Administration of MINE Protocol in Untreated Patients with Intermediate and High Grade Non-Hodgkin's Lymphoma

İsmet Aydoğdu[1], MD, Haluk Koç[2], MD, Osman İlhan[2], MD, Günhan Gürman[2], MD, Hamdi Akan[2], MD, Meral Beksaç[2], MD, Nahide Konuk[2], MD, Akın Uysal[2], MD

In recent years, more effective and less toxic treatment protocols have been developed to rise cure rates in intermediate and high grade non-Hodgkin's lymphoma (NHL). This study was undertaken to investigate the efficacy and toxicity of MINE (ifosfamide, mesna, mitoxantrone and etoposide) combination chemotherapy in patients with intermediate and high grade non-Hodgkin's lymphoma. Twenty-one patients (16 male, 5 female; aged between 26 and 70 years) with non-Hodgkin's lymphoma were included in the study. An overall response rate of 73% and complete response rate of 56% were achieved and survival rate for responding patients was 80% at 48th month. Side effects including mild myelosuppression, nausea-vomiting, and alopecia were observed. MINE combination seems to be effective and well tolerated without significant toxicity as a first-line therapy in patients with intermediate or high grade NHL. [Journal of Turgut Özal Medical Center 1997;4(1):59-62]

***Key Words**: Non-Hodgkin's lymphoma, combination chemotherapy*

Orta ve yüksek malignite eğilimli tedavi edilmemiş non-Hodgkin lenfomalarda MİNE protokolü uygulaması

Son yıllarda, orta ve yüksek malignite eğilimli non-Hodgkin lenfomalarda (NHL) etkili ve az toksik olan kemoterapi protokolleri kür oranını artırmak amacı ile geliştirilmiştir. Bu çalışma MİNE protokolünün NHL'daki etkinliğini araştırmak amacı ile yapılmıştır. Çalışmaya 16'sı erkek, 5'i kadın olmak üzere, yaşları 26-70 arasında değişen toplam 21 hasta alınmıştır. Hastaların %56'sında tam remisyon elde edilmiş olup, objektif yanıt %73 idi. Tedavi sırasında ılımlı myelosupresyon, bulantı, kusma ve alopesi dışında önemli ağırlıkta yan etki gözlenmedi. Bu çalışma NHL'da MİNE protokolünün, önemli bir yan etkisi olmaksızın, etkili olabilecek bir tedavi seçeneği oluşturduğunu göstermektedir. [Turgut Özal Tıp Merkezi Dergisi 1997;4(1):59-62]

***Anahtar Kelimeler**: Non-Hodgkin lenfoma, kombinasyon tedavisi*

Intermediate and high grade non-Hodgkin's lymphomas (NHL) are curable neoplasms. Cure can be achieved in approximately 45 percent of patients with disseminated intermediate or high-grade NHL with combination chemotherapy (1). Durable remissions have been achieved in an increasing proportion of patients with aggressive non-Hodgkin's lymphomas (NHL) and evidences suggest that remission rates and survival may be further improved by using intensive chemotherapeutic regimens (2).

Ifosfamide, an analogue of cyclophosphamide, has been shown to produce responses in lymphomas

[1] İnönü University School of Medicine Department of Hematology, Malatya
[2] Ankara University School of Medicine Department of Hematology, İbn-i Sina Hospital, Ankara

even in patients who were resistant to treatment with cyclophosphamide (3). On the other hand, mitoxantrone, an anthracenedione, has also been effective in a variety of lymphomas and, particularly, in patients who have been considered to be refractory to first-line treatment (4). Recently, combination of ifosfamide, mesna, mitoxantrone and etoposide (MINE) were used as a salvage regimen in the treatment of intermediate and high grade NHL (5).

The present study was designed to investigate the efficacy and toxicity of MINE regimen in previously untreated patients with intermediate and high grade NHL.

PATIENTS AND METHODS

Eligibility criteria : This study was performed as a cooperative study at the Hematology Departments of Ankara and İnönü Universities Medical Schools between May, 1992 and June, 1996. Twenty-one previously untreated patients with intermediate and high grade NHL were included in this study. Eligibility criteria were: 1- Patient's age; patients between the age of 18 and 70 years were selected for the study, 2-Diagnosis; confirmed diagnosis of intermediate or high grade NHL, stage II-IV according to the Ann Arbor staging system was sought, 3- Normal cardiac, hepatic and renal function, performance status of the patients according to ECOG criteria between 0 and 3. Of the 21 patients enrolled, 18 patients fulfilled the including criteria.

Patient characteristics : Their ages ranged from 26 to 70 (median 46.4) years and 16 of them were male, others were female. There were two patients in stage II, nine patients in stage III, and ten patients in stage IV. Among those patients with stage IV, 4 patients had bone marrow involvement (Table 1).

Chemotherapy regimen : The regimen consisted of mitoxantrone 12 mg/m^2 on one day, ifosfamide 1.33 gr/m^2, eight hourly infusion, on days 1 to 3, mesna 1.33 gr/m^2 on days 1 to 3, etoposide 65 mg/m^2 on days 1 to 3. This regimen was given six courses with 28 days between each course.

Table 1. Main clinical characteristics of patients

Total patients	21
Age (years) median	46.4
(Range)	26-70
Sex M/F	16/5
Histology	
Intermediate (%)	12 (57)
High (%)	9 (43)
Stage	
II (%)	2 (9)
III (%)	9 (43)
IV (%)	10 (48)
B symptoms (%)	15 (71)
LDH levels	
> 500 U/L (%)	7 (33)
< 500 U/L (%)	14 (67)
Bone marrow involvement	4 (19)

Criteria for response : Complete remission (CR) was defined as disappearance of tumor mass with a normal complete blood count in symptom-free patients. Partial remission (PR) was indicated in patients with tumor mass reduction of more than 50 % or significant tumor regression but incomplete recovery of blood counts (i.e. a platelet count less than 100.000/mm^3 and granulocyte count less than 1.000/mm^3). No response or a response less than PR after two courses of treatment was considered as stable disease. Disease progression (P) was indicated by the appearance of new lesions or by a 25% increase in the size of preexisting lesions. Toxicity has been classified according to the World Health Organization (WHO) criteria (6).

RESULTS

Response to treatment : Eighteen of the 21 patients completed therapy and were evaluated for response and toxicity. 3 of 21 patients were excluded because of early death (D). Complete and partial remissions were achieved in 10 (56%) and 3 (17%) of 18 patients respectively, with an overall response rate of 73%. Five patients had disease progression; all died after replacement of the treatment with new regimens. Overall survival was 38% at 48th month (Figure 1). Median duration of follow-up for those patients who have responded to treatment was 32 months (6-48 months). Five patients relapsed between 6 to 24 months following PR (+6, +12, +16) and CR (+12, +24). Response to chemotherapy was the most important prognostic factor. The complete responders had higher survival rates than those without CR (log-rank p=0.00001)

(Figure 2). Since the patient groups are small, other parameters such as age, sex, LDH were not studied for statistical analysis.

Toxicity : Leukopenia was the most common hematological toxicity, and two had life threatening toxicity of grade IV. One patient had gastrointestinal bleeding due to thrombocytopenia grade IV (Table 2). Partial alopecia was observed in 12 patients and 9 patients had nausea and vomiting. Dyspnea was observed in one patient during the ifosfamide infusion and died during second course of treatment. Cardiac functions were assessed and followed-up by echocardiography. Cardiac toxicity and hemorrhagic cystitis due to mitoxantrone (maximum dose of 72 mg/m^2) and ifosfamid were not observed.

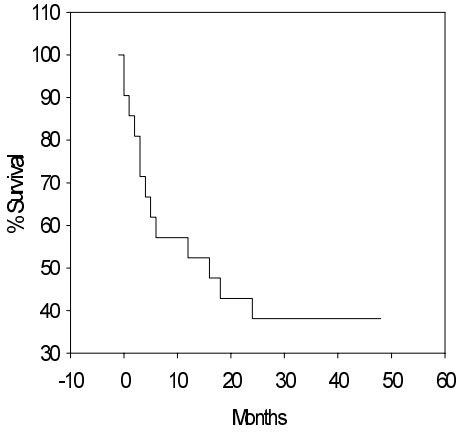

Figure 1. Overall survival in patients receiving MINE

DISCUSSION

The gold standard for first-line treatment in high grade NHL remains cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) combination chemotherapy (7-9). However, ideal treatment modality is not defined. With CHOP, the standard chemotherapy protocol of the last decade, complete remission was obtained in 50-60 percent of patients with high grade NHL (7,8). However, approximately half of these had poor prognosis and patients will eventually relapse. The more aggressive regimens gave better results than the CHOP regimen in patients with intermediate or high grade NHL (10-12). On the other hand, Fisher et al. have reported that the most aggressive regimens were not superior to CHOP (13).

MINE may be used as a potent salvage regimen (5,14). In this trial we tested the combination of MINE as a first-line therapy for aggressive non-Hodgkin's lymphoma. The main reasons for MINE application are to improve the survival and reduce

Table 2. Toxicity of the MINE treatment

	WHO Criteria				
Side effects	**0**	**1**	**2**	**3**	**4**
Anemia	15	2	3	1	-
Leukopenia	12	4	2	1	2
Thrombocytopenia	17	2	1	-	1
Nausea and vomiting	12	5	4	-	-
Alopecia	9	7	5	-	-
Hepatic toxicity	17	3	1	-	-
Dyspnea	20	-	-	1	-

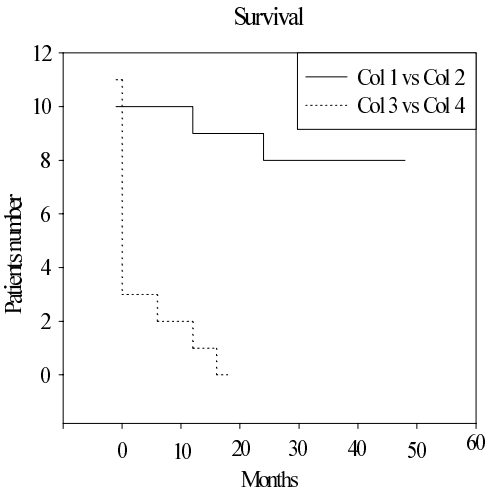

Figure 2. Overall survival according to the response

the toxicity. Ifosfamide and mitoxantrone are two of the most active single agents in the salvage treatment of NHL (3,4). A response rate of 82.5% was reported in previously untreated patients with NHL receiving combination chemotherapy including mitoxantrone (15). Combination of mitoxantrone, etoposide and ifosfamid regimen have been tested in patients with relapsed or aggressive NHL. CR was 42% in this study and overall

response rate was 60% (14). In another study, overall response rate was 75% in relapsed or refractory patients with aggressive NHL (16). Four out of seven previously untreated patients with intermediate or high grade NHL was achieved CR in a further study (17). Our study was performed in previously untreated patients with aggressive NHL. A complete response rate of 56% and overall response rate of 73% were documented in our patient population. Overall survival rate for responding patients was 80%. It seemed that the most important prognostic factor was response to chemotherapy.

Hematological and gastrointestinal side effects seen in this study were predictable and manageable. A major disadvantage of ifosfamide is the genitourinary toxicity. In our cases these side effect especially urothelial toxic effect of ifosfamide, was not observed. Prolonged infusion, hydration with diuresis concomitant administration of mesna may be an explanation for this result. One patient developed an anaphylactic type dyspnea during his first and second course of therapy. This toxicity appeared to be related to ifosfamide administration. Mitoxantrone was well tolerated without significant cardiac toxicity and can be used in the treatment of patients and patients having the risk of carditoxicity instead of doxorubicin.

Our results indicate that MINE treatment may be considered as an alternative first-line regimen, and since its side effects are quite tolerable, it may be a good alternative to doxorubicin containing combinations. In conclusion, larger patient numbers and longer follow-up are necessary to evaluate the final value of this regimen in the treatment of intermediate and high grade NHL.

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Correspondence address : İsmet AYDOĞDU, MD
İnönü University School of Medicine
Department of Haematology
44069 MALATYA