CHAPTER 5

DISCUSSION

Poor prognosis NHL as defined by the international prognostic index as the high- and high-intermediate risk-group remains one of the most difficult-to-treat hematologic malignancies. The proportion of newly diagnosed NHL patients that will fall into this category is generally at 30-40%[5]. With the current doxorubicin-based chemotherapy, the rate of CR and 5-year survival are 44-55% and 26-43%, respectively, in contrast to patients with the low-risk prognosis, the rate of CR and 5-year survival are 87% and 73%[5]. Intragumtornchai et al had recently analysed 84 newly diagnosed aggressive NHL patients (category F,G,H by the Working Formulation) treated at Chulalongkorn Hospital during 1988-1993[137]. The high- and high-intermediate risk groups together constituted 33.3% of the patients. The rate of CR and 5-year survival were 37.5% and 24.7%, respectively. The therapeutic outcome of the patients in this prognostic category therefore is unsatisfactory and more effective novel therapy is needed to improve the survival.

A number of studies had recently conducted in order to resolve the aforementioned clinical quest. Haioun et al randomized 236 poor prognosis patients who already obtained CR to receive either sequential chemotherapy (n = 111) or high-dose therapy and autologous bone marrow transplantation (n = 125). The results showed the superiority of the high-dose therapy with a higher 5-year survival rate (65%, 95% CI, 56 - 74% vs. 52%, 95% CI, 42 - 62%, P = 0.06)[132]. Gianni et al compared 50 patients receiving MACOP-B therapy with 48 patients treated with sequential high-dose chemotherapy followed by myeloablative treatment with autologous bone marrow transplantation[22]. At a median follow-up time of 55 months, the patients given high-dose therapy had significantly higher rate of CR (96% vs. 70%, P

= 0.001) and event-free survival (76% vs. 49%, P = 0.004). It is noteworthy that the prognostic features of the patients comprised in these two studies fared better than patients in our study. For instance, the proportion of patients considered as high-risk cases were 42% in Gianni's study and 22%, in Haioun's study whereas in our study, 63% of the patients were the high-risk cases. In addition, 12.6% of the patients in Gianni's study were in the low-intermediate risk-group whereas in our study the low-intermediate cases were excluded.

Our study had showed that tumor response in general fared superiorly with the high dose therapy compared to the conventional CHOP chemotherapy. Although the rate of CR were comparable (39% vs. 38%), the rate of disease progression was much less with high-dose therapy (0%, 95% CI, 0 - 37% vs. 40%, 95% CI, 19 - 64%, P = 0.063). The rate of PR was also higher in patients receiving the high-dose treatment although the difference was not significantly different (12%, 95% CI, 0.3 - 53% vs. 20%, 95% CI, 6 - 44%, P = 1.00). The CR rate in patients treated with high-dose therapy was increased to 64% if the analysis considered only on patients who did not violate the treatment protocol. This rationale might be acceptable as it was shown that the clinical features especially the prognostic features of the patients who were withdrawn/lost to follow-up were similar to the remaining patients (Table 12).

Although the high-dose treatment with PBPCT was considered as the much more aggressive form of treatment compared to the conventional CHOP chemotherapy, the death rate and the occurrence of febrile neutropenia did not significantly different in the two groups. This might be explained in part from the meticulous standard supportive care provided to the neutropenic patients which is currently practicing in the medical units. It is however notable that while the cause of death in patients receiving CHOP therapy was the disease progression, febrile neutropenia was the main therapeutic obstacle in patients receiving the high-dose therapy.

Table 20 demonstrated the degree of tumor response before randomization as the most significant factor predictive of the ability to obtain CR as well as the risk of death. The significant predictive factors for disease progression however could not be derived with the available sample size. Younger age was also fared better in term of achieving CR. The risk factors (high- vs. high-intermediate) had lost its power in predicting the therapeutic outcomes when the high-dose therapy was applied to the patients.

Our study had showed that 16.7% of the patients did not survive during the first three courses of CHOP which is higher than what had been expected before conducting the study. This implies a very aggressive nature of this subgroup of lymphoma. The main cause of mortality during this early phase was equally due to disease progression and febrile neutropenia. Together with the result obtained from the stepwise logistic regression analysis that the degree of tumor response after the first phase of therapy was the most important factor determining the outcome, the future plan of treatment should hence be directed or geared heavily on this early phase of treatment. This means that to yield a better outcome, the most effective therapy should be given to the patients as early as possible after the diagnosis was obtained.

One of the important obstacles in this study was the patients who were withdrawn or lost to follow-up. It is evident that patients who were receiving high-dose treatment could not strictly adhered to the treatment protocol as patients who were treated with CHOP chemotherapy. This could be explained mainly from the more complicated pattern of treatment administration in the high-dose therapy and also some side effects such as, nausea and vomiting. For example, to receive each course of ESHAP therapy, the patients needed to be admitted in the hospital for 5 days, compared to CHOP therapy in which the treatment can be given simply at the outpatient department. Although the pattern of treatment had been thoroughly explained to the patients before

entering the study, a portion of the patients still could not strictly adhere to the treatment plan.

It is noteworthy that our study had measured the reliabilty in the interpretation of the CT scan of the abdomen which was one of the mainstay procedure employed for determining the tumor response in the patients after receiving the assigned treatment. The degree of agreement (K coefficient) of the two radiologists indepedently blindly assessed a randomly selected CT of the patients was 0.91 which indicated a very high reliability in the interpretation of this test in the current study.

This study was only a part of the full treatment protocol. The more significant therapeutic outcomes lie on the long-term survival of the patients which is now being conducted. Comparison of the overall and event-free survival of the patients in the two treatment arms will reflect vividly the more novel therapy. Considering the very high-cost of the high-dose therapy, especially in the amidst of the economic crisis faced by the country, the economic appraisal of this study is of utmost important.