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MESNA/IFOSFAMIDE, MITOXANTRONE, ETOPOSIDE, BLEOMYCIN, VINCRISTINE, PREDNISONE (MINE-BOP) COMBINATION CHEMOTHERAPY IN THE TREATMENT OF REFRACTORY AND RELAPSED NON-HODGKIN'S LYMPHOMA

DİLEK DİNÇOL, FİKRİ İÇLİ, HANDAN KARAOĞUZ, FİLİZ ÇAY, ALİ ARICAN, AHMET DEMİRKAZIK and HAKAN AKBULUT

Twenty-one consecutive patients with refractory or relapsed non-Hodgkin's lymphomas were treated with a novel combination chemotherapy (MINE-BOP), comprising myelosuppressive (ifosfamide, mitoxantrone, etoposide) and non-myelosupressive (bleomycin, vincristine and prednisone) drugs. Median age of the patients was 42 years and all had intermediate or high-grade lymphoma. Fifteen patients had refractory disease. All patients had previously been treated with one or two regimens, containing anthracyclines. In all cases the duration between the last chemotherapy and the MINE-BOP regimen was shorter than 12 months. Response rate was 57% with 33% complete remission (CR). Median disease-free and overall survivals were 7 and 10 months respectively. The serum LDH level was the only significant prognostic factor in this study. The toxicity of this regimen was moderate with 24% of febrile neutropenia and 9% of microscopic hematuria. Toxic death due to febrile neutropenia was observed in one patient who had bone marrow involvement. To conclude, the addition of non-myelosuppressive drugs to the chemotherapy regimen and shortening the interval between the application of cytotoxic drugs as used in the present study did not show any improvement of response and survival in this group of patients.

Combination chemotherapy gives a cure rate of 30–40% in agressive lymphomas (1). On the other hand, the success of salvage chemotherapy in patients without complete remission (CR) with first-line chemotherapy or relapsed after first CR has been disappointing. CR rates with many different salvage chemotherapy regimens have ranged from 10% to 40% and the duration of response have been relatively short (2–4).

Ifosfamide is an oxazaphosphorine analogue of cyclophosphamide. Since it did not show any evidence of cross resistance with cyclophosphamide, it has been widely used in the salvage treatment of lymphomas. Cabanillas reported a response rate of 56% with mesna/ifosfamide/mitoxantrone/etoposide (MINE) combination treatment (5). The aim of the present study was to achieve higher response rates and longer durable CR by addition of non-myelosuppressive drugs to MINE regimen on the 14th day of treatment.

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From Ankara University, School of Medicine, İbni Sina Hospital, Section of Medical Oncology, Ankara (all authors), Turkey.
Correspondence to: Dr Dilek Dinçol, Ankara Üniversitesi İbni Sina Hastanesi, Tibbi Onkoloji Bilim Dali, TR-06100 Ankara, Turkey.

Material and Methods

Patient eligibility. Twenty-one patients with refractory or relapsing non-Hodgkin's lymphoma (NHL) were entered to this prospective trial. Also patients who had responded to first-line chemotherapy with partial remission (PR) and who showed no signs of further cytoreduction

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Table 1

Patient characteristics

No. of patients	21
Age	
median (range)	42 (15–67)
Sex (M/F)	11/10
Histology	
Diffuse small cleaved cell	5
Diffuse mixed small and large cell	6
Diffuse large cell	7
Immunoblastic	3
Stage	
I	1
II	7
III	6
IV	7
Symptoms	
A	8
B	13
Performance status (ECOG)	
0–1	13
2–4	8
Serum LDH level	
Normal	7
High	13
Undetermined	1
Disease status	
Relapsed	6
Refractory	15

after the first 4–6 courses of therapy were considered partially refractory to front-line management and were included in the study. Relapsed patients required disease-free survival (DFS) of less than 12 months with first-line chemotherapy. All patients had previously received one or two of the anthracycline-containing regimens, (one regimen ($n = 17$) and two ($n = 4$)). Likewise, three of the patients had undergone radiotherapy. Patients with low-grade, lymphoblastic or Burkitt's type lymphomas were excluded. Patients were eligible if they had normal renal and cardiac function. No exclusion was done as to age and performance status. The characteristics of the patients are shown in Table 1.

Chemotherapy program. The MINE-BOP regimen consisted of two distinct phases during each treatment cycle. A myelosuppressive phase of ifosfamide 1.3 g/m^2; mesna 1.3 g/m^2; etoposide 65 mg/m^2, on days 1–3 and mitoxantrone 20 mg on day 1 was followed by a non-myelosuppressive phase with bleomycin 15 mg/m^2; vincristine 2 mg, on day 14 and prednisone 40 mg/m^2, taken orally on days 14 through 21. The treatment was repeated every three weeks. In case of delayed recovery of bone marrow, the treatment was postponed untill the hematological parameters reached normal values. No dose reduction was done in the subsequent courses of the therapy because of myelo-response rates and survival. Evaluation of response followed WHO recommendations with physical examination before each treatment course and chest radiography, follow-up sonography and/or CT scan bimonthly (6). Other clinical examinations were performed if necessary. If progressive disease (PD) or lack of response was reported after the completion of 2 cycles, the treatment was changed to another salvage regimen, mostly to ESHAP (etoposide, cisplatinum, high dose cytosine arabinoside (Ara-C), and prednisone).

Statistical analysis. The univariate analysis between complete response and individual clinical features were analysed with Fisher's exact test. Overall survival (OS) of all patients was calculated from the beginning of MINE-BOP treatment to death or date last known alive, and disease-free survival of patients who achieved CR were estimated with the Kaplan-Meier method. Univariate associations between individual clinical features and overall survival were determined with the log-rank test. Independent factors associated with overall survival were identified in multivariate analysis by proportional hazard regression (7).

Results

All 21 patients were evaluable for response and toxicity of the treatment. CR was achieved in 7 patients (33%), and PR in 5 (24%), with a response rate of 57%. One CR was obtained after additional involved-field radiotherapy. The response rates of patients according to the stage, performance status, LDH and disease status are shown in Table 2. Only LDH level was found as a significant factor which affects the CR rate and overall survival ($p = 0.0223$ and $p = 0.0059$ respectively) and proved to be an independent prognostic factor of OS ($p = 0.0152$). Six patients relapsed during 25 months of follow-up. Median disease-free survival was 7 months (range 4–15 months). Ten of the

Table 2

Response rates according to prognostic factors

Prognostic factors	CR	PR	NR
Stage			
1–2	2 (25%)	–	6 (75%)
3–4	5 (38%)	5 (38%)	3 (23%)
Performance status			
0–1	6 (46%)	2 (16%)	5 (38%)
2–4	1 (13%)	3 (37%)	4 (50%)
Serum LDH level*			
Normal	5 (72%)	1 (14%)	1 (14%)
High	2 (15%)	3 (23%)	8 (62%)
Disease status			
Relapsed	3 (50%)	2 (33%)	1 (17%)
Refractory	4 (27%)	3 (20%)	8 (53%)

Table 3

Toxicity

	n (%)
Non-hematological	
Nausea-vomiting	8 (38%)
Mucositis	3 (14%)
Microscopic hematuria	2 (9%)
Acute renal failure	1 (5%)
Diarrhea	1 (5%)
Hematological	
Neutropenia	13 (61%)
Fever (neutropenic)	5 (24%)
Thrombocytopenia	1 (5%)
Anemia	1 (5%)

patients with recurrent or unresponsive disease after MINE-BOP were treated with ESHAP and only 2 PRs were achieved. Median duration of survival was 10 months. All deaths were related to progressive disease, except one toxic death. The DFS and OS curves of patients are shown in the Figure. Of five patients who are still alive, only one is still in CR with disease-free survival of 10 months.

Treatment was given in an out-patient clinic. Almost one-fourth of the patients experienced febril neutropenia and one of them, who had bone marrow involvement, died of septicemia. Nephrotoxicity from this regimen was moderate with 9% of microscopical hematuria and one reversible acute renal failure in a 60-year-old patient with febril neutropenia. No cardiac toxicity was observed.

Discussion

The largest study of salvage therapy in lymphomas is methyl-GAG/ifosfamide/methotrexate/etoposide (MIME) regimen used at the M.D. Anderson Cancer Center (2). Of 208 patients treated with MIME, 24% achieved CR and the response rate was 60%. Following a long-term follow-up the authors concluded that 25% of the patients achieving CR were cured. However, these good results of MIME treatment could not be confirmed by the study of the Swedish Lymphoma Group (8). They obtained a response rate of 38%, and four of the five patients achieving CR relapsed and died within 3 months. Many other studies in which ifosfamide-containing regimens were used showed 20–70% response rates and 10–41% CR rates (1) and in some of them the median survival was reported to be between 10 and 19 months.

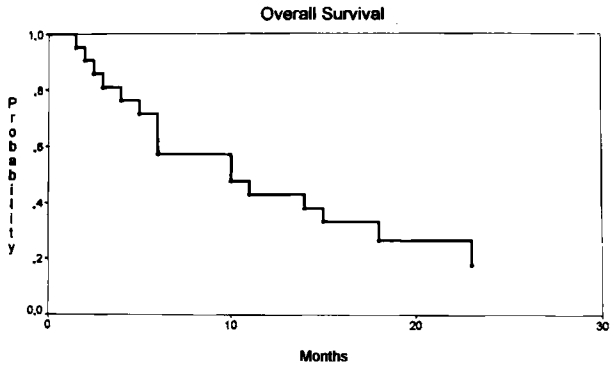

Figure. Overall survival calculated from the beginning of MINE-BOP for all patients.

The addition of non-myelosuppressive drugs to chemotherapy regimens could improve the results of salvage chemotherapies, especially in patients with rapidly progressive disease although it was shown of no use in front-line treatment (9). However, the response rate in this study (57%) was not superior to that of the original MINE study (56%) (5). Moreover, the duration of response was not longer than those reported with other salvage therapies in aggressive NHLs.

The evaluation of the patients according to the prognostic factors showed that only serum LDH level had an important effect on CR rate and OS. Clinical stage and performance status did not seem to affect the response to salvage chemotherapy ($p = 0.6556$ and $p = 0.1735$ respectively) in our study. One of the most important factors reported to determine the success of salvage chemotherapy is to achieve a long durable CR (longer than 12 months) with first-line chemotherapy. The duration of first CR was shorter than 12 months in all responding patients to front-line treatment in the present study and we did not find any difference of importance between the patients who achieved CR and those who did not during the front-line treatment in terms of response rate to salvage therapy ($p = 0.3543$).

Among the non-ifosfamide-containing salvage regimens, the results of the combination of cis-platinum and high-dose Ara-C have been encouraging (10). In our study, only two PRs were obtained with ESHAP in 10 patients who were refractory to MINE-BOP. This result is compatible with that by Johnson et al. (11) who found ESHAP combination ineffective in the heavily pretreated patients with lymphoma. However, Rodriguez et al. (12) reported 43% CR and 37% 2-year survival by sequential use of MINE and ESHAP. In the latter study, the patients who were refractory to a prior Ara-C/platinum regimen received only MINE and 18% of them achieved CR with an 18% 2-year survival. The best sequence of these combinations should be searched in a randomized study.

In conclusion, MINE-BOP regimen gave similar results when compared with other ifosfamide containing regimens with tolerable toxicity. More effective salvage therapies are necessary to prolong survival of the patients, especially those with bad prognostic factors, such as high serum LDH levels, and to cure some of them.

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