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METHYL-GAG, IFOSFAMIDE, METHOTREXATE AND ETOPOSIDE (MIME) AS SALVAGE THERAPY FOR NON-HODGKIN'S LYMPHOMAS

A Swedish national prospective study

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One hundred and two patients with recurrent or refractory non-Hodgkin's lymphoma (NHL) were treated with MIME (methyl-GAG, ifosfamide, methotrexate, etoposide) in accordance with a prospective protocol. Of 75 patients with high-grade malignant NHL (median age 57 years, range 21–79), 15 patients (20%) obtained a complete response (CR) and 27 patients (36%) a partial remission (PR), giving an overall response rate of 56%. The remissions were usually short when not consolidated with ABMT or radiotherapy. The probability of progression-free survival after 2 years was 13%, and the cause-specific survival was 23%. Of 27 patients with low-grade NHL (median age 46 years, range 37–86), 7% had a CR and 37% a PR giving a response rate of 44%. The remissions were again usually short when not consolidated, and the probability of progression-free survival at two years was 11%, and the cause-specific survival 26%. The main toxicity was hematological with septicemia in 20% of the patients and other severe infections in 19%. Fifteen patients (11 high-grade NHL and 4 low-grade NHL) were consolidated with high-dose therapy followed by ABMT, of whom 6 are in continuous CR. We conclude that MIME can induce remissions in NHL patients, and that the remission rates are comparable with those of many other salvage regimens. The remissions are, however, generally of short duration and need consolidation. There was considerable toxicity therefore patients not suitable for ABMT preferably should be treated with less toxic salvage regimens.

Patients with primarily refractory or recurrent high-grade malignant non-Hodgkin's lymphomas (NHL) generally have a poor prognosis. After failure of the first-line chemotherapy regimen, only a small proportion of patients achieve a durable second complete remission. One of the promising salvage regimens was MIME (methyl-GAG, ifosfamide, methotrexate, etoposide), originally developed by Cabanillas who reported a 60% response rate (1). When all MIME-treated NHL patients in Sweden between October 1984 and July 1988 were retrospectively analyzed, a response rate (complete and partial remissions) of 47% was observed. The remissions were usually very short (2). These apparently inferior results in the Swedish study could well be explained by the population-based nature in contrast to the probably more selective hospital-based material reported by Cabanillas et al. (1). The results inititated a nation-wide, prospective study of MIME as salvage regimen for high-grade malignant NHL. The aim was to investigate the antitumoral activity and the toxicity of the regimen when used as second-line therapy in the entire Swedish population. Also, it was a requirement from the Swedish Medical Products Agency that a prospective trial be performed in order to gain availability to the two non-registered drugs, methyl-GAG and ifosfamide.

In the retrospective study it was also found that patients with low-grade malignant NHL refractory to combination chemotherapy regimens containing doxorubicin obtained

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remissions with the MIME regimen (2). These patients were thus included in the prospective study in order to accurately assess remission rates in this group of patients also.

Material and Methods

Study design

All six health care regions in Sweden participated in the study, and patients were entered between July 1988 and December 1990. The clinician was responsibe for registration in the study and this might explain the relatively low number of patients included as compared with the number expected. The patients were registered and information about previous therapy and response was recorded. The MIME regimen was recommended as second-line therapy for all patients with primarily refractory or relapsing high-grade NHL, provided the patient was fit enough to tolerate further combination chemotherapy. Patients with relapsing or refractory NHL who were eligible for the Parma study (3) were excluded from the protocol but could receive MIME as third-line therapy. In patients with low-grade malignant NHL, the question of whether MIME treatment was appropriate was left to the discretion of the clinician. The patients should, however, have received and failed a doxorubicin-containing regimen.

For classification of NHL, the Kiel classification was used (4). The diffuse centroblastic/centrocytic (CB/CC) lymphomas were included among the high-grade NHL (5). The response was measured after every second cycle of MIME by performing the same examinations as those found to be pathological before initiation of MIME treatment. Complete response (CR) was defined as disappearance of all known disease and partial remission (PR) as disappearance of at least 50% of all disease. Patients obtaining CR or 'good' PR were recommended high-dose chemotherapy with bone-marrow rescue (ABMT), provided they were fit enough and below the age of 55. The ABMT was performed in accordance with local therapy protocols at three different centers, and details about the ABMT procedure were not stated in the program. If AMBT was not performed, it was recommended that CR patients be treated with two additional cycles of MIME after obtaining CR.

The MIME regimen

The MIME regimen consisted of infusion (1 h) of methyl-GAG (500 mg/m^2) on day 1 and day 14, infusion of ifosfamide (1 000 mg/m^2) on days 1–5, infusion of etoposide (100 mg/m^2) on days 1–3 and bolus injection of methotrexate (30 mg/m^2) on day 3. To prevent hemorrhagic cystitis, all patients received uromitexan (200 mg/m^2) at 0, 4 and 8 h, respectively, after the infusion of ifosfamide. The cycles were repeated every third week provided the peripheral blood counts were normalized. If the absolute leucocyte count was between 3 and 3.9 × 10^9/1 or the thrombocyte count between 75 and 100 × 10^9/1, the ifosfamide was given on days 1–4 only. If the absolute leucocyte count was between 2 and 2.9 × 10^9/1 or the thrombocyte count between 50 and 74 × 10^9/1, ifosfamide was given on days 1–3 and the etoposide and methotrexate dose treatment was reduced to 50%. If the absolute leucocyte count was $< 2.0 \times 10^9$/1 or the thrombocyte count $< 50 \times 10^9$/1, the treatment interval was prolonged by one week.

Table 1A

Histopathological diagnosis and response to MIME treatment in high-grade malignant NHL

	Total n (%)	CR n (%)	PR n (%)	PD n (%)
CB	29	7(24)	12(41)	10(35)
CB/CC, diffuse[1]	9	1	4	4
IB	7		3	4
LB	2	1		1
Transformed low-grade	7	3	2	2
NUD	21	3	6	12
Total	75	15(20)	27(36)	33(44)

Abbreviations: CB = centroblastic lymphoma, CB/CC = centroblastic/centrocytic lymphoma, IB = immunoblastic lymphoma, LB = lymphoblastic lymphoma, NUD = not classfied.
1) Included among clinically high-grade NHL (5).

Table 1B

Histopathological diagnosis and response to MIME treatment in low-grade malignant NHL

	Total n (%)	CR n (%)	PR n (%)	PD n (%)
CC	4		1	3
CLL	2			2
CB/CC, follicular	8		5	3
CB/CC, follicular and diffuse	4	1	1	2
IC	7	1	1	5
NUD	2		2	
Total	27	2(1)	10(37)	15(56)

Abbreviations: CC = centrocytic lymphoma, CLL = chronic lymphatic leukemia, CB/CC = centroblastic/centrocytic lymphoma, IC = immunocytic lymphoma, NUD = not classified.

Patients with high-grade malignant NHL

Seventy-five patients with high-grade malignant NHL were included in the study. The mean and median ages 55 and 57 years (range 21–79), respectively, and there was a

Table 2A

Results of MIME treatment in relation to response to previous therapy in patients with high-grade malignant NHL

	Total n (%)	CR n (%)	PR n (%)	PD n (%)
CR	34	6	14	14
PR	34	3	6	8
PD	9	2	2	5
⩾2 relapses	15	4	5	6
Total	75	15(20)	27(36)	33(44)

Table 2B

Results of MIME treatment in relation to response to previous therapy in patients with low-grade malignant NHL

	Total n (%)	CR n (%)	PR n (%)	PD n (%)
CR	2		1	1
PR	18	2	7	9
PD	3			3
⩾2 relapses	4		2	2
Total	27	2(7)	10(37)	15(56)

male predominance of 47 men to 28 women. The histopathological diagnoses are presented in Table 1A. All patients had received at least one combination regimen containing doxorubicin, mainly CHOP or MACOP-B. The reasons for starting MIME treatment are presented in Table 2A. In all patients with the exception of three, the responses were evaluated by radiological methods, such as computed tomography and ultrasonography, or with bone-marrow examination.

Patients with low-grade malignant NHL

Twenty-seven patients (17 men and 10 women) with low-grade malignant NHL were included. The mean and median ages were 56 and 46 (range 37–86) years, respectively. The histopathological diagnoses are presented in Table 1B. All patients had received at least one doxorubicin-containing regimen prior to MIME treatment. The reasons for starting MIME treatment are presented in Table 2B. In all cases with the exception of four, the responses were evaluated using the radiological methods or bone-marrow examination.

Statistical methods

Life table survival analysis with the log-rank significance test was performed (Statistica 3b). Progression-free survival and cause-specific survival were analyzed. Progression-free survival was defined as the time from starting MIME treatment until disease progression was established.

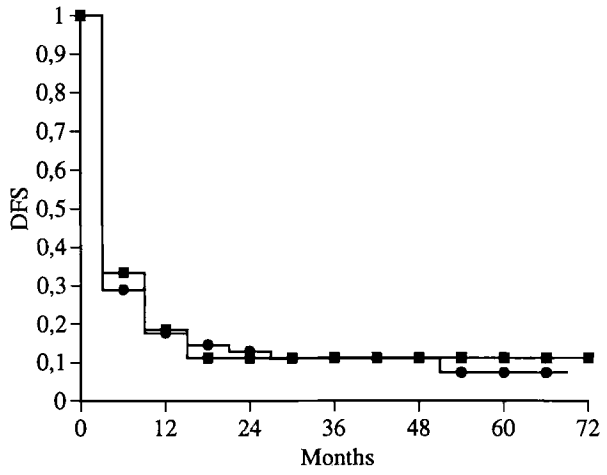

Fig. 1. Disease-free survival for patients with high grade and low grade non-Hodgkin lymphoma. —●—: High-grade; —■—: Low-grade.

In the cause-specific survival calculations, patients whoe died from causes other than NHL were excluded from the population at risk after their death, provided they were in CR, whereas patients with known NHL were considered as having died from NHL irrespective of the actual cause of death. The survival time was calculated from the start of MIME treatment to death, or to the latest clinical control. All patients were followed until death or until the last clinical control before October 1994, median 60 (33–72) months for living patients.

Results

High-grade malignant NHL

Fifteen patients (20%) obtained a CR and 27 (36%) a PR, giving a response rate of 56%. Responses to MIME treatment in relation to the results of previous therapy are presented in Table 2A. There were no differences in response rates in relation to results of previous chemotherapy. The responses were consolidated with ABMT in 11 patients and with radiotherapy in 2 patients. The duration of responses was generally short. For complete responders, including consolidated patients, the median response duration was 11 months (range 2–66+) and for partial responders the median response duration was 5 months (2–50+) giving a probability of progression-free survival of 13% after 2 years (Fig. 1) and a cause-specific survival of 23% (Fig. 2). When consolidated patients were excluded, the median complete response duration was 6 months (range 2–52+) and the median partial response duration was 4 months (range 2–19). In unconsolidated patients the 2-year probabilities of progression-free survival and cause-specific survival were 2% and 14%, respectively. In fact, only one patient who did not receive and

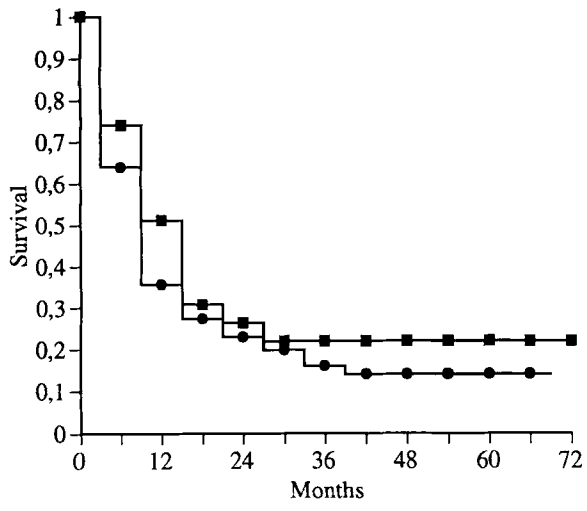

Fig. 2. Cause specific (lymphoma) survival for patients with high grade and low grade non-Hodgkin lymphoma. —●—: High-grade; —■—: Low-grade.

further treatment is alive and well, 52 months after the start of MIME treatment. Of all patients included in the study 6 are still alive and in CR, two after consolidation with ABMT, one after consolidation with radiotherapy and three who have received further chemotherapy and radiotherapy after failing MIME.

Since age was found to be an adverse prognostic factor in most studies, treatment results above and below the age of 60 were analyzed. The response rates were similar for both age groups with 22% CR and 34% PR in the younger and 18% CR and 38% PR in the older group. There were no significant differences in the outcome between young and old patients, or when either progression-free survival or cause-specific survival was analyzed ($p = 0.1$).

Low-grade malignant NHL

Two patients (7%) obtained CR and 10 (37%) PR, giving a response rate of 44%. The results of treatment are presented in Table 1B and 2B. The responses were consolidated with ABMT in three patients. The median response duration was 8 months (range 2–72+) for all patients and 6 months (range 2–12) for unconsolidated patients. The probability of disease-free survival and cause-specific survival after 2 years was 11% (Fig. 1) and 26% (Fig. 2) respectively. When consolidated patients were excluded, the probability of disease-free survival after 1 year was 0% and the probability of cause-specific survival after 2 years was 14%. There were no significant differences in disease-free survival of cause specific survival between low-grade and high-grade NHL, $p = 0.5$ and $p = 0.2$, respectively (Figs. 1 and 2).

Results of ABMT

Fifteen patients (11 high-grade and 4 low-grade malignant) were treated with high-dose therapy followed by ABMT. Of the high-grade malignant NHL patients, 6 obtained CR 4 PR and one obtained SD after MIME treatment. Before ABMT was performed, three of the partial responders and the patient with SD were treated with involved-field radiotherapy and one partial responder was treated with two courses of CHOP. Six patients had a relapse 1–18 months after ABMT (median 6

Table 3

Toxicity in all MIME-treated patients

Toxic side effect	< 60 years (n = 60) n(%)	> 60 years (n = 42) n(%)
TWBC		
(1.0 – 2.0 × 10^9/l or PMN 0.1–1.0 × 10^9/l)	13(22)	10(24)
(< 1.0 × 10^9/l or PMN < 0.1 × 10^9/l)	25(42)	23(55)
B-Thrombocytes (20–50 × 10^9/l)	8(13)	7(17)
B-Thrombocytes (< 20 × 10^9/l)	9(15)	8(19)
Septicemia	7(12)	14(33)
Other severe infection	11(18)	8(19)
Fever during or after treatment without infection	4(7)	5(12)
Mucositis (grade II–III)	9(15)	8(19)
Abdominal pain, diarrohea	8(13)	5(12)
Melena, gastric ulcer, bowel performation	0	3(7)
Circumoral stitches	4(7)	0
Muscular weakness	4(7)	4(10)
Pain and stitches in arms and legs	2	1
Nose bleeding	1	

Abbreviations: TWBC = total white blood cell count, PMN = polymorphonuclear cells.

months) and died of progressive lymphoma. Two patients died of infections during CR 4 and 9 months after ABMT, respectively, one patient died of myelodysplastic syndrome 60 months after ABMT and two patients are in continuous CR, 48 and 54 months after ABMT, respectively.

Four patients with low-grade malignant NHL were treated with BMT (one syngeneic and three autologous). The response to MIME treatment was CR in one patient, PR in two and SD in one. All patients are in continuous CR, 44–63 months after ABMT.

Toxicity

Pronounced hematological toxicity with leucopenia was observed in 70% of the patients. Twenty-one patients had septicemia and 19 had other severe infections related to the leucopenia. Thrombocytopenia was less common, with only three patients with bleeding associated with it (melena, ulcus and nose bleeding). Severe leukopenia and septicemia were more common in patients above the age of 60 (Table 3). In 10 patients only, it was possible to give the treatment as scheduled, whereas in all the other instances, dose reductions or prolongation of intervals due to toxic side effects (mainly leukopenia) were present.

There were 4 possible treatment-related deaths: 2 patients (66 and 73 years old respectively) died of 'deterioration' 1 week after their last (5th and 10th, respectively) course without evidence of disease at autopsy, one patient (72 years old), with a previous history of congestive heart disease, died of congestive heart failure after 1 day of MIME treatment and one patient (64 years old) died of bronchopneumonia in association with leucopenia, 1 week after the first course. There were no cases of hypoglycemia, hypothetically related to methyl-GAG, and no cases of urinary bladder symptoms related to ifosfamide, indicating a good protection with uromitexan.

Discussion

When this study was initiated the most promising salvage regimens for recurrent and refractory NHL were those containing ifosfamide had etoposide, e.g. IMPV-16 and MIME with remission rates of about 60% and complete remission rates of about 25%. In addition, a retrospective analysis of all MIME-treated patients with NHL in Sweden indicated acceptable antitumoral activity with a 47% remission (2).

The overall remission rates (56%) and survival in this study are similar to most salvage regimens based on ifosfamide, cisplatin and etoposide (6, 7). The results appear, however, poorer than those reported with VIM ± B (etoposide, ifosfamide and methotrexate with or without bleomycin) (8) and DICE (dexametasone, ifosfamide, cisplatin, and etoposide) (9) with 87% and 77% remission rates, respectively. Another regimen with apparently better results is the recently described EPOCH regimen (etoposide, vincristine, doxorubicin, cyclophosphamide and prednisone) with 96-h infusion of etoposide, vincristine and doxorubicin with a reported response rate of 87% (10). However, a number of aspects must be considered before any conclusions can be drawn about the relative activity of various regimens. None of the studies are controlled, they all contain a relatively limited number of patients and the great importance of patient selection on treatment results is usually entirely unrecognized.

In the present study patients were included and treated at a number of different oncolgical and hematological clinics throughout the country and virtually no selection of 'the youngest and fittest' was made. This is reflected in the high median age of the treated patients, almost 10 years higher than that in most other studies. In this context, the DICE study also has a high median age (10).

Another possible reason for the poor survival rate in this material could be a tendency towards palliative intention with the treatment, particularly in elderly patients, knowing that the possibility of cure is very low. This might have led to more pronounced dose reductions, and thus inferior treatment results. There were, however, no differences in remission rates between patients younger and older than 60 years in this study, but the toxicity was more pronounced and notably all four possibly treatment-related deaths occurred in patients above 60 years.

Less toxic combinations might be considered in patients not suitable for ABMT, e.g. single-drug idarubicin which gave 43% remission rate in a study of 31 patients with relapsed and refractory NHL (11), or single-drug methyl-GAG which gave remissions in 5/10 patients with relapsed or refractory NHL with AIDS (12). Another potentially less toxic regimen recently described in LEMP (lomustine, etoposide, methotrexate and prednisone), which, according to authors, gave 17 remissions in 22 treated patients (13) with minimal toxicity.

There was no difference in response to MIME in relation to response to previous therapy. Most other studies of salvage regimens report a better response rate in patients who at some time have responded to chemotherapy. The reason for this difference is not known but the indications are that patients who are 'apparently chemotherapy resistent' might also respond.

The literature dealing with treatment of patients with low-grade malignant NHL who have failed a doxorubicin-containing regimen is sparse. Recently, new purine analogues have been reported to induce remissions in 50–60% of pretreated patients (14).

We conclude that, when used for relapsed and refractory non-Hodgkin lymphomas the MIME regimen induces remissions that are not apparently inferior to other presently used regimens. The remissions are usually very short, therefore the regimen can be used mainly to select patients suitable for ABMT. In patients where subsequent ABMT

is not possible, the regimen is mainly palliative with only a minor chance of long-lasting remissions.

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