ANTICANCER DRUG UTILIZATION FOR THE TREATMENT OF BREAST CANCER AT REGIONAL CANCER CENTERS IN THAILAND

Miss Chaninun Ketkaew

A Dissertation Submitted in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy Program in Social and Administrative Pharmacy

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รูปแบบการใช้ยาต้านมะเร็งในโรคมะเร็งเต้านมที่ศูนย์มะเร็งภูมิภาคของประเทศไทย

นางสาวชนินันท์ เกตุแก้ว

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรดุษฎีบัณฑิต
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By	Miss Chaninun Ketkaew
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Thesis Advisor	Assistant Professor Niyada Kiatying-angsulee

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.....Dean of the Faculty of Pharmaceutical Sciences
(Assistant Professor Rungpetch Sakulbumrungsil)

THESIS COMMITTEE

.....Chairman
(Assistant Professor Rungpetch Sakulbumrungsil)

.....Thesis Advisor
(Assistant Professor Niyada Kiatying-angsulee)

.....Examiner
(Associate Professor Vithaya Kulsomboon)

.....Examiner
(Assistant Professor Puree Anantachoti)

.....External Examiner
(Kitisak Thepsuwan M.D.)

ชนินันท์ เกตุแก้ว : รูปแบบการใช้ยาต้านมะเร็งในโรคมะเร็งเต้านมที่ศูนย์มะเร็งภูมิภาคของประเทศไทย. (ANTICANCER DRUG UTILIZATION FOR THE TREATMENT OF BREAST CANCER AT REGIONAL CANCER CENTERS IN THAILAND) อ.ที่ปรึกษาวิทยานิพนธ์หลัก: ผศ. ภญ. ดร. นิยดา เกียรติยิ่งอังศุลี, 4 หน้า.

สิ่งที่ผู้เกี่ยวข้องตระหนักเกี่ยวกับการรักษาโรคมะเร็งด้วยยา คือ ต้นทุนค่ายาที่สูงขึ้น ยาตัวใหม่ที่มีราคาแพง นโยบายการเบิกจ่ายค่ารักษาพยาบาล แนวทางการรักษาที่มีหลากหลายและแตกต่างกัน และปัจจัยด้านอื่นๆที่จะทำให้เกิดการใช้งบประมาณสิ้นเปลือง การรักษาที่ไม่สอดคล้องกับแนวทางเวชปฏิบัติ อันจะนำไปสู่คุณภาพการให้บริการที่ลดลง เพื่อให้ทราบถึงสถานการณ์การใช้ยารักษาโรคมะเร็งเต้านม การศึกษาครั้งนี้มีวัตถุประสงค์เพื่อ อธิบายรูปแบบการใช้ยารักษาโรคมะเร็งเต้านม วิเคราะห์ความสมเหตุสมผลของการสั่งใช้ยา และค้นหาปัจจัยที่ส่งผลต่อรูปแบบการใช้ยา และความสมเหตุสมผลในการสั่งใช้ยา ทั้งนี้ในมุมมองของผู้ให้บริการ ทำการศึกษาแบบย้อนหลังจากใบสั่งยาผู้ป่วยนอกของผู้ป่วยโรคมะเร็งเต้านมที่มีการสั่งใช้ยาที่ศึกษา ณ ศูนย์มะเร็งภูมิภาค 7 แห่ง ระหว่างเดือนมกราคมถึงมิถุนายน 2553 จำนวน 7,520 ใบสั่งยา วิเคราะห์รูปแบบการสั่งใช้ยารักษาโรคมะเร็งโดยแบ่งเป็น 3 กลุ่ม คือ ยาเคมีบำบัด (3,485 ใบสั่งยา) ยาต้านฮอร์โมน (3,930 ใบสั่งยา) และยารักษาแบบมุ่งเป้า (105 ใบสั่งยา) ประเมินความสมเหตุสมผลในการสั่งใช้ยา 3 รายการ คือ Docetaxel, Letrozole และ Trastuzumab การค้นหาปัจจัยที่มีผลต่อรูปแบบการสั่งใช้ยาและความสมเหตุสมผลในการสั่ง ใช้ยาใช้สถิติวิเคราะห์ Chi-square, Man-Whitney U Test และ 2-Independent Sample Test สำหรับตัวแปรอิสระปัจจัยเดียว และใช้สถิติ Logistic Regression ในการวิเคราะห์ตัวแปรอิสระร่วมหลายปัจจัย

ผลการศึกษาแสดงรูปแบบของการสั่งใช้ยาดังนี้ พบการสั่งใช้ยาต้นแบบและยานอกบัญชียาหลักแห่งชาติมากที่สุดในกลุ่มยาต้านฮอร์โมน คิดเป็นร้อยละ 26.50 และ 9.35 ตามลำดับ ยาเคมีบำบัดมีการสั่งใช้ยาร่วมรักษามากที่สุด คิดเป็นร้อยละ 92.60 การสั่งใช้ยามีความสอดคล้องกับแนวทางปฏิบัติคิดเป็นร้อยละ 92.60 ร้อยละ 94.35 และร้อยละ 100.00 ในกลุ่มยาเคมีบำบัด กลุ่มยาต้านฮอร์โมน และกลุ่มยารักษาแบบมุ่งเป้าตามลำดับ มีเพียงยาเคมีบำบัดสูตร CMF (Cyclophosphamide, Methotrexate and Fluorouracil) สูตรเดียวเท่านั้นที่ค่ายาเฉลี่ยไม่เกินมูลค่าการจ่ายชดเชย ด้านการสั่งยาร่วมรักษาพบว่า มากกว่าร้อยละ 90 ของใบสั่งยากลุ่มยาต้านฮอร์โมนและกลุ่มยารักษาแบบมุ่งเป้าไม่เกิดความเสี่ยงจากอันตรกิริยาระหว่างยา อีกทั้งวิธีการบริหารยาเคมีบำบัดตามลำดับที่ถูกต้องพบความเสี่ยงของอันตรกิริยาระหว่างยาน้อยกว่าร้อยละ 1 การประเมินความสมเหตุสมผลในการสั่งใช้ยา พบว่าร้อยละ 49.72 ของยา Docetaxel ร้อยละ 80.76 ของยา Letrozole และ ร้อยละ 100.00 ของยา Trastuzumab มีความเหมาะสมในการสั่งใช้ยาตามเกณฑ์ทางคลินิก ยา Docetaxel และ Letrozole ยังมีการใช้แบบประเมินการสั่งใช้ยาน้อยมากเมื่อเทียบกับยา Trastuzumab ด้านปัจจัยพบว่า ปัจจัยที่มีผลต่อการสั่งใช้ยา คือ นโยบายยานอกบัญชียาหลักแห่งชาติ นโยบายยาต้นแบบ มาตรฐานความปลอดภัยด้านยาโรงพยาบาล และระบบการเบิกจ่ายค่ารักษาพยาบาล ปัจจัยที่มีผลต่อความสมเหตุสมผลในการสั่งใช้ยา Docetaxel คือ มาตรฐานความปลอดภัยด้านยาโรงพยาบาล ระบบเบิกจ่ายค่ารักษาพยาบาล ความเชี่ยวชาญเฉพาะของแพทย์ และอายุของผู้ป่วย ปัจจัยที่มีผลต่อความสมเหตุสมผลในการสั่งใช้ยา Letrozole คือ ความเชี่ยวชาญเฉพาะของแพทย์ และอายุของผู้ป่วย ด้านปัจจัยประกอบที่มีผลต่อรูปแบบและความเหมาะสมในการสั่งใช้ยาเป็นไปตามสมการความถดถอยโลจิสติก

ภาควิชา เภสัชศาสตร์สังคมและบริหาร ลายมือชื่อนิสิต .....

สาขาวิชา เภสัชศาสตร์สังคมและบริหาร ลายมือชื่อ อ.ที่ปรึกษาวิทยานิพนธ์หลัก .....

ปีการศึกษา 2556

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CHANINUN KETKAEW: ANTICANCER DRUG UTILIZATION FOR THE TREATMENT OF BREAST CANCER AT REGIONAL CANCER CENTERS IN THAILAND. ADVISOR: ASST. PROF. DR. NIYADA KIATYING-ANGSULEE, 4 pp.

All stakeholders realized that cost of medications, new innovative medicines, reimbursement policy, clinical practice guideline or other factors may cause the overuse of budget, deviation from the guideline and finally leading to low quality of treatment. To explore the situation of anticancer drug, this research was aimed to describe the pattern of use, examine the appropriated use and elaborate factors affected pattern and appropriate use of anticancer drugs in healthcare provider perspective. Retrospective study was conducted by collecting anticancer drugs prescriptions from out-patients department at seven regional cancer centers of Thailand between January to June 2010. There were 7,520 analyzed prescriptions by three groups (3,485 of Chemotherapy, 3,930 of Hormone therapy and 105 of Targeted therapy) for describing pattern of use and three anticancer drugs (Docetaxel, Letrozole and Trastuzumab) were selected to examine the appropriate use. Chi-square, Man-Whitney U test, 2-Independent Sample test and Logistic regression were used to analyze.

The results showed pattern of prescribing original drug and non-National list of Essential Drug (NLED) were most frequently in hormone therapy drug as 26.50% and 9.35% respectively. Chemotherapy prescriptions showed the highest average percentage of concomitant drugs prescribing (92.60%). Due to National Health Service Office (NHSO) cancer guideline, the percentage of prescriptions that complied with the guideline in each group was 92.60%, 94.35% and 100.00% in chemotherapy, hormone therapy and targeted therapy respectively. To compare average cost of chemotherapy regimen found that only cost CMF (Cyclophosphamide, Methotrexate and Fluorouracil) regimen was under reimbursed cost. More than 90% of hormone and targeted therapy prescription did not found drug interaction and the sequential of administration lead to prevent drug interaction in chemotherapy. Drug use evaluation (DUE) by clinical evaluation show 49.72%, 80.76% and 100.00% appropriate in Docetaxel, Letrozole and Trastuzumab respectively even DUE forms were not all completed. The factor affected patterns of prescribing were non-NLED policy, original drug policy, medication safety standard policy and health benefit scheme. The factor affected appropriated use of Docetaxel were medication safety standard policy, health benefit scheme, physician specialist and age. The factor affected appropriated use of Letrozole were physician specialist and age. The logistic regression equation of all factors were analyzed for predicting the pattern and appropriate use.

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Student's Signature .....
Advisor's Signature .....

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CHAPTER I

INTRODUCTION

1.1 Statement of the problem

Cancer is the uncontrolled division of cells leading to abnormal growth of tissue. It is the leading cause of death in almost all countries. Nearly 12.7 million new cancer cases and 7.6 million cancer deaths occurred in 2008 worldwide (Globocan, 2008). In Thailand, 56,058 people death from cancer (88.34/100,000 people, 4.671 case/month or 156 case/day), it increase about 10.7% in 2009 (compare with 2005) (Ministry of Public Health, 2010). In 2010, all cancer case in Thailand were 241,051 patients, or 120 (female) – 140 (male) per 100,000 cancer patients. There were 3,314 new cancer cases (Attasara P & Buasom R, 2009). The most frequent cancer in female was breast cancer, the uncontrolled proliferation of breast ductal or lobular epithelial cells. Nearly 1.4 million of breast cancer worldwide and 458,503 deaths occurred in 2008 (Globocan, 2008). The number of breast cancer in Thailand was rising to 20,000 cases in 2008, more than cervical cancer which used to be the top of case in women, 4,600 breast cancer deaths. The new case breast cancers were detected up to 37% of all new patients per year (Attasara P & Buasom R, 2009).

Cancer treatment is kind of multimodality such as chemotherapy, radiotherapy, surgery, hormonal therapy and immunotherapy, which depended on type and stage of cancer. In breast cancer, medication treatment such chemotherapy, hormonal therapy and immunotherapy were the main treatments. The chemotherapy aimed to kill of the tumor cell while at the same time limiting unacceptable toxicity (Mkele, 2010). Hormonal therapy aimed to reduce or stop the role of related hormone in stimulating tumor cell growth. Immunotherapy had a role in inhibiting the proliferation and survival of cancer cell by competitive binding with specific antibody receptor on the tumor cell membrane. The example of immunotherapy for treating breast cancer was Trastuzumab, a humanized monoclonal antibody, binds to the extracellular

juxtamembrane domain of HER2 and inhibits the proliferation and survival of HER2-dependent tumors (Hudis, 2007).

As we have already known about high cost of anticancer drug, the pharmaceutical products developed for cancer are rapidly growth. There are more than 300 candidates of anticancer drug in the pipeline, 41 product from pharmaceutical company and 269 products from biotechnology company (Thomas F, 2009). Almost all biotechnology drugs were costly. Biopharmaceutical drugs were the kind of monoclonal antibodies, recombinant enzymes, and cytokines, which produced using cellular or molecular processes. Leading the list of expensive biotechnology agents were chemotherapeutic drugs (24 items, 36.9%), which the cost of each item is more than 12,000 (US$) per year (Rader, 2008).

Prescription survey from 31 public hospitals in Thailand 2009 by the comptroller general department shown that, anticancer was the highest cost of drug group in civil servant medication benefit scheme (CSMBS). The data in Table 1 confirmed that high cost of anticancer drug particularly in developing country.

Table 1 Cost of drugs use in civil servant medication scheme (CSMBS), 2009

Drug group	Prescriptions(10 months)		Average
	Number of prescription	Cost (million baht)	Baht/prescription
Antilipidemia	855,000	1,467	1,715
Anticancers	129,000	1,441	11,170
NSAIDs/Anti-osteoarthritis	891,000	1.022	1,147
Drug affecting bone metabolism	190,000	738	3,884
Anti-ulcerant/variceal bleeding	646,000	715	1,107

Source: The comptroller general department report

Due to the complicated disease and high cost of treatment, the clinical practice guidelines for cancers were developed. Guidelines regarded as important tools to improve the quality of care in clinical practice. They provide clinical care based on the best evidence available. By reducing practice variation they may lead to cost saving and better quality of care (Ottevanger, De Mulder, Grol, van

Lier, & Beex, 2004). In breast cancer patients, there were a significant association between treatment adherence and prolonged recurrence free and overall survival (Wockel et al., 2010). However the implementation of clinical practice guideline for cancer was not smoothly. On case review, 22% of the non-compliant incidences were justified and 16% seemed to be due to variation in chemotherapy and radiotherapy guideline interpretation in breast cancer (Balasubramanian, Murrow, Holt, Manifold, & Reed, 2003). There were multiple factors resulted low adherence to guideline including credibility of guideline, transparency, timely update, lack of system support to clinician, disseminating and implementing. As we already mentioned, development of anticancer drug was rapidly growth, so effective use of the guideline would be continually monitored.

Another related topic with adherence to guideline that often published was off-label use of anticancer drug. Off-label prescribing was the prescription of a registered medicine for a use that not included in the product information (Gazarian et al., 2006). The off-label use was more common in cancer more than other disease because the number of cancer type. In fact, each anticancer drug may be useful in several cancer type and many widespread anticancer drugs had not got the label for all the indications (Casali, 2007).

Due to the definition of rational use of drug that require patients receive medication appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community (World Health Organization, 2002), anticancer drugs should be closely monitored. Drug utilization study was a tool to identify how rational use of drugs and project the situation of drug use.

There were many studies about anticancer drug utilization from foreign countries. Utilization pattern of cancer chemotherapy drug in Nepal shown the equal rate of adjuvant and palliative chemotherapy is 38.33%. The most common of chemotherapy was alkylating agent (66%) and the common drugs use was cisplatin (27%) (Mallik, Palaron, Alam, Mishru, & Ravi Shankar, 2006). In China the utilization study shown as the consumption sum of anticancer drugs

increased 1.7 times from the year 2003. The constituent ratios of drugs in descending orders were: anticancer Chinese herbal medicine other kinds of anticancer drugs, antimetabolite, the anticancer antibiotic, and alkylating agent (Guonong., Bin., & Lin, 2007). Furthermore there were the utilization studies for specific purpose such as to benchmark for evaluating quality of practice. The optimal chemotherapy utilization rate in breast, lung and colorectal cancer were generated for comparing with the actual practice (Jacob et al., 2010; Weng Ng, Delaney G. P., Jacob S, & Barton M. B., 2010). In some study we had seen the defined daily dose (DDD) to measure the utilization pattern of anticancer drug, but because of the individual dosing calculation, DDD may sometime inappropriate for anticancer drugs.

In Thailand anticancer drug utilization studies were less. Almost all studies related to measure the outcome of treatment belonged to clinical practice guideline such as response rate and adverse drug reaction. The result of anticancer drug study in Thailand would be used to suggestion in further treatment. The examples of study about anticancer drugs were discussed. In cervical cancer, the study from Siriraj Hospital shown that 65.3% of patients were treated according to hospital clinical practice guideline, 70.4% of all that patients had complete response at 3 months. The overall results of clinical practice guideline treatment were comparable to the result of cervical cancer treatment in the literature (Ieumwananonthachai, 2003). In breast cancer, the study of using mitixantrone as a single agent shown well tolerates and offers comparable efficacy with less tolerable toxicity than other effective agents currently used as single agent in the treatment of advanced breast cancer (Tepmongkol, 1989). The disease free survival rate of breast cancer patients who received CMF (Cyclophosphamide 100 mg/m^2 p.o. day 1-4, Methotreaxate 40 mg/m^2 i.v. day 1 and 8, 5-Fluorouracil 600 mg/m^2 i.v. day 1 and 8) as adjuvant chemotherapy for six cycles was 66.66%. CMF chemotherapy is inadequate for controlling the disease in premenopausal patients because of high risk of recurrence and metastases than postmenopausal patients (Veerasarn, 1996).

To develop the policy or any intervention to promote rational use of drug, the situation should be known. However clinical study of cancer as previous discussed could not be projected the overall situation of anticancer drugs use in Thailand. To provide the situation of anticancer drug utilization in for policy maker, that's why this research would be conducted. The pattern of use and quality of use in anticancer drug would be described. Furthermore to elaborate such pattern of anticancer drug use, the factor influencing utilization should be identified in this study. This is a kind of retrospective study in health care provider prospective that will be explored quantitative aspect. This research start in breast cancer first because there are many suffered patients, high cost and rapidly launched of new treatment. Regional cancer centers were selected as the site of study because they were tertiary care hospital responsible for only cancer patients, under the department of medical services, ministry of public health. The result of this research would be proposed to the policy maker and stakeholders for considering how the utilization situation would be beyond the present context and how to develop policy in the future.

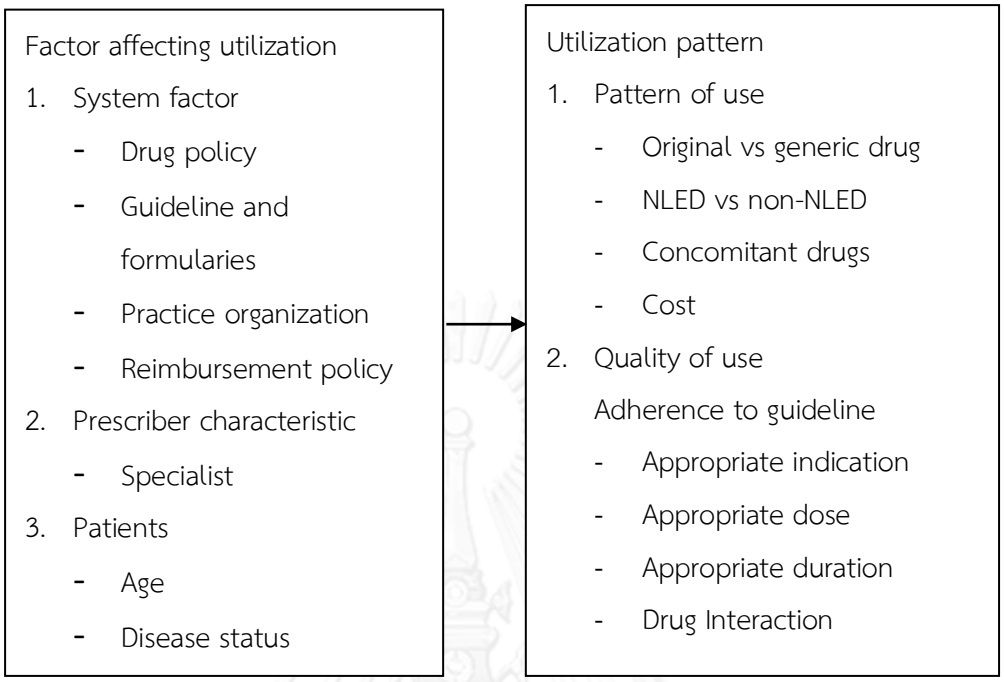
1.2 Research questions

1) What are the patterns of use of anticancer drugs?
2) How does the appropriate use of anticancer drugs?
3) What are the determinants affecting pattern of use and appropriate use of anticancer drug?

1.3 Objectives of study

1) To describe the pattern of use of anticancer drug
2) To examine the appropriate of use of anticancer drug
3) To elaborate the determinants affecting the pattern of use and the appropriate use of anticancer drug.

1.4 Conceptual Framework



The conceptual framework of this study was developed from factors influencing drug prescribing and the range of potential's outcome model (Lipton & Bird, 1993). This model was under the concept of drug utilization review (DUR) development program. The DUR program should be designed to correct the prescribing problems which may involve one or more the following: suboptimal choice of medication, wrong dosage, therapeutic duplication, inappropriate schedule or duration, potentially dangerous drug-drug interaction, lack of an acceptable indication for a drug, failure to prescribe a drug when one is needed, and prescribing expensive drugs when cheaper and equally effective agents were available. Underlying the development of DUR were assumptions regarding factors that either can improve or interrupt the quality of prescribing. These influences were identified in 3 components; system factor, prescriber characteristic and patients, all which affected the patients' outcome including adverse drug event, drug interaction and drug cost. The detail of conceptual framework will be discussed next.

Factors influencing utilization

1. System factor; exogenous or system factors, such as drug policies, formularies, reimbursement system, and medical/prescription record.

    1.1 Drug policies; Drug policies and utilization were related each other. When the policies were implemented, utilization pattern would be assumed to change and the utilization pattern will be served to the policy maker for developing the policy again (World Health Organization, 2003). The policies related to this study will be describe such the prior-authorization in anticancer drug, policy of cancer protocol, referred price that affected the selection of anticancer drug and national list of essential medicine. In this study drug policy and related factor were described as factor influencing utilization.

    1.2 Guidelines and formularies; The application of a carefully developed formulary theoretically provides the foundation for guiding clinicians in choosing the safest, most effective agents for treating particular medical problem. In USA, formulary development by the Joint Commission on Accreditation of Health Care Organization (JACHO) for more than 25 years was the process whereby a list of preferred drug product constructed and revised continuously to reflect pharmacologic improvement available in the market and clinical experience (T. D. Rucker & Schiff, 1990). In Thailand there was Thai National Formulary 2010 contained the criteria to prescribe anticancer drug which were the special access medicine. Formularies in cancer treatment were the subset of clinical practice guideline. Guideline was a tool to improve the quality of care in daily practice (Ottevanger et al., 2004). Many organizations developed the guideline of treatment breast cancer. In Thailand there were many source of guideline such as the national cancer institute incorporated with the royal college of medical oncology, the royal college of radiology and the royal college of surgery or the clinical practice guideline from national health security organization (NHSO). So the formularies and clinical practice guideline (CPG) were factor influencing prescribing and utilization in term of quality of use. In this study the formularies and CPG will

be described and use as the reference to evaluate the quality of anticancer drug use.

1.3 Practice organization; each hospital must have pharmaceutical and therapeutic committee (PTC) who set the hospital policy in all process of medication management. The goal of PTC was to ensure that patients received with the best possible cost-effective and quality of care through determining what medicines will be available, at what cost and how they will be use (Holloway K & Green T, 2003). The measures from PTC such as prescription policy, formularies due to the selection policy, and budget aspect. The practice organization may be affected by exogenous factor such national essential list and reimbursement system. The characteristic of practice organization will be observed to explain the pattern of utilization of anticancer drug.

1.4 Reimbursement Policy: To reimburse the medication expense in cancer was always strictly by payer because the high cost of treatment and sometime doubtful in indication. Many articles in USA had shown the controversy in reimbursing off-label of anticancer drug (Gazarian et al., 2006). In Thailand reimbursement policy in cancer treatment played role since 2007 by the Comptroller General Department in Civil Servant Medication Scheme (CSMBS). And the year later NHSO pronounced the cancer protocols which related to the condition of reimbursement. This study will explore how the reimbursement policy affected anticancer drug utilization by showing the pattern of anticancer drug use in each scheme.

2. Prescriber characteristic

2.1 Specialist; Knowledge-based mistakes were usually due to lack of knowledge about the relevant drug dose, coupled with difficulty accessing drug information (Nichols, Copeland, Craib, Hopkins, & Bruce, 2008). We might expect that physician with better; more extensive or more recent education would exhibit better, or at least different in prescribing practice (Christensen & Wertheimer, 1979). In cancer treatment physician should be the specialist

such as oncologist, radiologist or sergeants who were trained and has experience. In this study we collected the specialist of physicians who prescribe anticancer drug.

3. Patients; in this study the patients factor influencing utilization were age and the clinical disease status such as the stage of disease, size of tumor, the number of node-positive, hormone receptor status, menstrual condition and risk of recurrence. All clinical disease status would be the criteria for prescribing due to the guideline. In this study, age and the clinical disease status were collected from the medical record.

Utilization Pattern

1. Pattern of use: This covers the extent and profiles of drug and the trends in drug use and costs over time. This study measure the pattern of use such as following
   1) Pattern of use original drug and generic drug
   2) Pattern of use the drug in national list of essential medicine (NLED) and non-NLED
   3) Pattern of use anticancer drug belong to the guideline or formularies
   4) Pattern of use by cost; cost per regimen, cost per prescription
   5) Pattern of use concomitant drug; number of items, cost, ATC group of concomitant drug

2. Quality of use: This was determined using audits to compare actual use to national prescription guidelines or local drug formularies. Indices of quality of drug use may include the choice of drug (compliance with the guideline), drug cost (compliance with budgetary recommendation), drug dose (awareness of individual variation in dose requirement) and awareness of drug interaction and adverse drug interaction. The quality of anticancer drug use in this study was measure by drug utilization evaluation (DUE) system. Some anticancer drugs already had criteria in prescribing or DUE form.

1.5 Area of study

This was retrospective study in term of health care provider perspective. The study conducted in 7 regional cancer centers, Department of Medical Service, Ministry of Public Health.

1.6 Expected outcome

The situation of anticancer drug utilization in breast cancer in term of the pattern of use, the appropriate use and the determinant affecting utilization will be usefully for the policy maker to develop the intervention or policy for promoting the rational use of anticancer in Thailand.

CHAPTER II

LITERATURE REVIEW

This chapter reviewed about the burden and mortality of breast cancer around the world and Thailand, cancer drug situations, clinical practice guideline in breast cancer, rational use of anticancer drug, method of anticancer drug utilization and early related research about anticancer drug utilization in breast cacner.

2.1 World Cancer Situation (Globocan, 2008)

Nearly 12.7 million new cancer cases and 7.6 million cancer deaths occurred in 2008 worldwide. The number of new cancer cases ranges from 3.7 million in Eastern Asia. In men, the incidence of cancer is high in Northern America (ASR 334 per 100,000), Australia/New Zealand (ASR 356.8) and in Northern and Western Europe (ASRs 288.9 and 335.3 respectively) as a consequence of the high rates of prostate cancer in these regions (ASRs greater than 80 per 100,000 in all). As in males, the regions with the highest incidence rates in females were Northern America (ASR 274.4 per 100,000), Australia/New Zealand (ASR 276.4) and Northern and Western Europe (ASRs 257.8 and 250.5 respectively) as a consequence of the high rates of breast cancer in these regions (ASRs greater than 75 per 100,000). The lowest cancer incidence rates were in Middle and Western Africa and in South-Central Asia for men and in Middle and Northern Africa for women (ASRs less than 100 per 100,000). The ratios of ASRs of incidence between developed and developing regions were 1.8 in men and 1.6 in women, while the same ratios for mortality were much lower, 1.2 and almost 1.0 in woman. Women living in sub-Saharan Africa had the same risk of dying from cancer as women living in Central and Eastern Europe (ASRs greater than 90 per 100,000 in all). A number of common cancers in developed countries were associated with reasonably high survival (prostate, breast and colorectal cancers), whereas several common cancers with poorer prognoses (liver, stomach and esophageal cancers) were more common in less developed regions. The data show in Table 2.1.

2.1.1 Breast Cancer Incidence and Mortality Worldwide

Breast cancer was by far the most frequent cancer among women with an estimated 1.38 million new cancer cases diagnosed in 2008 (23% of all cancers), and ranks second overall (10.9% of all cancers). It was now the most common cancer both in developed and developing regions with around 690,000 new cases estimated in each region (population ratio 1:4). Incidence rates varied from 19.3 per 100,000

women in Eastern Africa to 89.7 per 100,000 women in Western Europe, and were high (greater than 80 per 100,000) in developed regions of the world (except Japan) and low (less than 40 per 100,000) in most of the developing regions. The range of mortality rates was much less (approximately 6-19 per 100,000) because of the more favorable survival of breast cancer in (high-incidence) developed regions. As a result, breast cancer ranked as the fifth cause of death from cancer overall (458,000 deaths), but it still the most frequent cause of cancer death in women in both developing (269,000 deaths, 12.7% of total) and developed regions, where the estimated 189,000 deaths was almost equal to the estimated number of deaths from lung cancer (188,000 deaths). The data show in Figure 2.1

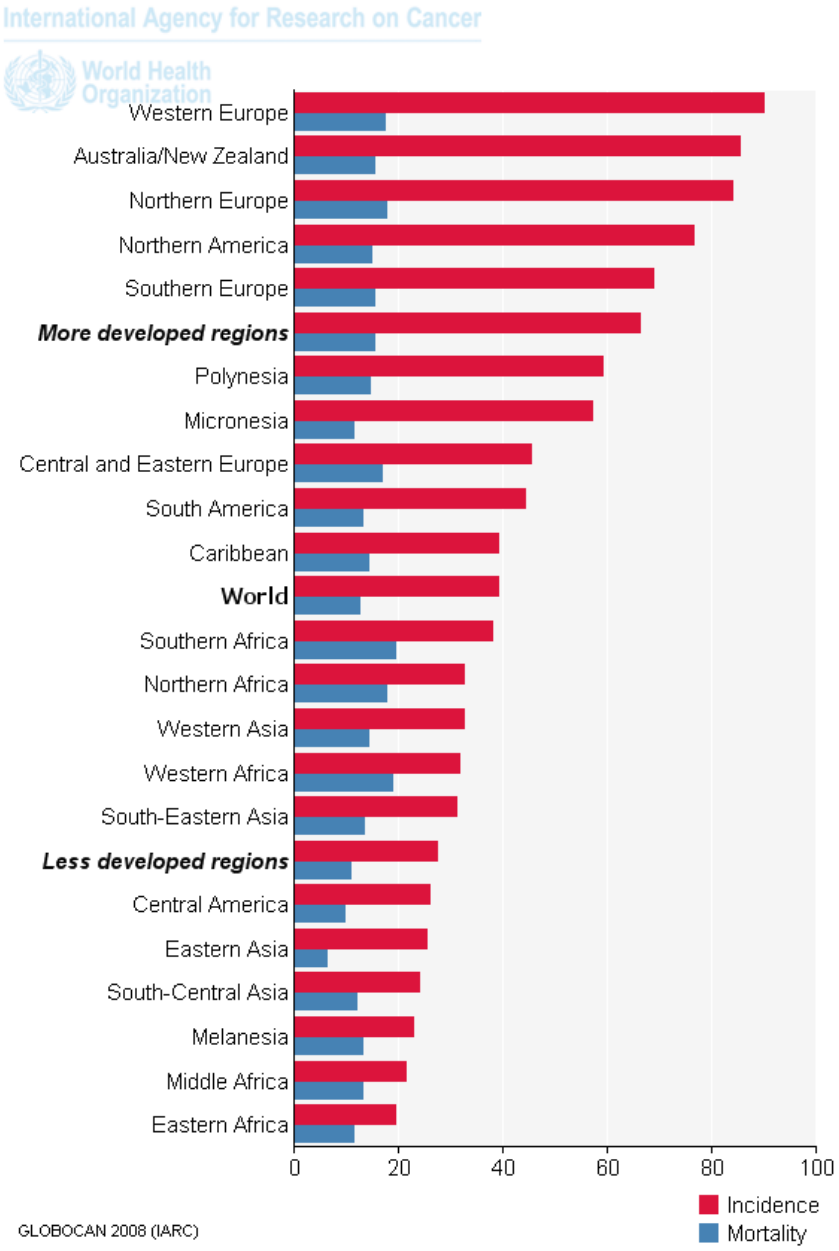
Table 2 Cancer Incidence and Mortality worldwide in 2008

Estimated numbers (thousands)	Men		Women		Both sexes	
	Cases	Deaths	Cases	Deaths	Cases	Deaths
World	6,617	4,219	6,044	3,345	12,661	7,564
More developed regions	2,964	1,522	2,591	1,222	5,555	2,744
Less developed regions	3,653	2,697	3,453	2,122	7,106	4,819
WHO Africa region (AFRO)	253	209	318	226	571	435
WHO Americas region (PAHO)	1,276	611	1,233	568	2,509	1,179
WHO East Mediterranean region (EMRO)	214	169	214	144	428	313
WHO Europe region (EURO)	1,812	1,038	1,610	822	3,422	1,860
WHO South-East Asia region (SEARO)	742	567	910	565	1,652	1,132
WHO Western Pacific region (WPRO)	2,316	1,621	1,755	1,016	4,071	2,637
IARC membership (21 countries)	3,073	1,612	2,817	1,352	5,890	2,964
United States of America	745	294	692	271	1,437	565
China	1,622	1,222	1,194	736	2,816	1,958
India	430	321	518	312	948	633
European Union (EU-27)	1,324	693	1,119	540	2,443	1,233

ASRs: Age-standardized incidence rates per 100,000 populations

Source: WHO report 2008

Figure 2.1 Breast Cancer Incidences and Mortality Worldwide in 2008(Globocan, 2008)



Source: (Globocan, 2008)

2.1.2 The cancer burden in Asia

In 2002, 4.2 million new cancer cases, 39% of new cases worldwide were diagnosed among 3.2 billion persons (48% of the world population) living in the fifteen most highly developed countries in South, East, and Southeast Asia: Japan, Taiwan, Singapore, South Korea, Malaysia, Thailand, China, Philippines, Sri Lanka,

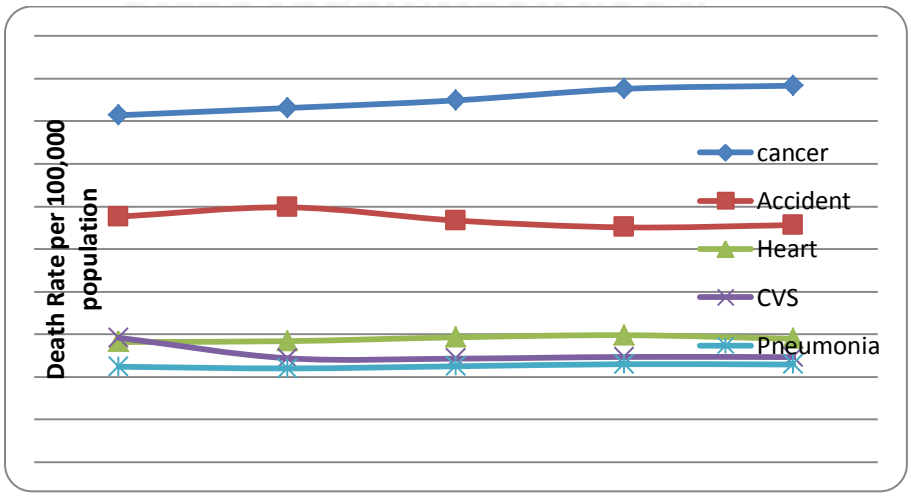
Vietnam, Indonesia, Mongolia, India, Laos, and Cambodia. China and India, together accounting for 37% of the worldwide population, reported 3 million of these newly diagnosed cancer cases. In 7 of these Asian countries, lung cancer was the highest incidence rate (age-standardized) of all cancers in males, and breast cancer was the highest incident cancer for females. Lung cancer was the highest death rate (age-standardized) for males in the majority of these Asian countries, and breast cancer ranks among the top-five mortality rate cancers for females in all.

There are 3.6 million males and 4.0 million females living with cancer in these Asian countries; China alone had 1.6 million male and 1.5 million female cancer survivors. Although the United States had a much smaller population than China (303 million), it had 50% more cancer survivors (2.4 million males and 2.3 million females living with cancer). In most of the Asian countries, cancer of the colon and rectum were the most common among male cancer survivors; among female survivors, breast cancer was the most common in most Asian countries.

2.2 Thailand cancer situation

In Thailand, cancer is the major cause of death since 2005. There were 56,058 people death from cancer (88.34/100,000 people, 4.671 case/month or 156 case/day), it increased about 10.7% in 2009 (compare with 2005) (Ministry of Public Health, 2010). Figure 2.2 show that cancer is the major cause of death.

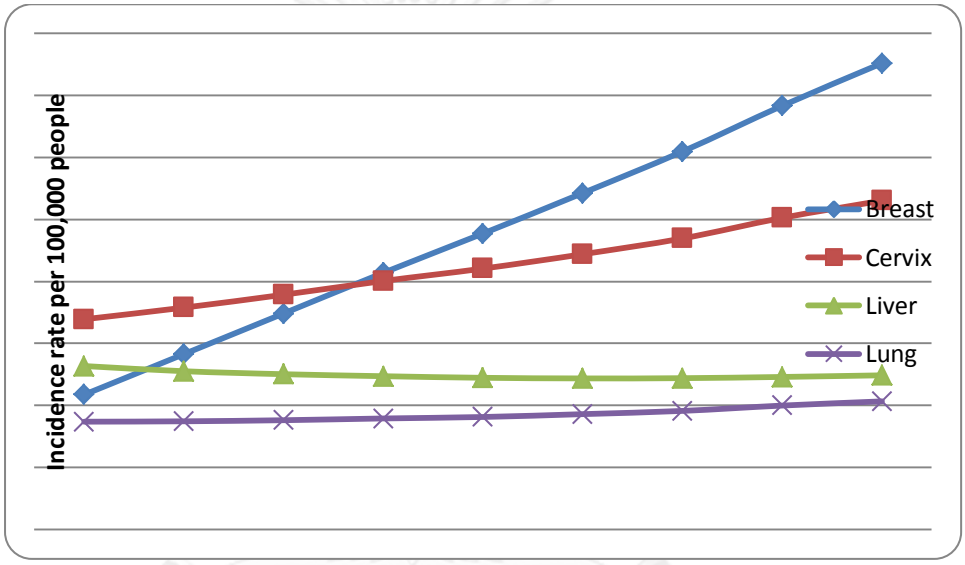
Figure 2.2 Death Rate per 100,000 populations by the leading cause of death in Thailand 2005-2009



Source : (Ministry of Public Health, 2010)

In 2010, all cancer case were 241,051 patients, or 120 (female) – 140 (male) per 100,000 cancer patients. The most frequent cancer in female was breast cancer that was the uncontrolled proliferation of breast ductal or lobular epithelial cells. The number of breast cancer in Thailand would be rising to 37.6 cases per 100,000 in 2013-2015, more than cervical cancer which used to be the top of case in female.

Figure 2.3 Incidence rate per 100,000 people of each type of cancer in female since 1989 – 2015



Source: (Attasara P & Buasom R, 2009)

2.3 Anticancer drug situation worldwide

There were many aspects of the study about anticancer drug around the world such as new drug development, cost, affordability, utilization and reimbursement policy.

1) Anticancer drug development

Cancer chemotherapy celebrated its sixtieth anniversary in 2005. It was in 1945 that wartime research on the nitrogen mustards, which uncovered their potential use in the treatment of leukemia and other cancers, was first made public. Fifty year later, more than sixty drugs have been registered in the USA for the treatment of cancer (Connors, 1996).

In 1950 more alkylating agent were developed, and with better success. To this day, chlorambucil, melphalan, and busulphan still the major roles in treating haematological cancers. The subsequent discovery and use of nitrosoureas and antimetabolites such as 5-fluorouracil quickly followed. Other class that have also been developed include anthracyclines, antitumor antibiotics that interfere with DNA replication enzymes, topoisomerase inhibitors that also target enzymes critical for DNA replication, as well as plant alkaloid-based mitotic inhibitors.

A further key discovery came in 1965, when platinum compounds were discovered in experiment investigating whether bacteria can grow in electric fields. The electrodes used in these experiments were coated with platinum, and while electricity alone did not impact cell division, the platinum and buffer liquid reacted together to form a highly toxic compound that halted bacteria cell division. The first platinum salt that was approved for use as an anticancer was cisplatin (DeVita & Chu, 2008).

In 1997 the first monoclonal antibody was approved, Imatinib. Since then there were many biological product discovered and approved. Biological products include a wide ranges of products such as vaccines, blood and blood components, allergenic, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. Biologics can be composed of sugar, proteins, or nucleic acids or complex combinations of these substances, or maybe living entities such as cells and tissues. Biologics were isolated from a variety of natural sources such human, animal, or microorganism and may be produced by biotechnology methods and other cutting edge technologies. In general the term “drugs” includes therapeutic biologic product. The data on the approval of new molecular entities (NMEs) approved by the U.S. Food and Drug Administration (FDA) for the treatment of cancer. The examines products, which included both drugs and vaccines, were those included in the U.S. National Cancer Institute (NCI) “alpha list” of cancer drugs. The July 2011 version of the alpha list includes 100 unique molecular entities, as well as a number of new formulations of combinations and chemotherapeutic

regimens (Miano P, 2011). Table 2.2 shown the number of new molecular entities as biological drugs registered by the period of time.

Table 3 The number of new molecular entities registered since 1952

Year	1952-1989	1990-1999	2000-2010	2010-2011	Total
Numbers	21	27	45	7	100

2) Cost of anticancer drugs

As the U.S. FDA had a huge increase in investigational agents studied in cancer, from 925 investigational new drug applications in 2003 to 1440 in 2008. Innovative drug development was slow and expensive. From 5000 to 10,000 compounds in pre-clinical trials, only 0.1% reaches clinical trial stage and of these, only 10-20% were finally approved with typical development times of 15 years (Schickedanz, 2010). The high cost of bringing a novel biologic drug to market had been estimated at 800 million US dollar in 2006. As a result, the American drugs budget rose four times in the decade 1998-2008 (Adams & Brantner, 2006).

Ambulatory cancer care seems to be the driver for the increase in costs. The USA Medicare spending on drugs administrator in a doctor's office, the vast majority of which was cancer treatment, rose from 3 billion US dollar in 1997 to 11 billion US dollar in 2004, a 267% increase while overall Medicare spending rose by only 47% over the same period (N. L. Rucker, 2007). The American data was confirmed in Europe. In France, the cancer drugs budgets had been doubling every 4 years, rising from €474 million in 2004 to €975 million in 2008 (Hillner & Smith, 2009).

Cost problem in cancer care were universal. In the Republic of Korea, cancer patients may face huge bills because the Korean National Health Insurance Scheme covers only 75% of the cost. The Republic of Korea had the highest out-of-pocket spending of any OECD country, with 36% of total health expenditure coming directly from patients' payment at the point of

service in 2007. In 2007, an estimated 3% of all households in the country suffered catastrophic expenditure, defined by the WHO as an obligatory disbursement greater than or equal to 40% of residual household income after basic needs had been met (Cornes P, 2008).

As an example of the effect of novel drugs on the costs of cancer care, the cost of treatment using standard of chemotherapy regimen evidenced by randomized trials for metastatic colon cancer was compared over time. Using the Mayo clinic regimen of 5-fluorouracil and leucovorin as a benchmark at 63 US dollar for drugs for 8 weeks treatment the costs rose with each improvement. Second generation regimens containing irinotecan or oxaliplatin cost 9,497 US dollar to 11,899 US dollar for 8 weeks treatment, while third generation regimens containing bevacizumab or cetuximab cost 21,330 US dollar to 30,790 US dollar. The data shown in Table 2.3, while some argument that this cost represented value for the improvement outcome, other point out the clinical benefit were not proportionate to the rise in cost of drugs.

Table 4 Cost of treatment metastatic colon cancer in USA

Treatment Era	**Drug regimens**	Cost of 8 weeks treatment in US dollar
1st Generation	Mayo clinic regimen of 5-fluorouracil and leucovorin	63
2nd Generation	Regimens containing irinotecan or oxaliplatin	9,497 – 11,899
3rd Generation	Regimens containing biologic drug: bevacizumab or cetuximab	21,399 – 30,790

3) Off-label use of anticancer drug

There were many articles around the world mentioned about off-label anticancer drug use. The off-label use of anticancer drugs had been estimated to reach 50% particularly in pediatric cancer. Off-label uses of anticancer drug often had evidence based and therefore fall within the state of art. In principle, a drug can be off-label under three conditions.

a) Because steps to extend the approval have not been made, although evidence of efficacy is available
b) Because it falls into the “gray zone” of evidence based medicine, within which high-level evidence was difficult to reach even for treatments which were likely effective
c) Because the drug was ineffective or at least there was no reason to believe in the effectiveness. The off-label use was more common in cancer more than other disease because the number of cancer type. In fact, each anticancer drug may be useful in several cancer type and many widespread anticancer drugs had not got the label for all the indications (Casali, 2007).

Many studies shown off-label use of anticancer drug, from self-reported practices and attitudes of US oncologists regarding off-protocol therapy, ninety-three percent of oncologists responded reported ever discussing and eighty-one percent ever prescribing off-protocol. Especially for academic oncologists who were more likely than community oncologists to have ever prescribed off-protocol (89% vs. 75%), to discuss off-protocol at least once/month (41% vs. 19%), and to deny requests for off-protocol at least once/month (16% vs. 2%).

Another study that aimed to quantify the extent of off-label prescribing in a hospitalized oncology population in Australia, 1351 prescriptions from 130 patients were classified as licensed, off-label or unlicensed. In 293 (22%) of the prescriptions the drugs was either off-label (242, 18%) or unlicensed (51, 4%). Among the 130 patients, 110 (85%) received at least one drug that was prescribed off-label or that was unlicensed. Off-label dosing was the most frequent reason for a drug being off-label (139, 10% of all prescriptions). Off-label due to use for unapproved indication was found in 117 prescriptions (9%) and off-label due to unapproved route of administration was found in 38 prescriptions (3%) (Poole & Dooley, 2004).

In French teaching hospital, the perspective study evaluated proportion of off-label anticancer drug use in terms of indication, 6168 prescriptions were administered to 1206 patients. 415 (6.7%) prescriptions presented a drug used in an off-label manner (Leveque, Michallat, Schaller, & Ranc, 2005).

In anticancer drug, there were examples of off-label drug in various topic, which confirmed the previous discuss that off-label-use was common. Table 2.4 show the example of off-label of anticancer drug use (Leveque et al., 2005).

Table 5 Example of off-label anticancer drug use

Topic	Off-label practice
Type or subtype of cancer	- Oxaliplatin is a drug approved for colorectal cancer but used in breast cancer - Trastuzumab used in ERBB2-positive breast cancer - Liposomal doxorubicin is approved for metastatic breast cancer in patients with an increased cardiovascular risk but used in patients without this risk
Dose	- High dosing of carboplatin in intensive chemotherapies instead of the approved dose
Expression of dosing	- Fixed dose of trastuzumab prescribed instead of that adjusted for bodyweight
Association of drug approved as monotherapy	- Raltitrexed combined with irinotecan in metastatic colorectal cancer - Trastuzumab with chemotherapy in pretreated metastatic breast cancer
Drug approved in combination but given as single agent	- Bevacizumab administration for metastatic colorectal cancer
Type of association	- Trastuzumab given with vinorelbine instead of paclitaxel or docetaxel in untreated metastatic breast cancer
Schedule of administration	- Every week instead of every 3 weeks for paclitaxel and docetaxel
Duration of treatment	- Trastuzumab given beyond progression in metastatic breast cancer
Route of administration	- Intraperitoneal injection of cisplatin rather than intraveneous - Subcutaneous administration of alemtuzumab instead of intraveneous
Age	- Use of adult-approved drugs in children

Source : (Leveque et al., 2005)

2.4 Anticancer drug situation in Thailand

The cabinet already passed the Thai National Drug Policy 2011 and Strategies to Develop Nation Drug System 2011-2016 since March, 14 2011. The national Thai drug committee was assigned to indicate framework, target, indicators and the evaluation system to achieve that policy. The vision of Thai National Drug Policy was universal access to essential medicines, rational use of medicine and relies on ourselves (Ministry of Public Health, 2011). That concept was surely included anticancer drug. There were many intervention and related regulation due to promote accessibility and rational use of anticancer drug. It will be discussed further.

1) The government use of patents on the four-anticancer drug in Thailand

There were many new chemotherapeutic and targeted therapies that have been developed in the last decade. Most of these new anticancer drugs were patented, costly, and cannot be accessed by the poor, nor by many members of the middle class. Many of these new drugs were not included in the National List of Essential Drugs (NLED) due to their high price and not covered by the National Health Insurance system. Patients who try to pay their expense out of pocket will face the financial problem and maybe drop out from the treatment. The National Health Security Board realized that problems and find the way to provide universal access to essential medicine without financial barrier. In 2007 the implementation of the Government Use of Patents on the four anticancer drugs was based on the advised of the Subcommittee on Selecting Essential Drugs with Access Problem under the National Health Insurance schemes and was confirmed by the Committee to Support the Implementation of the Government Use of Patents. The only reason for the implementation of the Government Use of Patents was to allow universal access to essential medicines by all the beneficiaries of the National Health Security System. There were four anticancer drugs were used on patents as follow (National Drug Committee, 2008).

a) Docetaxel (trade name Taxetere) was used to treat lung, breast and prostate cancer. The price of 80 mg. injection of patented drug was 25,000

Baht, while the generic drug was only 4,000 baht, representing a price differential of more than 6 times.

b) Letrozole (trade name Femara) was used to treat breast cancer. The price of 2.5 mg. tablet was 230 Baht, while the generic drug was only 6-7 Baht, representing a price differential of more than 30 times.

c) Erlotinib (trade name Tarceva) was used to treat lung cancer. The price of 150 mg. tablet was 2,750 Baht, while the generic drug was only 735 Baht, representing a price differential of more than 4 times.

d) Imatinib (trade name Glivec) was used to treat chronic myeloid leukemia (CML) and gastrointestinal stromal tumor (GIST). The price of 100 mg. tablet was 917 Baht, while the generic drug was only 50-70 Baht, representing a price differential of more than 120 times.

In conclusion, these were four essential anticancer drugs can be made available at price ranging from 4 to 30 times lower than the patented drugs. These lower prices would be affordable to the National Health Insurance Schemes, which would provide the drug to all need them. There were 4 years after implementation, until now many cancer patients can access to drugs.

2) National List of Essential Medicine 2008(National Drug Committee, 2008)

The last update of the National List of Essential Medicine was launched in 2008 and updating continually online. The medicines used to treat cancer were under the group related to pharmacology. Anticancer was under category-8, drug uses for malignant disease and immunosuppression. Subgroup 8.1, cytotoxic drugs which contained 28 items, and subgroup 8.3, sex hormones and hormone antagonists in malignant disease contained 4 items of drugs. Almost all new anticancer drugs, especially biotechnology product were still out of the National List of Essential Medicine 2008 (National Drug Committee, 2008).

However for anticancer drug, there was The National Formulary 2010: special access to medicine of national list of essential medicine or TNF 2010 was launch in 2010. This manual was the tool for promoting rational use of medicine under the drug monitoring mechanism through the related central committee.

This manual contained the guideline of prescription, monitoring system and the collecting form when prescribing (Subcommittee of National Drug List of Essential Medicine 2010, 2010). Three items of anticancer drug were in this manual such Docetaxel, Letrozole and Imatinib. The manual aimed to use as reference in all health service schemes. Especially the National Health Security System which already implemented the reimbursement process due to TNF 2010.

More than 50% of anticancer drug items registered in Thailand were out of the list of national list of essential medicine 2008. The number of non-essential drug list of anticancer drug was much more than the number of essential drug list of anticancer drug. Are you sure that all cancer patients can access to anticancer drug? This study shows you the pattern of anticancer drug use between essential and non-essential anticancer drug.

3) Reimbursement system or health service scheme

In Thailand 2011, of 65 million population, there are 3 main health schemes such the National Health Scheme (NHS), the Social Security Service (SSS), the civil servant medication service scheme (CSMBS). The number of Thai population separated into any scheme show in the Table 2.4 (National Health Scheme, 2009).

Table 6 The number of Thai population separated into any scheme (million peoples)

Scheme	2002	2003	2004	2005	2006	2007	2008	2009
NHS	45.35	45.97	47.1	47.34	47.54	46.67	46.95	47.56
SSS	7.12	8.09	8.34	8.74	9.2	9.58	9.84	9.61
CSMBS	4.05	4.03	4.27	4.15	4.06	5.13	5	4.96

Source: (National Health Scheme, 2009)

The healthcare cost of NHS each year is presented in Table 2.5 and the healthcare cost of CSMBS is presented in Figure 2.5

Table 7 The amount of budget of NHS each year since 2003 - 2009

Budget Million Baht	2003	2004	2005	2006	2007	2008	2009
Scheme budget	56,091.23	61,212.39	67,482.60	82,023.00	91,366.72	101,984.10	108,065.09
Managemen t budget	1,600	1,021.32	625.00	647.00	810.96	807.96	936.75
Total	57,691.23	62,233.71	68,107.60	82,670.00	92,177.68	102,792.06	109,001.84

Source: (National Health Scheme, 2009)

Almost 50 million Thai people were under NHS which the total health expenditure around 109,000.01 million Baht per year. Whereas CSMBS covered only 5 million people but loaded the health expenditure almost 60,000 million Baht in 2008. While the Thailand National Drug Policy 2011 concerned about accessibility to essential medicine. There should not have any limited condition to access to anticancer drug especially that drugs are needed in all scheme, but there were different ratio of cost between NHS and CSMBS. However there were some regulations from any scheme which related to reimbursement system affect the prescribing pattern and utilization of anticancer drugs.

Reimbursement system of CSMBS was divided as out-patient department (OPD) and in-patients department (IPD). OPD was reimbursed by fee for service and IPD was reimbursed based on DRG (Diagnosis Related Group). Anticancer drug used in IPD was reimbursed all if they have drug code-X. The comptroller general department showed the retrospective data from 31 public hospitals for 10 months. Anticancer was in the list of high cost drug, while the number of prescriptions is lower than other group. It confirmed that anticancer was high cost themselves. The list was shown in Table 2.6

The comptroller general department created some regulation for hospital to review the process of prescribing and recording medical record to promote the rational use of medicine. If the hospital may not follow the regulations, they must pay back that cost return to the scheme. Those regulations were followed (The Comptroller General Department, 2011).

- Reviewed the treatment belong to the guideline
- Completely record all process of diagnosis and treatment in medical record
- Emphasized PTC to monitor and evaluate medicine use
- Reported the quantity of drug use and the result from the evaluation process

The situation like CSMBS, NHS had some regulation affect the prescribing and utilization pattern of anticancer drug. The regulation as cancer protocol, that physician must follow when treat the out patients department (OPD) in 8 type of cancer. This study will identify the pattern of anticancer drug use in any scheme beyond the regulations that assumed to be affected.

Table 8 Top-ten cost of drug use in CSMBS

Drug group	Total prescription		NED prescription		Expected save cost (Baht)	%
	No. of prescription (x 1000)	Cost (Million Baht)	No. of prescription (x 1000)	Cost (Million Baht)		
No. of prescription	16,648	15,248	6,617	10,040		
1. Anti-ulcerant/ variceal bleeding	646	715	261	666	599	3.9
2. NSAIDs/anti-osteoarthritis	891	1,022	671	993	415	2.7
3. Antilipidemia	855	1,467	377	1,266	1,009	6.6
4. Angiotensin converting enzyme (ACE) inhibitors	263	125	74	99	87	0.6
5. Angiotensin-II receptor blockers (ARBs)	327	622	280	558	158	1.0
6. Antiplatelets	475	468	24	37	376	2.5
7. Glucosamine	-	-	-	442	442	2.9
8. Drug affecting bone metabolism	190	738	187	712	712	4.7
9. Anticancers	129	1,441	21	647	647	4.2
Total	4,614	7,679	2,057	5,488	4,851	31.8

Source: (The Comptroller General Department, 2011)

2.5 Anticancer drug use in breast cancer

1) Medication Treatment of Breast Cancer

Chemotherapy

Chemotherapy was a cancer treatment that uses drugs to stop the growth of cancer cells, either by killing the cells or by stopping them from dividing. When chemotherapy was taken oral or injected intravenous or muscle, the drugs enter the bloodstream and can reach cancer cells throughout the body (systemic chemotherapy). When chemotherapy was placed directly into the cerebrospinal fluid, an organ, or a body cavity such as the abdomen, the drugs mainly affect cancer cells in those areas (regional chemotherapy). The way the chemotherapy was given depends on the type and stage of the cancer being treated.

Hormone therapy

Hormone therapy was a cancer treatment that removes hormones or blocks their action and stops cancer cells from growing. Hormones were substances produced by glands in the body and circulated in the bloodstream. Some hormones can cause certain cancers to grow. If tests show that the cancer cells have places where hormones can attach (receptors), drugs, surgery, or radiation therapy was used to reduce the production of hormones or block them from working. The hormone estrogen, which makes some breast cancers grow, was made mainly by the ovaries. Treatment to stop the ovaries from making estrogen was called ovarian ablation.

Hormone therapy with tamoxifen was often given to patients with early stages of breast cancer and those with metastatic breast cancer (cancer that has spread to other parts of the body). Hormone therapy with tamoxifen or estrogens can act on cells all over the body and may increase the chance of developing endometrial cancer. Women taking tamoxifen should have a pelvic exam every year to look for any signs of cancer. Any vaginal bleeding, other than menstrual bleeding, should be reported to a doctor as soon as possible.

Hormone therapy with an aromatase inhibitor was given to some postmenopausal women who have hormone-dependent breast cancer. Hormone-dependent breast cancer needs the hormone estrogen to grow. Aromatase inhibitors decreased the body's estrogen by blocking an enzyme called aromatase from turning androgen into estrogen.

For the treatment of early stage breast cancer, certain aromatase inhibitors may be used as adjuvant therapy instead of tamoxifen or after 2 or more years of

tamoxifen. For the treatment of metastatic breast cancer, aromatase inhibitors were being tested in clinical trials to compare them to hormone therapy with tamoxifen.

Targeted therapy

Targeted therapy was a type of treatment that uses drugs or other substances to identify and attack specific cancer cells without harming normal cells. Monoclona antibodies and tyrosine kinase inhibitors were two types of targeted therapies used in the treatment of breast cancer. PARP inhibitors were a type of targeted therapy being studied for the treatment of triple-negative breast cancer.

Monoclonal antibody therapy was a cancer treatment that uses antibodies made in the laboratory, from a single type of immune system cell. These antibodies can identify substances on cancer cells or normal substances that may help cancer cells grow. The antibodies attach to the substances and kill the cancer cells, block their growth, or keep them from spreading. Monoclonal antibodies were given by infusion. They may be used alone or to carry drugs, toxins, or radioactive material directly to cancer cells. Monoclonal antibodies may be used in combination with chemotherapy as adjuvant therapy.

Trastuzumab (Herceptin) was a monoclonal antibody that blocks the effects of the growth factor protein HER2, which sends growth signals to breast cancer cells. About one-fourth of patients with breast cancer have tumors that may be treated with trastuzumab combined with chemotherapy.

Tyrosine kinase inhibitors were targeted therapy drugs that block signals needed for tumors to grow. Tyrosine kinase inhibitors may be used in combination with other anticancer drugs as adjuvant therapy.

Lapatinib was a tyrosine kinase inhibitor that blocks the effects of the HER2 protein and other proteins inside tumor cells. It may be used to treat patients with HER2-positive breast cancer that has progressed following treatment with trastuzumab.

PARP inhibitors were a type of targeted therapy that block DNA repair and may cause cancer cells to die. PARP inhibitor therapy was being studied for the treatment of triple-negative breast cancer.

To consider the appropriate medication treatment in breast cancer patients, the clinical condition must be evaluated. The clinical condition such tumor size, the number of node positive, hormone receptor status, HER2 receptor status and other related condition were evaluated. The breast cancer patients would be separated into any group due to the endocrine responsiveness and risk of recurrence. Those

criteria were used to decide which treatment is appropriated. Table 2.8 and 2.9 showed how to separated breast cancer patients into each criteria.

Table 9 Assessment of endocrine responsiveness

Patients group	Definition	Explain
Endocrine responsive	ER and PR Positive	Get maximum advantage from hormonal therapy
Endocrine response uncertain	Patient show only one condition 1. ER + but PR – 2. Low level of hormone receptor (< 10% of cell positive) 3. HER2 positive 4. Metastasis to ≥ 4 nodes	Hormonal therapy combine with chemotherapy
Endocrine non-responsive	ER and PR Negative	Hormonal therapy is useless, chemotherapy will be uses alone

Source: (Hussain, Williams, Stevens, & Rea, 2004)

Table 10 The definition risk of recurrence level

Risk category	Definition
Low risk	No metastasis to lymph node and meet all this criteria 1. pT ≤ 2 cm. and 2. Histology grade 1 tumor and 3. No peritumoral vascular invasion and 4. HER2 Negative and 5. Age ≥ 35 years
Intermediate risk	No metastasis to lymph node but have only one of the criteria 1. pT > 2 cm. or 2. Histology grade 2-3 tumor or 3. Have peritumoral vascular invasion or 4. HER2 Positive and 5. Age < 35 years Have metastasis to lymph node 1-3 node and HER2 negative
High risk	Have metastasis to lymph node 1-3 node but HER2 positive or Have metastasis to lymph node ≥ 4 node

Source: (Hussain et al., 2004)

2) Clinical practice guideline in breast cancer

The standard definition of Clinical practice guidelines (CPGs) was systematically developed statements to assist practitioners and patient decisions about appropriate health care for specific circumstances (Field MJ & Lohr KN (Eds), 1990). Guidelines were designed to support the decision-making processes in patient care. The content of a guideline was based on a systematic review of clinical evidence - the main source for evidence-based care. Another type of guideline was clinical protocol. Clinical protocol can be seen as more specific than guidelines, defined in greater detail. Protocols provided a comprehensive set of rigid criteria outlining the management steps for a single clinical condition or aspects of organization.

Purpose of guideline

- To describe appropriate care based on the best available scientific evidence and broad consensus
- To reduce inappropriate variation in practice
- To provide a more rational basis for referral
- To provide a focus for continuing education
- To promote efficient use of resources
- To act as focus for quality control, including audit
- To highlight shortcomings of existing literature and suggest appropriate future research

Guidelines were regarded as important tools to improve the quality of care in clinical practice. They were produced to provide care based on the best evidence available. By reducing practice variation they may lead to cost saving and better quality of care (Ottevanger et al., 2004). After a clinical practice guideline were developed and implemented, evaluation of adherence to guideline was required. Clinical practice guideline may take time for implement.

In 1993, after implement a clinical practice guideline program for breast and colon cancer in French cancer center, the compliance rate with CPG for breast cancer was significantly higher in 1995 compared with 1993 (54% vs 19%). The compliance rate with CPG for colon cancer was also significant higher in 1995 than in 1993 (70% vs 50%). Change in adherence rate surely affected the quality of anticancer drug utilization. Furthermore, non-adherence to guideline may lead to higher cost of treatment (Ray-Coquard et al., 1997).

A retrospective review of charts of 160 consecutive patients with breast cancer from July 1996 till June 1997 was made. The approved protocol (P) was cyclophosphamide, methotrexate and fluorouracil (CMF). The majority (78.8%) of the total 160 patients or 93.9% of those given antineoplastic drug were prescribed the approved protocol. Nonprotocol (NP) drug included epirubicin, paclitaxel, etoposide and cisplatin. Decisions to change non-protocol treatment appeared to be dictated by the type of payment and the stage of disease. Cost of non-protocol chemotherapy was 15 times higher per person or 20 times higher per visit. It was

suggested, from this review, that protocol evaluation should be done continuously by participants that may lead to optimum protocol. The adherence rates to guideline were vary because of many factor such as the credibility of guideline, the clinical setting, the method of developing, disseminating and implementing. Some study indicated the factors affected adherence rate of guideline (Achanond W et al., 2002).

The study compares care of woman with breast cancer with evidence from meta-analyses and US national Comprehensive Cancer Network (NCCN) clinical guideline. Records of 4,395 women with breast cancer were abstracted from practices of 19 surgeon oncologists in six specialty practices in the Philadelphia region during 1995-1999. Patients were followed through December 2001. Fewer than half the women received treatment reflecting meta-analysis results or NCCN guideline, by disease stage, TNM status. Adherence to either standard varied from 0% for LCIS to 87% for stages IIA or IIB node positive. There were multiple interactive reasons for low adherence to guidelines or meta-analyses result, including insufficient health system supports to clinicians, inadequate organization and delivery system and ineffective continuing medical education (Bloom, de Pouvourville, Chhatre, Jayadevappa, & Weinberg, 2004).

There were many guidelines for treatment breast cancer in around the world and in Thailand. The clinical practice guideline in breast cancer was discussed.

1) National Comprehensive Cancer Network (NCCN) Version 2, 2011
2) American Society of Clinical Oncology (ASCO)
3) Clinical Practice Guideline in Breast Cancer 2007 (Department of Medical Service, Ministry of Public Health, Thailand)
4) Cancer Protocol, Thailand Version 2010
5) The Clinical Practice Guideline or Protocol of each institute or hospital

In United State (USA) there were many clinical practice guidelines, protocol or sometime called compendia that the physicians use as reference. The different details between each guideline in USA were always getting into the problem and sometime maybe related to reimbursement policy. Table 2.8 the general description of each compendia showed the different in characteristic of guideline about

publisher, inception, version of release, edition assess, and electronic version update. Table 2.9 showed the purpose of each compendium such stated purpose, scope, condition for non-FDA approved indication and recognized by Center for Medicare and Medicaid Service (CMS) (Abernethy et al., 2009).

The risk of guideline that physicians should be considered, while make decision of treating cancer patients are:

Risk 1: Too many and Heterogeneous Guidelines

There were many guidelines available (more than 2,500 in Germany at the moment) and it was by no means clear to which clinical situation certain guidelines apply. There were guidelines of different quality with different level of evidence; and even for one disease, such as a particular cancer, different guideline exist from different medical societies.

Risk 2: Physicians are dispensable

The three main elements to joint clinical decision-making were: disclosure of information about the risks and benefits of therapeutic alternatives, exploration of the patient's evaluation of the therapy and potential outcome, and the actual decision. Again, this was particular important for older patients with advanced chronic disease, such as cancer. Ready to use guideline cannot be replaced the highly experienced, skillful and communicatively able physician. Doctors would be mutually interchangeable and physicians would be little more than skilled medical technocrats, who were responsible more for the diagnosis and less for treatment.

Risk 3: Evidence-based medicine does harm to the elderly, frail, and chronically sick

Evidence-based medicine was also not kind to the elderly. The guideline movement trusts only the products of randomized controlled trials, or preferably meta-analyses of those trials. However, subjects older than 75 years were rarely found in such trials. This population was invisible to scientific medicine. If we teach only what we known and if we know only what we can measure in clinical trials, then the care of the elderly seems to be of little importance. The same

often held true for patients in palliative care. However, we need to recognize that comfort and happiness of the patient were very important and might be adversely affected by medical diagnostics and treatment. Therefore, a willingness to make compromises, depending on changing circumstances and an ability to treat without diagnosing are necessary skills of a good physician, even though they do not have a place in evidence-based medicine. All of this would be found rather in the office of the doctor, who was able to consider the complexity.

Risk 4: Guideline do not work in complex clinical case

Deviation from guideline was often necessary when treating the individual patient. For example, a patient on a palliative care unit with advanced head and neck cancer would on the one hand have a low likelihood of cure with a certain recommended procedure and a statistically estimated survival. On the other hand, palliative treatment may not hold the chance of survival, but a certain time with little side effects and a reasonable quality of life until late in the disease. In this situation a hand-tailored calculation could provide the probabilities of moderate and severe side effects with palliative treatment. The resultant decision tree established for each patient would tell the physician the best possible solution to a problem, such as the preferred treatment procedure in a malignant disease. Decision analysis offered a repertoire of techniques, which may be useful for the evaluation of complex choices in clinical medicine. The following parameters and treatment aimed play a varying role in each clinical case

1. Probability of cure from radical treatment
2. Survival time for untreated patients
3. Life expectancy with palliative treatment
4. Life expectancy with radical treatment
5. Latency periods before complications develop, after curative of palliative treatment
6. Life expectancy for cured patients, quality factors and survival increments

Risk 5: Clinical trials do not represent the patient population

In addressing the patient's risk of adverse events without treatment and risk to harm with therapy, clinicians must recognize that patients were rarely identical to the average study patients. Differences between study participants and patients in real-world practice tend to be quantitative (differences in degree of risk or response to therapy), rather than qualitative (no risk or adverse response to therapy). Therefore, it was ironic to relate data of a poorly representative sample to the entire affected population.

Risk 6: Who decides which patient is represented by the study aim?

The applicability of clinical trials to individuals depends to a large extent on the outcome parameters used. In the case of cancer trials typical examples of such parameters are mortality rate, quality of life, or life prolongation. However, what was the best outcome parameter in the individual case and what was its relation to the realistic probabilities with a given treatment? For example, there was little room for regional modification of internationally established standards.

Risk 7: Failure to adhere to guidelines or use of wrong guidelines

Formulation and knowledge of guidelines did not necessarily mean that clinical behavior was being modified. Administrative support and other ways to established guidelines in everyday clinical practice have been undertaken. Among these efforts were to copy guideline and to include them into patient's charts and visits. Constant evaluation of and feedback on guideline adherence was therefore a key objective. In the hypothetical situation, a female patient may be treated for recurrent urinary tract infections (UTI). The family physician judged it an uncomplicated finding. However, over the months, recurrent infections of one kidney lead to unilateral nephrectomy. It came to a trials and the expert witness decides that it was not an uncomplicated but a complicated UTI, so that the application of guideline for the treatment of an uncomplicated UTI was wrong and rather guidelines for the treatment of a complicated UTI had to be implemented. The home physician would then be sentenced to payments, because he applied the wrong guidelines.

Risk 8: The role of the patient is neglected

The application of statistics drawn from clinical trials to the individual patient is very demanding. But what really made the experienced physician indispensable was taking into account factors such as the patient's wish and the patient's individual right of self-determination (patient autonomy) to decide in favor of or against a certain treatment.

Risk 9: Guidelines was not legally obligatory

Guideline were recommendations, they were not law. The legal implications of guidelines were therefore not clear at this point, at least from an international point of view. It was conceivable, however, and rather likely that published guidelines would be used if liability and insurance questions are raised.

Risk 10: Evidenced-based medicine was the basis for managed care

Managed care structures consider modern management concepts with the objective to directly influence patient and physician behavior. Of course, the instruments of evidence-based medicine as well as guidelines can be used, but they will typically only be utilized if they lead to a control of patient and physician behavior, cost reduction, and the optimization of processes in an economic framework. Thus, managed care did not necessarily aim at the improvement of treatment quality but at cost reduction and therefore cannot be compared with evidence-base medicine.

Taken together, the role of the physician was more important than ever, not only to have knowledge of the various guidelines in various diseases, but also to apply those guidelines and to convince the patient of the meaning of those guidelines. In that regard, there was still the need for the freedom of empirical decision making of the individual physician in the individual patient-physician relationship. This will probably remain like this as long as there are patients and doctors.

As we already known from the review that guideline may affected the utilization, this study will be show you how many guideline related to utilization and how different between all that guideline.

2.6 Rational use of anticancer drug

Rational use of medicines requires that “patients receive medication appropriate to their clinical needs, in dose that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community” (World Health Organization, 2002).

In treatment of cancer, there were main medication treatments such chemotherapy, hormonal therapy and immunotherapy. Chemotherapy was still important especially in breast cancer. The principles of cancer chemotherapy selection are as follow (Mkele, 2010).

a) The treatment plan

There were a number of factors that considered when choosing the most appropriate drugs to use for a chemotherapy regimen and these include

- The type of cancer being treated, because not all cancer cells respond to chemotherapy. The type of cancer will determine the drug to be used, in what combination and at what dose.
- The stage of cancer. The stage of cancer often determines whether monotherapy or combination therapy is required.
- The size of tumor. Large tumors tend to be unresponsive to cytotoxic drugs for two reasons: the tumor cell tend to be the resting phase that not respond to chemotherapy and the second reason is poor penetration of chemotherapy to tumor cell due to poor vasculature or insufficient to achieve the level of concentration of drug. These may cause the severe adverse reaction or toxicity instead.
- The sites of metastasis such as lymph node, bone, lung and liver.
- The patient’s age that may cause more severity in adverse reaction due to the physical condition and social circumstance.

- The patient's general state of health
- The presence of other serious co-morbidities such as heart, liver and kidney disease.
- Other type of treatment cancer given in the past.
- The cost of the drug treatment.

b) Single / Combination treatment

There were several different mechanisms by which chemotherapeutic drugs interfere with cell growth and division. The fact that these drugs differ in their mechanism of action provides the advantage of attacking the cancer cell in several stage of cell cycle. As a result, higher response rates with combination regimens and longer progression-free survival periods have been reported in practice and during clinical trials. Cancer cell has been known to mutate and resistant to a single agent. By using different drugs concurrently it was more difficult for the tumor to develop resistance to the combination.

c) High dose of chemotherapy

A consideration in using high dose chemotherapy in order to increase the therapeutic benefit of the drug. The dose of drug was increased and the time between treatment cycles reduced, this was known as dose-dense chemotherapy. The high dose of chemotherapy was however associated with increases adverse effects especially on the bone marrow and tolerability can become a limiting factor.

d) Route of administration

The most common routes of administration of cytotoxic drug were either intravenously (IV) and orally. Other routes of administration were rarely use due to the site of cancer, metastasis of cancer and the goal of treatment. Intrathecal methotrexate to the cranium for example was now routinely used with great success in preventing the central nervous system (CNS) involvement in some cancer.

An example study of rational use of anticancer drug study is 5-fluorouracil in Pakistan (K. T. Mehmood, K. Kiran, & Rana, 2010). 5-fluorouracil was the most

common chemotherapy drug using in many type of cancer especially in breast cancer. Most breast cancer case of this study received six cycles of FAC (5-fluorouracil + Doxorubicin + Cyclophosphamide) every three weeks, pre-medications were administered before chemotherapy every case but not at least half hour before chemotherapy. In all case 5-fluorouracil dose were calculated according to body surface area (BSA), no drug interaction was observed because regimen and approved protocol were used for chemotherapy in all hospitals. CBC, LFT's and RFT's were performed in all case before administered of each cycle. Dose adjustment was done in all case that has concomitant disease such hepatic disease. Site of infusion was usually rotated in all case. The duty nurses were not aware of the SOPs of chemotherapy administration in all hospital. Chemotherapy administration supervision by pharmacists was done only in one hospital. So the concept of rational use of drug is still under-defined in Pakistan. The irrational use practices remain a big challenge. Strategies should be developed as WHO guidelines on RUD. Health care professionals should play their role to promote rational use of drug to ensure better quality of life for cancer patients.

Another study about rational use of anticancer drug was conducted in Brazil base on the information on lawsuit field (Lopes, Barberato-Filho, Costa, & Osorio-de-Castro, 2010). 7 immunotherapy for cancer such bevacizumab, capecitabine, cetuximab, erlotinib, rituximab, imatinib and temozolamide accounted for expense over R$ 40 million to meet 1220 requests and lawsuit, at an average cost of R$ 33,500 per patient. 17% of requests and lawsuit did not provide evidence for the required indication and these amounted to inappropriate expense of at least R$ 6.8 million.

The rational use of anticancer drug still controversy in many countries so WHO advocates 12 key interventions to promote more rational use as follow

1. Establishment of a multidisciplinary national body to coordinate policies on medicine use
2. Use of clinical guideline
3. Development and use of national essential medicines list

4. Establishment of drug and therapeutic committees in districts and hospital
5. Inclusion of problem-based pharmacotherapy training in undergraduate curricula
6. Continuing in service medical education as a licensure requirement
7. Supervision, audit and feedback
8. Use of independent information on medicines
9. Public education about medicines
10. Avoidance of perverse financial incentives
11. Use of appropriate and enforced regulation
12. Sufficient government expenditure to ensure availability of medicines and staff

The twelve interventions aimed to promote the rational use of medicine. Before applying any intervention, the study of situation and pattern of medication use would be conducted.

2.7 Method to study anticancer drug utilization

Drug utilization review (DUR) was a tool to identify such common problems as inappropriate product selection, incorrect dosing, avoidable adverse drug reactions, and errors in drug dispensing and administration. DUR may then be used to implement action plans for change. DUR was an ongoing, planned, systematic process for monitoring, evaluating, and improving drug use and is an integral part of hospital efforts to ensure quality and cost effectiveness. More appropriate and more effective use of drugs ultimately results in improved patient care more efficient use of resource (World Health Organization, 2003). Drug utilization review in itself did not necessarily provide answers, but it contributed to rational drug use in important ways as described below.

Description of drug use pattern

1) It can be used to estimate the number of patients exposed to specified drugs within a given time period. Such estimates may either refer to all drug users,

regardless of when they start to use the drug (prevalence), or focus on patients who started to use the drug within the selected period (incidence).

2) It can describe the extent of use at a certain moment and/or in a certain area. (E.g. in a country, region, community or hospital). Such descriptions were most meaningful when they form part of continuous evaluation system i.e. when the pattern are followed over time and trends in drug use can be discerned.
3) Researcher can estimate (e.g. on the basis of epidemiological data on a disease) to what extent drug are properly used, overused or underused.
4) It can determine the pattern or profile of drug use and extent to which alternative drugs are being used to treat particular conditions.
5) It can be used to compare the observed patterns of drug use for the treatment of a certain disease with current recommendations or guidelines.
6) It can be used in the application of quality indications to patterns of drug utilization. An example was so-called DU90% (drug utilization 90%), a further development of the top-ten list. The DU90% segment reflect the number of drug that account for 90% of drug prescriptions and the adherence to the local or national prescription guidelines in this segment. This general indicator can be applied at different levels (e.g. individual prescriber, group of prescribers, hospitals, and region or country) to obtain a rough estimate of the quality of prescribing. The defined daily dose (DDD) and prescribed daily dose (PDD) can be used to evaluate the quality of use. In anticancer drug DDD many useless because the dose is individual due to body surface area (BSA). But DDD may be useful in hormonal therapy in breast cancer patients.
7) The number of case report of drug problem or adverse effects can be related to the number of patients exposed to the drug to assess the potential magnitude of the problem. If it was possible to detect that the reaction is more common in a certain age group, in certain conditions or at a given dose level, improving the information on indication, contraindication and appropriate dosage may be sufficient to ensure safer use and avoid withdrawal of the drug from the market.

The study about anticancer drug utilization was different in any pattern and by any country. The utilization of cancer chemotherapeutic agent in tertiary care

hospital in Nepal has shown the utilization pattern of 60 cancer patients (Mallik et al., 2006). Carcinoma of stomach was the common diagnosis seen in 10 (16.67%) of the patients. Adjuvant chemotherapy was given in 23 (38.33%) of the patients and palliative chemotherapy in 23 (38.33%). The common drug class used was alkylating agents (66%) and the common drug was Cisplatin accounting for 32 (27%) of the total drugs.

Another study conducted in Dr.Soetomo general hospital Surabaya, Indonesia, drug utilization study of chemotherapy in breast cancer patients. The result of this study has shown 75.9% of breast cancer patients are between 30-55 years old and the most common stage of breast cancer is IIIb (38.9%). The regimens of chemotherapy use were 5-fluorouracil + doxorubicin + cyclophosphamide (FAC) (57.4%), 5-fluorouracil + epirubicin + cyclophosphamide (FEC) (40.74%) and cyclophosphamide + methotrexate + 5-fluorouracil (CMF) (1.85%). Drug use for nausea and vomitting from chemotherapy were ondansetron (96.30%), tropisetron (90.74%), domperidone (7.40%) and ranitidine (70.37%). Another drug use for adverse reaction is dexamethasone (66.67%) for allergic reaction, ferrous sulfate (85.18%), erythropoietin alpha (22.22%) for anemia. The suggestions from this study are 1) the use of chemotherapy in breast cancer patients complied with guideline, 2) counseling to patients is needed to do continuously to get optimal result, 3) the efficacy and safety should be monitored due to therapy given, 4) the role of pharmacist in handling and preparing cytotoxic drugs.

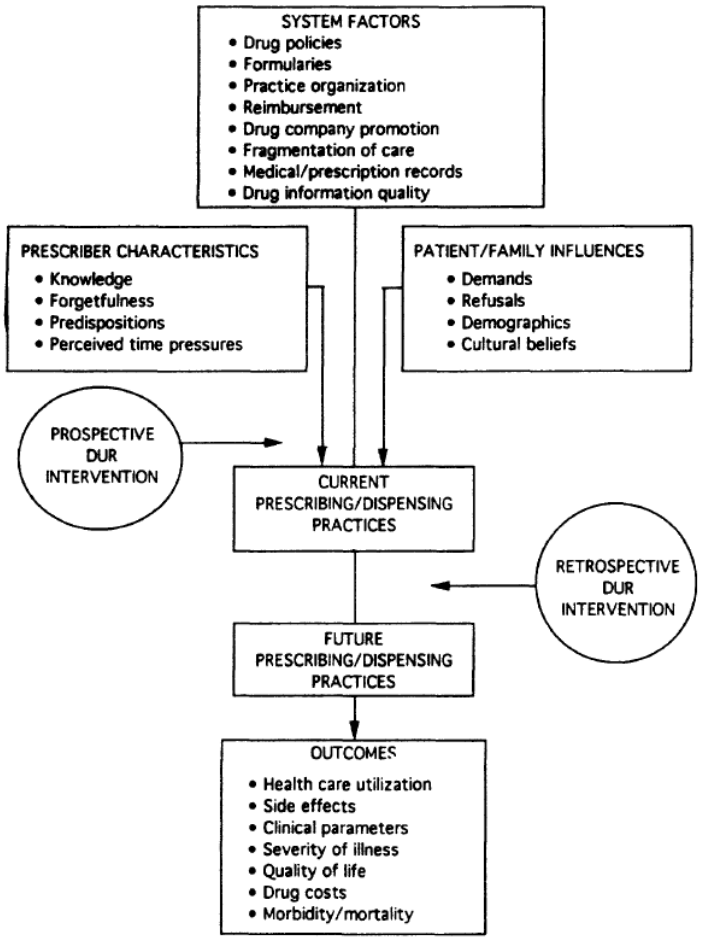
Two studies discussed above were type of pattern of use in term of descriptive study or quantitative aspect. There were another anticancer drug utilization study in term of outcome research. To compare the optimal chemotherapy utilization in any type of cancer was needed for benchmarking the quality of care. The optimal chemotherapy utilization model was constructed. Chemotherapy was indicated in 17 of the 24 possible clinical scenarios in the model. The estimated optimal proportion of breast cancer patients who should receive chemotherapy at least once was 68%. Sensitivity analysis showed that the range of optimal rate was 60-69%. The optimal rate appears to be substantially higher than the reported actual rate (29-49%) (Weng Ng et al., 2010). Furthermore there are some

studies in any type of cancer such lung cancer and colon cancer (Weng Ng et al., 2010).

Beside the pattern and quality of anticancer drug use, another type of drug utilization research was the determinant of use. The determinant of use or factor influencing prescribing/dispensing was affecting the utilization. The factors were identified in Figure 2.3 as patients and family factors, physician factors and system factors. The four factors and outcome will be discussed as follow (Lipton & Bird, 1993).

1) System factor
2) Physician factor
3) Patients/family factor
4) Outcome

Figure 2.4 Factor influencing prescribing/dispensing and DUR intervention



Source: (Lipton & Bird, 1993)

System factor

System factors composed of drug policies, formularies, practice organization, reimbursement, drug company promotion, fragmentation of care, medical/prescription record and drug information quality.

Physician factor

Physician factor was composed of knowledge, forgetfulness, predisposition and perceived time pressure.

Patient/family factor

Patients/family factor was composed of demand, refusal, demographic and cultural belief. Drug utilization related to patients and family influences include patients' unwillingness to take appropriate drugs and demand for inappropriate drug. Patient demographic characteristics and culture beliefs also many influence prescribing. For example, there was evidence that woman, regardless of age or symptoms receive more prescription than men. The general problem was patient lack of needed therapy or prescription of unnecessary therapy.

Outcome

Outcome was composed of healthcare utilization, side effect, clinical parameter, severity of illness, quality of life, drug cost and morbidity/mortality.

CHAPTER III

METHODOLOGY

3.1 Study Design

To answer the research question quantitative methods was used in this study. Quantitative method would be used for describing the pattern of anticancer drugs use and outcome by collecting data from the prescriptions. Some qualitative method would be used for exploring the factor affecting the anticancer drug prescribing and explain how the detail of drug use pattern. Retrospective data analysis was used in this study.

3.2 Population and sample size

Sample in this study was selected due to the objective of study and divided into three groups as discuss below. This is kind of purposive sampling.

1) Sample of prescription survey for exploring pattern of anticancer drug use

Pattern of anticancer drug use will evaluated from all prescriptions of breast cancer patients which contained chemotherapy drug, hormonal therapy and immunotherapy. The Table 3.7 shows the list of items of drug in each group.

Inclusion criteria

- Prescription contained only interested anticancer drug use in breast cancer
- Prescription were prescribed between January - June 2010
- All cycle of chemotherapy prescription will be collected

2) Sample of prescription survey in appropriate use of anticancer drug

There are three anticancer drug that will be evaluated for the appropriate use, Docetaxel, Letrozole and Trastuzumab. Docetaxel is a kind of chemotherapy drug, Letrozole is hormonal therapy and Trastuzumab is immunotherapy. The sample of each drug was collected from prescription contained each drug between January 1, 2010 to June 30, 2010.

3) Sample of stakeholder interview to explain the situation

All of stakeholder who related will be interviewed. The stakeholder in each setting composed of the hospital director, the chairman of pharmaceutical and therapeutic committee (PTC), the head of pharmacy department and the physicians. The Table 3.4 shows the number of physician in any subspecialty in each setting.

Table 11 Number of the physicians who will be interviewed in each setting

	Chonburi	Lopburi	Lumpang	Maha	Suratthani	Ubon	Udonthani
Oncologist	3	4	2	1	1	1	2
Radiologist	2	9	2	2	1	4	3
Sergeant	2	3	3	0	1	2	3
Total	7	16	7	6	3	7	8

Table 12 Study Design

Objectives	Design	Data source	Expected outcome
1. To describe the pattern of use	Prescription review	- Prescriptions	- Pattern of use original and generic drug - Pattern of use NLED and non-NLED - Pattern of use concomitant drug
2. To examine the appropriate use	Medical record review	- Prescription - Medical record	- Appropriate use of indication, dose and duration in 3 anticancer drugs; Docetaxel, Letrozole and Trastuzumab - Drug Interaction
3. To elaborate the determinants affecting drug utilization	Documentation Review	- Document - CPG, formularies - Hospital drug list	- Policy affected utilization - Guideline and formulation analysis - Practice organization
	Medical record review	- Medical record	- Scheme - Patients' age - Disease status
	Interview	- Director - Chairman of PTC - Head of pharmacist - Physicians	- Character of prescriber - Attitude of stakeholder

3.3 Study site

The study site included 7 regional cancer centers under the department of medical service, ministry of public health. Cancer center is the tertiary care hospital where have responsible for the cancer patients in their area. Those centers were assume as the same baseline competency such as number of bed not over 150 beds, high technology equipment in treating cancer and especially under the mission as cancer professional.

Table 13 The features of 7 regional cancer centers included this study

Features	Chonburi	Lopburi	Lumpang	Maha	Suratthani	Ubon	Udonthani
No of bed	144	176	137	88	90	100	133

3.4 Scope of the study:

The pattern of use and the appropriate use of anticancer drugs were study in breast cancer patients because it is the major cause of death in female. Both in-patients' prescription and out-patients' prescription were included in this study. The appropriate use of anticancer drug was evaluated in three drugs that already have the formal evaluation form. The medication uses in ovarian ablation were excluded.

3.5 Operational definition

Anticancer drug: Anticancer drug in this study is referred to chemotherapy drugs, hormonal therapy drugs and immunotherapy drugs use in treating breast cancer. The medications for ovarian ablation are excluded.

Table 14 List of items of anticancer drug in each group of this study

Chemotherapy	Hormonal therapy	Immunotherapy
FAC	Tamoxifen	Trastuzumab
AC	Letrozole	
FEC	Anastrozole	
CMF	Exemetane	
FAC follow by Paclitaxel		
FAC follow by Docetaxel		
TAC		

F = 5-fluorouracil, A = Doxorubicin, C = Cyclophosphamide, E = Epirubicin, M = Methotrexate, T = Docetaxel

Pattern of use: Pattern of use will be defined as use of original drug and generic drug, use of NLED and non-NLED, adherence to guideline, cost and concomitant drug.

Quality of drug use: Quality of use or an appropriate use is defined as the right indication, right dose and right duration. Furthermore, prescribing medication without drug interaction is measured.

Drug policy: Drug policies and utilization is related each other. When the policies were implemented, utilization pattern would be assumed to change and the utilization pattern will be served to the policy maker for developing the policy again (WHO, 2003). In this study drug policy would be referred to any policies that affect the utilization of anticancer drug especially the national level policy such as national list of essential medicine. Drug policies in this study were presented as non-NLED policy and original policy. Those policies were classified due to strictly level as policies dominate and non-policy dominates.

Formularies or guideline: Formularies provided the foundation for guiding clinicians in choosing the safest, most effective agents for treating particular medical problem. Formularies in cancer treatment are the subset of clinical practice guideline. Guidelines are tool to improve the quality of care in daily practice (P.B. Ottevanger, 2004). Many organizations developed the guideline of treatment breast cancer. In this study formularies and guideline referred to formularies and guideline only for treatment of breast cancer that affected the utilization such international guideline, national guideline, institutional guideline and the guideline of any setting.

Practice organization: Practice organization was originated from PTC of each cancer centers. They show as prescription policy, some regulatory and criteria in dispensing. The practice organization may be affected by exogenous factor such national essential list and reimbursement system. The characteristic of practice organization will be observed to explain the pattern of utilization of anticancer drug. Practice organization in this study was presented by medication safety standard score that all hospital evaluated themselves very year. The full score was 5.

Reimbursement policy: it is the reimbursement policy that affected utilization such cancer protocol from NHS, some regulation from CSMBS. After

describe the pattern of anticancer drug use in each scheme so analyzed how the reimbursement policy affected that pattern.

Prescriber characteristic: Only physician who prescribe anticancer drug will be identified their status such specialist. The specialists in this study were presented as 3 specialists; oncologist, radiologist and surgeon.

Age: Age of patients was presented by 2 groups as age ≤ 60 years old and age more than 60 years old.

Patients: Breast cancer patients who visit the regional cancer center in 2010 and undergo the medication treatment of chemotherapy, hormonal therapy and immunotherapy.

Drug interaction: Drug interaction in this study will be defined as drug-drug interaction appeared in the prescription selected.

Cost: Cost will be defined as the cost of each item, cost of regimen, cost of medication per prescription, cost of concomitant drug and cost compare with the guideline.

3.6 Ethics

Ethical approvals were obtained from each site of study.

3.7 Methods of data collection

Data collection in this study was collected in four phases

3.7.1 Documentation review; type of documentation and finding show in

Table 15 Document review and finding

Type of documentation	Finding
Hospital drug list	- Number of anticancer drug
	- Ratio of NLED and non-NLED in the list
Hospital policy about anticancer drug	- Prescribing policy
	- Dispensing policy
	- Drug utilization evaluation policy
PTC meeting report	- Meeting conclusion
Hospital CPG	- Compare hospital CPG and other guideline that the physician use as reference

3.7.2 Prescription review; there are three group of prescription were selected, the data obtained from prescription show in Table 3.9

Table 16 prescription review and finding

Type of prescription	Data obtained from prescription
Chemotherapy	- HN, Scheme, Physician
	- Drug item, Drug regimen, Dose
	- Identified the drug in original or generic
	- Identified the drug in NLED or non-NLED
	- Cost and sale price of each item or regimen
	- Concomitant drug; number, cost, NLED:non-NLED
	- Identified the couple of drug-drug interaction
	- Identified the severity of drug-drug interaction
Hormonal therapy	- HN, Scheme, physician
	- Drug item, Dose
	- Duration of prescribing (month)
	- Identified the drug in original or generic
	- Identified the drug in NLED or non-NLED
	- Cost and sale price of each item, per prescription
	- Concomitant drug; number, cost, NLED:non-NLED
	- Identified the couple of drug-drug interaction
	- Identified the severity of drug-drug interaction
Immunotherapy	- HN, Scheme, Physician
	- Drug item, Dose
	- Identified the drug in original or generic
	- Identified the drug in NLED or non-NLED
	- Cost and sale price of each item, per prescription
	- Concomitant drug; number, cost, NLED:non-NLED
	- Identified the couple of drug-drug interaction
	- Identified the severity of drug-drug interaction

3.7.3 Medical record review; after finished to collect data from prescription review, the medical record were selected by those prescription

Table 17 Medical record review and finding

Medical record	Data obtained from medical record
Demographic data	- Age
	- Underlying disease
	- Previous treatment
Disease status	- Stage of disease
	- Tumor size (cm)
	- Number of node-positive
	- Hormone receptor status
	- HER2 receptor status
	- Risk of recurrence
	- Menopausal status

3.7.3 The appropriate use of Docetaxel, Letrozole and Trastuzumab were be collected from prescription review and medical record. The data will be recorded in official DUE form and will be analyzed to identify how appropriate use.

3.7.4 Interview the stakeholders

Table 18 Stakeholder interview and finding

Stakeholder	Topic to interview
Hospital director	- Perception about national policy of anticancer drug - Hospital policy and direction in rational use - Attitude to determinant affected utilization pattern and quality of drug use - Suggestion
Chairman of PTC	- Perception about national policy of anticancer drug - Role of PTC in rational use of anticancer drug - Policy from PTC - Attitude to determinant affected utilization pattern and quality of drug use - Suggestion
Head of pharmacy department	- Perception about national policy and hospital policy - Role of pharmacist in rational use of anticancer drug - Attitude to determinant affected utilization pattern and quality of drug use - Suggestion
Physicians	- Perception about national policy and hospital policy - Role of physician in rational use of anticancer drug - Attitude to determinant affected utilization pattern and quality of drug use - Suggestion

3.8 Data analysis:

The data obtained from the study were be analyzed by using Microsoft Excel 2003 and SPSS statistical package version 17.0 for Window

Statistics: Descriptive statistics were used to describe the characteristic of patients, disease status, and physician specialist and utilization pattern. Independent t-test will be used to compare mean of the utilization pattern in term of number. Chi-square will be used to find the association between factor affecting utilization and utilization in term of pattern of use and quality of use.

CHAPTER IV

RESULTS

There are four sections of results. The first section describes characteristics of information using descriptive statistic. The second section presents the result of pattern of anticancer drug use derived from analysis of each dependent variable. The third section presents drug use evaluation of three anticancer; Docetaxel, Letrozole and Trastuzumab. The fourth section presents the result of factor affecting anticancer drug use and appropriated use through cross analysis using chi-square, independent T-test, Man-Whitney U Test and logistic regression model.

4.1 Demographic data

4.1.1 Character of studied sites

Seven regional cancer centers had different context in details of policy in term of non-NLED policy, original drug policy and medication safety standard policy. To classified cancer center as different level of each policy, percentage of non-NLED and original drugs in hospital formularies were identified. For medication safety standard policy, the self-assessment of quality standard score conducted by the Bureau of Health Administration, Ministry of Public Health in 2010 was identified.

Table 19 Character of policy of cancer centers

Center	1	2	3	4	5	6	7	Mean ± SD	Median
Percentage of non-NLED of anticancer drug	1.60	8.80	5.20	1.40	1.50	12.10	10.00	5.25 ± 4.512	5.25
Percentage of original drugs of anticancer drug	8.00	19.30	18.30	11.50	6.70	23.80	4.70	13.19 ± 7.303	11.50
Quality standard score of medication safety	3.38	2.62	3.42	4.44	3.15	3.34	3.08	3.350 ± 0.554	3.35

Cancer center were classified into different level of policy due to mean and median in Table 4.1. Non-NLED policy were identified by mean of non-NLED items of anticancer drug in hospital formulary, if any cancer center has more than 5.25% of non-NLED anticancer drug items, there were classified as non-NLED policy dominate group and the lower were classified as non-NLED policy non-dominate group. So center 2, 6 and 7 were classified as non-NLED policy dominate and center 1, 3, 4 and 5 were classified in non-NLED policy non-dominate group. Same as non-NLED policy classification, original policy and medication safety standard policy use the same method to identify. Table 4-2 showed the conclusion of policy classification of each cancer center.

Table 20 Summary of policy classification group

Type of policy	Center classification	
	Policy Dominate	Policy Non-Dominate
non-NLED	2, 6, 7	1, 3, 4, 5
Original drug	2, 3, 6	1, 4, 5, 7
Quality standard of medication safety	1, 3, 4	2, 5, 6, 7

4.1.2 Character of studied prescriptions

Anticancer drug prescriptions were collected from 7 regional cancer centers between January to June 2010. Table 4-3 shows the character of studied prescription by each center.

There were 7,520 prescriptions from out-patient department of 3,544 breast cancer patients. Those were separated into 3 groups; 3,485 prescriptions (46.35%) of chemotherapy drug, 3,940 prescriptions (52.26%) of hormone therapy drug and 105 prescriptions (1.40%) of targeted therapy drugs. The average age of patients was 51.24 $\pm$ 10.574 years old. The financial schemes of patients were UC scheme (65.19%), CSMBS scheme (18.04%) and SSS scheme (12.85%) respectively.

Table 21 Characters of studied prescription

Center	1	2	3	4	5	6	7	Total
Number of prescriptions	1,667	2,407	561	973	282	1,006	624	7,520
Number of breast cancer patients	660	1,117	258	474	151	528	356	3,544
Age (Mean±SD)	50.01 ±10.642	52.12 ±10.574	51.46 ±9.412	49.86 ±10.962	49.99 ±11.222	51.91 ±10.693	51.32 ±10.113	51.24 ±10.574
Number of chemotherapy prescriptions (%)	742 (44.50)	1,120 (46.53)	290 (51.70)	436 (44.81)	135 (47.88)	421 (41.85)	341 (54.65)	3,485 (46.35)
Number of hormone therapy prescriptions (%)	913 (54.70)	1,269 (52.73)	259 (46.17)	530 (54.47)	144 (51.07)	552 (54.87)	263 (42.15)	3,930 (52.26)
Number of targeted therapy prescriptions (%)	12 (0.70)	18 (0.75)	12 (2.14)	7 (0.72)	3 (1.07)	33 (3.28)	20 (3.21)	105 (1.40)
Health benefit scheme								
- CSMBS (%)	237 (14.20)	402 (16.71)	145 (25.85)	107 (11.0)	60 (21.28)	241 (23.96)	164 (26.29)	1,356 (18.04)
- SSS (%)	280 (16.80)	238 (9.89)	45 (8.03)	326 (33.51)	12 (4.26)	29 (2.89)	36 (5.77)	966 (12.85)
- UC (%)	1,036 (62.10)	1,707 (70.92)	371 (66.14)	519 (53.34)	197 (69.86)	693 (68.89)	379 (60.74)	4,902 (65.19)

CSMBS (Civil Servant of Medical Benefit Scheme), SSS (Social Security Scheme), UC (Universal Coverage Scheme)

4.2 Pattern of prescription

To describe the pattern of prescribing, WHO criteria suggested to evaluate from each prescriptions in term of average number of drugs per prescription, percentage of drug prescribe by generic name, percentage of encounter resulting in prescription of antibiotic, percentage of encounters resulting in prescription of an injection, percentage of drug prescribed from essential drug list or formulary and average drug cost per encounter. This study selected some criteria and adapted criteria for clearly describe pattern of anticancer drug use.

4.2.1 Average number of drugs per prescription

Studied prescriptions were analyzed by average number of all drug items, median, mode and range in each prescription and presented in group of anticancer drug. Table 4-4 shows the detail of analysis.

Table 22 Number of all drug items in 3 types of cancer therapy

Number of drug items (items)	Type of prescriptions		
	Chemotherapy	Hormone therapy	Targeted therapy
Mean ± SD	8.54 ± 2.768	1.36 ± 0.767	2.96 ± 1.227
Median	9.00	1.00	3.00
Mode	9.00	1.00	3.00
Min - Max	2 - 18	1 - 5	1 - 5

The average number of all drug items (mean ± S.D.) were 8.54 ± 2.768, 1.36 ± 0.767 and 2.96 ± 1.227 in chemotherapy prescription, hormone therapy prescriptions and targeted therapy prescription respectively. It was not surprising because chemotherapy prescriptions always compose of chemotherapy regimen, pre-medication and sometime home medication. While hormone therapy prescriptions were always prescribed as single medication. Targeted therapy created less adverse drug reaction so the average numbers of all drug items were less than chemotherapy prescriptions.

4.2.2 Original drugs prescribing pattern

Another topic represent pattern of prescribing anticancer drug was original drug prescribing pattern because anticancer drug always be innovative product that rapidly launched especially in targeted therapy. Table 4-5 shows the pattern of

prescribing original drug by percentage of prescription contained original drug, range of percentage by each cancer center, average number of original drug, median, mode, minimum and maximum item of original drug prescribed.

Table 23 Original drugs prescribing pattern

Number of drug items	Type of prescriptions		
	Chemotherapy	Hormone therapy	Targeted therapy
Percentage of prescription contained original drug (%)	14.40 (4.69 – 23.75)	26.50 (12.34 – 34.17)	100.00
- Center 1 (%)	7.96	34.17	100.00
- Center 2 (%)	19.29	28.13	100.00
- Center 3 (%)	18.27	33.07	100.00
- Center 4 (%)	11.47	21.51	100.00
- Center 5 (%)	6.67	17.36	100.00
- Center 6 (%)	23.75	12.34	100.00
- Center 7 (%)	4.69	30.42	100.00
Average item of original drug (Mean ± SD) (items)	1.34 ± 0.684	1.15 ± 0.495	1.28 ± 0.702
- Median (items)	1	1	1
- Mode (items)	1	1	1
- Min - Max (items)	1 - 6	1 - 5	1 - 5

Table 4-5 showed average percentages of original drug prescription were 100.00%, 26.50% and 14.40% in targeted therapy, hormone therapy and chemotherapy prescription respectively. In Thailand 2010, there was not having generic targeted therapies yet and limited original hormone therapy in the market. For chemotherapy, there were many generic drugs in the market. The range of percentage of prescription contained original drug show variation pattern of each center. The average items of original drug in three groups were likely.

4.2.3 non-NLED prescribing pattern

Another topic represent pattern of prescribing anticancer drug was non-NLED prescribing pattern because some anticancer drug not always is listed in National List of Essential Medicine (NLED) especially in targeted therapy. Table 4-5 shows the pattern of prescribing non-NLED by percentage of prescription contained non-NLED, range of percentage by each cancer center, average number of non-NLED, median, mode, minimum and maximum item of non-NLED prescribed.

Table 4-6 showed average percentages of non-NLED prescription were 100.00%, 9.35% and 6.28% in targeted therapy, hormone therapy and chemotherapy prescription respectively. In Thailand 2010, all of targeted therapy did not listed in NLED yet, while chemotherapy and hormone therapy were mostly listed in NLED. For chemotherapy, there was National Health Security Office (NHSO) protocol was used as the guideline, all of chemotherapy items in protocol were listed in NLED. The range of percentage of prescription contained non-NLED show variation pattern of each center. The average items of non-NLED in three groups were likely. This study try to identify average cost of non-NLED per prescription, but the data were not normal distribution so median and range (minimum – maximum) were used to describe.

Table 24 Pattern of prescribed non-NLED

Number of non-NLED items	Type of prescriptions		
	Chemotherapy	Hormone therapy	Targeted therapy
Percentage of prescription contained non-NLED (%)	6.28 (1.48 – 12.11)	9.35 (2.07 – 23.41)	100.00
- Center 1 (%)	1.65	7.34	100.00
- Center 2 (%)	8.75	4.18	100.00
- Center 3 (%)	5.17	12.99	100.00
- Center 4 (%)	1.38	2.07	100.00
- Center 5 (%)	1.48	13.19	100.00
- Center 6 (%)	12.11	23.41	100.00
- Center 7 (%)	9.97	20.91	100.00
Average item of non-NLED (Mean ± SD) (items)	1.88 ± 0.585	1.20 ± 0.484	1.24 ± 0.883
- Median (items)	1	1	1
- Mode (items)	1	1	1
- Min - Max (items)	1 – 9	1 – 4	1 – 4
Average cost of non-NLED (Baht)			
- Median (Baht)	7,267	23,850	97,222
- Mode (Baht)	15,700	30	97,200
- Min - Max (Baht))	2 – 94,407	7 – 97,223	62,938 – 194,446

4.2.4 Number of prescription contained concomitant drugs

Concomitant drug refer two or more medication taken at the same time of specific medication. For instance, chemotherapy always have concomitant drug item to prevent adverse drug reaction or other drugs that prescribed for other objective which can harm or not to the patients. Another topic represent pattern of prescribing anticancer drug was concomitant drug prescribing pattern. Table 4-7 shows the pattern of prescribing concomitant drugs by percentage of prescription contained concomitant drug, average number of concomitant drug, median, mode and range (Minimum – Maximum) of item of concomitant drug prescribed.

Table 25 Number of prescription contained concomitant drugs

Number of drug items	Type of prescriptions		
	Chemotherapy	Hormone therapy	Targeted therapy
Percentage of prescription contained concomitant drugs (%)	92.60 (83.72 – 98.53)	23.52 (5.69 – 82.11)	85.71 (33.33 – 100.00)
- Center 1 (%)	89.44	5.69	33.33
- Center 2 (%)	97.86	12.77	94.44
- Center 3 (%)	96.89	13.78	100.00
- Center 4 (%)	83.72	82.11	57.14
- Center 5 (%)	96.29	18.75	33.33
- Center 6 (%)	86.94	27.77	100.00
- Center 7 (%)	98.53	25.48	95.00
Average number of prescribed concomitant drug (Mean ± SD) (items)	6.02 ± 2.432	1.56 ± 0.821	3.74 ± 0.083
- Median (items)	6	1	3
- Mode (items)	6	1	3
- Min - Max (items)	1 - 15	1 - 4	1 - 4

The data in table 4-7 showed the average percentage of prescription contained concomitant drug were 92.60%, 85.71% and 23.52% in chemotherapy, targeted therapy and hormone therapy prescription respectively. Normally in chemotherapy prescription should be contain concomitant drug such as pre-medication or other for prevent and relieve acute and delay side effect of chemotherapy. So there did not show wide variation in percentage of concomitant drug between the centers. Those related to number of concomitant drug that highest in chemotherapy too (6.02 ± 2.432 items). Targeted therapy sometime show side effect, so concomitant drug were slightly prescribed. Hormone therapy was normally prescribed as single agent. So the average numbers of concomitant drug were less than other.

4.2.5 Pattern of prescribe chemotherapy

The studied prescription were separately analyzed by three group (chemotherapy, hormone therapy and targeted therapy) to describe the pattern of chemotherapy prescription in this study refer to NHSO cancer protocol version 2010. The table 4-8 shows the pattern by regimen CMF, AC, FAC, FEC/EC, TAC/TC and other in each cancer center. The abbreviations of each chemotherapy regimen are shown below.

CMF	=	Cyclophosphamide + Methotrexate + Fluorouracil
AC	=	Doxorubicin + Cyclophosphamide
FAC	=	Fluorouracil + Doxorubicin + Cyclophosphamide
FEC/EC	=	Fluorouracil + Epirubicin + Cyclophosphamide
TAC/TC	=	Docetaxel + Doxorubicin + Cyclophosphamide

Table 4-8 show the pattern of chemotherapy regimens. 3,485 chemotherapy prescriptions were analyzed. There were 3,211 prescriptions (92.14%) adherence to the protocol. FAC (Fluorouracil + Doxorubicin + Cyclophosphamide) was the most common prescribed regimen (1,260 prescription; 36.15%). 165 prescriptions (4.73%) were out of protocol such as Gemcitabine, Vinorelbine and liposomal-Doxorubicin.

Table 26 Pattern of prescribe chemotherapy regimen

Center	1	2	3	4	5	6	7	Total
Complied with NHSO protocol 2010								
CMF	167	224	11	45	0	24	92	563
(%)	(22.51)	(20.00)	(3.79)	(10.32)		(5.70)	(26.98)	(16.15)
AC	42	140	58	63	22	119	73	517
(%)	(5.66)	(12.50)	(20.00)	(14.45)	(16.30)	(28.27)	(21.41)	(14.84)
FAC	343	354	91	152	70	168	82	1,260
(%)	(46.23)	(31.61)	(31.38)	(34.86)	(51.85)	(39.90)	(24.05)	(36.15)
Paclitaxel	46	168	41	101	30	0	54	440
(%)	(6.20)	(15.00)	(14.14)	(23.17)	(22.22)		(15.84)	(12.63)
Docetaxel	40	41	64	2	5	0	18	170
(%)	(5.39)	(3.66)	(22.07)	(0.46)	(3.70)		(5.28)	(4.88)
Capecitabine	4	82	18	46	8	101	2	261
(%)	(0.54)	(7.32)	(6.21)	(10.55)	(5.93)	(23.99)	(0.59)	(7.49)
Total	642	1,009	283	409	135	412	321	3,211
(%)	(86.53)	(90.09)	(97.59)	(93.81)	(100)	(97.86)	(94.15)	(92.14)
Not complied with NHSO protocol 2010								
FEC/EC	0	67	1	0	0	3	0	71
(%)		(5.98)	(0.34)			(0.71)		(2.04)
TAC/TC	0	23	0	0	0	0	9	32
(%)		(2.05)					(2.63)	(0.92)
Paclitaxel +	1	4	0	1	0	0	0	6
Carboplatin	(0.13)	(0.36)		(0.23)				(0.17)
(%)								
Other	99	17	6	26	0	6	11	165
Chemo(%)	(13.34)	(1.52)	(2.07)	(5.96)		(1.43)	(3.22)	(4.73)
Total	100	111	7	27	0	9	20	274
(%)	(13.47)	(9.91)	(2.41)	(6.19)		(2.14)	(5.85)	(7.86)
Overall	742	1,120	290	436	135	421	341	3,485
prescription	(100)	(100)	(100)	(100)	(100)	(100)	(100)	(100)

4.2.6 Pattern of prescribe hormone therapy

To describe pattern of hormone therapy, NHSO cancer protocol was referred. The data show separately both of original and generic medication. The number of prescriptions and percentage were present by cancer centers.

Table 27 Pattern of prescribe hormone therapy drug

Pattern	Center							Total
	1	2	3	4	5	6	7	
Complied with NHSO protocol 2010								
SERM group								
Tamoxifen	601	838	168	388	116	435	184	2,730
(%)	(65.82)	(66.03)	(64.86)	(73.21)	(80.56)	(78.80)	(69.96)	(69.47)
Nolvadex®	62	0	28	34	0	0	1	125
(Tamoxifen original) (%)	(6.79)		(10.81)	(6.41)			(0.38)	(3.18)
AI group								
Letrozole	4	82	3	27	4	71	13	204
(%)	(0.44)	(6.46)	(1.16)	(5.09)	(2.78)	(12.86)	(4.94)	(5.19)
Femara®	175	308	30	49	13	18	56	649
(Letrozole original) (%)	(19.16)	(24.27)	(11.58)	(9.24)	(9.03)	(3.26)	(21.29)	(16.51)
Total	842	1,228	229	498	133	524	254	3,708
(%)	(92.22)	(96.77)	(88.42)	(93.96)	(92.36)	(94.93)	(96.58)	(94.35)
Not Complied with NHSO protocol 2010								
AI group								
Anastrozole®	55	27	15	5	7	27	7	143
(original) (%)	(6.02)	(2.12)	(5.79)	(0.94)	(4.86)	(4.89)	(2.66)	(3.64)
Exemestane®	9	14	15	5	4	1	2	50
(original) (%)	(0.98)	(1.10)	(5.79)	(0.94)	(2.78)	(0.18)	(0.76)	(1.27)
Other	7	0	0	22	0	0	0	29
hormone	(0.76)			(4.15)				(0.74)
(%)								
Total	71	41	30	32	11	28	9	222
(%)	(7.78)	(3.23)	(11.58)	(6.04)	(7.64)	(5.07)	(3.42)	(5.65)
Overall (%)	913	1,269	259	530	144	552	263	3,930
	(100)	(100)	(100)	(100)	(100)	(100)	(100)	(100)

The table 4-9 and detail are as follow. There were 3,930 prescriptions analyzed for the pattern of hormone therapy prescriptions due to the NHSO cancer protocol version 2010. 3,708 prescriptions (94.35%) were under the protocol. Tamoxifen (both original Nolvadex® and generic drug) was the most prescribed hormone therapy drug (2,855 prescription; 72.65%) and Letrozole (both original Femara® and generic drug) was the most prescribed in AIs group (Aromatase Inhibitor).

4.2.7 Pattern of prescribe targeted therapy drug

To describe the pattern of prescribe targeted therapy, Trastuzumab was separately describe as single agent because it was the first targeted therapy that was registered as a first agent in Thailand to treat breast cancer. Table 4-10 show the percentage of Trastuazumab and other targeted therapy.

Table 28 Pattern of prescribed targeted therapy drug

Pattern	Center							Total
	1	2	3	4	5	6	7	
Trastuzumab	10	17	12	2	3	33	20	97
(%)	(83.33)	(94.44)	(100)	(28.57)	(100)	(100)	(100)	(92.38)
Other	2	1	0	5	0	0	0	8
targeted	(16.67)	(5.56)	(0)	(71.43)	(0)	(0)	(0)	(7.62)
therapy (%)								
Total	12	18	12	7	3	33	20	105
(%)	(100)	(100)	(100)	(100)	(100)	(100)	(100)	(100)

There were 105 prescriptions of targeted therapy, 97 prescriptions (92.38%) was Trastuzumab. The other targeted therapy was Bevacizumab.

4.2.8 Cost of anticancer drug prescriptions

NHSO protocol was not only mentions for chemotherapy or hormone therapy regimen should be prescribed, but it mention for reimbursed cost of chemotherapy per cycle. Those budgets will pay back due to the actual cost but not over the reimbursed cost. Although the reimbursed cost was enforce mainly for UC scheme but all cancer centers normally set the same treatment fee in all scheme. The cost of chemotherapy described in this study was evaluated from all patients in all health benefit schemes.

Table 29 Cost of chemotherapy regimen compare with reimbursed cost from NHSO cancer protocol

Cost(Baht)	Chemotherapy regimen				
	CMF	AC	FAC	Paclitaxel	Capecitabine
Reimbursed cost (Baht)	1,700	1,750	2,000	19,650	14,200
Actual cost (Mean±SD)	1,506.65 ±433.004	2,039.89 ±513.087	2,184.32 ±583.502	21,100 ±9,321	15,700 ±2,761
Median (Baht)	1,442	2,047	2,070	16,700	16,300
Mode (Baht)	1,156	2,408	2,278	16,683	16,296
Minimum (Baht)	1,010	1,241	1,312	14,308	10,200
Maximum(Baht)	4,556	3,940	4,303	49,558	24,287
One-sample T-test ($p \leq 0.05$)	< 0.01	< 0.01	< 0.01	0.006	< 0.01

The table 4-11 shows significantly different ($p \leq .05$) in reimbursed cost and average actual cost of all chemotherapy regimens. Reimbursed cost of each chemotherapy regimen to compare with the average actual cost calculated from all centers, only average actual cost CMF regimen (1,506.65±433.004 Baht) was under the reimbursed cost (1,700 Baht) but the other were over. It seems to be losing with other chemotherapy regimen. However this was only overall result, the average cost by cancer center will be mention in the next paragraph.

4.2.9 Average actual cost of chemotherapy regimen by center

To describe the average cost of chemotherapy regimen by the center, the data show in table 4-12.

Table 30 Average actual cost of chemotherapy regimen by center

Chemotherapy Regimen	Average cost of each center (Baht)							Reimburse cost (Baht)
	1	2	3	4	5	6	7	
Regimen CMF								
Mean	**1,844.00**	1,312.60	1,427.50	1,414.50	NA	1,346.40	**1,775.20**	1,700
SD	273.73	218.99	123.99	247.02		329.76	410.33	
Regimen AC								
Mean	**2,608.76**	**2,330.60**	**1,777.77**	**1,814.54**	1,424.55	**1,798.63**	**1,927.37**	1,750
SD	869.58	204.43	593.33	196.95	254.47	557.79	354.76	
Regimen FAC								
Mean	**2,601.64**	**2,230.67**	1,726.35	1,959.16	1,552.16	1,850.55	**2,155.79**	2,000
SD	807.54	200.87	536.74	226.31	62.25	506.97	564.97	
Regimen Paclitaxel								
Mean	**22,245.45**	16,844.91	**20,163.63**	15,474.67	9,975.87	NA	10,638.84	19,650
SD	1,079.00	2,877.00	1,000.00	4,329.00	1,014.00		941.07	
Regimen Capecitabine								
Mean	**17,226.75**	**15,040.85**	**18,020.00**	13,707.37	**15,866.67**	**15,161.34**	**17,850.00**	14,200
SD	6,773.0	4,456.00	906.33	3,778.00	723.40	482.90	1,683.00	

From table 4-12, two regimens (AC and Capecitabine) show the higher actual average cost more than reimbursed cost within 6 of 7 cancer centers. While the CMF regimen tend to be the less losing and no chemotherapy regimen that show the average cost under the reimbursed cost. Because the dose of chemotherapy was related to BSA (Body Surface Area), so the cost of each prescription was differentiating. However to conclude that whether losing occurred or not, we will discuss in the next chapter.

4.2.10 Average actual cost of chemotherapy regimen by center

To describe cost of non-NLED per prescription, this study selected only prescription contained non-NLED items to analyze (6.30% of chemotherapy, 9.40% of hormone therapy and 100.00% of targeted therapy). Because of the data of non-NLED cost was not normal distribution so the table 4-13 presents the cost as a range of Baht. The costs of non-NLED were divided into 5 levels.

Table 31 Cost of non-NLED

Cost	Chemotherapy	Hormone therapy	Targeted therapy
Not prescribed non-NLED	3,254	3,557	0
(%)	(93.70)	(90.60)	(0.00)
Prescribe non-NLED	218	367	105
(%)	(6.30)	(9.40)	(100.00)
- 1 – 100 baht	54	97	0
(%)	(1.60)	(2.50)	(0.00)
- 101 – 1,000 Baht	43	76	0
(%)	(1.20)	(1.90)	(0.00)
- 1,001 – 5,000 Baht	10	23	0
(%)	(0.30)	(0.60)	(0.00)
- 5,000 – 10,000 Baht	1	39	0
(%)	(0.00)	(1.00)	(0.00)
- > 10,000 Baht	110	132	105
(%)	(3.20)	(3.40)	(100.00)

The maximum cost of non-NLED found in targeted therapy in range of more than 10,000 Baht because all targeted therapy was non-NLED themselves and very expensive drug. Unlike other group, some regimen was not non-NLED themselves but show the cost of non-NLED in range of more than 10,000 Baht too. The higher cost may cause by non-NLED concomitant drug such as some of GCSF (Granulocyte Colony Stimulating factor) or EPO (Erythropietin).

4.2.11 Cost of concomitant drugs

To describe cost of concomitant drugs per prescription, this study selected only prescription contained concomitant drugs (93.20% of chemotherapy, 23.50% of hormone therapy and 88.90% of targeted therapy) items to analyze. Because of the data of concomitant drugs cost was not normal distribution so the table 4-14 presents the cost as a range of Baht. The costs of concomitant drugs were divided into 5 levels.

Table 32 Cost of concomitant drugs

Cost	Chemotherapy	Hormone therapy	Targeted therapy
Not prescribe	237	3,000	9
Concomitant drugs (%)	(6.80)	(76.50)	(11.10)
Prescribe	3,248	924	72
Concomitant drug (%)	(93.20)	(23.50)	(88.90)
- 1 – 100 baht	594	213	47
(%)	(16.70)	(5.40)	(58.00)
- 101 – 1,000 Baht	2,327	589	15
(%)	(67.00)	(15.00)	(18.50)
- 1,001 – 5,000 Baht	287	80	2
(%)	(8.30)	(2.00)	(2.50)
- 5,000 – 10,000 Baht	1	6	0
(%)	(0.03)	(0.02)	(0.00)
- > 10,000 Baht	39	36	8
(%)	(1.12)	(0.90)	(9.90)

Almost all the cost of concomitant drug of chemotherapy and hormone therapy prescriptions was between 101 – 1,000 Baht (67.00% of all chemotherapy prescriptions and 15.00% of hormone therapy prescriptions). In targeted therapy prescription, the cost of concomitant drugs was between 1 – 100 Baht.

4.2.12 The number of couple drug interaction

To describe the number of couple drug interaction, the software was used to evaluate each prescription. The couple of drug interactions were detected by not considered whether harm happen to patients. Because it's mean there have a risk of adverse drug interaction from miss administration. The number of couple drug interaction show in table 4-15

Table 33 Number of couple drug interaction in any severity

Pattern	Chemotherapy	Hormone therapy	Targeted therapy
Number of couple drug interaction			
None	848	3,721	94
(%)	(25.01)	(99.92)	(90.38)
≥ 1 couple	2,543	3	10
(%)	(74.99)	(0.08)	(9.62)
1 couple	631	3	3
(%)	(18.60)	(0.08)	(2.88)
2 couples	974	0	4
(%)	(28.72)		(3.85)
3 couples	855	0	1
(%)	(25.21)		(0.96)
4 couples	79	0	2
(%)	(2.32)		(1.93)
5 couples	4	0	0
(%)	(0.14)		

Because of more items in chemotherapy prescriptions, the highest couple of drug interactions were shown in this group. There were 53.93% of chemotherapy shows 2 -3 couples of drug interaction. In targeted therapy there were 6.73% of prescription show 1 – 2 couples of drug interaction. And there were only 0.08% of hormone therapy prescription show only 1 couple of drug interaction. However this topic did not mention about severity and harm to patients. It will be discussed in the next paragraph.

4.2.13 The severity of drug interaction

To describe the severity of drug interaction, the result present into three level of severity; minor, moderate and major. Because of sequential administration belong to standard guideline of chemotherapy, the couple of drug interaction in the guideline were excluded. The table 4-16 show number of suspected drug interaction.

Table 34 The maximum severity of all couple drug interaction

Severity drug interaction	No of suspected drug interaction		
	Chemotherapy	Hormone therapy	Targeted therapy
Minor	0	0	0
Moderated	7	1	0
- Morphine+Dimenhydrinate	2	-	-
- Morphine+Lorazepem	2	-	-
- Phenobarbital+Metoclopramide	1	-	-
- Antacid+Dexamethasone	1	-	-
- Docetaxel+Filgrastim	1	-	-
- Paclitaxel+Tamoxifen	1	1	-
Major	4	2	0
- Haloperidol+Ondansetron	2	-	-
- Haloperidol+Metoclopramide	2	-	-
- Tamoxifen+Celecoxib	-	2	-
Total	11	3	0

The data of drug interaction were analyzed by the list of drug in each prescription. The data in table 4-16 had shown the couple of drug interaction and severity. There were 11 times of suspected of moderate interaction from chemotherapy; Morphine + Dimenhydrinate, Morphine + Lorazepam, Phenobarbital + Metoplopramide, Antacid + Dexamethasone, Docetaxel + Filgrastim and Paclitaxel + Tamoxifen. We found 4 times of major severity of drug interaction; Haloperidol + Ondansetron, Haloperidol + Metoplopramide and Tamoxifen + Celecoxib (hormone therapy). No suspect drug interaction detected in targeted therapy.

4.3 Assessing appropriate use of anticancer drugs

Three anticancer drug; Docetaxel, Letrozole and Trastuzumab were selected from each group of anticancer (Chemotherapy, Hormone therapy and Targeted therapy) for evaluating appropriate use. The criteria evaluation for Docetaxel and Letrozole referred as TNF (Thai National Formulary) version 2010. The criteria for Trastuzumab referred from the comptroller general department or prior authorization program (OCPA).

4.3.1 Docetaxel

Before describe the appropriate use of Docetaxel, the demographic data of prescription were declared. There were 179 prescription of Docetaxel in 56 patients. Average age of patients who was prescribed Docetaxel was 53.39 ± 12.528 year olds. Almost all patients were in CSMBS (45.80%) and UC scheme (49.20%). 59.70% of patients have ER and/or PR positive and 3.90% cannot be found this data. Number of first time prescribed was 22.30%, the other were between the treatments. The limitation of Docetaxel administration was not more than 8 cycle. Due to the recommendation, 81.00% of prescription shown the pattern of every 3 weeks of Docetaxel.

The patients who disease developed to metastasis were 78.20%. 75.40% of prescriptions belong to patients who failed to anthracycline or contra-indication with anthracycline. Performance status was evaluated as ECOG, 54.70% of prescriptions were in ECOG 0 – 2 and much was not identified. None of prescription belongs to terminal ill patients, incorrect dose and incorrect pre-medication. The adverse drug reaction reported for 34.60% of prescriptions. Only 42.17% of prescription attached complete DUE form (Drug Use Evaluation) in the medical record.

Table 35 Demographic data of Docetaxel prescriptions

Demographic data	Center							Total
	1	2	3	4	5	6	7	
Number of prescriptions (%)	42 (23.46)	22 (12.29)	66 (36.87)	2 (1.12)	9 (5.03)	33 (18.44)	5 (2.79)	179
Number of patients (%)	8 (14.29)	8 (14.29)	19 (33.93)	2 (3.57)	3 (5.36)	11 (19.64)	5 (8.93)	56
Age of patients	53.39 $\pm$ 12.528 years (Maximum = 77, Minimum = 33)							
Scheme								
- CSMBS (%)	82 (45.80)							
- UC (%)	88 (49.20)							
- SSS (%)	7 (3.90)							
- Other (%)	2 (1.10)							
Hormone receptor								
- ER(+)/PR(+) (%)	62 (34.60)							
- ER(+)/PR(-) (%)	40 (22.30)							
- ER(-)/PR(+) (%)	5 (2.80)							
- ER(-)/PR(-) (%)	65 (36.30)							
- Not known	7 (3.90)							
Number of cycle								
- 1 (New case) (%)	40 (22.30)							
- 2 (%)	36 (20.10)							
- 3 (%)	31 (17.30)							
- 4 (%)	26 (14.50)							
- 5 (%)	20 (11.20)							
- 6 (%)	16 (8.90)							
- 7 (%)	5 (2.80)							
- 8 (%)	5 (2.80)							
Interval of cycle								
- Every 3 week (%)	145 (81.0)							
- Every 1 week (%)	34 (19.0)							

Criteria for Docetaxel DUE	Number of prescriptions
Indication: Metastasis breast cancer	
- Yes (%)	140 (78.20)
- No (%)	39 (21.80)
Indication: Be prescribed after anthracyclin	
- Yes: Failed anthracyclin (%)	126 (70.40)
- No: Contraindication to anthracyclin (%)	9 (5.0)
- No: Adjuvant therapy (%)	27 (15.10)
- Data not available (%)	17 (9.50)
Indication: Not in terminal ill	
- No (%)	179 (100)
Indication: Performance status ECOG = 0 – 2	
- Yes (%)	98 (54.70)
- Not record (%)	81 (45.30)
Correct dose	
- Yes (%)	179 (100)
- No (%)	0
Correct duration	
- Yes (%)	179 (100)
- No (%)	0
Adverse drug reaction	
- Yes (%)	62 (34.60)
- No (%)	117 (65.40)
Use dexamethasone as pre-medication	
- Yes (%)	179 (100)
- No (%)	0
Completed DUE form was founded in medical record	
- Yes (%)	35 (42.17)
- No (%)	48 (57.83)

Table 4-18 present how to evaluate the appropriate use of Docetaxel due to all 8 criteria. Criteria 1 – 7 were clinical criteria and criteria 8 was system criteria.

Table 36 Summary of evaluating appropriateness of Docetaxel

Criteria	Summary Assessing appropriateness	Number of appropriate prescriptions		
		Include	Exclude	Total
	Number of all Docetaxel prescriptions			179
1	**Metastasis Breast Cancer (N = 179)**	140	39	179
2	**Indication (N = 140)**			140
	1. Prescribe after anthracycline	114	0	
	2. Contraindication to anthracycline	9	0	
	3. Cannot identify indication =	0	17	
3	**Performance status (N = 123)**			123
	1. ECOG 0 – 2	83	0	
	2. Data cannot be found	0	40	
4	**Patient not in terminal ill (N = 83)**	83	0	83
5	**Prescribe dexamethasone as pre-medication (N = 83)**	83	0	83
6	**Dose interval (N = 83)**			83
	- Every 3 week	66	0	
	- Every 1 week	17	0	
7	**Correct dose (75 mg/m^2) (N = 83)**	83	0	83
8	**Found evidence paper of DUE form (N = 83)**			83
	- Yes	35	0	
	- No	0	48	
Summary 1	**Appropriate use from all prescription (Completed criteria 1 - 7) (%)**	83 (46.37)	96 (53.63)	179 (100.00)
Summary 2	**Appropriate use from all prescription (Completed all 1 - 8 criteria) (%)**	35 (19.55)	144 (80.45)	179 (100.00)

The Docetaxel prescription would be evaluated as appropriate due to the clinical criteria if they pass all 1 – 7 criteria, so the prescriptions were excluded stepwise if they did not meet the criteria. Finally 46.37% of Docetaxel prescriptions were appropriate due to the clinical criteria. Another system criteria of DUE form was proved that each center had completed all process of prescribing. There were only 19.55% of Docetaxel prescriptions that found evidence paper of DUE form in medical record and passed all 8 criteria.

4.3.2 Letrozole

Before describe the appropriate use of Letrozole, the demographic data of prescription were declared. Table 4-19 are as follow. There were 681 prescription of Letrozole from 254 patients. Average age of patients who was prescribed Letrozole was 58.60 $\pm$ 10.002 year olds. Almost all patients were in UC (77.70%), UC and SSS were 18.50% and 8.70% respectively. Only 10.60% were first time prescribed of Letrozole. Oncologist was frequently being specialist who prescribed Letrozole. Average amount of tablet per prescription was 57.80 $\pm$ 40.109 tablets.
The patients whose disease developed to metastasis were 78.20%. 75.40% of prescriptions belong to patients who failed to anthracycline or contra-indication with anthracycline. Performance status was evaluated as ECOG, 54.70% of prescriptions were in ECOG 0 – 2 and much was not identified. None of prescription belongs to terminal ill patients, incorrect dose and incorrect pre-medication. The adverse drug reaction reported for 34.60% of prescriptions. Only 42.17% of prescription attached complete DUE form (Drug Use Evaluation) in the medical record.

There were 96.00% of prescriptions that show ER and/or PR receptor positive. 91.00% of prescriptions show that patients were in post-menstrual status. The indications of Letrozole were for advance breast cancer for 25.99% and adjuvant therapy for 74.01%. Adverse drug reaction of Letrozole was reported as 1.60%. Calcium supplement was prescribed as concomitant drug for 19.40%. The evidence paper of DUE founded in medical record was 26.40% of all Letrozole prescriptions.

Table 37 Demographic data of Letrozole prescriptions

Demographic data	Center							Total
	1	2	3	4	5	6	7	
Number of prescriptions (%)	156 (22.91)	301 (44.20)	24 (3.52)	15 (2.20)	16 (2.35)	83 (12.19)	86 (12.63)	681
Number of patients (%)	51 (20.80)	85 (33.46)	12 (4.72)	8 (3.15)	9 (3.54)	37 (14.57)	52 (20.47)	254
Age of patients	58.60 ± 10.002 years (Maximum = 84, Minimum = 34)							
Scheme								
- CSMBS (%)	126 (18.50)							
- UC (%)	488 (77.70)							
- SSS (%)	59 (8.70)							
- Other (%)	8 (1.20)							
First prescribed								
- Yes (%)	72 (10.60)							
- No (%)	609 (89.40)							
Prescriber specialist								
- Oncologist %)	558 (81.90)							
- Med (%)	6 (0.90)							
- Radiologist (%)	93 (13.70)							
- Surgeon (%)	24 (3.50)							
Amount of prescribed tablets								
- Mean ± SD	57.80 ± 40.109							
- Maximum	212							
- Minimum	10							
- Mode	30							

Criteria of Letrozole	Number of prescriptions
Hormone receptor	
- ER(+)/PR(+) (%)	423 (62.10)
- ER(+)/PR(-)(%)	204 (30.0)
- ER(-)/PR(+)(%)	27 (4.0)
- ER(-)/PR(-)(%)	6 (0.90)
- Not known (%)	21 (3.10)
Menstrual status	
- Post-menstrual status from any cause; (%)	620 (91.04)
1) Age > 60 years (%)	245 (36.00)
2) Ovarian ablation (%)	44 (6.50)
3) LMP > 1 years before diagnosed of cancer (%)	331 (48.70)
	30 (4.40)
- Pre-menstrual status (%)	31 (4.60)
- Not known (%)	0
Terminal ill	
- No (%)	681 (100.00)
Indication	
- Advanced breast cancer (%)	177 (25.99)
- Adjuvant therapy (Start with tamoxifen + letrozole) (%)	284 (41.70)
- Adjuvant therapy (Start with letrozole + tamoxifen) (%)	220 (32.31)
Correct dose: 2.5 mg/day (%)	681 (100)
Adverse drug reaction	
- Yes (%)	11 (1.60)
- No (%)	670 (98.40)
Prescribed calcium supplement	
- Yes (%)	132 (19.40)
- No (%)	549 (80.60)
Completed DUE form was founded in medical record	
- Yes (%)	180 (26.40)
- No (%)	501 (73.60)

Table 38 Summary of evaluating appropriateness of Letrozole

Criteria	Summary Assessing appropriateness	Number of appropriate prescriptions		
		Inculde	Exclude	Total
	Number of all prescriptions			681
1	**Hormone receptor positive (ER/PR) (N = 681)**	654	27	681
2	**Post-menopause (N = 654)**	599	55	654
3	**Indication (N = 599)**	(571)	(28)	599
	1. Advance breast cancer	123	25	
	2. Adjuvant therapy (Start with tamoxifen)	243	3	
	3. Adjuvant therapy (Start with letrozole)	205	0	
4	**Duration**:Tamoxifen+ Letrozole $\leq$ 60	(550)	(21)	571
	months**(N=571)**	114	9	
	1. Advance breast cancer	231	12	
	2. Adjuvant therapy (Start with tamoxifen)	205	0	
	3. Adjuvant therapy (Start with letrozole)			
5	**Correct dose: 2.5 mg/Day (N = 550)**	550	0	550
6	**Complete DUE form (N = 550)**	(157)	(393)	550
	1. Advance breast cancer	22	92	
	2. Adjuvant therapy (Start with tamoxifen)	93	138	
	3. Adjuvant therapy (Start with letrozole)	42	163	
Summary 1	**Appropriate use from all prescription**	550	131	681
	(Completed criteria 1 - 5) (%)	(80.76)	(19.24)	(100.00)
Summary 2	**Appropriate use from all prescription**	157	524	681
	(Completed all 1 - 6 criteria) (%)	(23.05)	(76.95)	(100.00)

The Letrozole prescription would be evaluated as appropriate due to the clinical criteria if they pass all 1 – 5 criteria, so the prescriptions were excluded stepwise if they did not meet the criteria. Finally 80.76% of Letrozole prescriptions were appropriate due to the clinical criteria. Another system criteria of DUE form was proved that each center had completed all process of prescribing. There were only 23.05% of Docetaxel prescriptions that found evidence paper of DUE form in medical record and passed all 6 criteria.

4.3.3 Trastuzumab

Before describe the appropriate use of Docetaxel, the demographic data of prescription were declared in table 4-21.

Table 39 Demographic data of Trastuzumab prescriptions

Demographic data	Center							Total
	1	2	3	4	5	6	7	
Number of prescriptions	10	17	12	2	3	33	20	97
(%)	(10.31)	(11.53)	(12.37)	(2.06)	(3.09)	(34.02)	(20.62)	(100.00)
Number of patients	2	4	4	2	1	8	4	25
(%)	(8.0)	(16.0)	(16.0)	(8.0)	(4.0)	(32.0)	(16.0)	(100.00)
Age of patients	52.05 ± 12.111 years (Maximum = 71, Minimum = 31)							
Scheme								
- CSMBS (%)	97 (100.00)							
- NHSO (%)	0 (0.00)							
- SSS (%)	0 (0.00)							
- Other (%)	0 (0.00)							
Prescriber specialist								
- Oncologist (%)	69 (71.10)							
- Radiologist (%)	28 (28.90)							
Metastasis breast cancer								
- Yes (%)	25 (25.80)							
- No (%)	72 (74.20)							
Resectable								
- Complete (%)	87 (89.70)							
- NA (%)	10 (10.30)							
Previous Hormone Therapy								
- Yes (%)	20 (20.60)							
- No (%)	77 (79.40)							
HER-2 receptor								
- Positive 2 (%)	97 (100)							
- Negative (%)	0 (0.00)							
- NA (%)	0 (0.00)							
HER-2 Test by								
- FISH (%)	82 (84.50)							
- IHC (%)	15 (15.50)							

Demographic data	Number of prescriptions
Type of use	
- New case (%)	12 (12.40)
- Continue case (%)	85 (87.60)
Performance status ECOG = 0 – 2	97 (100.0)
- Yes (%)	0
- No (%)	
Indication	
- 1st line therapy (%)	0
- 2nd line therapy (%)	92 (94.8)
- 3rd line therapy (%)	5 (5.20)
- Re-prescribed after 1 year (%)	0
Cardiac function	
- LVEF $<$ 50% (%)	0
- LVEF $\geq$ 50% (%)	97 (100.00)
Cardiovascular Disease	
- Yes (%)	22 (22.70)
- No (%)	69 (71.10)
- NA (%)	6 (6.20)
Disease Status	
- Complete respond (%)	0
- Partial respond (%)	12 (12.37)
- Stable disease (%)	67 (69.07)
- Progress disease (%)	0
- NA (%)	18 (18.56)
Adverse drug reaction	
- Yes (%)	14 (14.40)
- No (%)	83 (85.60)
Completed DUE form	
- Yes (%)	86 (88.70)
- No (%)	11 (11.30)
OCPA Pre-authorization (%)	97 (100.0)

From the table 4-21 the data show. There were 97 Trastuzumab prescriptions of 25 patients for analysis. Average age of patients was 52.05 ± 12.111 years old and all of them were in CSMBS scheme. The oncologists were frequently prescribed as 71.10%, other prescribed by the radiologists. The indications shown 74.20% use in adjuvant therapy and 25.80% use in metastasis breast cancer. There were 89.70% of prescription were the patients who undergone complete resectable of tumor, 89.40% of prescription were the patients who never been prescribed hormone therapy before. The tumor marker use for confirm the efficacy of Trastuzumab were identified as HER2 receptor positive for all prescriptions 100.00%. There were 87.60% prescriptions of continuing treatment, only 12.40% of first time prescribed. Trastuzumab was prescribed as first and second line of treatment. Because cardio toxicity from Trastuzumab, cardiac function was evaluated before and between treatments. Only 22.70% of prescriptions had undelying of cardiac diseas and all patients (100.00%) were monitored cardiac function by LVEF% every 3 months (not more than 50%). Before prescribe next cycle, responsiveness was evaluate, 69.07% shown stable disease. Adverse drug reaction was reported for 14.40%. Although all of prescriptions undergo OCPA program before prescribing, but 11.30% of prescription did not found the evidence paper of DUE form in medical record.

The Table 4-22 summarized evaluation of appropriate use of Trastuzumab. Trastuzumab prescriptions would be evaluated as appropriate due to the clinical criteria if they pass all 1 – 6 criteria, so the prescriptions were excluded stepwise if they did not meet the criteria. Finally 100.00% of Trastuzumab prescriptions were appropriate due to the clinical criteria. Another system criteria of DUE form was proved that each center had completed all process of prescribing. There were 88.66% of Docetaxel prescriptions that found evidence paper of DUE form in medical record and passed all 7 criteria.

Table 40 Summary of evaluating appropriateness of Trastuzumab

Criteria	Summary Assessing appropriateness	Number of appropriate prescriptions		
		Include	Exclude	Total
	Number of all prescriptions			97
1	Indication (N = 97)	(97)		97
	1. Metastasis breast cancer	25	0	
	2. Adjuvant therapy	72	0	
2	HER-2 receptor positive (N = 97)	97	0	97
3	ECOG 0-2 (N = 97)	97	0	97
4	LVEF ≥ 50% (N = 97)	97	0	97
5	Recommend Dose (N = 97) (Maintenance Dose 6 mg/kg)	97	0	97
6	Appropriated duration (N = 97)	97	0	97
7	Complete DUE form (N = 97)	86	11	97
Summary 1	Appropriate use from all prescription (Completed criteria 1 - 6) (%)	97 (100.00)	0	97 (100.00)
Summary 2	Appropriate use from all prescription (Completed all 1 - 7 criteria) (%)	86 (88.66)	11 (11.34)	97 (100.00)

4.4Factors affecting pattern of prescribed

4.4.1 The relationship between non-NLED policy center and non-NLED prescribing pattern

To analyze the relation between non-NLED policies which were classified into 2 group (non-NLED policy dominate and non-NLED policy non-dominate) and non-NLED prescribing pattern. The researcher use chi square test for analyze with the hypothesis below. The result show in table 4-23.

Hypothesis

Ho: non-NLED policy of cancer center not related to non-NLED prescribing pattern

H1: non-NLED policy of cancer center related to non-NLED prescribing pattern

Table 41 The relationship between non-NLED policy and non-NLED prescribing pattern

Policy classification	non-NLED prescribing pattern		Total	χ^2	Sig. $p \leq 0.05$
	Prescribed non-NLED (prescription)	Not prescribed non-NLED (prescription)			
Chemotherapy					
non-NLED policy dominate (%of total)	183 (5.30)	1,699 (48.90)	1,882 (54.20)	82.878	<0.01
non-NLED policy non dominate(%of total)	35 (1.00)	1,555 (44.80)	1,590 (45.80)		
Total (%of total)	218 (6.30)	3,254 (93.70)	3,472 (100.00)		
Hormone therapy					
non-NLED policy dominate (%of total)	237 (6.10)	1,846 (47.00)	2,083 (53.10)	21.477	<0.01
non-NLED policy non dominate(%of total)	130 (3.30)	1,711 (43.60)	1,841 (46.90)		
Total (%of total)	367 (9.40)	3,557 (90.60)	3,924 (100.00)		
Targeted therapy					
non-NLED policy dominate (%of total)	71 (67.60)	0 (0.00)	71 (67.60)	N/A	N/A
non-NLED policy non dominate(%of total)	34 (32.40)	0 (0.00)	34 (32.40)		
Total	105 (100.00)	0 (0.00)	105 (100.00)		

Percentage of chemotherapy prescription that contained non-NLED was only 6.30%, 5.30% of those prescriptions were in non-NLED policy dominate group and

1.00% were in non-NLED policy non-dominate group. There was 93.70% of chemotherapy prescriptions not contained non-NLED. Hypothesis test for relation between non-NLED policy and non-NLED prescribing pattern at $p \leq 0.05$ show significantly different at Sig. = <0.01. Hypothesis Ho was rejected, so at statistical significant 0.05, non-NLED policy and non-NLED prescribing pattern of chemotherapy prescriptions show the relationship.

Percentage of hormone therapy prescription that contained non-NLED was only 9.40%, 6.10% of those prescriptions were in non-NLED policy dominate group and 3.30% were in non-NLED policy non-dominate group. There was 90.60% of hormone therapy prescriptions not contained non-NLED. Hypothesis test for relation between non-NLED policy and non-NLED prescribing pattern at $p \leq 0.05$ show significantly different at Sig. = <0.01. Hypothesis Ho was rejected, so at statistical significant 0.05, non-NLED policy and non-NLED prescribing pattern of hormone therapy prescription show the relationship.

Percentage of targeted therapy prescription that contained non-NLED was 100.00%, 67.60% of those prescriptions were in non-NLED policy dominate group and 32.40% were in non-NLED policy non-dominate group. Hypothesis test for relation between non-NLED policy and non-NLED prescribing pattern at $p \leq 0.05$ cannot show anything because non-NLED prescribing pattern was constant. So the researcher cannot identify the relation non-NLED policy and non-NLED prescribing pattern of targeted therapy prescriptions. The cause such pattern because all targeted drug still listed in non-NLED.

4.4.2 The relationship between non-NLED policy and number of prescribed non-NLED

To compare the different number of non-NLED items between non-NLED policy group (non-NLED policy dominate and non-NLED policy non-dominate) the independent sample T-test was use with the hypothesis below. The result show in table 4-24

Ho : $\mu_{\text{policy dominate}} = \mu_{\text{policy non-dominate}}$

Number of non-NLED item in non-NLED policy dominate group was not different from number of non-NLED item in non-NLED policy non-dominate group

H1 : $\mu_{\text{policy dominate}} \neq \mu_{\text{policy non-dominate}}$

Number of non-NLED item in non-NLED policy dominate group was different from number of non-NLED item in non-NLED policy non-dominate group

Table 42 The relationship between non-NLED policy and number of prescribed non-NLED

Group of policy	N	Number of non-NLED items		t-value	P-value
		X	S.D.		p≤0.05
Chemotherapy					
Non-NLED policy dominate	183	1.92	1.891	-0.775	0.439
Non-NLED policy non-dominate	35	1.66	1.697		
Hormone therapy					
Non-NLED policy dominate	237	1.22	0.496	-1.015	0.311
Non-NLED policy non-dominate	130	1.16	0.463		
Targeted therapy					
Non-NLED policy dominate	71	1.23	0.513	0.213	0.832
Non-NLED policy non-dominate	34	1.26	1.377		

In chemotherapy prescriptions, the mean of non-NLED items in non-NLED policy dominate group was 1.92 $\pm$ 1.891 items, non-NLED policy non-dominate group was 1.66 $\pm$ 1.697 items and p value was 0.439. In hormone therapy prescriptions, the mean of non-NLED items in non-NLED policy dominate group was 1.22 $\pm$ 0.496 items, non-NLED policy non-dominate group was 1.16 $\pm$ 0.463 items and p value was 0.311. In targeted therapy prescriptions, the mean of non-NLED items in non-NLED policy dominate group was 1.23 $\pm$ 0.513 items, non-NLED policy non-dominate group was 1.26 $\pm$ 1.377 items and p value was 0.832.

Hypothesis test for compare men between non-NLED policy and number of non-NLED items at $p \leq 0.05$ show not significantly different for all chemotherapy, hormone therapy and targeted therapy prescription. Hypothesis Ho was accepted, so at statistical significant 0.05, number of non-NLED items between non-NLED policy dominate and non-NLED policy non-dominate was not significantly different in all 3 group of cancer drugs.

4.4.3 The relationship between non-NLED policy and cost of non-NLED

To compare the different median cost of non-NLED items between non-NLED policy group (non-NLED policy dominate and non-NLED policy non-dominate) 2-independent sample test (Man-Whitney U test) was use with the hypothesis below because the data was not normal distribution. The result show in table 4-25

Ho : μpolicy dominate = μpolicy non-dominate
Cost of non-NLED item in non-NLED policy dominate group was not different from cost of non-NLED item in non-NLED policy non-dominate group

H1 : μpolicy dominate ≠ μpolicy non-dominate
Cost of non-NLED item in non-NLED policy dominate group was different from cost of non-NLED item in non-NLED policy non-dominate group

Table 43 The relationship between non-NLED policy and cost of prescribed non-NLED

Group of policy	N	Cost of non-NLED items	Test statistics		
		Mean Rank	Mann-Whitney U	Wilcoxon W	Asymp. Sig. (2-tailed)
Chemotherapy					
Non-NLED policy dominate	183	117.34	1767.500	2397.500	<0.01
Non-NLED policy non-dominate	35	68.50			
Hormone therapy					
Non-NLED policy dominate	237	185.51	15046.000	23561.000	0.712
Non-NLED policy non-dominate	130	181.24			
Targeted therapy					
Non-NLED policy dominate	71	63.01	496.000	1091.000	<0.01
Non-NLED policy non-dominate	34	32.09			

In chemotherapy prescriptions, the mean rank cost of non-NLED items in non-NLED policy dominate group was 117.348 and in non-NLED policy non-dominate was 68.50. In hormone therapy prescriptions, the mean rank cost of non-NLED items in non-NLED policy dominate group was 188.51 and in non-NLED policy non-dominate was 181.24. . In targeted therapy prescriptions, the mean rank cost of non-NLED items in non-NLED policy dominate group was 63.01 and in non-NLED policy non-dominate was 32.09. Chemotherapy and targeted therapy showed significantly relation as <0.01.

So hypotheses Ho were rejected, it's mean that the median cost between non-NLED policies dominate and non-NLED policy non-dominate were significantly different in chemotherapy and targeted therapy.

4.4.4 The relationship between original drugs policy and original drugs prescribing pattern

To analyze the relation between original drug policy which were classified into 2 group (original drug policy dominate and original drug policy non-dominate) and original drug prescribing pattern. The researcher use chi square test for analyze with the hypothesis below. The result show in table 4-26.

Ho: Original drug policy not related to original drug original drug prescribing pattern

H1: Original drug policy related to original drug original drug prescribing pattern

Table 44 The relationship between original drugs policy and original drugs prescribing pattern

Policy classification	Original drug prescribing pattern		Total	χ^2	Sig.
	Prescribed original (prescription)	Not prescribed original (prescription)			
Chemotherapy					
Original drug policy dominate (%Total)	369 (10.60)	1,462 (42.10)	1,831 (52.70)	101.60	<0.01
Original drug policy non dominate (%Total)	133 (3.90)	1,508 (43.40)	1,641 (47.30)		
Total (%Total)	502 (14.50)	2,970 (85.50)	3,472 (100.00)		
Hormone therapy					
Original drug policy dominate (%Total)	509 (13.00)	1,565 (39.90)	2,074 (52.90)	8.690	0.003
Original drug policy non dominate (%Total)	531 (13.50)	1,319 (33.60)	1,850 (47.10)		
Total (%Total)	1,040 (26.50)	2,884 (73.50)	3,924 (100.00)		
Targeted therapy					
Original drug policy dominate (%Total)	63 (60.00)	0 (0.00)	63 (60.00)	N/A	N/A
Original drug policy non dominate (%Total)	42 (40.00)	0 (0.00)	42 (40.00)		
Total (%Total)	105 (100.00)	0 (0.00)	105 (100.00)		

Percentage of chemotherapy prescription that contained original drug was only 14.50%, 10.60% of those prescriptions were in original drug policy dominate group and 3.90% were in original drug policy non-dominate group. There was 85.50% of chemotherapy prescriptions not contained original drug. Hypothesis test for relation between original drug policy and original drug prescribing pattern at $p \leq 0.05$ show not significantly different at Sig. = <0.01. Hypothesis Ho was rejected. It can summarize that at statistical significant 0.05, original drug policy and original drug prescribing pattern of chemotherapy prescriptions show the relationship.

Percentage of hormone therapy prescription that contained original drug was only 26.50%, 13.00% of those prescriptions were in original drug policy dominate group and 13.50% were in original drug policy non-dominate group. There was 73.50% of hormone therapy prescriptions not contained original drug. Hypothesis test for relation between original drug policy and original drug prescribing pattern at $p \leq 0.05$ show not significantly different at Sig. = 0.003. Hypothesis Ho was rejected. It can summarize that at statistical significant 0.05, original drug policy and original drug prescribing pattern of hormone therapy prescriptions show the relationship.

Percentage of targeted therapy prescription that contained original drug was 100.00%, 60.00% of those prescriptions were in original drug policy dominate group and 40.00% were in original drug policy non-dominate group. Hypothesis test for relation between original drug policy and original drug prescribing pattern at $p \leq 0.05$ cannot show anything because original drug prescribing pattern was constant. So the researcher cannot identify the relation original drug policy and original drug prescribing pattern of targeted therapy prescriptions. The cause of such pattern because all targeted drug were original drugs.

4.4.5 The relationship between medication safety standard policy and non-NLED prescribing pattern

To analyze the relation between medication safety standard policy which were classified into 2 group (medication safety standard policy dominate and medication safety standard policy non-dominate) and non-NLED prescribing pattern. The researcher use chi square test for analyze with the hypothesis below. The result show in table 4-27.

Hypothesis Ho: Medication safety standard policy not related to non-NLED prescribing pattern

H1: Medication safety standard policy related to non-NLED prescribing pattern

Table 45 The relationship between medication safety standard policy and non-NLED prescribing pattern

Policy classification	non-NLED prescribing pattern		Total	χ^2	Sig.
	Prescribed non-NLED (prescription)	Not prescribed non-NLED (prescription)			
Chemotherapy					
Policy dominate to higher standard (%Total)	33 (1.00)	1,422 (41.00)	1,455 (41.90)	68.466	<0.01
Policy dominate to lower standard(%Total)	185 (5.30)	1,832 (52.80)	2,017 (58.10)		
Total (%Total)	218 (6.30)	3,254 (93.70)	3,472 (100.00)		
Hormone therapy					
Policy dominate to higher standard(%Total)	111 (2.80)	1,586 (40.40)	1,697 (43.20)	27.884	<0.01
Policy dominate to lower standard(%Total)	256 (6.50)	1,971 (50.20)	2,227 (56.80)		
Total (%Total)	367 (9.40)	3,557 (90.60)	3,924 (100.00)		
Targeted therapy					
Policy dominate to higher standard(%Total)	31 (29.50)	0 (0.00)	31 (29.50)	N/A	N/A
Policy dominate to lower standard(%Total)	74 (70.50)	0 (0.00)	74 (70.50)		
Total (%Total)	105 (100.00)	0 (0.00)	105 (100.00)		

Percentage of chemotherapy prescription that contained non-NLED drug was only 6.30%, 1.00% of those prescriptions were in medication safety standard policy

dominate group and 5.30% were in medication safety standard policy non-dominate group. There was 93.70% of chemotherapy prescriptions not contained non-NLED drug. Hypothesis test for relation between medication safety standard policy and non-NLED drug prescribing pattern at $p \leq 0.05$ show significantly different at Sig. = 0.000. Hypothesis Ho was rejected. It can summarize that at statistical significant 0.05, medication safety standard policy and non-NLED drug prescribing pattern of chemotherapy prescriptions show the relationship.

Percentage of hormone therapy prescription that contained non-NLED drug was only 9.40%, 2.80% of those prescriptions were in medication safety standard policy dominate group and 6.50% were in medication safety standard policy non-dominate group. There was 90.60% of hormone therapy prescriptions not contained non-NLED drug. Hypothesis test for relation between medication safety standard policy and non-NLED drug prescribing pattern at $p \leq 0.05$ show significantly different at Sig. = 0.000. Hypothesis Ho was rejected. It can summarize that at statistical significant 0.05, medication safety standard policy and non-NLED drug prescribing pattern of hormone therapy prescriptions show the relationship.

Percentage of targeted therapy prescription that contained non-NLED drug was 100.00%, 29.50% of those prescriptions were in medication safety standard policy dominate group and 70.50% were in medication safety standard policy non-dominate group. Hypothesis test for relation between medication safety standard policy and non-NLED drug prescribing pattern at $p \leq 0.05$ cannot show anything because non-NLED drug prescribing pattern was constant. So the researcher cannot identify the relation between medication safety standard policy and non-NLED drug prescribing pattern of targeted therapy prescriptions. The cause of such pattern because all targeted drug were non-NLED drugs.

4.4.6 The relationship between health benefit scheme and non-NLED prescribing pattern

To analyze the relation between health benefit schemes which were classified into 3 group (CSMBS or Civil Servant of Medication Benefit Scheme, SSS or Social Security Scheme, UC or Universal Coverage) and non-NLED prescribing pattern. The researcher use chi square test for analyze with the hypothesis below. The result show in table 4-28.

Hypothesis Ho: Health benefit scheme not related to non-NLED prescribing pattern

H1: Health benefit scheme related to non-NLED prescribing pattern

Table 46 The relationship between health benefit schemes and non-NLED prescribing pattern

Policy classification	non-NLED prescribing pattern		Total	χ^2	Sig.
	Prescribed non-NLED (prescription)	Not prescribed non-NLED (prescription)			
Chemotherapy					
CSMBS	120	333	453		
(%Total)	(3.60)	(9.90)	(13.40)	427.10	<0.01
SSS	41	451	492		
(%Total)	(1.20)	(13.40)	(14.60)		
UC	40	2,393	2,433		
(%Total)	(1.20)	(40.80)	(72.00)		
Total	201	3,177	3,378		
(%Total)	(6.00)	(94.00)	(100.00)		
Hormone therapy					
CSMBS	184	619	803		
(%Total)	(4.90)	(16.60)	(21.60)	250.90	<0.01
SSS	32	437	469		
(%Total)	(0.90)	(11.70)	(12.60)		
UC	115	2,337	2,452		
(%Total)	(3.10)	(62.80)	(65.80)		
Total	331	3,393	3,724		
(%Total)	(8.90)	(91.10)	(100.00)		
Targeted therapy					
CSMBS	105	0	105		
(%Total)	(100.00)	(0.00)	(100.00)	N/A	N/A
SSS	0	0	0		
(%Total)	(0.00)	(0.00)	(0.00)		
UC	0	0	0		
(%Total)	(0.00)	(0.00)	(0.00)		
Total	105	0	105		
(%Total)	(100.00)	(0.00)	(100.00)		

Percentage of chemotherapy prescription that contained non-NLED drug was only 6.00%, 3.60% of those prescriptions were in CSMBS, 1.20% were in SSS and

1.2% were in UC. There was 94.00% of chemotherapy prescriptions not contained non-NLED drug. Hypothesis test for relation between health benefit scheme and non-NLED drug prescribing pattern at $p \leq 0.05$ show significantly different at Sig. = 0.000. Hypothesis Ho was rejected. It can summarize that at statistical significant 0.05, health benefit schemes and non-NLED drug prescribing pattern of chemotherapy prescriptions show the relationship.

Percentage of hormone therapy prescription that contained non-NLED drug was only 8.90%, 4.90% of those prescriptions were in CSMBS, 0.90% were in SSS and 3.1% were in UC. There was 91.10% of hormone therapy prescriptions not contained non-NLED drug. Hypothesis test for relation between health benefit scheme and non-NLED drug prescribing pattern at $p \leq 0.05$ show significantly different at Sig. = 0.000. Hypothesis Ho was rejected. It can summarize that at statistical significant 0.05, health benefit schemes and non-NLED drug prescribing pattern of hormone therapy prescriptions show the relationship.

Percentage of targeted therapy prescription that contained non-NLED drug was 100.00% in CSMBS. Hypothesis test for relation between health benefit scheme and non-NLED drug prescribing pattern at $p \leq 0.05$ cannot show anything because non-NLED drug prescribing pattern was constant. So the researcher cannot identify the relation between health benefit scheme and non-NLED drug prescribing pattern of targeted therapy prescriptions.

4.4.7 The relationship between health benefit scheme and original drug prescribing pattern

To analyze the relation between health benefit schemes which were classified into 3 group (CSMBS or Civil Servant of Medication Benefit Scheme, SSS or Social Security Scheme, UC or Universal Coverage) and original drug prescribing pattern. The researcher use chi square test for analyze with the hypothesis below. The result show in table 4-29.

Hypothesis Ho: Health benefit scheme not related to original drug prescribing pattern

H1: Health benefit scheme related to original drug prescribing pattern

Table 47 The relationship between health benefit schemes and non-NLED prescribing pattern

Policy classification	Original drug prescribing pattern		Total	χ^2	Sig.
	Prescribed original drug (prescription)	Not prescribed original drug (prescription)			
Chemotherapy					
CSMBS	174	279	453		
(%Total)	(5.20)	(8.30)	(13.40)	263.60	<0.01
SSS	83	409	492		
(%Total)	(2.50)	(12.10)	(14.60)		
UC	229	2,204	2,433		
(%Total)	(6.80)	(65.20)	(72.00)		
Total	486	2,892	3,378		
(%Total)	(14.40)	(85.60)	(100.00)		
Hormone therapy					
CSMBS	385	418	803		
(%Total)	(10.30)	(11.20)	(21.60)	264.70	<0.01
SSS	126	343	469		
(%Total)	(3.40)	(9.20)	(12.60)		
UC	463	1,989	2,452		
(%Total)	(12.40)	(53.40)	(65.80)		
Total	974	2,750	3,724		
(%Total)	(26.20)	(73.80)	(100.00)		
Targeted therapy					
CSMBS	105	0	105		
(%Total)	(100.00)	(0.00)	(100.00)	N/A	N/A
SSS	0	0	0		
(%Total)	(0.00)	(0.00)	(0.00)		
UC	0	0	0		
(%Total)	(0.00)	(0.00)	(0.00)		
Total	105	0	105		
(%Total)	(100.00)	(0.00)	(100.00)		

Percentage of chemotherapy prescription that contained original drug was only 14.40%, 5.20% of those prescriptions were in CSMBS, 2.50% were in SSS and 6.80% were in UC. There was 85.60% of chemotherapy prescriptions not contained original drug. Hypothesis test for relation between health benefit scheme and original drug prescribing pattern at $p \leq 0.05$ show significantly different at Sig. = 0.000. Hypothesis Ho was rejected. It can summarize that at statistical significant 0.05, health benefit schemes and original drug prescribing pattern of chemotherapy prescriptions show the relationship.

Percentage of hormone therapy prescription that contained original drug was 26.20%, 10.30% of those prescriptions were in CSMBS, 3.40% were in SSS and 12.40% were in UC. There was 72.80% of hormone therapy prescriptions not contained original drug. Hypothesis test for relation between health benefit scheme and original drug prescribing pattern at $p \leq 0.05$ show significantly different at Sig. = 0.000. Hypothesis Ho was rejected. It can summarize that at statistical significant 0.05, health benefit schemes and original drug prescribing pattern of hormone therapy prescriptions show the relationship.

Percentage of targeted therapy prescription that contained original drug was 100.00% in CSMBS. Hypothesis test for relation between health benefit scheme and original drug prescribing pattern at $p \leq 0.05$ cannot show anything because original drug prescribing pattern was constant. So the researcher cannot identify the relation between health benefit scheme and original drug prescribing pattern of targeted therapy prescriptions.

4.4.8 The relationship between health benefit scheme and concomitant drugs prescribing

To analyze the relation between health benefit schemes which were classified into 3 group (CSMBS or Civil Servant of Medication Benefit Scheme, SSS or Social Security Scheme, UC or Universal Coverage) and concomitant drug prescribing pattern. The researcher use chi square test for analyze with the hypothesis below. The result show in table 4-30.

Hypothesis Ho: Health benefit scheme not related to concomitant drug prescribing pattern

H1: Health benefit scheme related to concomitant drug prescribing pattern

Table 48 The relationship between health benefit schemes and concomitant drugs

Policy classification	Concomitants drug prescribing pattern Prescribed concomitant drug (prescription)	Not prescribed concomitant drug (prescription)	Total	χ^2	Sig.
Chemotherapy					
CSMBS	428	25	453		
(%Total)	(12.70)	(0.70)	(13.40)	8.002	0.018
SSS	469	23	492		
(%Total)	(13.90)	(0.70)	(14.60)		
UC	2,243	190	2,433		
(%Total)	(66.40)	(5.60)	(72.00)		
Total	3,140	238	3,378		
(%Total)	(93.00)	(7.00)	(100.00)		
Hormone therapy					
CSMBS	246	557	803		
(%Total)	(6.60)	(15.00)	(21.60)	115.30	<0.01
SSS	183	286	469		
(%Total)	(4.90)	(7.70)	(12.60)		
UC	459	1,993	2,452		
(%Total)	(12.30)	(53.50)	(65.80)		
Total	888	2,836	3,724		
(%Total)	(23.80)	(76.20)	(100.00)		
Targeted therapy					
CSMBS	90	15	105		
(%Total)	(86.500	(13.50)	(100.00)	8.310	0.016
SSS	0	0	0		
(%Total)	(0.00)	(0.00)	(0.00)		
UC	0	0	0		
(%Total)	(0.00)	(0.00)	(0.000		
Total	90	15	105		
(%Total)	(86.50)	(13.50)	(100.00)		

Percentage of chemotherapy prescription that contained concomitant drug was only 93.00%, 12.70% of those prescriptions were in CSMBS, 13.90% were in SSS and 66.40% were in UC. There was 7.00% of chemotherapy prescriptions not contained concomitant drug. Hypothesis test for relation between health benefit scheme and concomitant drug prescribing pattern at $p \leq 0.05$ show significantly different at Sig. = 0.018. Hypothesis Ho was rejected. It can summarize that at statistical significant 0.05, health benefit schemes and concomitant drug prescribing pattern of chemotherapy prescriptions show the relationship.

Percentage of hormone therapy prescription that contained concomitant drug was 23.80%, 6.60% of those prescriptions were in CSMBS, 4.90% were in SSS and 12.30% were in UC. There was 76.20% of hormone therapy prescriptions not contained concomitant drug. Hypothesis test for relation between health benefit scheme and concomitant drug prescribing pattern at $p \leq 0.05$ show significantly different at Sig. = 0.000. Hypothesis Ho was rejected. It can summarize that at statistical significant 0.05, health benefit schemes and concomitant drug prescribing pattern of hormone therapy prescriptions show the relationship.

Percentage of targeted therapy prescription that contained concomitant drug was 86.50% in CSMBS. 13.50% was not prescribed concomitant drug. Hypothesis test for relation between health benefit scheme and concomitant drug prescribing pattern at $p \leq 0.05$ show significantly different at Sig. = 0.016. Hypothesis Ho was rejected. It can summarize that at statistical significant 0.05, health benefit schemes and concomitant drug prescribing pattern of targeted therapy prescriptions show the relationship.

4.4.9 Logistic regression analysis of factors affecting non-NLED prescribing pattern

To evaluate if many factors affected non-NLED prescribing pattern, the direction of relationship and level of association, logistic regression analysis was useful. There were 3 independent variables; non-NLED policy, original drug policy and medication safety standard policy. Non-NLED prescribing pattern was evaluated as 2 group of prescribed non-NLED and not prescribed non-NLED.

Independent variable

X1 = non-NLED policy (Dominate/non-Dominate)

X2 = Original drug policy (Dominate/non-Dominate)

X3 = Medication safety standard policy (Dominate/non-Dominate)

X4 = Health benefit scheme (CSMBS/SSS/UC)

X5 = Physician specialist (Oncologist/Radiologist/Surgeon)

X6 = Age of patient (Years)

Dependent variable

Z = non-NLED prescribing pattern (Prescribed/not prescribed)

Logistic regression equation

$$Z = \beta_0 + \beta_1X_1 + \beta_2X_2 + \beta_3X_3 + \beta_4X_4 + \beta_5X_5 + \beta_6X_6$$

Table 49 Logistic regression analysis of factors affecting non-NLED prescribing pattern of chemotherapy prescriptions

Model summary

Step	-2 log likelihood	Cox & Snell R square	Nagelkerke R square
1	1054.915	0.120	0.313

Variables in Equation

Step 1	B	S.E.	Wald	Df	Sig.	Exp(B)
Non-NLED policy	1.225	0.775	2.495	1	0.114	3.403
Original policy	1.027	0.262	15.409	1	0.000	2.792
Medication Safety Policy	0.418	0.767	0.297	1	0.586	1.519
Health benefit scheme	-1.518	0.097	243.095	1	0.000	0.219
Physician specialist	0.554	0.164	11.441	1	0.001	1.741
Age	-0.010	0.008	1.636	1	0.201	0.990
constant	-2.178	0.827	6.940	1	0.008	0.113

The regression model was shown below.

Z = -2.178 + 1.027X2 - 1.518X4 + 0.554X5

The level and the direction of relationship were shown as the coefficient. The logistic regression model equation show significant relationship between non-NLED prescribing pattern and three factors (original policy, health benefit scheme and age) in chemotherapy prescriptions.

Table 50 Logistic regression analysis of factors affecting non-NLED prescribing pattern of hormone therapy prescriptions

Model summary

Step	-2 log likelihood	Cox & Snell R square	Nagelkerke R square
1	1684.422	0.118	0.240

Variables in Equation

Step 1	B	S.E.	Wald	Df	Sig.	Exp(B)
Non-NLED policy	-0.187	0.313	0.355	1	0.551	0.830
Original policy	0.410	0.164	6.251	1	0.012	1.507
Medication Safety Policy	-0.979	0.300	10.616	1	0.001	0.376
Health benefit scheme	-0.851	0.068	158.658	1	0.000	0.427
Physician specialist	0.365	0.040	82.713	1	0.000	1.441
Age	0.039	0.006	47.107	1	0.000	1.040
constant	-2.924	0.466	39.406	1	0.000	0.054

The regression model was shown below.

$Z = -2.924 - 0.187X1 + 0.410X2 - 0.979X3 - 0.851X4 + 0.365X5 + 0.039X6$

The level and the direction of relationship were shown as the coefficient. The logistic regression model equation show significant relationship between non-NLED prescribing pattern and six factors in hormone therapy prescriptions.

4.4.10 Logistic regression analysis of factors affecting original drug prescribing pattern

To evaluate if many factors affected original drug prescribing pattern, the direction of relationship and level of association, logistic regression analysis was useful. There were 3 independent variables; non-NLED policy, original drug policy and medication safety standard policy. Original drug prescribing pattern was evaluated as 2 group of prescribed original drug and not prescribed original drug. Independent variable

X1 = non-NLED policy (Dominate/non-Dominate)
X2 = Original drug policy (Dominate/non-Dominate)
X3 = Medication safety standard policy (Dominate/non-Dominate)
X4 = Health benefit scheme (CSMBS/SSS/UC)
X5 = Physician specialist (Oncologist/Radiologist/Surgeon)
X6 = Age of patient (Years)

Dependent variable

Z = Original drug prescribing pattern (Prescribed/not prescribed)

Logistic regression equation

$$Z = \beta_0 + \beta_1X_1 + \beta_2X_2 + \beta_3X_3 + \beta_4X_4 + \beta_5X_5 + \beta_6X_6$$

Table 51 Logistic regression analysis of factors affecting original drug prescribing pattern of chemotherapy prescriptions

Model summary

Step	-2 log likelihood	Cox & Snell R square	Nagelkerke R square
1	2104.370	0.109	0.195

Variables in Equation

Step 1	B	S.E.	Wald	Df	Sig.	Exp(B)
Non-NLED policy	0.180	0.436	0.170	1	0.680	1.197
Original policy	1.316	0.164	64.367	1	0.000	3.728
Medication Safety Policy	0.515	0.421	1.497	1	0.221	1.674
Health benefit scheme	-0.994	0.065	232.183	1	0.000	0.370
Physician specialist	0.207	0.134	2.375	1	0.123	1.229
Age	0.022	0.005	16.122	1	0.000	1.022
constant	-2.709	0.487	30.998	1	0.000	0.067

The regression model was shown below.

Z = -2.709 + 1.316X2 – 0.994X4 + 0.022X6

The level and direction of relationship were show as the coefficient. The logistic regression model equation show significant relationship between original drug prescribing pattern and three factors (original policy, health benefit scheme and age) in chemotherapy prescriptions.

Table 52 Logistic regression analysis of factors affecting original drug prescribing pattern of hormone therapy prescriptions

Model summary

Step	-2 log likelihood	Cox & Snell R square	Nagelkerke R square
1	2950.516	0.156	0.230

Variables in Equation

Step 1	B	S.E.	Wald	Df	Sig.	Exp(B)
Non-NLED policy	0.423	0.276	2.352	1	0.125	1.526
Original policy	-0.210	0.123	2.889	1	0.089	0.811
Medication Safety Policy	0.907	0.257	12.425	1	0.000	2.476
Health benefit scheme	-0.864	0.051	282.748	1	0.000	0.421
Physician specialist	0.161	0.033	24.291	1	0.000	1.174
Age	0.053	0.004	144.711	1	0.000	1.054
constant	-2.717	0.367	54.688	1	0.000	0.066

The regression model was shown below.

Z = -2.717 + 0.907X3 - 0.864X4 + 0.161X5 + 0.053X6

The level and direction of relationship were show as the coefficient. The logistic regression model equation show significant relationship between original drug prescribing pattern and four factors (medication safety standard policy, health benefit scheme, physician specialist and age) in hormone therapy prescriptions.

4.5Factor affecting appropriate use

4.5.1 The relationship between medication safety standard and appropriate use

To analyze the relation between medication safety standard which were classified into 2 groups (Policy dominate to higher standard and policy dominate to lower standard) and assessment of appropriate use. The researcher use chi square test for analyze with the hypothesis below. The result show in table 4-34.

Hypothesis Ho: Medication safety standard not related to assessment of appropriate use

H1: Medication safety standard related to assessment of appropriate use

Table 53 The relationship between medication safety standard and appropriate use

Policy classification	Assessment of appropriate use		Total	χ^2	Sig.
	Appropriate use (prescription)	Not appropriate use (prescription)			
<u>Docetaxel</u>					
Policy dominate to higher standard (%Total)	64 (35.80)	46 (25.70)	110 (61.50)	16.013	<0.01
Policy dominate to lower standard(%Total)	19 (10.60)	50 (27.90)	69 (38.50)		
Total (%Total)	83 (46.40)	96 (53.60)	179 (100.00)		
<u>Letrozole</u>					
Policy dominate to higher standard(%Total)	165 (24.50)	29 (4.30)	194 (71.20)	3.132	0.077
Policy dominate to lower standard(%Total)	379 (56.30)	100 (14.90)	479 (28.80)		
Total (%Total)	129 (80.80)	544 (19.20)	673 (100.00)		
<u>Trastuzumab</u>					
Policy dominate to higher standard(%Total)	24 (24.70)	0 (0.00)	24 (24.70)	N/A	N/A
Policy dominate to lower standard(%Total)	73 (75.30)	0 (0.00)	73 (75.30)		
Total (%Total)	97 (100.00)	0 (0.00)	97 (100.00)		

Percentage of Docetaxel prescription that were evaluated as appropriate use was 46.40%, 35.30% were in group of policy dominate to higher medication safety standard and 10.60% were in group of policy dominate to lower medication safety standard. There were 53.60% of Docetaxel prescriptions be evaluated as not appropriated use. Hypothesis test for relation between medication safety standard policy and appropriate use of Docetaxel at $p \leq 0.05$ show significantly different at Sig. = 0.000. Hypothesis Ho was rejected. It can summarize that at statistical significant 0.05, medication safety standard policy and appropriate use of Docetaxel prescriptions show the relationship.

Percentage of Letrozole prescription that were evaluated as appropriate use was 80.80%, 24.50% were in group of policy dominate to higher medication safety standard and 56.30% were in group of policy dominate to lower medication safety standard. There were only 19.20% of Letrozole prescriptions be evaluated as not appropriated use. Hypothesis test for relation between medication safety standard policy and appropriate use of Letrozole at $p \leq 0.05$ show not significantly different at Sig. = 0.077. Hypothesis Ho was accepted. It can summarize that at statistical significant 0.05, medication safety standard policy and appropriate use of Letrozole prescriptions do not show the relationship.

Percentage of Trastuzumab prescriptions that were evaluated as appropriate use was 100.00%. 24.70% were in group of policy dominate to higher medication safety standard and 75.30% were in group of policy dominate to lower medication safety standard. Hypothesis test for relation between medication safety standard policy and appropriate use of Trastuzumab at $p \leq 0.05$ cannot be evaluated because appropriate use was constant. So the researcher cannot identify the relation between medication safety standard and appropriate use of Tratsuzumab.

4.4.11 The relationship between health benefit scheme and appropriate use

To analyze the relation between health benefit schemes which were classified into 3 groups (CSMBS, SSS and UC) and assessment of appropriate use. The researcher use chi square test for analyze with the hypothesis below. The result show in table 4-35.

Hypothesis Ho: Health benefit schemes not related to assessment of appropriate use

H1: Health benefit schemes related to assessment of appropriate use

Table 54 The relationship between health benefit scheme and appropriate use

Health benefit scheme	Assessment of appropriate use		Total	χ^2	Sig.
	Appropriate use (prescription)	Not appropriate use (prescription)			
Decetaxel					
CSMBS	25	57	82		
(%Total)	(14.10)	(32.20)	(46.30)		
SSS	5	2	7		
(%Total)	(2.80)	(1.10)	(4.00)		
UC	52	36	88	15.813	<0.01
(%Total)	(29.40)	(20.30)	(49.70)		
Total	82	95	177		
(%Total)	(46.30)	(53.70)	(100.00)		
Letrozole					
CSMBS	108	18	126		
(%Total)	(16.00)	(2.70)	(18.70)		
SSS	51	8	59		
(%Total)	(7.60)	(1.20)	(8.80)	4.320	0.115
UC	385	103	488		
(%Total)	(57.20)	(15.30)	(72.50)		
Total	544	129	673		
(%Total)	(80.80)	(19.20)	(100.00)		
Trastuzumab					
CSMBS	97	0	97		
(%Total)	(100.00)	(0.00)	(100.00)		
SSS	0	0	0		
(%Total)	(0.00)	(0.00)	(0.00)	N/A	N/A
UC	0	0	0		
(%Total)	(0.00)	(0.00)	(0.00)		
Total	97	0	97		
(%Total)	(100.00)	(0.00)	(100.00)		

Percentage of Docetaxel prescription that was evaluated as appropriate use was 46.30%, 14.10% were in CSMBS, 2.80% were in SSS and 29.40% were in UC. There were 53.70% of Docetaxel prescriptions be evaluated as not appropriated use. Hypothesis test for relation between health benefit scheme and appropriate use of Docetaxel at $p \leq 0.05$ show significantly different at Sig. = 0.000. Hypothesis Ho was rejected. It can summarize that at statistical significant 0.05, health benefit schemes and appropriate use of Docetaxel prescriptions show the relationship.

Percentage of Letrozole prescription that was evaluated as appropriate use was 80.80%, 16.00% were in CSMBS, 7.60% were in SSS and 57.20% were in UC. There were 19.20% of Letrozole prescriptions be evaluated as not appropriated use. Hypothesis test for relation between health benefit scheme and appropriate use of Letrozole at $p \leq 0.05$ show not significantly different at Sig. = 0.115. Hypothesis Ho was accepted. It can summarize that at statistical significant 0.05, health benefit schemes and appropriate use of Letrozole prescriptions do not show the relationship.

Percentage of Trastuzumab prescriptions that were evaluated as appropriate use was 100.00% and all of those were in CSMBS. Hypothesis test for relation between health benefit schemes and appropriate use of Trastuzumab at $p \leq 0.05$ cannot be evaluated because appropriate use was constant. So the researcher cannot identify the relation between health benefit schemes and appropriate use of Tratsuzumab.

4.4.12 The relationship between physician specialist and appropriate use

To analyze the relation between physician specialists which were classified into 3 groups (oncologist, radiologist and surgeon) and assessment of appropriate use. The researcher use chi square test for analyze with the hypothesis below. The result show in table 4-36.

Hypothesis Ho: Physician specialist not related to assessment of appropriate use

H1: Physician specialist related to assessment of appropriate use

Table 55 The relationship between physician specialist and appropriate use

Physician specialist	Assessment of appropriate use		Total	χ^2	Sig.
	Appropriate use (prescription)	Not appropriate use (prescription)			
<u>Decetaxel</u>					
Oncologist	81	81	162		
(%Total)	(45.30)	(45.30)	(90.50)		
Radiologist	2	15	17	9.045	0.003
(%Total)	(1.10)	(8.40)	(9.50)		
Total	83	96	179		
(%Total)	(46.40)	(53.60)	(100.00)		
<u>Letrozole</u>					
Oncologist	476	81	557		
(%Total)	(70.70)	(12.00)	(82.80)		
Radiologist	50	42	92	49.868	<0.01
(%Total)	(7.40)	(6.20)	(13.70)		
Surgeon	18	6	24		
(%Total)	(2.70)	(0.90)	(3.60)		
Total	544	129	673		
(%Total)	(80.80)	(19.20)	(100.00)		
<u>Trastuzumab</u>					
Oncologist	76	0	76		
(%Total)	(78.40)		(78.40)		
Radiologist	8	0	8	N/A	N/A
(%Total)	(8.20)		(8.20)		
Surgeon	13	0	13		
(%Total)	(13.40)		(13.40)		
Total	97	0	97		
(%Total)	(100.00)		(100.00)		

Percentage of Docetaxel prescription that was evaluated as appropriate use was 46.40%. 45.30% were prescribed by oncologists and 1.10% was prescribed by radiologists. There were 53.70% of Docetaxel prescriptions be evaluated as not appropriated use. Hypothesis test for relation between physician specialist and appropriate use of Docetaxel at $p \leq 0.05$ show significantly different at Sig. = 0.003. Hypothesis Ho was rejected. It can summarize that at statistical significant 0.05, physician specialist and appropriate use of Docetaxel prescriptions show the relationship.

Percentage of Letrozole prescription that was evaluated as appropriate use was 80.80%. 70.70% were prescribed by oncologists, 7.40% was prescribed by radiologists and 2.70% was prescribed by surgeon. There were 19.20% of Letrozole prescriptions be evaluated as not appropriated use. Hypothesis test for relation between physician specialist and appropriate use of Letrozole at $p \leq 0.05$ show significantly different at Sig. = 0.000. Hypothesis Ho was rejected. It can summarize that at statistical significant 0.05, physician specialist and appropriate use of Letrozole prescriptions show the relationship.

Percentage of Trastuzumab prescription that was evaluated as appropriate use was 100.00%. 78.40% were prescribed by oncologists, 8.20% was prescribed by radiologists and 13.40% was prescribed by surgeon. Hypothesis test for relation between physician specialist and appropriate use of Trastuzumab at $p \leq 0.05$ cannot be evaluated because appropriate use was constant. So the researcher cannot identify the relation between physician specialist and appropriate use of Tratsuzumab.

4.4.13 The relationship between age of patients and appropriate use

To analyze the relation between age of patients which were classified into 2 groups (Age $\leq$ 60 year olds and age $>$ 60 year olds) and assessment of appropriate use. The researcher use chi square test for analyze with the hypothesis below. The result show in table 4-37.

Hypothesis Ho: Age of patients not related to assessment of appropriate use

H1: Age of patients related to assessment of appropriate use

Table 56 The relationship between age of patients and appropriate use

Policy classification	Assessment of appropriate use		Total	χ^2	Sig.
	Appropriate use (prescription)	Not appropriate use (prescription)			
<u>Decetaxel</u>					
Age ≤ 60 years old	77	63	140		
(%Total)	(43.00)	(35.20)	(78.20)		
Age > 60 years old	6	33	39	19.250	<0.01
(%Total)	(3.40)	(18.40)	(21.80)		
Total	83	96	179		
(%Total)	(46.40)	(53.60)	(100.00)		
<u>Letrozole</u>					
Age ≤ 60 years	288	110	398		
old	(42.80)	(16.30)	(59.10)		
(%Total)				45.103	<0.01
Age > 60 years	256	19	275		
old	(38.00)	(2.80)	(40.90)		
(%Total)					
Total	544	129	673		
(%Total)	(80.80)	(19.20)	(100.00)		
<u>Trastuzumab</u>					
Age ≤ 60 years	70	0	70		
old	(72.20)	(0.00)	(72.20)		
(%Total)				N/A	N/A
Age > 60 years	27	0	27		
old	(27.80)	(0.00)	(27.80)		
(%Total)					
Total	97	0	97		
(%Total)	(100.00)	(0.00)	(100.00)		

Percentage of Docetaxel prescription that was evaluated as appropriate use was 46.40%. 43.00% were the prescriptions of patient age ≤ 60 year olds and 3.40% were the prescriptions of patient age > 60 year olds. There were 53.60% of Docetaxel prescriptions be evaluated as not appropriated use. Hypothesis test for relation between age of patients and appropriate use of Docetaxel at p ≤ 0.05 show significantly different at Sig. = 0.000. Hypothesis Ho was rejected. It can summarize that at statistical significant 0.05, age of patients and appropriate use of Docetaxel prescriptions show the relationship.

Percentage of Letrozole prescription that was evaluated as appropriate use was 80.80%. 42.80% were the prescriptions of patient age ≤ 60 year olds and 38.00% were the prescriptions of patient age > 60 year olds. There were 19.20% of Letrozole prescriptions be evaluated as not appropriated use. Hypothesis test for relation between age of patients and appropriate use of Letrozole at p ≤ 0.05 show significantly different at Sig. = 0.000. Hypothesis Ho was rejected. It can summarize that at statistical significant 0.05, age of patients and appropriate use of Letrozole prescriptions show the relationship.

Percentage of Trastuzumab prescription that was evaluated as appropriate use was 100.00%. 72.20% were the prescriptions of patient age ≤ 60 year olds and 27.80% were the prescriptions of patient age > 60 year olds. Hypothesis test for relation between age of patients and appropriate use of Trastuzumab at p ≤ 0.05 cannot be evaluated because appropriate use was constant. So the researcher cannot identify the relation between age of patients and appropriate use of Tratsuzumab.

4.4.14 Logistic regression analysis of factors affecting appropriate use

To evaluate if many factors affected appropriate, the direction of relationship and level of association, logistic regression analysis was useful. There were 4 independent variables; medication safety standard policy, health benefit scheme, physician specialist and age of patients. Assessment of appropriate use was evaluated as 2 groups of appropriate use and not-appropriate use.

Independent variable

X1 = non-NLED policy (Dominate/non-Dominate)

X2 = Original drug policy (Dominate/non-Dominate)

X3 = Medication safety standard policy (Dominate/non-Dominate)

X4 = Health benefit scheme (CSMBS/SSS/UC)

X5 = Physician specialist (Oncologist/Radiologist/Surgeon)

X6 = Age of patient (Years)

Dependent variable

Z = Appropriate use (Appropriate/not appropriate)

Logistic regression equation

$$Z = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_4 X_4 + \beta_5 X_5 + \beta_6 X_6$$

Table 57 Logistic regression analysis of factors affecting appropriate use of Docetaxel prescriptions

Model summary

Step	-2 log likelihood	Cox & Snell R square	Nagelkerke R square
1	105.513	0.544	0.726

Variables in Equation

Step 1	B	S.E.	Wald	Df	Sig.	Exp(B)
Non-NLED policy	3.401	1.223	7.728	1	0.005	29.983
Original policy	-5.398	0.946	32.576	1	0.000	0.005
Medication Safety Policy	0.847	1.091	0.603	1	0.437	2.334
Health benefit scheme	1.619	0.545	8.824	1	0.003	5.049
Physician specialist	-0.129	0.950	0.018	1	0.892	0.879
Age	-0.115	0.035	10.797	1	0.001	0.891
constant	2.261	1.710	1.748	1	0.186	9.594

The regression model was shown below.

$$Z = 2.261 + 3.401X1 - 5.398X2 + 1.619X4 - 0.115X6$$

The level and direction of relationship were show as the coefficient. The logistic regression model equation show significant relationship between appropriate use and four factors (non-NLED policy, original policy, health benefit scheme and age of patients) in Docetaxel prescriptions.

Table 58 Logistic regression analysis of factors affecting appropriate use of Letrozole prescriptions

Model summary

Step	-2 log likelihood	Cox & Snell R square	Nagelkerke R square
1	575.771	0.115	0.184

Variables in Equation

Step 1	B	S.E.	Wald	Df	Sig.	Exp(B)
Non-NLED policy	-2.929	0.625	21.974	1	0.000	0.053
Original policy	0.824	0.321	6.601	1	0.010	2.280
Medication Safety Policy	2.795	0.584	22.906	1	0.000	16.358
Health benefit scheme	0.030	0.213	0.019	1	0.889	1.030
Physician specialist	-1.012	0.186	29.660	1	0.000	0.363
Age	0.063	0.012	28.411	1	0.000	1.065
constant	-2.058	0.838	6.023	1	0.014	0.128

The regression model was shown below.

$Z = -2.058 - 2.929X1 + 0.824X2 + 2.795X3 - 1.012X5 + 0.063X6$

The level and direction of relationship were show as the coefficient. The logistic regression model equation show significant relationship between appropriate use and five factors (non-NLED policy, original policy, medication safety standard, physician specialist and age of patients) in Letrozole prescriptions.

4.6 Summary of factor affecting pattern and appropriate use of anticancer drugs

Table 59 Summary of factor affecting pattern of prescribing anticancer drug

Independent Variable	Dependent Variable	Group of anticancer	Sig. ($p \leq 0.05$)
Non-NLED policy	Non-NLED prescribing pattern	Chemotherapy	<0.01*
		Hormone therapy	<0.01*
		Targeted therapy	N/A
	Number of non-NLED items	Chemotherapy	0.439**
		Hormone therapy	0.311**
		Targeted therapy	0.832**
	Cost of non-NLED items	Chemotherapy	<0.01***
		Hormone therapy	0.712***
		Targeted therapy	<0.01***
Original policy	Original prescribing pattern	Chemotherapy	<0.01*
		Hormone therapy	0.003*
		Targeted therapy	N/A
Medication safety standard policy	Non-NLED prescribing pattern	Chemotherapy	<0.01*
		Hormone therapy	<0.01*
		Targeted therapy	N/A
Health benefit scheme	Non-NLED prescribing pattern	Chemotherapy	<0.01*
		Hormone therapy	<0.01*
		Targeted therapy	N/A
Health benefit scheme	Original prescribing pattern	Chemotherapy	<0.01*
		Hormone therapy	<0.01*
		Targeted therapy	N/A
Health benefit scheme	Concomitant drug prescribing pattern	Chemotherapy	0.018*
		Hormone therapy	<0.01*
		Targeted therapy	0.016*

*Chi-square test at significant $p \leq 0.05$, ** Independent sample T-Test at significant $p \leq 0.05$, ***Nonparametric (2-Independent sample test (Man-Whitney U Test) at significant $p \leq 0.05$

Table 60 Summary of factor affecting appropriate use of evaluated anticancer drug

Independent Variable	Dependent Variable	Group of aniticancer	Sig. ($p \leq 0.05$)
Medication safety standard policy	Appropriate use	Docetaxel	< 0.01*
		Letrozole	0.077
		Trastuzumab	N/A
Health benefit scheme	Appropriate use	Docetaxel	< 0.01*
		Letrozole	0.115
		Trastuzumab	N/A
Physician specialist	Appropriate use	Docetaxel	0.003*
		Letrozole	< 0.01*
		Trastuzumab	N/A
Age of patients	Appropriate use	Docetaxel	< 0.01*
		Letrozole	< 0.01*
		Trastuzumab	N/A

*Chi-square test at significant $p \leq 0.05$

Table 61 Logistic regression analysis of multifactor affecting pattern of use

Independent variable	Dependent variable	Logistic regression equation
Chemotherapy		
X1 = non-NLED policy X2 = Original drug policy X3 = Medication safety policy X4 = Health benefit schemes X5 = Physician specialist X6 = Age	Non-NLED prescribing pattern	Z = -2.178 + 1.027X2 - 1.518X4 + 0.554X5
Hormone therapy		
X1 = non-NLED policy X2 = Original drug policy X3 = Medication safety policy X4 = Health benefit schemes X5 = Physician specialist X6 = Age	Non-NLED prescribing pattern	Z = -2.924 – 0.187X1 + 0.410X2 – 0.979X3 – 0.851X4 + 0.365X5 + 0.039X6
Chemotherapy		
X1 = non-NLED policy X2 = Original drug policy X3 = Medication safety policy X4 = Health benefit schemes X5 = Physician specialist X6 = Age	Original drug prescribing pattern	Z = -2.709 + 1.316X2 – 0.994X4 + 0.022X6
Hormone therapy		
X1 = non-NLED policy X2 = Original drug policy X3 = Medication safety policy X4 = Health benefit schemes X5 = Physician specialist X6 = Age	Original drug prescribing pattern	Z = -2.717 + 0.907X3 - 0.864X4 + 0.161X5 + 0.053X6

Table 62 Logistic regression analysis of multifactor affecting appropriate use

Independent variable	Dependent variable	Logistic regression equation
Docetaxel		
X1 = non-NLED policy	Appropriate use	Z = 2.261 + 3.401X1 - 5.398X2
X2 = Original drug policy		+ 1.619X4 – 0.129X5
X3 = Medication safety policy		– 0.115X6
X4 = Health benefit schemes		
X5 = Physician specialist		
X6 = Age		
Letrozole		
X1 = non-NLED policy	Appropriate use	Z = -2.058 – 2.929X1+ 0.824X2
X2 = Original drug policy		+ 2.795X3 – 1.012X5
X3 = Medication safety policy		+ 0.063X6
X4 = Health benefit schemes		
X5 = Physician specialist		
X6 = Age		

CHAPTER 5

DISCUSSION, CONCLUSION, LIMITATION AND RECOMMENDATION

5.1 Discussion:

The research finding of this study is discussed in three different heading of pattern of use, appropriate use and factor affecting anticancer drug use.

5.1.1 Anticancer drug Utilization

1) Context of regional cancer center

Although all center had responsibility to serve for all type of cancer, DMS assigned the strategies to all centers for serving specific health problem by incidence of cancer. So that main responsibility would be related to medication management policy and hospital formularies. The different context of each centers showed as different number of prescription and different level of policy classification. To evaluate which cancer centers were classified in which level of policy, the hospital formularies and medication safety policy were analyzed. Different context in each cancer center related to different pattern of utilization.

2) Original drug prescribing pattern

Original drug prescribing pattern of chemotherapy drug in this study showed higher percentage in center 2, 3 and 6 that related to policy classification in original drug policy dominate group. Many studies showed different efficacy and safety between original and generic drug of anticancer chemotherapy that might be the factors of hospital drug selection criteria, such as Paclitaxel(Sagara et al., 2009; Takahara, Yamamoto, Tokushima, & Shiba, 2009; Takahashi, Hosoda, Takahashi, & Todo, 2010) and Docetaxel (Poirier et al., 2014). The data of Paclitaxel shown similar efficacy and safety between original and generic drug but the data of generic Docetaxel shown little serious febrile neutropenia more than original drug.

Same as chemotherapy prescriptions, hormone therapy prescriptions had comparative data between efficacy and safety between original and

generic Tamoxifen(Blencowe, Reichl, Gahir, & Paterson, 2010). The data shown Nolvadex® had lower arthralgia than generic Tamoxifen. In Thailand there were many generic Tamoxifen but none of AIs generic except Letrozole under government procurement due to compulsory license. So the ratio of prescribing original drug in hormone therapy was more than chemotherapy but this pattern did not related with policy classification.

Other factors that caused different pattern of original drug prescribing were the number of registered product in the market. There were many generic of chemotherapy drug, few generic hormone therapy drug and none of targeted therapy drug in market. So the percentage of prescribing original drug in chemotherapy was more than hormone.

3) Non-NLED drug prescribing pattern

The regulation of the ratio between non-NLED : NLED of drug item in general hospital formulary should be closed to 30:70. WHO(El Mahalli, 2012) indicated the criteria for evaluate the appropriated use of drug as the drug should be prescribed from essential drug list. After reviewed NLED 2009, more chemotherapy drugs were listed in NLED, 2 hormone therapy drugs were listed and none of targeted therapy was listed in NLED. As cancer centers where delivered specific treatment and rapidly developed of innovation in cancer treatment, so the anticancer drugs selected into hospital formularies may deviated from general hospital and different pattern of non-NLED prescribing occurred. So the study shown only 6.28% and 9.35% in chemotherapy and hormone therapy prescriptions contained non-NLED respectively.

4) The concomitant drug prescribing pattern

Chemotherapy regimens in breast cancer were highly adverse drug reaction as acute and delay type of onset. Common pre-medication was anti-emetics drug such as antihistamines, dopamine-receptor antagonists, serotonin-receptor antagonists, and neurokinin-receptor antagonists (Georgy, Neceskas, & Goodin, 2007). It was not surprisingly that 92.60% of chemotherapy prescriptions have at least one concomitant drug per all

prescriptions. Other data showed some concomitants drugs such as melatonin hormone which was prescribed for decrease toxicity and increase efficacy of chemotherapy in poor clinical patients(Lissoni et al., 1999), such pattern did not found in this study. While hormone therapy was usually not prescribe concomitant drug because it did not have serious adverse effect. However long term use of AI (Aromatase Inhibitor) cause worse of bone health (Bundred, 2009). So calcium and vitamin D supplement were sometimes prescribed in hormone therapy. In patients with early stage and bone metastasis breast cancer, bisphosphonate group were prescribed such as Zoledronic acid for inhibit bone loss (M. F. Gnant et al., 2007; Tabane & Vorobiof, 2011). In this study not much bisphosphonate group was prescribed in early stage breast cancer, but only prescribed in metastasis stage(M. Gnant, 2012).

This study shows many couples of drug interaction risk especially in chemotherapy. However chemotherapy drugs were administered by order as the guideline suggested so drug interactions were ignored.

5) Chemotherapy Utilization

As compare with the NHSO cancer protocol version 2010, the top three most common prescribed chemotherapy regimens under protocol were FAC (36.15%), CMF (16.15%) and AC (14.84%) respectively. Although the recent studied show the decline in use of anthracycline-base regimen (Campone, Fumoleau, Bourbouloux, Kerbrat, & Roche, 2005; Giordano, Lin, Kuo, Hortobagyi, & Goodwin, 2012). In Thailand, it was not surprisingly founded because those regimens were the first-line therapy in early stage breast cancer. Those three regimens might be shifted to other if patients did not response to the first regimen. Paclitaxel was prescribed followed by AC as first-line therapy and as single agent followed by FAC as second-line therapy. While Docetaxel and Capcitabine always prescribed as second-line chemotherapy. As oral form, Capecitabine was easily for administration. It seems to be more prescribed of Capecitabine than other. And some study shown that Capecitabine regimen was more favorable outcome regarding treatment side effect and quality of life

than Paclitaxel and Docetaxel regimen in both first and second-line therapy in metastasis breast cancer(Schwartzberg, Cobb, Walker, Stepanski, & Houts, 2009). The possible reasons caused our study show different data from the early research. There were many generic drug of Paclitxel in Thailand while Capecitabine was only one brand. Many generic product of Paclitaxel caused more choices for hospital to procure. The cost will be discussed in the next section.

274 prescriptions (7.86%) of chemotherapy regimen prescribed out of protocol such as FEC/EC, TAC/TC, Vinorelbine, Gemcitabine, liposomal-doxorubicin and Paclitaxel+Carboplatin. Many evidence shown the efficiency of use non-protocol regimen in another context (Au et al., 2009). In Thailand those chemotherapy drugs were not listed in NLED such as Vinorelbine and Epirubicin(Bonneterre et al., 2005). Liposomal-Doxorubicin (Smith et al., 2010) was the drug of choice in patients who have problem in cardiac function. Some were listed in NLED but they have only one brand and high cost. Prescribing chemotherapy out of protocol was occurred in some exception case.

6) Hormone Therapy Utilization

3,930 prescriptions of hormone therapy were analyzed for determine the pattern of use. Common clinical guidelines recommend that women with hormone-receptor positive breast cancer should receive hormone therapy (selective estrogen receptor modulators [SERMs] or aromatase inhibitors [AIs])(Santen, Brodie, Simpson, Siiteri, & Brodie, 2009) for five years after diagnosis. Many study shown different pattern of prescribing hormone therapy (Kawakami, Saji, & Toi, 2004). Almost study aboard shown trend of prescribing AI much more SERM (Luftner, Scheller, Kolm, & Possinger, 2008). Big studied (ATAC trial) show cost-effectiveness of AI (Anastrozole) over SERM (Tamoxifen)(Rocchi & Verma, 2006). In Thailand there were some SERMs such as Tamoxifen which was listed in NLED and Raloxifene as non-NLED. AIs in Thailand were Letrozole (NLED; J-2 category), Anastrozole and Exemestane (both non-NLED).

Some study shown age was related to pattern of prescribing hormone therapy, especially in elderly that physician tend to prescribe AIs more than SERMs in Medicare Part D in United State(Riley, Warren, Harlan, & Blackwell, 2011).

This research show different result with the early studies. Tamoxifen (SERMs) was always prescribed more than AIs. We assume this result had caused by low cost generic name of Tamoxifen and the enforcement of NHSO cancer protocol. In Thailand, protocol indicated reimbursed cost for 6 Baht/Tamoxifen 20 mg 1 tablet and reimbursed Letrozole by VMI (Vender Managed Inventory). Other hormone drugs were not allowed to reimburse.

7) Targeted therapy

105 prescriptions of targeted therapy were analyzed. Trastuzumab was the most common prescribed 97 prescriptions (92.38%). Other targeted therapy 8 prescriptions (7.62%) was Bevacizumab. In Thailand 2010, Trastuzumab was already approved indication in metastasis breast cancer but Bevacizumab still not. There was the prior-authorization system before prescribing Trastuzumab in breast cancer, worked by the comptroller general department. Like other early research (Ray, Bonthapally, McMorrow, Bonafede, & Landsman-Blumberg, 2013) that Trastuzumab and Bevacizumab were prescribed in breast cancer.

5.1.2 Appropriate use of anticancer drug

Three anticancer drugs were evaluated appropriate use by DUE form as a tools. Docetaxel was represented chemotherapy, Letrozole was represented hormone therapy and Trastuzumab was represented targeted therapy. DUE form of Docetaxel and Letrozole came from Thai National Formulary 2011 (TNF) because both of drugs were in J2 category. DUE of Trastuzumab came from OCPA pre-authorization online program by the Comptroller General Department.

1) Docetaxel

Docetaxel was chemotherapy in taxane group that listing in NLED as J2 category. Only 83 prescriptions (46.36%) were rely on clinical DUE criteria, but only 19.55% of prescriptions found evidence paper of DUE form in medical record. Some unclear indication was discussed between practitioners because in TNF manual indicated that Docetaxel had only indication in metastasis breast cancer. Many strong evidence shown efficacies in adjuvant indication and this used drugs can already reimbursed from the scheme. However this study must use the published reference (TNF 2011). The prescription did not meet the criteria were excluded stepwise.

It seems to be surprisingly that few appropriated use was not interesting anymore. But the unclear guideline, missing data in medical record and uncompleted DUE process were problematic for Docetaxel. Those factors caused misunderstanding of the appropriated use evaluations. The researcher propose the solutions for the pharmaceutical and therapeutic committee (PTC) in reviewing the DUE criteria and assign for strictly recording data with the setting. However as the cancer center, the setting should propose this problem to TNF or NLED committee to review the indication of this drug.

2) Letrozole

Letrozole was aromatase inhibitors (AIs) use in treating breast cancer. 550 prescriptions met the clinical DUE criteria while only 157 prescriptions were perfectly completed all DUE processes. Letrozole must be prescribed only in ER (and/or) PR positive and in post-menstrual status. 27 prescriptions were excluded due to ER (and/or) PR negative or this data not available. ER/PR receptors were used to predict responsiveness to Letrozole. Sometime the data could be change so the physicians may request to review it. After excluded non post-menopause status, 599 prescriptions were remained. The interested topics in appropriate use of Letrozole were duration and average number of tablet prescribed per time. Many studies and NHSO cancer protocol indicated that duration of Tamoxifen plus Letrozole in early breast cancer should not more than 5 years(Morandi et al., 2004). Patients started with Tamoxifen for 2 – 3 years and shifted to AIs for not more than 2 years. There were 12 prescriptions that prescribed for longer duration that leaded to lose from rejected reimbursement if those prescriptions were under UC scheme. For

number of prescriptions, NHSO indicated not more than 60 tablets per visit because it was the ceiling number of reimbursement by medicine. The average tablets of Letrozole was 57.80 $\pm$ 40.109 tablets. There were 11 prescriptions prescribed more than 180 tablets and the maximum was 212 tablets. However there was not having any data to indicate how many appropriate amount of prescribing. But closely monitored and evaluated breast cancer patients should be done.

3) Trastuzumab

Trastuzumab was the targeted drug used in breast cancer, by inactivating the signaling pathway of proliferation by HER2 receptor(Mohd Sharial, Crown, & Hennessy, 2012). This drug already was set the pre-authorization approval by the Comptroller General Department as OCPA program. This study used the OCPA application as the DUE form of Trastuzumab. The studies aboard shown indication approved for Trastuzumab as both metastasis and adjuvant therapy(Freedman et al., 2013; Zhu, Zhang, Chen, & Li, 2013). This study found both indications prescribed and already approve although the OCPA manual did not mention in adjuvant therapy. This regulation made a physician little confuse but finally they prescribed Trastuzumab relied on the OCPA online approval program. Every prescription met all DUE appropriated use criteria; indication, HER2 receptor positive, ECOG 0-2, correct dose, appropriate duration, patients not in terminal ill and safety cardio toxicity. So all prescribed Trastuzumab in this study were appropriately used.

However the researcher noticed that only patients under CSMBS schemes were prescribed Trastuzumab, although 15 – 23% of all breast cancer patients over expressed HER2 positive(Mohd Sharial et al., 2012). How about the patients in other schemes could access to this drug? Because CSMBS scheme had obviously channel of access to Trastuzumab through OCPA online program, whereas other schemes did not. If this pre-authorization already done, the reimbursed cost of Trastuzumab was guaranteed. For other scheme, Trastuzumab still in the list of non-NLED, so it did not an obviously channel to access this drug. If Trastuzumab was prescribed in UC or SSS schemes, the cost

of Trastuzumab might be responsible of healthcare provider or patients. Finally it was not normally prescribed in UC and SSS scheme.

After evaluating appropriate use of three anticancer drugs; Docetaxel, Letrozole and Trastuzumab, there were many uncompleted clinical data in medical record such as performance status (ECOG). So many missing data made the researcher judge that prescriptions were not appropriated. The appropriate indications of three drugs were slightly mentioned because this study was framed only in breast cancer, so off-label used were not found. The similar topic interested in all drug were how to complete DUE process. Although more prescriptions met the DUE clinical criteria but only few DUE forms were completed in Docetaxel and Letrozole, while all completed in Trastuzumab. As we already known DUE form was the tool for encouraging rational use of drugs(Navarro, 1989) and monitoring unexpected cost(Vukusic & Culig, 2005). DUE form of Docetaxel and Letrozole were the system assigned by Thai National Formulary (TNF 2011) and related with the reimbursement of UC scheme. The reason why DUE form of Docetaxel and Letrozole had not been completed, because system did not have strictly external auditing system. Although UC scheme drug reimbursement system related to DUE form but not immediately effected when drug prescribed. Unlike OCPA system in CSMBS scheme which generated the pre-authorization code for reimbursement when Trastuzumab was prescribed. However each setting should have policy for DUE and setting tools for facilitating DUE process such as online approved system. This idea might be possible because anticancer drugs were not life-saving drugs but they could be plan, prepare and monitor by the cycle. As three anticancer drugs

5.1.3 Determinant affected anticancer drug utilization

1) Policy

Different context of each setting were assumed that different pattern of prescriptions. The data shown significantly pattern of prescribing in each centers, however many factors caused this pattern. Different contexts were discussed below.

A. Non-NLED policy

There was significantly different between pattern of non-NLED prescription between non-NLED policy dominate and non-NLED policy non-dominate. The percentage of prescriptions contained non-NLED within non-NLED policy non-dominate was more than in non-NLED policy dominate. The reasons of such patterns were caused from rapidly development of new drugs especially in targeted therapy and chemotherapy drug respectively. New anticancer drugs still not listed in NLED because waiting for enough data or pharmacoeconomic study will be consumed long duration.

B. Medication safety standard policy

Medication safety standard policy was significantly different with pattern of prescribing. Medication safety standard was classified by hospital self-assessment score in any topic. Normally medication standard policy always related with pattern and appropriate of drug use. Sometime this result would be in-depth studied because self-assessment may be bias.

2) Health benefit scheme

Main financial statuses were CSMBS, UC and SSS. It significantly different pattern of use in any schemes except prescribing concomitant drug in chemotherapy prescriptions. For appropriate use of anticancer, scheme was significantly different between schemes. Furthermore the number of prescribed Letrozole was significantly different too. Different guideline and conditions of prescribing between health benefit schemes were caused of such pattern.

3) Age

Age was the factor affected pattern of use chemotherapy prescription. The elderly who have many underlying disease were supposed to prescribe low less adverse drug reaction regimen. This study similar as other that CMF regimen always prescribed more in elderly. For hormone therapy, age was the factor in clinical DUE criteria. Breast cancer patients who aged more than 60 and pots-menopause should be prescribed Letrozole.

In term of age related choosing chemotherapy regimen, the early research always shown substandard chemotherapy in elderly(Hancke et al., 2010) and some regimen was common prescribed in elderly due to the safety reasons(Kadakia, Rajan, Abughosh, Du, & Johnson, 2013). Our data shown the same result as early research, CMF and Capecitabine were prescribed mostly in patients age more than 60 years old due to the low risk of side effect and easily administration reasons.

5.1.4 Cost

1) Cost of chemotherapy compare with NHSO cancer protocol

The actual cost of chemotherapy regimens were more than the reimbursed cost especially AC (Doxorubicin and Cyclophosphamide) and Capecitabine. The reimburse cost was set as average ceiling cost even the patients had any BSA (body surface area), so if patients had more than average BSA it tended to be lose. But if the patients had less BSA than average, the real cost was reimbursed. Cancer centers received a little gap of profit rely on the formula of regulation from the comptroller general department. Because the period of study was same as the started period of NHSO protocol regulation, some setting still not analyzed the cost of anticancer drugs or they still have the high cost batch inventory. Cancer centers should adjust themselves in procurement policy, prescribing policy and admission policy for keeping the quality of treatment and good financial status of the centers. The procurement policy was reviewed by cost of NHSO protocol; the actual cost should be forecasted and evaluated to protect the

loss. Other tools for setting drugs cost were reference price index form DMSIC or reference price from provincial procurement. Prescription and admission policy should be reviewed and compromised between actual cost of out-patients and in-patients department. PTC or the occasional committee might be set for discussion. Some intervention may occur such as setting some chemotherapy regimens for only in-patients department. Further study should monitor and compare cost of reimbursement before and after the NHSO launched.

2) Cost of concomitant drugs

As already discussed in above section that chemotherapy prescriptions had more concomitant drugs items than hormone and targeted therapy. The concomitant drugs of chemotherapy prescriptions were pre-medication, home-medication (prevent and treatment delayed ADR) and drug treatment underlying disease. Pre-medication of chemotherapy were anti-emetic agent, steroids and anti-histamine, those were common, cheap and always set as standing prescriptions. Different chemotherapy regimens were prescribed different pre-medication. Home medications were prescribed after the physician evaluated individual patients' ADR. In hormone therapy prescriptions, breast cancer patients should be continuity prescribed neither serious ADR occurred, so concomitant drugs were less items and less cost. Same as hormone therapy, targeted therapy commonly less ADR so less items of pre-medication and low cost.

5.2Conclusion

Anticancer drug utilization pattern represented in term of non-NLED prescribing pattern, original drug prescribing pattern, concomitant drug, comparison with protocol, cost of anticancer and appropriate use of anticancer drugs. The results showed into 3 groups of chemotherapy, hormone therapy and targeted therapy. Hormone therapy and targeted therapy drugs showed higher percentage in non-NLED and original drug prescribing pattern while chemotherapy drug showed the higher percentage

of concomitant drugs prescribing pattern. There were lower percentage of non-complied prescribing due to the cancer protocol in both chemotherapy and hormone therapy. Almost all chemotherapy regimens were over than reimbursed cost. The evaluation of Trastuzumab was most appropriated because of the pre-authorization system. There were 46.37% and 80.76% of appropriate use in Docetaxel and Letrozole respectively. Lower percentage of DUE completed form in both Docetaxel and Letrozole. Almost all studied factors affected pattern of anticancer drug prescribing except non-NLED policy versus number of prescribing non-NLED. All studied factors were affected appropriate use except medication safety policy and health benefit schemes only in hormone therapy. The logistic regression equation were conducted to predict the pattern of prescribing and appropriate use of anticancer drug due to any factors.

5.3Limitations:

There were few limitations in this study.

1) The pattern of anticancer drug utilization was study from prescriptions that do not have clinical data of patients. So the researcher cannot analyze the pattern of use related to the clinical data. We recommend in the future research to use the electronic data instead.
2) This study was not analyzed the pattern of use as the line of therapy in each patient. This was the interested topic that can compare with other research to reach some point of view such as volume of prescribed and cost(Ray et al., 2013).
3) To compare the pattern of anticancer drug use so this study do only in out-patients department, there were some patients alter between out-patients department and in-patients department in course of treatment or regimen. So the researcher could miss some prescriptions. The electronic data base will be correct this problem in the future research.

5.4Recommendation:

5.4.1 Policy recommendation:

The researcher strongly recommend in few areas as follow.

1) Cost analysis of chemotherapy drug in each center should be done and compare with the cancer protocol. Because this study showed higher costs of each regimen more than reimburse cost. Further strategy would be suggested such as central procurement for controlling cost.
2) Propose the factor affected pattern and appropriate use of anticancer drugs for developing desire pattern of use and more appropriate use of anticancer drug.
3) Review process of DUE in each center for improving higher percentage of completed DUE form. Some strategies would be suggested such as electronic applied DUE.

5.4.2 Research recommendation:

1) The period of study should be retrospect and extended before and after the NHSO protocol was announced, so the research would compare the pattern of prescribed due to the effect from protocol. More appropriated period should be 1 year before and after the protocol announced.
2) The pattern of prescribing concomitant drugs should be separately studied in the further research. Because researcher can deeply analyzed in many dimension such as drug interaction, appropriated use of pre-medication or cost analysis.

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APPENDIX

Data Collection Form 1:

Prescription Analysis of Breast Cancer Patient

(ใช้ในการเก็บข้อมูลจากใบสั่งยาผู้ป่วยมะเร็งเต้านม)

1. Center
   ❑1)Chonburi ❑2)Lopburi ❑3)Lumpang❑4)Pathum
   ❑5)Surat❑6)Ubon❑7)Udorn
2. Type of patient ❑1)OPD ❑2)IPD
3. Right ❑1)CSMBS ❑2)SSS ❑3)NHSO ❑4)CASH
   ❑5)Support ❑6)Other
4. Date of prescription .....(Date/Month/2010)
5. Gender❑1)Female ❑2)Male
6. Age .....Years
7. Physician Name
   ❑1)Doctor A ❑2)Doctor B ❑3)Doctor C ❑4)Doctor D ❑5)Doctor E
8. Specialist
   ❑1)Oncologist❑2)Onco-Haemato❑3)Onco-surg
   ❑4)Surgeon ❑5)Radiologist ❑6)Other
9. No of all drug items .....items
10. Cost of all drug .....Baht
11. No of ED .....items
12. Cost of ED .....Baht
13. No of NED .....items
14. Cost of NED .....Baht
15. Drug/Regimen

    Chemotherapy

    ❑1) FAC❑2) FEC❑3) AC❑4) Paclitaxel ❑5) Docetaxel ❑6) CMF
    ❑7) TAC❑8) Pac/Carbo ❑9) Xeloda❑10) Navelbine❑11) other chemo

    Hormone

    ❑12) Tamoxifen ❑13)Nolvadex❑14)Anastrozole❑15) Arimidex
    ❑16) Letrozole ❑17)Femara ❑18) Exemestane❑19)Other Hormone

Targeted Therapy

❑20)Herceptin ❑21)Avastin ❑22)Other Targeted Therapy.....

16. Amount(Tablet) For Hormone only .....Tablets
17. Cost of Drug/Regimen .....Baht
18. Are there any original items in this prescription?

❑1)Yes ❑2)No

19. Ratio of Original items : All items ..... :.....
20. Are there any concomitant drug? ❑1)Yes ❑2)No
21. No of concomitant drug .....items
22. Cost of concomitant drug .....Baht
23. No of ED-concomitant drug .....items
24. Cost of ED-concomitant drug .....Baht
25. No of NED-concomitant drug .....items
26. Cost of NED-concomitant drug .....Baht
27. Identify concomitant drug in ATC code
    1) Drug name.....ATC Code.....
    2) Drug name.....ATC Code.....
    3) Drug name.....ATC Code.....
    4) Drug name.....ATC Code.....
    5) Drug name.....ATC Code.....
    6) Drug name.....ATC Code.....
    7) Drug name.....ATC Code.....
    8) Drug name.....ATC Code.....
    9) Drug name.....ATC Code.....
    10) Drug name.....ATC Code.....
28. No of couple of DI .....Couples Please Identify Generic name & Severity
    1) .....VS.....

    ❑1)Major ❑2)Moderate ❑3)Minor ❑4)Major/Moderate ❑5)Minor/Any

    2) .....VS.....

    ❑1)Major ❑2)Moderate ❑3)Minor ❑4)Major/Moderate ❑5)Minor/Any

3) .....VS.....

❑1)Major ❑2)Moderate ❑3)Minor❑4)Major/Moderate❑5)Minor/Any

4) .....VS.....

❑1)Major ❑2)Moderate ❑3)Minor❑4)Major/Moderate❑5)Minor/Any

5) .....VS.....

❑1)Major ❑2)Moderate ❑3)Minor❑4)Major/Moderate❑5)Minor/Any

Rating on Clinical Significance of Drug Interaction (Reference: Drug Interaction Facts)

Significant Level	Severity of Drug Interaction	Evidence Base
1	Major	Suspected or >
2	Moderate	Suspected or >
3	Minor	Suspected or >
4	Major/Moderate	Possible
5	Minor	Possible
	Any	Unlikely

Data Collection Form 2:

Anticancer drug utilization in breast cancer patients: data collection form

Part 1 Demographic data and disease status of patient

1	**Center** ❑01 ❑02 ❑03 ❑04 ❑05 ❑06 ❑07
2	**Date of prescription**...../...../.....
3	**Type** ❑ 01 OPD ❑ 02 IPD
4	**Scheme** ❑01CSMBS ❑02 NHSO ❑03 SSS ❑04 Cash ❑05 other .....
5	**Date of Birth**...../...../.....
6	**Age**.....year ❑01 1-20 ❑02 21-40 ❑03 41-60 ❑04 61-80 ❑05 > 80
7	**Gender** ❑ 01 Male ❑ 02 Female
8	**Body wt**.....kg **Height**.....cm **BSA**.....m^2
9	**Stage** ❑01 Stage I ❑02 Stage II ❑03 Stage III ❑04 Stage IV ❑05 Stage 0 ❑06 Unknown
10	**TNM Staging**.....(if available)
11	**Nodes positive** ❑01 ≥4 nodes ❑02 1-3 nodes ❑03 nodes negative ❑04 not know
12	**Tumor size** ❑01 ≤ 5cm ❑02 = 5 cm ❑03 > 5 cm ❑04 not know
13	**Hormone receptor** ❑01 ER(+)/PR(+) ❑02 ER(+)/(PR-) ❑03 ER(-)/PR(-)
14	**Her-2 receptor** ❑01 Positive ❑02 Negative (confirm by FISH/IHC)
15	**Risk of recurrence** ❑01 Low risk ❑02 Intermediate risk ❑03 High risk
16	**Assessment of endocrine responsiveness** ❑01 Endocrine responsive ❑02 Endocrine responsive ❑03 Endocrine non-responsive
17	**Menstrual condition** ❑01 Premenopausal ❑02 Postmenopausal
18	**Prescriber characteristic: specialty** ❑01 Medical oncologist ❑02 Medical doctor ❑03 Radiologist ❑04 Onco Sergeant ❑05 Sergeant ❑06 other.....

Data Collection form 2:

Anticancer drug utilization in breast cancer patients: data collection form

Part 2 DUE for Letrozole (Reference from Thai National Formulary 2010)

	สั่งใช้ยา Letrozole ครั้งนี้เป็นครั้งแรก ❑ 01 Yes ❑ 02 No
	Terminal ill ❑ 01 Yes ❑ 02 No
	วินิจฉัยตามเกณฑ์ พบว่าเป็นโรคมะเร็งเต้านมที่มี Hormone receptor + ❑ 01 Yes ❑ 02 No
	Hormone receptor ❑ 01 Yes ❑ 02 No
	Postmenopause(ใช่ อย่างน้อย 1 ข้อ) ❑ 01 อายุมากกว่า 60 ปี ❑ 02 ผู้ป่วยได้รับการผ่าตัดรังไข่ออกหมด ❑ 03 หมดประจำเดือนตามธรรมชาติ ก่อนเกิดมะเร็งเต้านม นานมากกว่า 1 ปี ❑ 04 ระดับ FSH .....mIU/ml (Postmenopausal 25.8-134.8 mIU/ml) ❑ 05 ระดับ Estradiol .....pg/ml (Postmenopausal <5.00-54.7 pg/mL)
	Indication ❑ 01 Advance Breast Cancer ❑ 02 Early Breast Cancer/ Adjuvant Therapy (Start Tamoxifen → Letrozole ไม่เกิน 60 เดือน) ❑ 03 Early Breast Cancer/ Adjuvant Therapy (Start Letrozole → Tamoxifen ไม่เกิน 60 เดือน) ❑ 04 Other.....
	กรณี Early Breast Cancer ที่ได้รับ Tamoxifen มาก่อน ระยะเวลาที่ได้รับ Tamoxifen มาก่อน เป็นเวลา.....เดือน
	รวมระยะเวลาทั้งหมด Tamoxifen + Letrozole เป็นเวลา.....เดือน
	สั่งใช้ยาตาม Recommend dose 2.5 mg/day ❑ 01 Yes ❑ 02 No
	Original Drug ❑ 01 Yes ❑ 02 No
	Amount of Drug .....**Tab**
	Cost/Tab.....**Baht**
	ADR ❑ 01 Yes ❑ 02 No Identify.....
	ผู้ป่วยยังคงตอบสนองต่อยาและทนผลข้างเคียงได้สมควรให้ยาต่อ ❑ 01 Yes ❑ 02 No
	Calcium supplement ❑ 01 Yes ❑ 02 No Identify.....
	มีการใช้แบบฟอร์มกำกับการใช้ยาโดยกรอกข้อมูลและลงนามสมบูรณ์ ❑ 01 Yes ❑ 02 No

Data Collection form 2:

Anticancer drug utilization in breast cancer patients: data collection form

Part 2 DUE for Docetaxel (Reference from Thai National Formulary 2010)

1	**สั่งใช้ยา Docetaxel ครั้งนี้เป็นครั้งแรก** ❑ 01 Yes ❑ 02 No
2	**Cycle** ❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ 6 ❑ 7 ❑ 8 ❑ **>8**
3	**เหตุผลที่ให้ยาครั้งนี้** ❑ 01 เป็นการให้ยาต่อเนื่องจากครั้งแรก ❑ 02 ให้ยาซ้ำหลังจากหยุดยาชั่วคราว
4	**Terminal ill** ❑ 01 Yes ❑ 02 No
5	**วินิจฉัยตามเกณฑ์ พบว่าเป็นโรคมะเร็งเต้านมระยะลุกลาม** ❑ 01 Yes ❑ 02 No
6	**ผู้ป่วยรายนี้สมควรได้รับ Docetaxel ด้วยเหตุผลใด** ❑ 01 ไม่สามารถใช้ Anthracycline ได้ เพราะ..... ❑ 02 ใช้ Anthracycline แล้วไม่ได้ผล (ระบุช่วงเวลา.....ถึง.....)
7	**มีการแพร่กระจายของโรค** ❑ 01 Yes ❑ 02 No 1. ตับ ❑ 01 Yes ❑ 02 No 2. สมอง ❑ 01 Yes ❑ 02 No 3. ปอด ❑ 01 Yes ❑ 02 No 4. กระดูก ❑ 01 Yes ❑ 02 No 5. อื่นๆระบุ..... ❑ 01 Yes ❑ 02 No
8	**ECOG** ❑ 01 ECOG=0 ❑ 02 ECOG=1 ❑ 03 ECOG=2 ❑ 04 ECOG=3 ❑ 05 ECOG=4 ❑ 06=NA
9	**Body wt**.....kg **Height**.....cm **BSA**.....m^2
10	**Dose** of Docetaxel.....mg (คิดเป็น.....mg/ m^2) ❑ 01 Yes ❑ 02 No Recommend dose = 75 mg/ m^2 หรือระหว่าง 60 – 100 mg/ m^2
11	**Every 3 week** ❑ 01 Yes ❑ 02 No
12	**Combine with Chemotherapy** ❑ 01 Yes (Identify.....) ❑ 02 No
13	**Original Drug** ❑ 01 Yes ❑ 02 No
14	**Amount of Drug 80 mg .....ขวด** **Amount of Drug 20 mg .....ขวด**
15	**Cost/80 mg 1 ขวด**.....**Baht(1)** **Cost/20 mg 1 ขวด**.....**Baht(2)** **Total**.....**Baht(1)+(2)**
16	**ADR** ❑ 01 Yes (Identify.....) ❑ 02 No or Not record
17	**ผู้ป่วยยังคงตอบสนองต่อยาและทนผลข้างเคียงได้สมควรให้ยาต่อ** ❑ 01 Yes ❑ 02 No
18	**มีการใช้ Dexamethasone เป็น pre-medication** ❑ 01 Yes ❑ 02 No
19	**มีการใช้แบบฟอร์มกำกับการใช้ยาโดยกรอกข้อมูลและลงนามสมบูรณ์** ❑ 01 Yes ❑ 02 No

Data Collection form 2:

Anticancer drug utilization in breast cancer patients: data collection form

Part 2 DUE for Trastuzumab (Reference from OCPA)

	เป็นผู้ป่วยรายเก่าหรือรายใหม่ ❑ รายเก่า(มารับยาต่อเนื่อง) ❑ รายใหม่(ได้ยาครั้งแรก)
	Indication ❑ 1st line ❑ 2nd line ❑ 3rd line ❑ กลับมาใช้ใหม่หลังครบ 1 ปี
	ECOG ❑ 01 ECOG=0 ❑ 02 ECOG=1 ❑ 03 ECOG=2 ❑ 04 ECOG=3 ❑ 05 ECOG=4 ❑ 06=NA
	LVEF .....%**(ไม่เกิน 6 เดือน** Date..... ❑ 01 MUGA ❑ 02 Echocardiogram
	Previous Chemotherapy ❑ 01 Yes ❑ 02 No
	Adjuvant/Neoadjuvant Chemotherapy ❑ 01 Yes ❑ 02 No
	Metastasis Chemotherapy ❑ 01 Yes ❑ 02 No
	Regimen of Adjuvant/Neoadjuvant Chemotherapy ❑ 00 None ❑ 03 Paclitaxel ❑ 06 Gemcitabine ❑ 01 CMF ❑ 04 Docetaxel ❑ 07 Vinorelbine ❑ 02 FAC/FEC/AC ❑ 05 Capecitabine ❑ 08 Other.....
	Regimen of Metastasis Chemotherapy ❑ 00 None ❑ 03 Paclitaxel ❑ 06 Gemcitabine ❑ 01 CMF ❑ 04 Docetaxel ❑ 07 Vinorelbine ❑ 02 FAC/FEC/AC ❑ 05 Capecitabine ❑ 08 Other.....
	Previous Hormone ❑ 01 None ❑ 02 Tamoxifen ❑ 03 AI.....
	Resectatble ❑ 01 None ❑ 02 Complete resectable ❑ 03 Partial resectable
	Tissue diagnosis ❑ 01 Cytology ❑ 02 Histology
	Hormone receptor ❑01 ER(+)/PR(+) ❑02 ER(+)/(PR-) ❑03 ER(-)/PR(-)
	Her-2 = 3+ by FISH /IHC(+) ❑ 01 Yes ❑ 02 No
	Her-2 Test Date.....by ❑ 01 FISH ❑ 02 IHC
	Underlining cardiovascular disease ❑ 01 Yes ❑ 02 No
	Body wt.....kg **Height**.....cm **BSA**.....m^2
	Recommend Dose ❑ 01 Yes ❑ 02 No
	Disease status หลังใช้ยา ❑ 01 CR ❑ 02 PR ❑ 03 SD ❑ 04 PD
	ADR ❑ 01 Yes (Identify.....) ❑ 02 No or Not record
	ผู้ป่วยยังคงตอบสนองต่อยาและทนผลข้างเคียงได้สมควรให้ยาต่อ ❑ 01 Yes ❑ 02 No
	มีการใช้แบบฟอร์มกำกับการใช้ยาโดยกรอกข้อมูลและลงนามสมบูรณ์ ❑ 01 Yes ❑ 02 No

แบบสัมภาษณ์เพื่อการวิจัยเรื่อง

ANTICANCER DRUG UTILIZATION FOR THE TREATMENT OF BREAST CANCER AT REGIONAL CANCER CENTERIN THAILAND

คำชี้แจง

1. แบบสัมภาษณ์นี้มีวัตถุประสงค์เพื่อศึกษา รูปแบบการใช้ยาต้านมะเร็งในโรคมะเร็งเต้านมที่ศูนย์มะเร็งภูมิภาค 7 แห่ง ของประเทศไทย เพื่อสัมภาษณ์กลุ่มตัวอย่าง คือ
   1) ผู้อำนวยการศูนย์มะเร็งภูมิภาค
   2) ประธานคณะกรรมการเภสัชกรรมและการบำบัด(PTC)
   3) แพทย์ผู้สั่งใช้ยา
   4) หัวหน้ากลุ่มงานเภสัชกรรม
2. แบบสอบถามฉบับนี้แบ่งออกเป็น 3 ตอน คือ
   2.1 ตอนที่ 1 หนังสือยินยอมให้สัมภาษณ์
   2.2 ตอนที่ 2 คำถามเกี่ยวกับสถานภาพของผู้ตอบแบบสอบถามจำนวน 3 ข้อ
   2.3 ตอนที่ 3 หัวข้อคำถามในการสัมภาษณ์

ผู้วิจัยขอขอบพระคุณท่านในการเสียเสละเวลาในการให้สัมภาษณ์ โดยคำตอบของท่านจะถูกนำไปประมวลผลโดยไม่เปิดเผยตัวบุคคล และสถานที่ปฏิบัติงาน แต่จะเป็นประโยชน์ในการศึกษารูปแบบการสั่งใช้ยา เพื่อเป็นข้อมูลสำหรับผู้เกี่ยวข้องในการส่งเสริมการใช้ยาอย่างสมเหตุผล

นางสาวชนินันท์ เกตุแก้ว
นิสิตระดับปริญญาดุษฎีบัณฑิต
หลักสูตรเภสัชศาสตร์สังคมและการบริหาร
คณะเภสัชศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย

หนังสือแสดงความยินยอมการให้สัมภาษณ์แก่นักวิจัย
(Informed consent form)

โครงการวิจัยเรื่องรูปแบบการใช้ยาต้านมะเร็งในโรคมะเร็งเต้านมที่ศูนย์มะเร็งภูมิภาคของประเทศไทย
ผู้วิจัย นางสาวชนินันท์ เกตุแก้ว นิสิตหลักสูตรเภสัชศาสตร์สังคมและการบริหาร
รหัสประจำตัวนิสิต 5177101033 คณะ เภสัชศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
ตำแหน่ง เภสัชกรชำนาญการ หัวหน้ากลุ่มงานเภสัชกรรม หน่วยงานต้นสังกัด ศูนย์มะเร็ง ชลบุรี

****

ข้าพเจ้าได้รับฟังคำอธิบายจากผู้ทำวิจัยว่าได้ทำการศึกษาเรื่องรูปแบบการใช้ยาต้านมะเร็งในโรคมะเร็งเต้านมที่ศูนย์มะเร็งภูมิภาคของประเทศไทยซึ่งมีวัตถุประสงค์จะนำข้อมูลจากการสัมภาษณ์นี้ไปใช้ทำการวิจัยในรายวิชาวิทยานิพนธ์ หลักสูตรวิทยาศาสตรดุษฎีบัณฑิต สาขาเภสัชศาสตร์สังคมและการบริหาร ซึ่งเป็นการใช้ข้อมูลเพื่อประโยชน์ทางการศึกษาเท่านั้น และการให้สัมภาษณ์นี้ข้าพเจ้าให้สัมภาษณ์ด้วยความสมัครใจโดยไม่มีค่าตอบแทนใดๆตลอดจนทราบดีว่าจะสามารถถอนตัวจากการมีส่วนร่วมในการศึกษานี้เมื่อใดก็ได้

การให้สัมภาษณ์นี้ ผู้วิจัยได้อธิบายให้ข้าพเจ้าทราบเกี่ยวกับโครงการวิจัยโดยละเอียดแล้ว ไม่มีสิ่งใดปกปิด ผู้วิจัยยินดีตอบคำถามทุกคำถามของข้าพเจ้า และผู้วิจัยให้คำรับรองกับข้าพเจ้าว่าจะเก็บข้อมูลเกี่ยวกับข้าพเจ้าเป็นความลับและจะเปิดเผยเฉพาะในรูปที่เป็นการสรุปการวิจัย โดยไม่ระบุตัวบุคคลผู้เป็นเจ้าของข้อมูล

ข้าพเจ้าได้อ่านและเข้าใจคำอธิบายข้างต้นแล้ว จึงได้ลงนามยินยอมนี้ด้วยความเต็มใจ

❑ ยินดีให้สัมภาษณ์และอนุญาตบันทึกเสียง ❑ ยินดีให้สัมภาษณ์แต่ไม่อนุญาตให้บันทึกเสียง ❑ ไม่ยินดีให้สัมภาษณ์

ลายมือชื่อผู้ให้สัมภาษณ์.....

(.....)

ลายมือชื่อผู้วิจัย.....

(.....)

ลายมือชื่อพยาน.....

(.....)

ลายมือชื่อพยาน.....

(.....)

วันที่.....เดือน.....พ.ศ. .....

<u>ตอนที่ 2</u> สถานภาพของผู้ตอบแบบสอบถาม กรุณาทำเครื่องหมาย ✓ ลงในช่อง ❑

1	**ตำแหน่ง** ❑ 01 ผู้อำนวยการศูนย์มะเร็ง ❑ 02 ประธานPTC ❑ 03 แพทย์ผู้สั่งใช้ยา ❑ 04 หัวหน้ากลุ่มงานเภสัชกรรม
2	**เพศ** ❑ 01 ชาย ❑02 หญิง
3	**ท่านเป็นแพทย์เฉพาะทางสาขา(กรณีไม่ใช่แพทย์ ไม่ต้องตอบข้อนี้)** ❑01 Medical oncologist ❑02 Medical doctor ❑03 Radiologist ❑04 Onco Sergeant ❑05 Sergeant ❑06 other.....

ตอนที่ 3 หัวข้อคำถามและประเด็นในการสัมภาษณ์

การสัมภาษณ์ใช้เวลาไม่เกิน 30 นาที

1. นโยบายการการจัดการด้านยาในโรงพยาบาล
   - มีการกำหนดนโยบายด้านการสั่งใช้ยามะเร็งอย่างไร(เช่น ใช้เฉพาะ Medical Oncologists)
   - ดูแลโดยคณะกรรมการชุดใด
   - นโยบายครอบคลุมในเรื่องใดบ้าง (เช่น การคัดเลือก การจัดซื้อ การสั่งใช้)
   - การกำหนดนโยบายนั้นมีที่มาอย่างไร ทำเพื่ออะไร
   - ได้รับความร่วมมือหรือไม่ เกิดปัญหาและอุปสรรคอย่างไร
   - มีนโยบายด้านราคายาหรือไม่ อย่างไร
   - มีนโยบายเกี่ยวกับการสั่งใช้ยาต้นแบบ และยาเลียนแบบอย่างไร
   - นโยบายการสั่งใช้ยาเกี่ยวกับสิทธิการรักษาหรือไม่ อย่างไร
   - นโยบายการสั่งใช้ยาตามแนวทางเวชปฏิบัติ Guideline, Protocol มีหรือไม่ อย่างไร ได้รับความร่วมมือหรือไม่ มีปัญหาอย่างไร ข้อดี/ข้อเสีย ข้อเสนอแนะ
2. ความคิดเห็นต่อปัจจัยที่มีผลต่อการใช้ยาต้านมะเร็งในโรคมะเร็งเต้านม(ทั้งด้านผลเชิงบวกและลบ)
   - ปัจจัยภายนอกโรงพยาบาล ตัวอย่างคำถามได้แก่ โรงพยาบาลของท่านได้รับถ่ายทอดนโยบายด้านยาจากส่วนกลาง/นำมาปฏิบัติอย่างเคร่งครัด จริงจังหรือไม่/ปฏิบัติแล้วมีปัญหาหรือข้อติดขัดหรือไม่/
   - ปัจจัยภายในโรงพยาบาล ตัวอย่างคำถาม ได้แก่ โรงพยาบาลของท่านมีการกำหนดนโยบายด้านการใช้ยารักษาโรคมะเร็งบ้างหรือไม่ / มีที่มาอย่างไร / อะไรบ้าง / อย่างไร / มีการปฏิบัติอย่างจริงจังเคร่งครัดหรือไม่ / มีปัญหาอุปสรรคหรือไม่ อย่างไร

3. ความตระหนักต่อปัญหา
   - คิดว่าการสั่งใช้ยามะเร็งในปัจจุบันมีปัญหาหรือไม่ ในโรงพยาบาลของท่าน ในประเทศไทย และผลต่อคนไข้
4. ระบบรายงานถึงสภาพการใช้ยาในโรงพยาบาลของท่านมีหรือไม่ ท่านทราบหรือไม่ รายงานรูปแบบไหน ใครเป็นผู้รับผิดชอบรายงาน ท่านมีส่วนร่วมในรายงานนั้นอย่างไร เอาผลจากรายงานไปใช่ประโยชน์หรือไม่ อย่างไร
5. มีกระบวนการทำ DUE ในโรงพยาบาลหรือไม่ ผลเป็นอย่างไร ใครทำ ท่านมีส่วนร่วมหรือไม่อย่างไร ท่านคิดว่าการทำ DUE มีประโยชน์หรือไม่ เพราะอะไร ควรทำต่อไปหรือไม่
6. โรงพยาบาลมีนโยบายด้านการส่งเสริมการใช้ยาอย่างสมเหตุผลหรือไม่ อย่างไร กำหนดเป็นเพียงนโยบายหรือปฏิบัติเคร่งครัด ทำเพราะอะไร มีใครบังคับมา ใครมีส่วนร่วมบ้าง ทำแล้วประสบความสำเร็จแค่ไหน ใช้ตัวชี้วัดอะไร
7. ปัญหาการนำเครื่องมือต่างๆ มาใช้ ได้แก่ Guideline DUE Protocol และคิดว่ามีประโยชน์หรือไม่ มีความเป็นปัจจุบันหรือทันสมัยหรือไม่ ท่านยินดีปฏิบัติตามหรือไม่ ถ้าไม่เหมาะสมหรือมีข้อติดขัด ท่านมีข้อเสนอแนะอย่างไร
8. ข้อกังวลใจในการสั่งจ่ายยา เช่น คุณภาพยา ราคา ผลข้างเคียง กองทุนต่างๆ
   - มีอะไรบ้างที่ท่านรู้สึกเป็นห่วงเมื่อสั่งจ่ายยาให้คนไข้มะเร็ง
9. ข้อเสนอแนะ ภายในโรงพยาบาล และต่อนโยบายรัฐ, ท่านคิดว่านโยบายควรเป็นอย่างไร ผู้ป่วยจึงจะได้ประโยชน์สูงสุด

จบการสัมภาษณ์

.....

VITA

Name –Surname : Chaninun Ketkaew

Date of Birth : December 10, 1977

Address : 11 Krungthepkreetha 20 Krungthepkreetha Rd. Sapansoong Province, Bangkok 10250

Work Place : Chonburi Cancer Hospital 300 Moo.2 Prayasajja Rd. Samed province A.Muang Chonburi 20000

Position : Head of Pharmacy Department

Work Experiences : Chonburi Cancer Hospital (2001 - 2014)

Education Background : BSc. (Pharm), Chulalongkorn University, Thailand (2001)

MBA, Burapha University, Thailand (2008)

Publication

1. THE STUDY ON THE EFFECT S OF SERVICE FACTORS OF CHAIN DRUG STORES AND INDEPENDENT DRUG STORES OF PEOPLE AT CHONBURI PROVINCE (2010)

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