CHAPTER 4

RESULTS

4.1 Demographic Data

There were a total of 54 patients enrolled in the study. Fifty patients were accrued at Chulalongkorn Hospital and 4 patients were entered from Pramongkutkloa Hospital. The baseline clinical features of the patients is shown in Table 10.

The mean age of the patients was 35.8 years (range, 17 - 55 years). Twenty-four percent of the patients were older than 45 years. There was a slightly preponderance of male over female (53.7 vs 46.3%). The diffuse large-cell subtype was the most common histologic entity encountered in 79.6% of the patients. Forty-six percent of the patients had far advanced disease (stage III, IV) and most patients (88.5%) experienced systemic B symptoms at presentation. The distribution of the patients' performance status (PS) according to the ECOG criteria were 3.7, 14.8, 25.9, 42.6 and 13.0% for the PS of grade 0, I, 2, 3 and 4, respectively. Bulky disease i.e., harboring mass with the diameter greater than 10 cms at presentation was found in 38.9% of the patients. Other features indicating poor prognostic features, namely, bone marrow involvement, presence of $\geq$ 2 extranodal sites and serum LDH of > 450 u/l were found in 37, 55.6, and 96.3% of the patients, respectively. According the international prognostic risk-group index, 63% of the patients were categorized as the high-risk cases and 37% as the high-intermediate group.

Table 10 Clinical characteristics of the patients (N = 54)

	N	%
Age (mean, years)	35.8 (17 - 55)	
Male	29	53.7
Distribution of histologic subtypes		
Diffuse mixed small and large cells	11	20.4
Diffuse large cells	43	79.6
Distribution of stage		
Stage I	3	5.6
Stage II	5	9.3
Stage III	9	16.7
Stage IV	37	68.5
B symptoms	46	88.5
Distribution of performance status (PS)		
PS 0	2	3.7
PS 1	8	14.8
PS 2	14	25.9
PS 3	23	42.6
PS 4	7	13.0
Bulky disease	21	38.9
Bone marrow involvement	20	37.0
$\geq$ 2 extranodal sites	30	55.6
serum LDH > 450 u/l	52	96.3
Distribution of risk-group		
High-intermediate	20	37.0
High	34	63.0
Hemoglobin level (mean, g/dl)	10.1 $\pm$ 2.7 (5.8 - 15.2)	
Platelet count (mean, x 10^9/l)	54.0 $\pm$ 266.7 (2.2 - 696.0)	
Total birilubin level (mean, mg/dl)	1.9 $\pm$ 5.4 (0.09 - 35.0)	
Serum albumin level (mean, g/dl)	3.5 $\pm$ 0.8 (1.7 - 5.2)	

The laboratory markers also indicated the high severity of lymphoma in this patient cohort. Eighty-one percent of the patients were anemic (hemoglobin level < 13.0 g/dl) and 31.5% were thrombocytopenic (platelet count < 150 x 10^9/l). Jaundice was present in 10.4% of the patients. Low serum albumin (< 3.5 g/dl) was seen in 47.9% of the patients.

4.2 Tumor Responses after the First Three Courses of CHOP Therapy

Tumor responses after the first 3 courses of CHOP therapy could be assessed in 44 patients. One patient was lost to follow-up after the third course of treatment before the evaluation of tumor response. Nine patients (16.7%) died during this phase of therapy indicating the highly aggressiveness of the disease. The main reasons of death in these patients were febrile neutropenia after chemotherapy occurred in 44.4% and progression of the lymphoma in 55.6% of the patients. Of the evaluable 44 patients, CR, PR, SD and PD were documented in 26.7, 55.6, 6.7, and 11.1% of the patients, respectively.

4.3 Randomization

The surviving 44 patients were stratified randomized to receiving the two treatment arms according to the features that were likely to affect the treatment outcome, i.e., age, the risk-group and tumor response after 3 courses of CHOP. Twenty-two patients were randomized to continue with CHOP therapy whereas another 22 patients were assigned to the high-dose treatment with PBPCT. Table 11 compares the important prognostic features pertaining to these two groups of patients. Statistical significant differences in the proportion of patients according to these characteristics between the two groups were not observed.

Table 11 Comparison of the important clinical features in patients receiving CHOP and high-dose therapy

	CHOP therapy	High-dose therapy	P-value
No	22	22	
% age > 45 years	27.5	22.7	1.00
% high-risk group	59	50	0.76
% tumor response after 3rd CHOP			
CR	22.7	37.9	0.74
PR	63.6	50.0	0.34
SD	4.5	9.0	1.00
PD	9.0	9.0	1.00
% PS 2 - 4	77.3	81.8	1.00
% stage III - IV	81.8	81.8	1.00
% bulky disease	20.0	17.0	0.41
% bone marrow involvement	31.8	36.4	1.00
% $\geq$ 2 extranodal sites	50.0	50.0	1.00
% serum LDH > 450 u/l	100.0	90.9	1.00

4.4 Therapeutic Outcome

4.4.1 Rate of complete remission

Of the 44 patients who had been randomized to the two treatment arms, 5 patients were still not completed the treatment at the time of evaluation. Of the remaining 39 patients, 21 were treated with CHOP chemotherapy and 18 were receiving high-dose therapy. In patients enrolled to the high-dose therapy, 4 (22.2%) were lost to follow-up during the ESHAP therapy i.e., before being treated with PBPCT and another three patients refused to continue with the treatment. The clinical features of these 7 patients were not significantly different from the remaining 11 patients who had completed the high-dose treatment (Table 12). One patient in the CHOP arm was lost to follow-up after receiving the fourth cycle of CHOP.

Table 12 Comparison of the clinical features in patients who were and were not withdrawn (lost to follow-up, refused the treatment) in the high-dose treatment

	Not withdrawn patients	Withdrawn patients	P-value
No.	11	7	
% age > 45 years	9	27.3	0.24
% high-risk group	45.4	57.1	1.00
% tumor response of CR + PR after 3rd cycle of CHOP			
	72.7	85.7	0.68
% stage III, IV	72.7	100.0	0.24
% PS 2 - 4	81.8	85.7	1.00
% serum LDH > 450 u/l	90.9	85.7	1.00

As the statistical approach on the treatment outcome were based on the intention-to-treat analysis, the rate of CR of each arm was calculated as the number of patients who attained CR divided by the total number of patients enrolled in that arm although some were protocol violated. As demonstrated in Table 13, the rate of CR in patients receiving CHOP and high-dose therapy were 38% and 39%, respectively. The 95% confidence interval of the true difference in the CR rates in the two groups included the value of 1 (-.30 - .31).

Table 13 Rate of CR and the 95% confidence interval of the true difference in CR rate of the two treatment modalities

	N	Rate of CR	95% CI	P-value
All patients	39	.38	.23 - .55	
CHOP therapy	21	.38	.18 - .61	
High-dose therapy	18	.39	.17 - .64	
Rate difference		.008	-.30 - .31	1.00
Odds ratios		1.03	.29 - 3.68	

However, as it is shown that the clinical features as well as the prognostic index of the patients who were withdrawn or lost to follow-up were not significantly differed from those who had completed the treatment, it is conceivable that the therapeutic results obtained from the evaluable patients could represent the outcome of the cohort. With this rationale, the CR rate of the high-dose treatment group was 64%. The 95% confidence interval of the CR rate in the two groups however were not significantly different (Table 14).

Table 14 Rate of CR and the 95% confidence interval of the CR rates of the two group analysed on patients completing the treatment

	N	Rate of CR	95% CI	P-value
All patients	31	.48	.30 - .67	
CHOP therapy	20	.40	.19 - .64	
High-dose therapy	11	.64	.31 - .89	
Rate difference		.24	-.11 - .59	0.27
Odds ratios		2.62	.60 - 11.4	

4.4.2 Rate of progressive disease and death

Of the total 39 randomized patients, 7 patients (18%) died. Four cases were in the CHOP arm and another three, in the high-dose therapy. The rate of death and progressive disease were analysed only on the evaluable patients (N = 31) as the results might be diluted if the patients who were withdrawn/lost to follow-up were also included. Table 15 showed the data on the rate and 95% confidence interval of the death rates pertaining to the two groups. Table 16 showed the main causes of death in the two groups. It is notable that progressive disease was the main cause of death in patients receiving CHOP treatment.

Table 15 Rate of death and the 95% confidence interval of the true difference in the rate of death in the two treatment modalities

	N	Rate of death	95%CI	P-value
All patients	31	.22	.09 - .41	
CHOP therapy	20	.20	.06 - .44	
High-dose therapy	11	.27	.06 - .61	
Risk difference		.07	-.24 - .39	0.68
Odds ratios		1.5	.30 - 7.73	

Table 16 Causes of death in the patients*

	CHOP therapy	High-dose therapy
No.	4	3
Febrile neutropenia	1	2
Progressive disease	3	0
Non-treatment-related	0	1

*P-value of the difference in causes of death in the 2 groups was 0.49

Of the 11 patients treated with the high-dose therapy, 3 patients died before completing the treatment (1 from febrile neutropenia during ESHAP chemotherapy, 1 from febrile neutropenia during PBPCT and 1 from unrelated cause during ESHAP therapy). Thus, tumor response could be assessed in 8 patients. Of these 8 patients, none showed progressive disease. In contrast, 8 patients (40%) in the CHOP arm had progressive disease. The 95% confidence interval of the true difference in the rate of progressive disease in these 2 groups was almost significant (Table 17).

Table 17 Rate of progressive disease and the 95% confidence interval of the true difference in the rate of progressive disease in the two treatment modalities

	N	Rate of PD	95% CI	P-value
All patients	28	.29	.13 - .49	
CHOP therapy	20	.40	.19 - .64	
High-dose therapy	8	0	0 - .37*	
Risk difference		-.4	-.61 - -.18	0.06
Odds ratios		0		

* One-tailed, 97.5% CI

4.4.3 Overall tumor response

Table 18 showed the overall tumor response in the two treatment arms.

It is evident that the rate of disease progression was significantly higher in the CHOP treatment arm. However, the rate of partial response was comparable in the two groups.

Table 18 Overall tumor response

	CHOP therapy	High-dose therapy	95% CI for the true difference
Rate of CR	.40	.64	-.11 - .59
Rate of PR	.20	.12	-.36 - .21
Rate of PD	.40	0	-.61 - -.18

4.4.4 Rate of febrile neutropenia

Febrile neutropenia occurred in 19% of patients receiving CHOP and 27%, in the high-dose therapy (Table 19). There was no statistical significant in the rate of this complication in the two groups.

Table 19 Rate of febrile neutropenia (FN) in the two treatment groups

	N	Rate of FN	95% CI	P-value
All patients	39	.23	.11 - .39	
CHOP therapy	21	.19	.05 - .42	
High-dose therapy	18	.27	.09 - .53	
Risk difference		.09	-.17 - .35	0.71
Odds ratios		1.63	.39 - 6.85	

4.4.5 Prognostic features

The important clinical features of the patients were analysed for prediciting the main therapeutic outcomes i.e., the likelihood to obtain CR, the risk of progressive disease and death. The features selected for entering as the independent factors were the risk group, age, tumor response before randomization and the treatment the patients received. While all 39 randomized patients were entered in the analysis of the ability to obtain CR (with those who were withdrawn/lost to follow-up were regarded as not obtaining CR), only those 31 patients who were not protocol violated were analysed for the likelihood of progressive disease and death. By using the stepwise logistic regression, the degree of tumor response before randomization was the most important factor determining the therapeutic outcomes (CR and death) (Table 20). Age was also significantly affected the ability to obtain CR in the patients. There were no factors shown as independently affecting the risk of PD.

Table 20 Significant prognostic factors predicting CR, PD and death

	Likelihood to obtain		
	CR	PD	Death
Age	OR = .91 95% CI = .85-.99	-	-
Tumor response before randomization	OR = .25 95% CI = .07-.78	-	OR= 3.41 95% CI =1.2-9.6
Risk-group	-	-	-
Treatment arm	-	-	-

4.5 Reliability in the interpretation of the procedure used in the assessment of tumor response

As CT abdomen was one of the most used staging procedures of the patients in this study and the assessment of the degree of tumor response after treatment rested heavily on the interpretation of this investigation, we had conducted the measurement of the reliability in the interpretation of this test. A randomly selected 24 CT abdomen studied in the patients were independently intrerpretated by two radiologists who had no knowledge regarding the clinical data as well as the therapeutic option of the patients. The assessment was to verify whether there were abnormalities pertaining to lymphomatous process. The K coefficient of the interpretation between the two observers was 0.91 which was very high (Table 21).

Table 21 The results of the interpretation of CT abdomen by two radiologists

		Observer 2		
		Normal	Abnormal	Total
Observer 1	Normal	10	0	10
	Abnormal	1	13	14
		11	13	24