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Massive Chemotherapy with non-Frozen Autologous Bone Marrow Transplantation in 13 Cases of Refractory Hodgkin's Disease

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Abstract—*A group of 13 patients with advanced, diffuse Hodgkin's disease, poorly responding to the most widely employed primary chemotherapy regimens, were treated with massive chemotherapy (MCH) followed by rescue with non-frozen autologous bone marrow infusion (ABMT). Complete remission (CR) was obtained in 8/13 patients (61.5%) and partial remission in two. Hematopoietic recovery occurred in 12 cases. These preliminary results would seem to indicate that MCH with non-frozen ABMT may be successfully used in patients with resistant or relapsed Hodgkin's disease.*

INTRODUCTION

SIGNIFICANT progress has been made in the treatment of Hodgkin's disease (HD) in the last decade, and represents one of the most remarkable achievements of modern cancer treatment. Despite this progress, few patients fail to achieve complete remission (CR), or relapse early. In these cases the prognosis is very poor.

In an attempt to overcome the problem of primary drug resistance and early relapse, our group has designed a MCH protocol with ABMT in advanced HD patients. In this report we present the preliminary results in 13 refractory or relapsed HD patients.

MATERIALS AND METHODS

From May 1981 to June 1984, 13 patients with histologically confirmed HD were entered in this study. There were eight males and five females. Median age was 29.6 yr (range 15-40 yr). All cases except one had extranodal relapses (stage III or IV according to the Ann Arbor Classification). All patients received first-line chemotherapy of CcVPP (CCNU, vinblastine, procarbazine, prednisone), MOPP or MOPP + ABVD + CEP with radiotherapy and all failed or relapsed (Table 1). Prior to MCH, all patients had at least one measurable indicator lesion to serve as an objective parameter of response therapy. Radiographic findings were acceptable, provided clear-cut measurements could be made. Clearly defined defects measuring at least 5 cm in diameter on radionuclide, computed tomographic or ultrasound examination of the liver were also considered acceptable measurable parameters. Biopsy proof of liver involvement by HD was required if the liver was considered as the sole area of measurable disease. Pretreatment laboratory test requirements included WBC count $\geq$4000/mm^3, platelet count $\geq$150,000/mm^3, Hb $\geq$ 12 g%, total serum bilirubin $\leq$1.0 mg/dl, serum creatinine $\leq$1.5 mg/dl. No case had evidence of tumor involvement of the marrow in multiple bone marrow biopsy specimens. Except for one case (case 04, Table 2), all marrow specimens had normal cellularity at the time of BM harvesting. In all cases the BM suspension was refrigerated at 4°C for 41 hr (range 36-48 hr) until reinfusion and was not cryopreserved.

Under general anesthesia BM was aspirated from the anterior and posterior iliac crest by previously described techniques [1]. The aspirated marrow was anticoagulated with preservative-free

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Table 1. Pre-ABMT patient characteristics and therapeutic response

Case	Age/sex	Stage at diagnosis and histology	Previous therapy	Prior response	No. of relapses	Type of relapse	Duration of unmaintained first RC (months)	Stage prior MCH	Type of MCH	Complications	Type of response	Status on 31.5.84 (duration in months)
01	36/N	IVB L+ (MC)	CcVPP × 6cy MOPP × 6cy RT 'mantle'	NR	—	—	—	IVB L+	BCNU (700 mg/m²)	*E*: liver *L*: lung fibrosis	CR	alive CR (34)
02	25/F	IIIA (MC)	MOPP × 4cy RT 'mantle + ipsilon' ABVD × 4cy	CR	2	nodes	64	IIIB	BCNU (600 mg/m²)	—	CR	alive CR (25)
03	35/M	IIB (NS)	MOPP/ABVD × 6cy RT 'mantle + ipsilon'	NR	—	—	—	IVB L+ B+ (CM)	CVB	*E*: liver	CR	alive, relapse (3)
04	24/F	IIB (NS)	MOPP/ABVD × 6cy CEP × 3cy RT 'mantle'	CR	1	lung nodes	10	IVB L+	CVB	—	PR	died in aplasia
05	25/M	IIA (NS)	MOPP × 6cy ABVD × 6cy vindesine × 2cy RT 'mantle + ipsilon'	CR	2	lung nodes	18	IVA L+	CVB	*E*: liver	CR	alive, relapse (4)
06	28/M	IVB L+ H+ (MC)	MOPP/ABVD × 6cy MOPP × 5cy CEP × 6cy RT 'mantle'	NR	—	—	—	IVB L+ H+	CVB	*E*: liver	NR	died
07	27/M	IIIB (NS)	MOPP/ABVD × 6cy CEP × 3cy RT 'mantle'	CR	2	lung nodes	14	IVB L+	CVB	*E*: liver	CR	alive CR (12)

08	40/F	IVB L+ B+ (MC)	MOPP/ABVD × 6cy RT 'mantle'	NR	—	—	—	IVB L+ B+ H+	CVB	*E*: liver	CR	alive CR (8)
09	40/M	IVB H+ L+ (NS)	MOPP/ABVD × 5cy CEP × 6cy RT 'mantle + ipsilon'	CR	1	lung liver nodes	9	IVB H+ L+	CVB	*E*: liver	PR	died
10	37/M	IIB (MC)	MOPP/ABVD × 6cy CEP × 3cy RT 'mantle'	PD	1	lung nodes	10	IVB L+	CVB	—	CR	alive CR (4)
11	21/M	IVB L+ (LD)	MOPP/ABVD × 8cy CEP × 6cy RT 'mantle'	CR	1	—	10	IVB L+	CVB	*E*: liver	NR	died
12	15/F	IVB L+ (MC)	MOPP/ABVD × 4cy RT 'mantle' CEP × 2cy	CR	1	lung	7	IVB L+	CVB	—	PD	died
13	23/F	IIIA (NS)	RT 'mantle + ipsilon' MOPP × 6cy ABVD × 4cy	CR	2	lung	14	IVB L+	CVB	*E*: liver	CR	alive CR (2)

E = early; *L* = late; L = lung; B = bone; H = liver; PD = progressive disease; NR = no response; PR = partial remission; CR = complete remission; CVB = cyclophosphamide (5 g/m²) + VP-16 (400 mg/m²) + BCNU (600 mg/m²); NS = nodular sclerosis; MC = mixed cellularity; LD = lymphocytic depletion; RT 'mantle' = 4000 rads; RT 'ipsilon' (inverted Y) = 4000 rads.

Table 2. Number of nucleated cells and CFU-GM: harvesting data

Case	Volume collected (ml)	Nucleated cells collected ($\times 10^8$/kg)	Total CFU-GM collected ($\times 10^4$/kg)	No. of cells grafted ($\times 10^8$/kg)	CFU-GM grafted ($\times 10^4$/kg)	Granulocytes (0.5×10^3)	Pt (5×10^4)
1	900	1.8	15.7	0.7	11.3	16	25
2	500	1.2	1.3	1.1	1.0	9	15
3	1000	2.2	3.1	2.3	2.9	11	15
4	900	0.4	0.6	0.4	0.3	aplasia	
5	900	2.6	5.8	1.8	4.0	13	16
6	900	1.2	N.D.	0.9	N.D.	26	31
7	900	1.8	2.2	1.6	1.7	14	34
8	950	2.4	N.D.	1.6	N.D.	19	21
9	900	1.4	0.9	1.5	0.6	16	20
10	1000	1.9	5.8	1.1	3.4	20	30
11	900	3.8	4.3	2.6	2.8	14	42
12	900	2.9	1.2	1.6	0.9	17	40
13	900	2.0	1.5	1.8	1.1	17	22

N.D. = not done.

heparin (20 units/ml final concentration). The marrow was passed through stainless steel screens and collected in polyethylene bags; the volume obtained averaged 900 ml and contained 2.2×10^8 cells (range $0.4\text{-}3.8 \times 10^8$). The bag containing the marrow was centrifuged at 1000 *g* for 10 min following which a portion of the supernatant containing suspended fat was removed. The final volume averaged 600 ml and had a packed red cell volume of 45-55%. The mean recovery granulocyte-monotype colony-forming cell (CFU-C) was $71 \pm 11\%$ (range 50-94%).

High-dose modality therapy

The pretransplant conditioning regimen consisted in two patients of BCNU alone (600 mg/m^2) and in 11 patients of BCNU (600 mg/m^2), Cy 5 g/m^2, and etoposide (VP-16) (400 mg/m^2). The patients were hydrated beginning from day 1 up to 5 days after MCH.

Urine output was maintained at 150 ml/hr. A central venous catheter was inserted 12 hr prior to the MCH and was removed 48 hr later. All patients were maintained in single rooms and received oral non-absorbable antibiotics; prior to MCH, all cases received diazepam and metoclopramide.

Bone marrow infusion (Table 2)

The patients received a mean of 1.4×10^8 bone marrow cells/kg (range $0.4\text{-}2.6 \times 10^8$) containing 2.3×10^4 CFU-C/kg (range $0.3\text{-}11.3 \times 10^4$).

Post-ABMT evaluation

Blood cell counts were done daily and bone marrow aspiration and biopsy were performed weekly. Every 10 days the patients were evaluated with liver and kidney function tests.

Criteria of response

Patients were considered to have achieved a complete remission (CR) if all signs and symptoms of disease disappeared and if values of biochemical and radiologic parameters returned to normal for at least 4 weeks. Reduction >50% in the product of the longest perpendicular diameters of all measurable lesions was considered as partial remission (PR). Duration of CR was measured from the time of maximal response until the time of progression. Survival was calculated from the onset of MCH.

RESULTS

Tumor response

CR was obtained in eight cases (61.5%) and PR in two. Two CR patients subsequently relapsed within 3 and 4 months, although they are still alive at the present time; all other responsive patients are in CR 2-34 months from MCH-ABMT. Overall survival of all patients is given in Fig. 1. However, the results can be summarized as follows: (a) three refractory patients died of disseminated HD; (b) one patient died of a

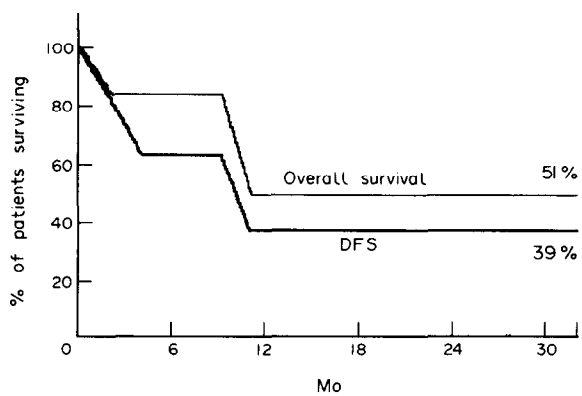

Fig. 1. Autologous BMT in advanced HD (13 patients, Genova 1984).

therapy-related complication, i.e. *Pseudomonas aeruginosa* septicemia; and (c) ten patients (76.1% of the total group) are still alive without treatment 2-34 months after MCH, but only six are also in a non-maintained CR.

Hematopoietic reconstitution

All patients had WBC counts of $0.5 \times 10^9/l$ or less and platelet counts of 10×10^9 or less 10-20 days after MHC. Marrow recovery occurred in 12 patients, while one case died 40 days after ABMT of bone marrow aplasia. In the other cases the WBC count was $1 \times 10^9/l$ or more a median of 16 days (range 9-26 days) following ABMT and the platelet count was $50 \times 10^9/l$ or more a median of 23 days post-ABMT (range 15-42 days) (Table 2).

Non-marrow toxicity

All patients had elevations in liver enzymes and/or alkaline phosphatase; they usually returned to normal within 2-5 months. One patient with bilateral lung infiltrations had clinical and radiological evidence of lung fibrosis. Cardiotoxicity, as assessed by clinical evaluation, echocardiography and calculation of pre-ejection period/left ventricular ejection time, was not observed.

DISCUSSION

Our results show a high response rate to MCH-ABMT, a high proportion of long-term survivors and a low proportion of early therapy deaths in 13 very bad prognosis resistant or relapsed HD patients. These preliminary results also confirm previous reports showing that ABMT is capable of restoring hematopoiesis in patients given MCH as a short half-life single agent and in combination chemotherapy which is capable of inducing severe life-threatening bone marrow hypoplasia [2-14]. As compared to marrow cryopreservation, the infusion of non-frozen bone marrow is shown to be an easier procedure which consistently provides successful and fast hematologic reconstitution.

The optimal management of HD patients who develop progressive or recurrent disease after primary chemotherapy remains to be clearly established. At present, 4-60% of resistant or relapsed HD patients can enter CR following first-generation regimens of salvage chemotherapy without ABMT, with a median duration of 10-14 months [15-21]. Recently, the Milan NCI and Sloan-Kettering Cancer Center have developed second-generation regimens of salvage chemotherapy (CEP and CAD)* and the initial experience appears promising, since the total response (CR + PR) was observed in 54 and 46% of refractory or relapsed advanced HD patients respectively [22, 23].

The efficacy of first- or second-generation regimens of salvage chemotherapy for those patients with advanced HD relapsing after MOPP is dependent on several prognostic factors. One factor is the period of time between the initial response to MOPP and the relapse. As reported by Fisher *et al.* [24], MOPP reinduced a CR in a high proportion of patients that relapsed more than 1 yr after the initial remission, and this salvage chemotherapy is undoubtedly less effective when the recurrence takes place in major extranodal sites (such as lung, liver or bone) rather than being confined to lymph nodes [17]. The same observation applies to other salvage regimens. Another important factor is whether patients are treated in their first relapse or after multiple relapses; salvage chemotherapy is less effective for the latter group of patients.

Although it is known that patients with advanced HD may still respond to salvage chemotherapy, it must nevertheless be pointed out that, in these series, effective regimens, such as MOPP, ABVD, alone or in an alternating scheme, and CEP, had already been employed with no response or remissions of brief duration. In addition, a single treatment would seem to be less unpleasant for the patient and patient compliance to a long treatment would not be a problem. At present it is very difficult to interpret reports of MCH and ABMT in HD patients because of the efficacy of both primary and salvage chemotherapy. In two recent reports 6/15 (40%) and 8/17 (47%) HD patients obtained CR after MCH-ABMT despite primary resistance to relapse from first line chemotherapy [25, 26]. Unfortunately prolonged CR were uncommon also because toxic deaths were frequent, due to fatal infections [26] and interstitial pneumonitis following total-body irradiation (TBI) [25].

This excessive toxicity could probably be avoided if such treatment were given earlier in the course of the disease before the accumulation of iatrogenic effects, and if TBI were avoided in the conditioning regimen of patients who received prior mantle radiotherapy. TBI was not employed in our cases because all patients had received prior mantle radiotherapy.

In conclusion, the high percentage of remissions obtained in these advanced patients proves the validity of such treatment attempts in poor prognosis HD. Whether MCH-ABMT will eventually supersede conventional and/or new salvage chemotherapies, especially in advanced HD, may be answered only after controlled clinical trials.

*CEP: CCNU, etoposide, prednimustine; CAD: CCNU, melphalan, vindesine.

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