

High dose chemotherapy and autologous bone marrow transplantation in refractory Hodgkin's disease

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Summary Seventeen patients with Hodgkin's disease (HD) were treated with high-dose chemotherapy followed by autologous bone marrow transplantation (ABMT). Eleven patients were resistant to initial therapy. Three patients had relapsed and were still responders to second or third line therapy. Three patients had relapsed but were progressing under second or third line therapy. Pre-ABMT chemotherapy included high dose cyclophosphamide in all patients (50 mg Kg⁻¹ day⁻¹ bolus for 4 days), most often associated with BCNU or CCNU, aracytine and 6 thioguanine. Four patients received additional TBI (10 Gy). In 9 patients complete remission (CR) was achieved, 4 failed to respond and 4 cases were not evaluable due to early death. Among CR patients, 2 died from late toxicity, 4 relapsed between the 2nd and 5th months, but 3 patients remain in CR, off therapy at 25+, 43+, and 66+ months, including 1/11 initially resistant and 2/6 who had relapsed. There were 9 treatment related deaths: 6 due to infection, 1 cardiac failure and 2 multiorgan failure.

The high complete response rate in these heavily pretreated patients suggests that there may be an indication for high dose therapy earlier in resistant HD. Moreover under such conditions, treatment related morbidity would be expected to be lower.

Hodgkin's disease (HD) is one of the most therapy-sensitive malignant lymphomas and in several long term studies more than 80% of the patients have been considered cured following radiotherapy, chemotherapy or usually a combination of both. Nevertheless, irrespective of age, initial presentation, stage or histologic subgroup, a few patients remain resistant to treatment. These can present, either with initial resistance, an incomplete response to chemotherapy, or early and often multiple, relapses (Teillet-Thiebaud *et al.*, 1984). For this small group of refractory patients, even though some response can be obtained by changing the therapeutic regimen, survival is very poor (Boccacio *et al.*, 1983). As HD is highly chemosensitive, several teams have examined the role of high-dose combined modality therapy for these patients, with the support of autologous bone marrow transplantation (ABMT). However, reported results have been rather rare, due to the small number of cases, and are usually part of larger series which include a variety of solid tumours or haematological malignancies (Jagannath *et al.*, 1984; Phillips, 1983a,b; Spitzer *et al.*, 1983; Schmeizer, 1983).

In order to have a clearer idea of the results of ABMT in HD, an inquiry was made among French teams, by the French Autologous Bone Marrow Grafting Group. Results of this study are reported herein and include 17 cases treated in 9 different centres.

Materials and methods

Patients

Clinical data and prior therapy are summarized in Table I. One case has been previously reported (Gorin *et al.*, 1981). Ages were between 10 and 45 (median 22). Stages at diagnosis included IA (1), IIA (2), IIB (2), IIIA (2), IIIB (1), and IVB (9). Among the IVB patients, 2 had initial bone marrow involvement and 8 had lung involvement.

Eleven patients were considered to have refractory disease and had never achieved complete remission despite combination chemotherapy and radiotherapy (see details in Table I). The other six had relapsed from CR (1st to the 6th relapses), 2 off therapy and 4 on therapy, and presented at time of ABMT with disease still responsive to rescue protocols (cases 3, 5 and 17) or not responsive to rescue protocols (cases 4, 6 and 7). Patients had

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Table I Patients treated by high dose chemotherapy and autologous bone marrow transplantation

Case	Age/Sex	Stage at diagnosis	First line treatment	Response	Treatment at relapse (salvage therapy)	Response to the last salvage therapy prior to ABMT
1	17/M	IV B BM	MOPP × 6	PR	ABVD × 6	PD
2	36/M	IV B Lung	MOPP × 6	PR	ABVD × 6	PD
3	22/F	III A	MOPP × 6 + RT	CR	MOPP × 6, ABVD × 3	PR
4	21/M	IV B Lung	MOPP × 6 + RT	CR	CVPP CCNU, ABVD × 8	PD
5	15/M	III A	MOPP × 6 + RT	CR	ABVD × 4	PR
6	24/M	II A	MOPP × 3 + RT	CR	MOPP × 3, ABVD × 3	PD
7	27/M	IV B Lung	MOPP × 4 ABVD × 4 + RT	CR	ABVD × 3, MOPP × 3	PD
8	22/M	IV B Lung	MOPP × 6	PR	RT	PD
9	27/M	IV B Lung	MOPP × 6	PR	CVPP × 10, Eldesine, + RT	PD
10	34/F	II A	MOPP × 9	PR	ABVD × 2, Eldesine, + RT	PD
11	12/F	IV B Lung	MOPP × 4	PR	ABVD × 4	PD
12	16/M	II _e B	MOPP × 3	PR	ABVD × 3 + RT	PD
13	31/M	IV B Lung, BM	MOPP × 6	PR	ABVD × 6	PD
14	33/M	IV B Lung	MOPP × 6	PR	ABVD × 6	PD
15	45/M	II B	MOPP × 4	NR	ABVD × 4 + RT	NR
16	35/M	III B	MOPP × 4	PR	ABVD × 2	PD
17	13/M	I A	MOPP × 4 + RT	CR	ABVD × 6	CR

CR = complete remission; PR = partial response; NR = no response; RT = radiotherapy.

been treated for a median period of 24 months prior to ABMT.

At the time of grafting, stages were II (3), III (2) and IV (12) (Table I). All patients except three (Table I) were progressing at time of ABMT.

Bone marrow freezing and storage

All patients had uninvolved bone marrow at the time of harvesting and *in vitro* purging was not attempted. The harvest was done under general anaesthesia and in all cases bone marrow was cryopreserved according to the usual procedure (Gorin *et al.*, 1983, Herve *et al.*, 1981). The number of nucleated cells collected for each case is described in Table II. For some patients, 2 harvests were necessary, due to prolonged previous therapy.

High dose therapy and autologous engraftment

Several types of combined modality therapy were used, the details of which are summarized in Table III. Each patient except one received cyclophosphamide and apart from 2, all received either CCNU or BCNU. Nine patients received the TACC or BACT combinations, as often used in non-Hodgkin's lymphomas, and one of these also

received TBI (12 Gy). The 8 other patients were given various regimens, as detailed in Table III. Three of these 8 were given TBI (10 Gy). Bone marrow was reinfused 48 h after the last dose of cyclophosphamide, 12 h after TBI and 72 h after BCNU or CCNU. Patients received a median of 1.2×10^8 nucleated cells kg^{-1} and were nursed in single rooms until haematologic reconstitution.

Post-treatment evaluation

Patients were evaluated at day 30 and thereafter on a monthly basis. They were considered to have had a complete remission only if clinical, radiology and laboratory tests, including the sedimentation rate, became normal. Patients who died less than 30 days after the first day of treatment were not considered evaluable for tumour response unless there was clear evidence of progressive disease or autopsy evidence of remission. No patient received maintenance chemotherapy after ABMT.

Results

Anti-tumour effect (Table IV)

Four patients were not evaluable (death on day 4,

Table II Number of nucleated cells reinfused, time to hematologic recovery, and other toxicity

Case no.	$\times 10^8$ kg	< 1000 WBC mm^{-3} (days)	$< 50\,000$ pl mm^{-3} (days)	Other toxicities
1	1.5	32	28	Haemolytic uraemic syndrome
2	1.2	NE (>6)	NE (>6)	Cardiomyopathy ^a
3	1.3	18	16	Herpes simplex
4	1	NE (>15)	NE (>15)	Cardiomyopathy; renal failure ^a
5	1.7	12	12	Herpes simplex
6	0.5	11	NE (>20)	Septicemia, gastric ulcer, CNS complications ^a
7	0.9	17	22	Septicemia, lung fibrosis ^a
8	1.9	17	19	Vomiting
9	1	19	20	Septicemia, herpes, cardiomyopathy
10	1	18	8	Herpes, encephalitis
11	2	NE (>21)	NE (>21)	Septicemia ^a
12	1.2	39	13	Pneumocystis
13	1.5	25	30	Late pulmonary disease (CMV) after recovery ^a
14	0.5	NE (>4)	NE (>4)	Septicemia ^a
15	1.5	20	NE (>35)	(Aspergillosis) ^a
16	0.02	NE (>21)	NE (>21)	Renal failure ^a
17	1.5	NE (>17)	NE (>17)	(Aspergillosis) ^a

^aFatal.**Table III** Summary of protocols

	TACC	BACT	VACC	CAC	COAC	COMAC	COCM	CCP	VP16-C	VP16-A-M
Cyclophosphamide	●	●	●	●	●	●	●	●	●	
Aracytin	●	●	●							●
CCNU	●		●	●	●	●	●	●		
BCNU		●								
6-Thioguanine	●	●								
Vindesine			●				●			
Vincristine					●	●				
Adriamycin				●	●	●				
Caryolysine						●				
Melphalan							●			●
Procarbazine								●		
Etoposide									●	●

Cyclophosphamide 40–50 mg kg⁻¹; aracytin 200–400 mg m⁻²; B or CCNU 200–400 mg m⁻²; 6 thioguanine 200–400 mg m⁻²; vindesine 2.5 mg m⁻²; vincristine 2 mg m⁻²; adriamycin 60–100 mg m⁻²; caryolysine 6 mg m⁻²; melphalan 100–140 mg m⁻²; procarbazine 200 mg m⁻²; etoposide 100–600 mg m⁻².

6, 17 and 20); 3 of these, however, showed a partial clinical remission before death. Four patients failed to respond and died within the first month with progressive disease. Nine achieved CR, although 2 of these died from treatment related toxicity (cases 4 and 13), but CR was confirmed at autopsy. Four out of the 8 survivors subsequently relapsed at 3, 4 and 5 months and died within 12 to 17 months. Nevertheless, 3 long-term survivors are presently free of disease, and off therapy for more than 25, 43 and 66 months, respectively.

Toxicity (Table II)

Haematopoietic reconstitution is detailed in Table II.

Seven patients had culture proven sepsis either during the period of aplasia (5) or within the following 3 months (2). Organisms isolated included 2 pseudomonas, 2 escherichia coli, 2 aspergillosis, and 1 cytomegalovirus and were lethal in 6 patients. In 1 case, an acute cardio-respiratory failure developed possibly due to the toxicity of a

Table IV Results and follow-up

Case no.	Indication for high dose therapy	Stage before the last salvage therapy prior to ABMT	Massive therapy protocol ^b	Result post ABMT	Outcome (M = months; D = days)
1	Resistant disease	III B	TACC	CR	Alive in CR M66
2	Resistant disease	IV B	TACC	NE	Death D6
3	2nd relapse off treatment	II A	BACT	CR	Alive in CR M43
4	Resistant disease	IV B BM + L + Bone +	BACT + TBI 12	CR ^a	Death D15
5	1st relapse off treatment	IV A L + Bone +	BACT	CR	Alive in CR M25
6	Resistant disease	IV A L + Lung +	TACC	NE	Death D20
7	Resistant disease	IV B Lung +	TACC	NR	Death D30
8	Resistant disease	IV B Lung +	CAC	CR	Relapse M5 death M17
9	Resistant disease	IV B Lung +	BACT	CR	Relapse M5 death M16
10	Resistant disease	IV B Lung +	BACT	CR	Relapse M4 death M12
11	Resistant disease	IV B Lung +	CCP	NR	Death D21
12	Resistant disease	II B	VACC	CR	Relapse M3 death M14
13	Resistant disease	IV B Lung +	COMAC + TBI 10	CR	Death in CR M3
14	Resistant disease	IV B Lung +	COMAC + TBI 10	PR ^a	Death D4
15	Resistant disease	II B Med +	COC Melph.	NR	Death D35
16	Resistant disease	III B	VP16-C + TBI 10	NR	Death D21
17	3rd relapse off treatment	IV B	VP16-A-M	NE	Death D17

^aAnatomic post-mortem data; ^bDetails on protocol Table II; + Involvement of BM (bone marrow), Bone, Mediastinum (Med), L (liver) and Lung (Lung +).

protocol including both cyclophosphamide and total body irradiation. Other toxicities are summarized in Table II.

Discussion

In Hodgkin's disease conventional therapy leads to cure in such a high percentage of cases that more toxic regimens are not required for the great majority of patients. Refractory patients, however, are rarely cured, even when different conventional regimens are attempted as salvage therapy (Bonadonna *et al.*, 1982; Santoro *et al.*, 1982; Canellos, 1985). The most optimistic report concerning the use of ABVD emanated from Milan (Santoro *et al.*, 1982). The series consisted of a particularly favourable patient population at relapse which achieved a 59% CR rate with 38% of these free of disease at 5 years (i.e. 15% overall survival at 5 years). Early series composed of heavily pretreated patients failed to confirm these results and it is now quite clear that long term survival is rare and usually limited to those who relapse off therapy and with limited lymph nodes involvement. The relapse patients studied in this report consisted of 11 who never reached CR in the course of the disease, 3 who relapsed on therapy and 3 who relapsed off therapy. However, even if the result of second line treatment must be interpreted with caution ours is a bad prognosis group with conventional rescue protocol (Santoro, 1985).

As HD is very sensitive to both radiotherapy and chemotherapy, it might be anticipated that a dose response effect could lead to better results with more intensive schedules. Although there are few long term survivors in this series it is an important conclusion for future studies that 9 out of 17 such heavily treated patients achieved a complete remission. Response in 7 out of 11 patients with progressive disease, previously resistant to conventional therapy is clear evidence for a dose effect relationship in HD.

An antitumour effect has been observed by other teams using either cyclophosphamide+TBI (Appelbaum *et al.*, 1985; Phillips *et al.*, 1984) Melphalan (Corringham *et al.*, 1983) BCNU (Carella *et al.*, 1983, 1984) or CBV (Spitzer *et al.*, 1983). Including this report a total of 48 patients have been treated so far with high dose combination chemotherapy regimens. Twenty eight patients (58%) achieved CR. Of these 10 relapsed within 6 months and 4 died early in remission due to complication of the transplant procedure. An assessment of disease-free survival in the 14 patients still free of disease is limited because of the short observation period (5 were observed for 12 months

or less). However there are 9 survivors in remission at 24+, 25+, 25+, 34+, 38+, 39+, 43+ and 66+ months.

There may be lessons to be learned from experience in Non Hodgkin's Lymphoma (NHL) where a similarly high CR rate was achieved after ABMT in phase I studies but durable remission was rare (Philip *et al.*, 1983, 1984, 1985). The concept of resistant relapse and non resistant relapse seems to be important (Philip *et al.*, 1984): in NHL only relapsed patients who are still chemosensitive to salvage therapy are likely to be cured by massive therapy. The situation could be similar in HD (2/3 such patients being long term survivors in this report).

The issue of the need for ABMT after regimens not including TBI is often raised. Whilst it is probable that myeloreconstitution will occur after high dose melphalan or BACT, it has been demonstrated that ABMT reduced the duration of aplasia (Appelbaum, 1978). Where tumour reinfusion is not thought to be a likely problem there seems little reason not to try and reduce morbidity by the use of ABMT. Allogenic bone marrow transplantation could also be used (Appelbaum *et al.*, 1985).

The toxicity of these high dose treatment regimens, even with the support of ABMT, must be considered a serious problem (Dumont *et al.*, 1984) since 7 patients, in this series, died of sepsis or cardio-respiratory failure. In other reports, early deaths due to interstitial pneumonitis, sepsis or other toxicities were common in protocols including CP+TBI (Goldstone, 1984). However, in the 48 patients reported so far in the literature, 11 (22%) died of toxicity, a treatment related death ratio comparable to similar studies in NHL (Philip *et al.*, 1985). Almost all patients have, however, been previously given intensive chemotherapy and often extensive irradiation, and it is likely that less toxicity would be observed if ABMT was performed earlier in the course of the disease. Initially resistant patients, such as those only in partial remission after short therapeutic attempts (Ferme *et al.*, 1984) and early or second relapses, could be suitable candidates. These patients are unlikely to achieve a complete durable remission with conventional therapy and would be the best candidates for a high dose regimen.

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