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MIME COMBINATION CHEMOTHERAPY IN RECURRENT OR REFRACTORY LYMPHOPROLIFERATIVE MALIGNANCIES

A phase II study

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Abstract

Seventy-two patients with recurrent or refractory malignant lymphoproliferative diseases were treated with MIME combination chemotherapy (methyl-GAG, ifosfamide, methotrexate, etoposide) and concurrent mesna to prevent urothelial toxicity; 41 patients had high/intermediate-grade non-Hodgkin's lymphoma (NHL), 18 low-grade NHL/chronic lymphocytic leukemia (CLL), and 13 Hodgkin's disease (HD). The overall response rates were 56% in high/intermediate-grade NHL, 11% in low-grade NHL/CLL, and 69% in HD respectively. Median survival in the same 3 groups was 7, 2 and 10 months respectively. Neither previous type of response to chemotherapy nor previous amount of treatment predicted the outcome of MIME chemotherapy. Toxicity was modest, hemorrhagic cystitis did not occur, and only one therapy-related death occurred. Although MIME appears to be a safe treatment with considerable activity in recurrent or refractory lymphoproliferative disease very few patients become long-term survivors. However, MIME is well suited for remission induction in patients intended for subsequent autologous bone-marrow transplantation.

Key words: Lymphoma, recurrent, chemotherapy, MIME, non-Hodgkin's lymphoma, Hodgkin's disease

In general, patients with non-Hodgkin's lymphomas (NHL), recurring after standard first-line chemotherapy, or showing primary refractoriness to the same treatment, have shown a poor response to second-line chemotherapy. With single drugs overall response rates tend to be around 25–35% and most responses are brief and partial. Similar overall response rates of 30–32% have been observed with a number of chemotherapy combinations not containing ifosfamide (1, 2).

In five studies of ifosfamide + etoposide + methotrexate with or without methyl-GAG or bleomycin, overall response rates have been reported from 60–79% (3–7). Unfortunately, these results are contradicted by other studies of similar ifosfamide-containing regimens in which low overall response rates were noted from 18–36% (8–10).

The largest of the studies mentioned above was reported by Cabanillas et al. (4) and comprised 208 patients treated with the MIME regimen (methyl-GAG, ifosfamide, etoposide, methotrexate). An overall response rate of 60% was obtained. In comparison, the following overall response rates were found with the individual drugs included in MIME: 33% with VP-16 (11), 34% with ifosfamide (12, 13), 37% with methyl-GAG (14), and 41% with methotrexate (15).

Because of the uncertainty regarding the efficacy of ifosfamide-containing regimens we conducted a phase II study of MIME in patients with recurrent and refractory lymphoproliferative malignancies.

Material and Methods

Adult patients of any age with relapsing refractory lymphoproliferative malignancies were eligible for treatment with MIME, regardless of performance status or number of drugs given previously. There were 41 patients with NHL of high or intermediate grade (International Working Formulation), 9 patients with NHL of low grade, 9 patients with chronic lymphocytic leukemia (CLL), and 13 patients with Hodgkin's disease (HD). These 72 patients were evaluable for both response and toxicity. In

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Table 1

Response to MIME in relation to intial performance score

Performance status		NHL excluding low-grade cases			Low-grade NHL plus CLL			Hodgkin's disease		
Score	n	CR	PR	NC/PD	CR	PR	NC/PD	CR	PR	NC/PD
0	0	–	–	–	–	–	–	–	–	–
1	29	5	6	2/2	–	2	3/1	2	3	2/1
2	31	4	8	2/3	–	–	2/7	2	2	1/0
3	9	–	–	2/5	–	–	1/1	–	–	–
4	3	–	–	0/2	–	–	1/0	–	–	–
Total	72	9	14	6/12	0	2	7/9	4	5	3/1

Abbreviations: NHL = non-Hodgkin's lymphoma; CLL = chronic lymphocytic leukemia; CR = complete remission; PR = partial remission; NC = no change; PD = progressive disease.

addition, 5 patients with NHL had MIME as first-line chemotherapy (due to cardiac problems contraindicating anthracyclines), 3 patients with relapsing ALL received MIME as induction or maintenance treatment, and one patient with NHL was given MIME as adjuvant treatment following radiotherapy. These 9 patients were also considered to be evaluable for toxicity.

The median age of the patients was 57 years (range 20–91 years). The number of drugs given previously was as follows: 1–3 drugs: 6 cases, 4–5 drugs: 44 cases, and 6+ drugs: 22 cases. In general, patients with high/intermediate-grade NHL had CHOP or a CHOP-like regimen as first treatment, while patients with low-grade NHL or CLL had an alkylating agent initially, followed by CVP or CHOP on relapse. Most patients with Hodgkin's disease had alternating COPP/ABVD as first treatment. Performance scores at the start of MIME treatment are given in Table 1

Initially, the doses reported by Cabanillas et al. (4) were employed, but severe bone marrow toxicity was observed in the first 10 patients treated, with one toxic death. For this reason, the doses of the various drugs were reduced by 15–25%, resulting in the following dose schedule: Methyl-GAG 400 mg/m^2 i.v. on days 1 and 14, ifosfamide 750 mg/m^2 i.v. days 1 through 5, followed by mesna, 20% of ifosamide dose i.v. 0, 4 and 8 h after ifosfamide, methotrexate 25 mg/m^2 i.v. on day 3, and etoposide 100 mg/m^2 orally days 1 through 3. Courses were repeated every 4 weeks for 6–9 courses or until disease progression occurred. After the completion of treatment, patients were seen every 2 months.

In case of marrow toxicity, doses of ifosfamide, methotrexate and etoposide were reduced by 25–50%, and in case of mucositis the dose of methyl-GAG was reduced correspondingly. Doses were similarly reduced in patients over 70 years of age. In some cases of fast-growing tumors with evidence of kinetic resistance the courses were given every 2–3 weeks without methyl-GAG on day 14. Toxicity was graded according to WHO (16).

Complete response (CR) was defined as the disappearance of all signs and symptoms of disease for a minimum of 2 months. Partial response (PR) was defined as a >50% reduction in the sum of all tumor measurements lasting for at least 1 month. Any response less than PR, including mixed responses, was considered as no change (NC) if it lasted for at least 2 months. Progressive disease (PD) was defined as an increase of any measurable lesion by >25%, or a response less than PR lasting for less than 2 months. Actuarial survival and actuarial survival without progression for all patients was calculated from the initiation of therapy to death or last follow-up and time to progression of disease or death respectively. Actuarial survival without progression was also calculated for the subgroup of patients who obtained complete or partial remission; in this subgroup it was calculated from the time the response was first noted and until PD or death.

Results

Table 1 shows the remission rates that were obtained in relation to disease type and performance score. Since the treatment results in low-grade NHL and CLL were similar these two groups, which are also biologically related, have been combined throughout. A total of 34 responses occurred in all 72 patients (47%). In the group with high or intermediate grade NHL, 23 of 41 patients had a response (56%), of which 22% were CRs. In contrast, in the group of low-grade NHL + CLL only 2 out of 18 patients had a PR (11%). In HD 9 or 13 patients responded (69%) with 4 CRs. One of the latter occurred in a 91-year-old female. None of the 12 patients with performance score 3 or 4 had a response.

The response rates according to response to previous chemotherapy are shown in Table 2. Of patients with recurrent disease 19/41 (46%) responded, while 15/31 (48%) patients with primary refractory disease responded. When related to the number of drugs given previously the

Table 2

Response to MIME in relation to previous treatment response

	n	CR	PR	NC	PD
Recurrent disease					
NHL excl. low-grade	15	5	4	2	4
Low-grade NHL + CLL	14	0	2	5	7
Hodgkin's disease	12	4	4	3	1
Total	41	9	10	10	12
Refractory disease					
NHL excl. low-grade	26	4	10	4	8
Low grade NHL + CLL	4	0	0	2	2
Hodgkin's disease	1	0	1	0	0
Total	31	4	11	6	10

Abbreviations: NHL = non-Hodgkin's lymphoma; CLL = chronic lymphocytic leukemia; CR = complete remission; PR = partial remission; NC = no change; PD = progressive disease.

following response rates were observed: 1–3 drugs: 4/6 (67%), 4–5 drugs: 20/44 (45%), 6+ drugs: 10/22 (45%). There were no significant differences between the three groups of patients treated (Table 3). Thus, neither previous type of response to chemotherapy nor previous amount of treatment predicted the outcome of MIME therapy. Interestingly, 4 out of the 5 patients who had MIME as intial treatment for high/intermediate-grade NHL obtained CR. The one patient who did not respond had performance score 4 and died on day 7 after the start of treatment.

Fig. 1 shows survival, survival without progression and survival with progression for responding patients with high or intermediate-grade NHL. At 15 months 25% were alive, 13% without diesease progression. Median duration of response was 6 months, and median survival 7 months.

The same data are shown for low-grade NHL + CLL in Fig. 2. Although performance score was 1–2 in 15/18 patients, median survival was only 2 months, due to the

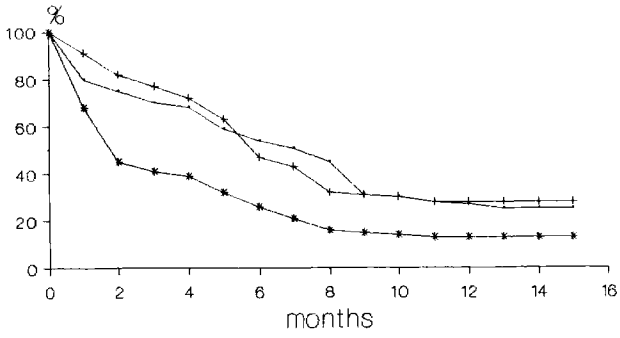

Fig. 1. High/intermediate-grade non-Hodgkin's lymphoma (n = 41): Survival (—●—) and survival without progression (—×—) for all patients. Survival without progression (—┼—) for patients obtaining complete plus partial remission.

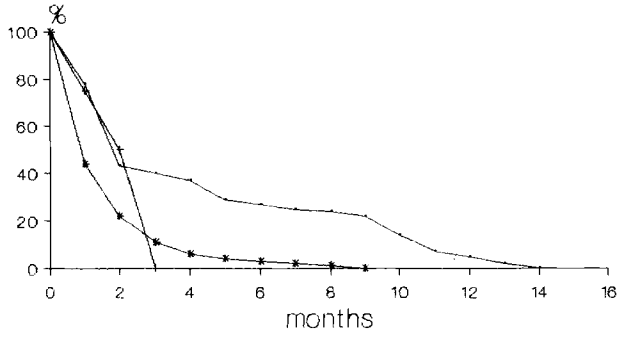

Fig. 2. Low-grade non-Hodgkin's lymphoma plus chronic lymphocytic leukemia (n = 18): Survival (—●—) and survival without progression (—×—) for all patients. Survival without progression (—┼—) for patients obtaining complete plus partial remission.

fact that the majority of these patients were heavily pretreated with terminal transformation of their disease.

In contrast, Fig. 3 shows that cases of HD had the least unfavorable prognosis of all patients treated with MIME with 44% alive at 15 months and 21% still without progression. Median duration of response was 7 months, and median survival 10 months respectively.

Table 3

Response to MIME in relation to number of drugs given previously

Number of drugs	CR + PR/all patients treated			CR + PR %
	NHL excl. low-grade	Low-grade NHL + CLL	Hodgkin's disease	
0–3	3/3	0/2	1/1	67
4–5	15/29	2/12	3/3	45
6+	5/9	0/4	5/9	45

Abbreviations: NHL = non-Hodgkin's lymphoma; CLL = chronic lymphocytic leukemia; CR = complete remission; PR = partial remission; NC = no change; PD = progressive disease.

Table 4

Percentage of patients reaching a given WHO toxicity level at any time during treatment

Toxicity grade	Hgb	Leukocytes	Platelets	Nausea/ vomiting	Mucositis	Infections
0	19	21	56	17	40	51
1	44	9	7	41	22	12
2	27	19	9	35	26	12
3	9	33	7	7	11	22
4	1	18	21	0	1	3
Average*	0.6	0.9	0.5	0.8	0.5	0.6

* average score throughout treatment.

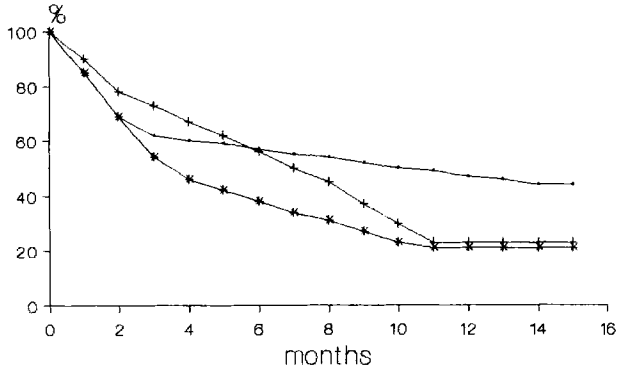

Fig. 3. Hodgkin's disease (n = 13): Survival (—●—) and survival without progression (—×—) for all patients. Survival without progression (—|—) for patients obtaining complete plus partial remission.

The number of courses given was 1.0 in PD, 2.35 in NC, 3.85 in PR, and 6.15 in CR respectively. Table 4 shows the percentage of patients reaching a given toxicity level at any time during treatment. Grade 3 + 4 leukopenia was reached by 51% and 28% grade 3 + 4 thrombocytopenia. Twenty-five percent reached the same level as regards infections, and one patient died of treatment-related sepsis. Generally, however, toxicity was not a significant problem, as shown by the low average scores between 0.5 and 0.8 for all individual toxicity manifestations. Due to the use of mesna no cases of cystitis were observed, and only one patient had microscopic hematuria.

Discussion

Although the overall response rate with MIME was only 47%, this result was mainly due to the fact that only 2 out of 18 terminal patients with low-grade NHL or CLL responded to the treatment. In high/intermediate-grade NHL and in HD the response rates were 56% and 69% respectively. Further, the exclusion of NHL patients with performance scores of 3 and 4 would have increased the response rate for high/intermediate-grade NHL from 56% to 72%. Thus, to a considerable extent the response rates that are obtained are dependent on the selection of patients. No doubt this factor accounts for the differences in results between various studies of very similar treatments. Somewhat surprisingly, response rates did not differ between recurrent and refractory disease, or between cases having received few or many drugs.

Disregarding the results in low-grade NHL, our results with MIME agree well with the results reported by Cabanillas et al. (4) for NHL and by Hagemeister et al. (17) in HD, using the same drug combination in 15–25% higher doses and without mesna. Presumably, these differences explain why the percentages of toxic deaths and cystitis were 6% and 20% respectively, in the study by Cabanillas et al. (4), as against 1% and 0% respectively, in the present study.

It is not possible to determine from the available data the relative contribution of the individual drugs in the MIME combination. Cabanillas et al. (3) reported a 62% overall response rate with ifosfamide/methotrexate/etoposide, but Sangster et al. (8) and Hagberg et al. (10) obtained overall response rates of only 18% and 19% respectively, with the same combination. Again, the combination of ifosfamide/methotrexate/etoposide/bleomycin has been reported to produce response rates of 61%, 62% and 79% respectively in 3 smaller studies (5–7). Thus, there is some indication that at least ifosfamide, methotrexate and etoposide are required in order to obtain a significant level of remissions.

Although MIME has considerable activity in recurrent or refractory lymphoma, very few patients become long-term survivors. Clearly, MIME, like all other 'salvage' treatments, is only of limited value in itself. However, by combining remission induction with MIME with subsequent autologous bone-marrow transplantation it might be possible to obtain more durable remissions in a number of patients. MIME is well suited for this setting since it does not contain drugs with cardiac or pulmonary toxicity which may compromise the use of adjuvant cytoreductive radiotherapy.

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