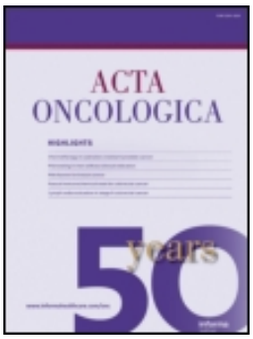

Acta Oncologica

ISSN: 0284-186X (Print) 1651-226X (Online) Journal homepage: informahealthcare.com/journals/ionc20

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To cite this article: G. Enblad, B. Glimelius, H. Hagberg & C. Lindemalm (1990) Methyl-Gag, Ifosfamide, Methotrexate and Etoposide (Mime) as Salvage Therapy for Hodgkin's Disease and Non-Hodgkin's Lymphoma, Acta Oncologica, 29:3, 297-301, DOI: 10.3109/02841869009090001

To link to this article: https://doi.org/10.3109/02841869009090001

Published online: 08 Jul 2009.

Acta Oncologica 29 (1990) Fasc. 3

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

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Abstract

One hundred and three patients with recurrent or refractory Hodgkin's disease (HD) or non-Hodgkin's lymphoma (NHL) treated with MIME (methyl-GAG, ifosfamide, methotrexate, etoposide) were retrospectively studied. Thirty-seven of the 44 patients with HD, 34/47 with high-grade malignant and 9/12 with low-grade malignant NHL were evaluable for response. Of the 37 evaluable patients with HD, 16 (43%) achieved complete remission (CR) and 4 partial remission (PR), giving a total response rate of 54%. Of the 34 evaluable patients with high-grade NHL, 5 achieved CR and 8 PR, giving a response rate of 38%. Of 9 evaluable patients with low-grade NHL, 2 achieved CR. The main toxicity was leukopenia, trombocytopenia and infections. Twenty-six per cent of the patients developed septicaemia, which was fatal in 6 cases (6%). We conclude that MIME as salvage regimen can induce complete remissions in lymphoma patients, particularly in HD with previous heavy treatment, and that it is relatively well tolerated.

Key words: Hodgkin's disease, non-Hodgkin's lymphoma, salvage therapy, methyl-GAG, ifosfamide, etoposide.

Patients with Hodgkin's disease (HD) or high-grade malignant non-Hodgkin's lymphoma (NHL) who fail to respond to first-line chemotherapy or who relapse after having obtained complete (CR) or partial remission (PR), have a poor prognosis. A number of chemotherapeutic combinations have been developed with variable, though usually disappointing results (1–3). Only a small proportion of these patients has attained long-lasting remissions. A combination designated MIME (metyl-GAG, ifosfamide, methotrexate and etoposide) has recently been shown to give a relatively high proportion of responding patients in both HD (4) and in high-grade malignant NHL (5), but there is no literature confirming these initial results reported from the group at MD Anderson Hospital, Houston, USA.

MIME has been used in Sweden as a salvage regimen for malignant lymphomas since the end of 1984. The aim of this retrospective study was to evaluate therapeutic effect and toxicity of the MIME-regimen, when treatment was given on a routine basis in a great number of hospitals.

Material and Methods

Since the combination contains 3 non-registered drugs, the number of patients treated with MIME at each hospital could be identified via the Swedish National Board of Health and Welfare, Department of Drugs. Between October 1984 and July 1988, 105 patients with HD and NHL were treated with MIME. The records of 103 patients could be traced and examined. The treatment was performed in 26 hospitals including all 9 Swedish university hospitals. All information about the medical history, the histopathological diagnosis, the side effects and the

Accepted for publication 15 May 1989.

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responses was collected from the patient records. In case there was any doubt about the treatment results, additional information was obtained from the responsible physician. In some cases, the radiograms were re-examined. All 103 patients were followed to death or to October 1988. Complete remission was defined as the disappearance of all evidence of disease and partial remission as more than a 50% reduction of disease. The histopathological diagnosis of NHL was made according to the Kiel classification (6). The diffuse centroblastic/centrocytic (CB/CC) lymphomas were included among the 'high-grade' malignant NHL (7).

Patient characteristics. Of the 103 MIME-treated patients, 44 patients had HD (15 women and 29 men), median age 36 years (range 18–77) (Table 1). All these patients had previously been treated with both MOPP (mustine, vincristine, procarbazine and prednisone) and ABVD (doxorubicin, bleomycin, vinblastine and DTIC), and either failed to respond or relapsed after having achieved a complete remission (CR).

Forty-seven patients had high-grade malignant NHL (15 women and 32 men), median age 49 years (range 23–77) (Table 1). Three patients received MIME but not as salvage therapy, and were therefore not considered in the response evaluations. One of these patients had an acute myocardial infarction on day 1 of MACOP-B (methotrexate with leucovorin rescue, doxorubicin, cyclophosphamide, vincristine, prednisone and bleomycin) (8) and was afterwards treated with MIME and two patients received MIME as consolidation before high-dose chemotherapy requiring bone marrow rescue (ABMT). The remaining 44 patients had previously been treated with various chemotherapy combinations, all including doxorubicin; mainly CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) (9) MACOP-B or a modification of MACOP-B also including etoposide and ara-C. All had either failed to achieve CR on initial therapy or relapsed after having been in CR.

Twelve patients with low-grade malignant NHL, all men, median age 59 years (range 45–70) (Table 1), were all treated with MIME due to treatment-refractory disease, and had received a number of cytostatic combinations, at least one including an antracycline, mainly CHOP or a combination of etoposide, mitoxantrone, ara-C and prednisone.

Information about performance status, extent of the disease and presence or absence of systemic symptoms were not available in every patient at the time of MIME treatment initiation, and no exact figures can be given. Of patients thoroughly investigated and with the information available in the clinical records, almost all patients had advanced disease (stage III or IV). Between 40 and 50% had extranodal engagement and the same proportion had systemic symptoms with a tendency to higher figures in NHL compared to HD.

Table 1

Histopathological diagnosis in all patients treated with MIME and in patients considered evaluable for response

Hodgkin's disease	No. of patients	Evaluable
Nodular sclerosis	26	22
Mixed cellularity	7	5
Lymphocytic predominance	2	2
Lymphocytic depletion	1	1
Unclassifiable	8	7
Total	44	37
Non-Hodgkin's lymphoma		
High-grade malignant		
CB	19	15
CB/CC, diffuse	4	2
IB	5	4
LB	2	2
T-cell	1	1
Transformed low-grade	7	4
Unclassifiable	9	6
Total	47	34
Low-grade malignant		
CLL	4	3
CC, small cell	1	0
CB/CC, follicular	1	1
CB/CC, follicular and diffuse	1	1
IC	1	0
Unclassifiable	4	4
Total	12	9

Abbreviations. CB = Centroblastic lymphoma, CB/CC = Centroblastic/centrocytic lymphoma, IB = Immunoblastic lymphoma, LB = Lymphoblastic lymphoma, CLL = Chronic lymphocytic leukemia, CC = Centrocytic lymphoma and IC = Immunocytic lymphoma.

Chemotherapy. The MIME regimen consisted of infusion (1 h) of methyl-GAG (500 mg/m^2) day 1 and 14, infusion (1 h) of ifosfamide (1 000 mg/m^2) days 1–5, infusion (1 h) of etoposide (100 mg/m^2) days 1–3 and bolus injection of methotrexate (30 mg/m^2) day 3. To prevent haemorrhagic cystitis, all patients received Uromitexan (200 mg/m^2) at 0, 4 and 8 h respectively after the infusion of ifosfamide. The cycle was repeated every third week provided that the peripheral blood counts were acceptable. If not, the treatment interval was prolonged to 4 weeks. Further interval prolongations and/or dose reductions due to haematological and other toxicities were performed by routine and varied between hospitals.

Results

Number of cycles given. A total of 388 cycles were given (range 1–9); 186 to patients with HD and 202 to patients with NHL. In 20 (20%) patients, MIME treatment was

terminated during or after the first treatment cycle (6 HD, 11 high-grade malignant and 3 low-grade malignant NHL). These patients were not considered evaluable for objective response but were evaluated with respect to toxicity. They received at most one cycle due to rapidly progressive disease in 17 cases (4 HD and 13 NHL), patient refusal in 2 cases (HD) and as consolidation before ABMT in one patient (NHL). Of the patients with rapidly progressive disease, 15 died within 3 months without receiving further cytostatic treatment, two patients received additional treatment; one died after 5 months and the other one is still alive, although not in CR.

Toxicity. Toxicity was evaluated in all 103 patients where MIME treatment was initiated (Table 2). Myelosuppression was the most common toxicity and occurred in the majority of the patients (peripheral blood counts were not regularly performed between treatment cycles and the exact proportion can thus not be estimated). Septicaemia was described in 39 instances (27 patients); in 6 patients it contributed to the patient's death. Fever for unknown reason during treatment or between cycles occurred in 19 patients. Abdominal pain, diarrhoea or intestinal atonia was described in 12 patients.

Response in Hodgkin's disease. Thirty-eight patients with HD received more than one cycle of MIME. One of these patients could not be evaluated for response since diffuse infiltration of the liver was the only known manifestation and no biopsy was performed. Thirty-seven patients with a median age of 36 years (range 18–73) were thus evaluable for response. Of these patients, 16 (43%) achieved CR and 4 PR; an overall response rate of 54% (Table 3). If all 44 patients with HD in whom MIME therapy was initiated, were considered, the total response rate was 45%. The median age of the responding patients was 35 years (range 23–73). There was no apparent difference in frequency of responses between patients with extranodal disease or with nodal disease only. Six patients attaining CR received ABMT as consolidation and two patients were consolidated with involved field radiotherapy. Three of the CR patients relapsed after 2.8 and 21 months respectively, the latter after ABMT. The other 13 patients are still in CR after 1–25 months of follow-up (median 3 months).

Table 2

Toxocity in 103 patients treated with MIME

Toxic effect	No. of patients	Percentage
Septicaemia	27 (39 episodes)	26
Other serious infection	6	6
Fever of unknown origin	19	18
Nausea	16	16
Mucositis	7	7
Abdominal pain, diarrhoea	12	12
Hematuria	3	3
Circumoral paresthesia	3	3
Muscular weakness	1	1

Table 3a

Effect of MIME-treatment in patients with Hodgkin's disease evaluable for response. Results are presented with respect to response to previous therapy

Response to first-line treatment	No. of patients	CR	PR	SD + PD
Failure	11	5(1*)	1	5
CR ≤ 12 months	4	3(3*)		1
CR > 12 months	4	2	1	1
CR + failure[1]	4			4
≥ 2 relapses	14	6(2*)	2	6
Total	37	16	4	17

Table 3b

Effect of MIME-treatment in patients with NHL evaluable for response. Results are presented with respect to previous therapy

Response to first-line treatment	No. of patients	CR	PR	SD + PD
High-grade malignant				
Failure	12	2	2	8
CR[2]	12	2	4	6
CR + failure[1]	5	1	1	3
≥ 2 relapses	5		1	4
Total	34	5	8	21
Low-grade malignant				
Failure	9	2(1*)		7

* Autologous bone marrow transplantation after achieving complete remission on MIME treatment.
1) CR on first-line treatment, failure on second-line treatment.
2) One patient had a duration of the first CR of more than one year.
Abbreviations: CR = complete remission, PR = partial remission, SD + PD = stationary or pregressive disease.

Response in high-grade malignant NHL. Thirty-six patients received more than one cycle of MIME. Two were excluded from the response evaluation; one patient had two cycles as consolidation before ABMT and one received 5 cycles as primary treatment. The remaining 34 patients were all evaluable for response. The median age of the evaluable patients was 49 years (range 23–77). Five (15%) patients achieved CR and 8 PR; total response rate 38% (median age of responding patients was 56 years, range 40–77). If also patients who received one cycle only were included, the total response rate was 30%. No consolidation therapy was given. Of the 5 complete responders 4 have relapsed and died within 3 months while one is still alive in CR after 3 months of follow-up. The patient who was treated with MIME as primary treatment achieved CR and has no evidence of disease 10 months after termination of treatment. Patients with nodal disease only tended to

respond more often but responses were also seen in patients with extranodal disease.

Response in low-grade malignant NHL. Of 9 patients evaluable for response, two patients obtained CR, with duration of 5+ and 18+ months respectively, the latter one consolidated with ABMT. The remaining 7 patients had stationary or progressive disease and 5 are dead (Table 3).

Discussion

The encouraging initial results reported with MIME as salvage therapy for malignant lymphomas (4, 5) contributed to an increasing popularity for MIME treatment in Sweden. In HD, besides MIME, CEP (CCNU, etoposide and prenimustine) (10) was recommended as 'third-line' therapy after failure on MOPP and ABVD (11). Initially, CEP was more often used than MIME, but with increasing experience of MIME, CEP was reserved for palliative purpose only. In NHL, MIME was initially used as a last resort only, but with increasing experience it became used as 'second-line' therapy. This development and the retrospective nature of the study must be kept in mind when evaluating the present report. The results give, however, an idea of the potential of the regimen, when used on a routine basis in a great number of hospitals.

The retrospective nature of the study made it difficult to accurately estimate some clinical features of the patients. The performance status of the patient was available in a few cases only. There were also difficulties in obtaining information about presence or absence of systemic symptoms before MIME treatment. MIME treatment was often initiated in immediate connection with failure of a previous cytostatic combination and it was not possible to retrospectively analyse whether systemic symptoms then were present. Many patients with far advanced disease were treated with MIME during this period and the extent of the disease were in those cases not thoroughly investigated.

Due to the fact that many patients were treated with MIME as a last resort, we decided to exclude patients who only received one treatment course from the objective response evaluations. Although this selection can be criticized, we believe that by excluding such patients a more fair idea of the anti-tumour effect of the regimen was achieved. However, figures for all patients starting on MIME-treatment are given as well.

Based upon the present results, MIME appears to have considerable antitumour effect in patients with Hodgkin's disease after failure on both MOPP and ABVD. The overall response rate of 54% is comparable to the 63% response rate reported by Hagemeister et al. (4), and the results of Reitz et al. (12) who reported CR in 4 out of 5 treated patients. The duration of the remissions obtained in the present study cannot be properly assessed, since the follow-up time is short. Furthermore, consolidation with ABMT had been performed in 6 patients. It is, however, promising that so far only 2 out of 10 patients with a CR not followed by ABMT have relapsed. The age of the patients did not seem to influence treatment outcome and there was no difference in median ages between the patients who achieved CR and those who did not.

In contrast to HD, the patients with NHL formed an heterogeneous group where the previous treatment, the accomplishment, and the intention to treat, varied considerably. The treatment results in this group are therefore hard to interpret. The response rate was, however, lower than in the study of Cabanillas et al. (5) who reported 60% response rate in NHL patients. In the present material, 38% (30%, if all patients were included) of the patients with high-grade malignant NHL responded, but the remissions were short. MIME seems, however, to be superior to IVM (ifosfamide, etoposide and methotrexate), which gave a response rate of 24% when used on a routine basis in a great number of Swedish hospitals as salvage regimen for high-grade malignant NHL (13). Two few patients with low-grade malignant NHL have been treated with MIME, to draw valid conclusions, although the two patients with CR (one consolidated with ABMT) are in continuous remission.

The toxicity of MIME appeared to be of moderate severity and well in accordance with previous reports of MIME (4, 5) and of other salvage regimens (2). Mild toxicity such as nausea and mild stomatitis is extremely difficult to evaluate retrospectively, since it is often not recorded. One can, however, assume that information about moderate to severe toxicity is seldom missing in the records, because medical care is often required.

In summary, we conclude that MIME is a salvage regimen which, with relatively moderate toxicity, can induce complete remissions in previously heavily treated lymphoma patients. MIME can be of importance in achieving a complete remission before ABMT both in patients with HD and NHL. Treatment results appear to be better in HD than in NHL, although the retrospective nature of the investigation does not allow firm conclusions.

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