Eur J Cancer Clin Oncol, Vol. 24, No. 3, pp. 483–486, 1988.
Printed in Great Britain

0277–5379/88$3.00+0.00

Ifosfamide and VP-16213 Combination Chemotherapy Combined with Ablative Chemotherapy and Autologous Marrow Transplantation as Salvage Treatment for Malignant Lymphoma

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Abstract—*Eighteen patients with high-grade malignant lymphoma were treated with ifosfamide–VP16213 combinations after failing to respond completely or after relapsing on CHOP-like therapy. Responders to the salvage therapy were subsequently treated with ablative chemotherapy (BCNU, VP-16213, Ara-C and melfalan) and autografted. Of these 18 patients six were in relapse, six were partial responders and six failed CHOP-like therapy. There were two complete remissions and seven partial responses to the ifosfamide–VP-16213 combinations. Of them, eight patients were transplanted, together with one non-responder. Four of these nine patients were disease-free survivors 18–34 months after autografting. There were two early deaths: one before and one during the autografting procedure.*

Using one of the best salvage therapy combinations followed by high-dose chemotherapy and autografting is feasible. The results in this pilot study suggest that an appreciable number of patients may be cured by this procedure.

INTRODUCTION

THE RESULTS obtained with chemotherapy in patients having diffuse large-cell lymphoma have changed dramatically in the last 10 years. Complete response rates of about 80% with few relapses afterwards, leading to an actuarial survival of approx. 70% are reported in a number of single-institute studies [1, 2]. However, results of salvage therapy for patients not achieving remission on first-line treatment or for relapsing patients are poor. Ifosfamide and VP-16213 containing regimens like IMVP-16 and MIME are among the most useful salvage regimens but only a few patients experience durable remissions [3, 4]. Recently, it has been shown that high-dose chemotherapy with autologous marrow rescue is capable of inducing complete remission in patients who failed to respond completely to or relapsed on conventional chemotherapy [5]. This study reports the combined use of IMVP-16 or MIME and high-dose chemotherapy followed by autologous marrow transplantation in such patients.

Accepted 12 October 1987.
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MATERIALS AND METHODS

Patient characteristics

Between February 1984 and November 1985, 18 patients who had failed to respond completely or who had relapsed after front-line therapy were included in the study. Initial stages were: two stage II, five stage III and 11 stage IV. The front-line therapy consisted of CHOP or CHVM26P. In some patients adjuvant radio- or combination chemotherapy had been used. The histologic diagnoses (Working Formulation) were: large non-cleaved diffuse eight, large cleaved-non-cleaved diffuse three, large cleaved diffuse one, true histiocytic two,

immunoblastic two, lymphoblastic-non-convoluted two.

Chemotherapy

Fifteen patients received IMVP-16 and three MIME. The two regimens were given as published [3, 4] with minor alterations: IMVP-16 consisted of ifosfamide 1 g/m^2 daily for 5 days, VP-16213 100 mg/m^2 daily for 3 days and methotrexate 30 mg/m^2 daily for 2 days. MIME was given as IMVP-16 supplemented by methyl-GAG 500/mg/m^2 for 1 day. Proper hydration and alkalinization of the urine were included together with mesna for prevention of hemorrhagic cystitis. One to three courses were given with 4 week intervals. Response was evaluated after every course.

High-dose chemotherapy with autologous marrow rescue

Patients who showed a complete or partial response to IMVP-16 or MIME were eligible, if age and physical and psychological conditions permitted the procedure. None of them had bone marrow involvement before initial or salvage chemotherapy. Nine patients were treated with a high-dose regimen (BEAM) consisting of BCNU 300 mg/m^2 on day 1, VP-16213 100 mg/m^2 and Ara-C 200 mg/m^2 on days 2, 3, 4 and 5 and melphalan 140 mg/m^2 on day 6 followed by autologous marrow infusion on day 7.

Bone marrow procedures

Marrow harvesting was done before the first or after the second course of IMVP-16 or MIME after excluding marrow involvement by scrutinizing bone marrow biopsies. Bone marrow cells were collected by multiple bone marrow aspirations under general anesthesia into heparin-containing bottles. The median yield of nucleated cells was 2.08 × 10^8/kg (range 1.11–3.07). A buffy-coat suspension was prepared and subsequently a mononuclear fraction obtained by Ficoll Isopaque (1.079 g/cm^3) density-gradient centrifugation on the IBM Cell Washer (type 2991-2). This fraction was frozen until rapidly thawed at the bedside and reinfused through a single-lumen Hickman right atrial catheter.

Supportive care

Seven patients who underwent transplantation were nursed in a laminar-air-flow room. The other two were nursed in single rooms with conventional reverse isolation. All patients received parenteral alimentation, irradiated blood component support (30 Gy), oral antibiotics for partial decontamination of the intestinal tract and systemic antibiotic therapy as required.

Evaluation of response

Complete remission (CR) was defined as the disappearance of all evidence of disease for a minimum of 1 month. A partial response (PR) was defined as a more than 50% reduction of the measurable tumors. Duration of survival was measured from the end of treatment with IMVP-16 or MIME or from the date of bone marrow reinfusion in the transplanted patients.

RESULTS

Response to IMVP-16–MIME (Table 1)

Six patients were treated because of relapsing disease. One achieved CR, one a partial response and four patients had treatment-resistant relapse.

Six patients were treated because of disease resistant to first-line chemotherapy. Of these patients none achieved CR, two patients showed a partial response, and three did not respond at all. There was one therapy-related death in this group.

Six patients were treated after having experienced a partial response to first-line chemotherapy. One achieved CR, four had a partial response and one showed no further improvement after treatment with IMVP-16 or MIME.

Toxicity of IMVP-16–MIME

Nausea, vomiting and mucositis were mild, and did not exceed WHO grade 2. Hemorrhagic cystitis did not occur. Gross liver and renal dysfunctions were not observed. Pancytopenia was common with platelet counts below 20 × 10^9/l and granulocyte counts below 0.5 × 10^9/l in 17 of 18 patients. Recovery was fast, mostly within 21 days. During pancytopenia, there were two documented episodes of septicemia (*Listeria monocytogenes* and *Salmonella*). One patient had fever of unknown origin accompanied by hemorrhagic diathesis and died. This patient initially had bone marrow invasion by lymphoma and responded to treatment with long-standing and severe pancytopenia.

Response to BEAM and autografting

Of the nine patients responding to IMVP-16 or MIME, eight were eligible for BEAM and autografting. One patient achieving CR after IMVP-16 was considered too old for the procedure. Seven of these eight patients had a partial response and one a complete remission after two or three cycles of IMVP-16 or MIME. One patient with progressive disease was also transplanted and included in the analysis (Table 1). Age ranged from 17 to 59 years. The patient with progressive disease died during the procedure. Four patients are alive without evidence of disease, 18, 24, 32 and 34 months after transplantation. Three of these four patients received IMVP-16 initially because of a partial response on first-line therapy. Two patients

Table 1. *Characteristics of patients*

No.	Age	Histology*	Initial† therapy	Response‡	Status at time salvage‡	Salvage therapy§	Response	Auto-grafting	Status‡ after salvage therapy ± autografting Immediate	→ present
1	43	cl/non cl[1]	COP[1] × 6 CHOP[2] × 6	CR[1]	Relapse	MIME[1] × 2	PR	Yes	Res	Died of disease day 64
2	17	Non cl[2]	CHOP × 6 COP × 12	CR	Relapse	IMVP[2] × 2	Res	No	Res	Died of disease day 62
3	54	Non cl	CHOP × 8 RT[3]	CR	Relapse	IMVP × 2	Res	No	Res	Died of disease day 51
4	58	Non cl	CHOP × 7 RT	CR	Relapse	IMVP × 3	Res	No	Res	Died of disease day 118
5	32	Non cl	CHVP[4] × 6	CR	Relapse	MIME × 2	Res	Yes	NE	Died of sepsis day 15
6	26	Immunobl[3]	CHOP × 6	Res[2]	Res	IMVP × 1	NE[4]	No	NE	Died of hemorrhage day 13
7	59	Non cl	CHOP × 6	Res	Res	MIME × 2	Res	No	Res	Died of disease day 65
8	55	cl/non cl	CHOP × 8	PR[3]	PR	IMVP × 2	PR	Yes	CR	Well month 32
9	19	Lymphobl[4]	CHOP × 6	CR	Relapse	IMVP × 3	CR	Yes	CR	Relapsed day 73 Died of disease month 13
10	17	Lymphobl	CHVP × 8	Res	Res	IMVP × 2	PR	Yes	PR	Died of disease month 11
11	36	cl/non cl	CHOP × 5	PR	PR	IMVP × 2	PR	Yes	CR	Well month 34
12	22	Histioc[5]	CHOP × 6	PR	PR	IMVP × 1	Res	No	Res	Died of disease day 71
13	47	cl[6]	CHOP × 4	PR	PR	IMVP × 2	PR	Yes	CR	Well month 24
14	22	Non cl	CHOP × 6	PR	PR	IMVP × 2	PR	Yes	CR	Relapsed month 9 died of disease month 10
15	32	Immunobl	CHOP × 3	Res	Res	IMVP × 1	Res	No	Res	Died of disease day 18
16	16	Histioc	CHVP × 6	Res	Res	IMVP × 3	Res	No	Res	Died of disease day 68
17	64	Non cl	CHOP × 8	PR	PR	IMVP × 7	CR	No	CR	Well month 17
18	59	Non cl	CHOP × 4	Res	Res	IMVP × 3	PR	Yes	CR	Well month 18

*Histology: [1]large cell, cleaved/non-cleaved, diffuse; [2]large cell, non-cleaved, diffuse; [3]immunoblastic; [4] lymphoblastic non-convoluted; [5] histiocytic; [6]large cell, cleaved, diffuse.
†Initial therapy: [1]cyclofosfamide, vincristine, prednisone; [2]cyclofosfamide, adriamycin, vincristine, prednisone; [3]involved field radiotherapy; [4]cyclofosfamide, adriamycin, VM-26, prednisone.
‡Response: [1]complete remission; [2]resistant disease; [3]partial response; [4]not evaluable.
§Salvage therapy: [1]methyl-GAG, ifosfamide, VP-16213, MTX; [2]ifosfamide, VP-16213, MTX.

relapsed after achieving complete remission, one showed a partial response and one had resistant disease. These four patients all died of disease.

Toxicity of BEAM

Nausea and vomiting were mild and readily manageable by antiemetic therapy. Stomatitis and diarrhea occurred in all patients. It was mild except in one patient who experienced severe mucosal toxicity and gastrointestinal hemorrhage. BEAM therapy regularly resulted in severe pancytopenia with lowest platelet counts below 10×10^9/l and granulocyte counts essentially zero. Recovery was relatively fast with platelet counts reaching 50×10^9/l by 32 days (median; range 25–39) and granulocyte counts reaching 0.5×10^9/l by 29 days (median; range 22–36). One patient's platelet count did not recover. One patient died during the aplastic period of streptococcal septicemia. Four other patients also experienced a streptococcal sepsis. Three others had fever of unknown origin.

DISCUSSION

Ifosfamide- and VP-16213-containing combination chemotherapy like IMVP-16 and MIME are among the best salvage regimens for patients with high-grade malignant lymphoma who are resistant to or relapse after first-line CHOP-like therapy [3, 4]. The best results are obtained in patients relapsing 6 months or later after completing therapy. About 40% of such patients achieve CR, some of them durable [6]. Patients who only partially respond or failed to respond at all to CHOP-

like regimens achieve CR in only about 10% of cases [3, 4, 6].

Recently high-dose chemotherapy or chemo-radiotherapy has been shown to induce complete remissions and possible cures in an appreciable number of patients who failed to achieve CR or relapsed after conventional [5, 7, 8] therapy. In this study we combined both approaches, all patients received IMVP-16 or MIME and only those who showed a response to these regimens were subsequently transplanted. We chose a conditioning regimen without total body irradiation (TBI) because there does not seem to be a difference in efficacy between schemes with or without TBI while there is a trend to a higher proportion of toxic deaths with TBI-contaminating regimens [9].

In our study, response to IMVP-16 and MIME was as expected: nine patients (50%) showed a response, two of them achieved complete remission (11%). One of the complete remitters relapsed shortly after transplantation. The results in the patients who were transplanted are encouraging. The procedure was well tolerated, although all patients were given first-line chemotherapy, IMVP-16 or MIME and finally BEAM in a relatively short period of time. The one transplant-related death occurred in the patient who was transplanted despite progressive disease during MIME treatment. Although the follow-up is short, we wished to report our findings especially to show the feasibility of treating patients relapsing after or failing to respond completely to CHOP-like therapy, with one of the best salvage schemes followed by high-dose chemotherapy and autotransplantation. It is possible that, by increasing the amount of cycles of IMVP-16 or MIME in responding patients before going to auto-transplantation, results could be improved. Currently, we are following this protocol in patients with stage II, II, or IV high-grade malignant non-Hodgkin's lymphoma who are not in complete remission after the fourth course of CHOP–MTX [10].

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