CHAPTER 1

BACKGROUND AND RATIONALE

Non-Hodgkin's lymphoma (NHL) is a heterogenous group of diseases characterized by neoplastic transformation of cells which reside in the immune system. It is one of the most common hematologic malignancies in Thailand[1] and worldwide[2]. About sixty new cases are diagnosed each year at Chulalongkorn Hospital[1]. By the standard classification scheme known as the Working Formulation, the disease is divided into low-, intermediate- and high-grade according to the natural history[3].

Advances in the therapy for patients with diffuse aggressive NHL are one of the most important breakthroughs in oncology over the past 20 years. With currently available combination chemotherapy regimens, complete remission can be obtained in 60-80% of patients and long-term disease-free survival can be achieved in 30-50%[4]. However, in patients identified as "high-risk" group, the outcome is still unsatisfactory. With doxorubicin-based combination chemotherapy, the complete remission rate was 44% and five-year survival was obtained only in 26% for patients who had multiple poor prognostic features (age > 60 years, tumor stage III or IV, number of extranodal involvement > 1 site, the Eastern Cooperative Oncology Group (ECOG) performance status scale $\geq$ 2 and raised serum lactate dehydrogenase (LDH) level)[5]. In contrast to the "low" risk patients (one or none of the poor prognostic features), complete remission and five-year survival was achieved in 87% and 73% of the patients, respectively[5]. Therefore a more effective therapy is urgently needed in patients with poor prognostic features.

Experimental data and retrospective analysis of clinical studies and prognostic factors in patients with NHL suggest a correlation between

increased dose intensity and improved therapeutic outcome[6,7]. High-dose myeloablative chemotherapy followed by stem cell rescue is one form of therapy which takes advantage of the steep dose response curves displayed by several drugs which are active in treating lymphomas[8,9]. High-dose therapy with autologous bone marrow transplantation (ABMT) has now become an established treatment for patients with relapsed or resistant lymphomas. With combination chemotherapy at conventional dose, only 5-10% of these patients survive for long period[4] in contrast to results of several trials in patients with NHL in chemosensitive relapse receiving high-dose therapy and ABMT, a progression-free survival of 20-50% was reported [10-12].

Because of the encouraging results in patients with relapsing or recurrent lymphoma, high-dose therapy with stem cell rescue has now been carried out in patients who are at high-risk of failure on conventional therapy at their early phase of disease while the disease still respond to chemotherapy and the tumor burden is small. In addition, it had been shown that a slow response to conventional chemotherapy in patients with intermediate and high grade NHL is an unfavorable prognostic factor[13]. A number of studies has been attempted to administer high-dose therapy with stem cell rescue in poor prognosis aggressive NHL patients at the early phase of disease. The results of these uncontrolled trials showed a 80-95% long-term disease-free survival in the patients[14-17].

Myeloablative chemoradiotherapy with peripheral blood progenitor cells transplantation (PBPCT) rescue is increasingly used to treat cancer. An increasingly popular use is due to some practical advantages of the procedure over ABMT. The morbidity of the collection process is lower since there is no requirement for a general anaesthetic or multiple needle aspirations. The procedure can be considered in patients with marrow hypoplasia or malignant infiltration who were previously excluded from receiving ABMT[18]. But perhaps the most clearly established advantage is

the acceleration of hematopoietic reconstitution compared with BMT. A number of studies have suggested PBPCT produces a faster recovery of neutrophils and platelets over BMT. This leads to a corresponding reduction in antibiotic use, platelet dependence, hospitalization and cost[18-20].

High-dose therapy with PBPCT has recently been utilized intensively to treat patients with NHL. Reports have included patients with relapsed or refractory diseases and those who achieved complete remission and received PBPCT as a consolidation therapy. A series of 78 patients with intermediate and high grade NHL who were treated with high dose therapy and PBPCT was reported by Kessinger et al[21]. All patients had relapsed or refractory diseases and their bone marrow was considered unsuitable for autografting. Forty-two patients experienced a complete remission and eight patients had a partial response following high-dose therapy. At the time of analysis, 38 patients were dead, most of them as the result of progressive disease. Forty patients survived, but 6 had evidence of progression. Thirty-four (44%) patients remained in unmaintained progression-free survival at a median of 18 months (range, 4 to 79 months) after PBPCT. The actuarial event-free survival for all 78 patients at 80 months was 30%. Recently the results of a phase III trial assessing the efficacy of high dose chemotherapy and PBPCT as part of the initial treatment in 98 poor-risk patients according to the international index had been reported by Gianni et al[22]. Patients were randomized to receive either MACOP-B chemotherapy (methotrexate with leucovorin rescue, doxorubicin, cyclophosphamide, vincristine, prednisolone, and bleomycin) or high-dose sequential chemotherapy with autologous PBPCT. The event-free and overall survival rate (76% vs. 49%, $p = 0.004$; 81% vs. 55%, $p = 0.09$, respectively) were in favorable for patients in the transplant arm. The conclusion was that early high-dose therapy in high risk NHL patients might improve treatment results, as compared to conventional chemotherapy.