Eur J Cancer Clin Oncol, Vol. 22, No. 7, pp. 871–877, 1986.
Printed in Great Britain.

0277–5379/86$3.00+0.00
Pergamon Journals Ltd.

High Dose Therapy and Autologous Marrow Transplantation as Salvage Treatment for Patients with Diffuse Large Cell Lymphoma

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Abstract—*Twenty-nine patients with diffuse large cell lymphoma who failed traditional chemotherapy were treated with high dose chemotherapy with or without total body irradiation followed by infusion of cryopreserved autologous marrow. Complete response was achieved in* 11/29 *patients* (38%), *partial response in* 13/29 *patients* (45%) *and* 5/29 *patients* (17%) *had no response. Six complete responders remain well and free of disease for* 5+, 6+, 9+, 10+, 18+ and 25+ months, 3 *relapsed at* 2, 3 *and* 8 months *after marrow infusion, and* 2 *died from infectious complications. Complete response was seen more frequently with the absence of bulky tumor* (70 *vs* 21%, P = 0.03), *a total body irradiation containing regimen* (52 *vs* 0%, P = 0.03), *a history of complete remission with initial chemotherapy* (55% *vs.* 9%, P = 0.03), *and a performance status* ≥ 80 (56 *vs* 15%, P = 0.06). *High dose therapy had a high response rate* (83%) *in resistant diffuse large cell lymphoma and yielded durable complete responses in a minority of these patients.*

INTRODUCTION

THE MOST common aggressive non-Hodgkins' lymphoma is diffuse large cell lymphoma. Although highly chemotherapy responsive, the cure rate in large series with long follow-up has not exceeded 50%. Failure to achieve a complete remission with chemotherapy, or relapse after complete remission has been achieved, almost always means eventual death from lymphoma. Salvage chemotherapy regimens in this disease have been disappointing with only rare reports of cures [1].

A dose–response curve to chemotherapy has been demonstrated in a variety of tumors [2]. In addition, present cryopreservation technology has made reconstitution after reinfusion of frozen autologous marrow following marrow ablative therapy highly reproducible [3]. This allowed the study of dose escalation in lymphomas using agents with primarily marrow toxicity. Cures have been regularly reported in relapsed Burkitt's lymphoma with high dose therapy and autologous marrow transplantation [4]. Most reports to date of high dose therapy and autologous marrow transplantation in other lymphomas have studied the feasibility of the approach or looked at the use of a particular regimen while treating a mixture of histologic types [5–24]. This treatment has been reported in few patients with diffuse large cell lymphoma. We therefore reviewed all the patients with diffuse large cell lymphoma treated at our institutions in studies of high dose therapy and autologous marrow transplantation to gain insight into the tumor response rate and the tolerance of these generally older patients to this very intensive treatment approach.

PATIENTS AND METHODS

This report presents the results of high dose therapy and autologous bone marrow transplantation for all patients with *de novo* diffuse large cell lymphoma treated by the authors at their respective institutions through December 1984. These 29 patients were treated in a series of sequential studies utilizing different treatment regimens. Patients with all histologic subtypes of lymphoma were entered into these studies. Criteria for entry included demonstrated incurability with standard

Accepted 16 December 1985.
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chemotherapy and informed consent. Patients were considered incurable after failing a front-line, adriamycin containing chemotherapy regimen. However, in practice most patients had received one or more salvage chemotherapy regimens. Early in these studies patients were included if they had a Karnofsky score of ≥ 40, did not have bone marrow involvement, and were less than 55 yr of age. More recently patients up to 61 yr of age have been treated. The patient's clinical characteristics are presented in Table 1. All patients had active lymphoma at the time of high dose therapy.

The treatment regimens employed in these studies all utilized high dose chemotherapy with or without total body irradiation. The studies were sequential and included patients with all histologic types of lymphoma. We examined the possibility that patients with diffuse large cell lymphoma received a chemotherapy only regimen or a total body irradiation containing regimen based on prognostic factors (i.e. if sicker patients did not receive irradiation). There was not a significant imbalance between the patients receiving or not receiving total body irradiation for the prognostic variables high tumor bulk (62 vs 75%, $P = 0.81$), Karnofsky score .016 70 (38 vs 62%,, $P = 0.44$), or lack of complete remission to the initial chemotherapy regimen (33 vs 50%, $P = 0.68$). The treatment regimens utilized in the studies and the number of patients with diffuse large cell lymphoma were as follows:

1. (11 patients)
   cytarbine 3 g/m^2 i.v.every 12 hr for 6 doses (Days -10, -9, -8) (6 patients) or 8 doses (Days -8, -7, -3, -2 *or* Days -11, -10, -7, -6) (5 patients),
   cyclophosphamide 90 mg/kg i.v. for 1 dose (Day -8 *or* -6),
   total body irradiation 900 cGy in 1 dose (Day 0) (2 patients) or 250 cGy daily × 5 (Days -4, -3, -2, -1, 0) (9 patients).

2. (6 patients)
   melphalan 70 mg/kg i.v. daily for 2 doses (Days -6, -5)
   total body irradiation 170 cGy (4 patients) or 180 cGy (2 patients) twice daily for 5 doses (Days -2, -1, 0).

3. (4 patients)
   cyclophosphamide 60 mg/kg i.v. daily for 2 doses (Days -6, -5)
   total body irradiation 170cGy (3 patients) or 180 cGy (1 patient) twice daily for 5 doses (Days -2, -1, 0).

4. (8 patients)
   carmustine 300 mg/m^2 i.v. once (Day -6)
   etoposide 100 mg/m^2 (4 patients) or 125 mg/m^2 (4 patients) iv. every 12 hr for 6 doses (Days -6, -5, -4)
   plus
   cyclophosphamide 1.5 g/m^2 i.v. daily × 4 (Days -6, -5, -4, -3) (4 patients) ***or***
   amsacrine 225 mg/m^2 i.v. daily × 2 (Days -6, -5) (4 patients).

Marrow in each case was obtained from the posterior iliac crest and cryopreserved in liquid nitrogen. No patient had morphologically recognizable lymphoma in the marrow at the time of storage. The marrow was not treated *in vitro*. The time from marrow collection to reinfusion varied from < 1 to 14 months (median < 1 month). The quantity of marrow actually reinfused varied from 1.2×10^8 to 4.7×10^8 nucleated marrow cells per kg of recipient weight. The patients were nursed in reverse isolation (16 patients at the University of Nebraska) or laminar air flow rooms (13 patients at M.D. Anderson).

Complete response refers to the absence of tumor after completing therapy documented either by clinical or biopsy reevaluation of sites known previously to contain disease or at autopsy. Partial response refers to at least a 50% shrinkage of all known disease. All other patients were considered nonresponders. Bulky tumor was defined as a tumor mass of ≥ 5 cm or > three sites of involvement. Informed consent for participation in a study of high dose therapy and autologous marrow transplantation as approved by the Institutional Review Board at each institution was obtained in each case. Survival curves were generated using the Life Table method. Statistical significance of differences between groups was determined using the chi-square test with the Yates correction.

RESULTS

The overall survival of the 29 patients is presented in Figure 1. Seven patients are alive with a projected 1 yr survival of 36%. The response to therapy is presented in Table 2. Eleven (38%) of the 29 patients had a complete response, 13 (45%) had partial response and five patients (17%) had no response. Complete response was more likely with the absence of bulky tumor (70 vs 21%, $P = 0.03$), a total body irradiation containing regimen (52 vs 0%, $P = 0.03$), a history of complete remission with initial chemotherapy (55 vs 9%, $P = 0.03$), and a performance status ≥ 80 (56 vs 15%, $P = 0.06$).

Two of the 11 patients in whom the high dose therapy produced a complete response died of infections in the first month after therapy. Three other patients relapsed after 2, 3 and 8 months of follow-up. Six patients remain well and free of disease for 5+, 6+, 9+, 10+, 18+ and 25+ months

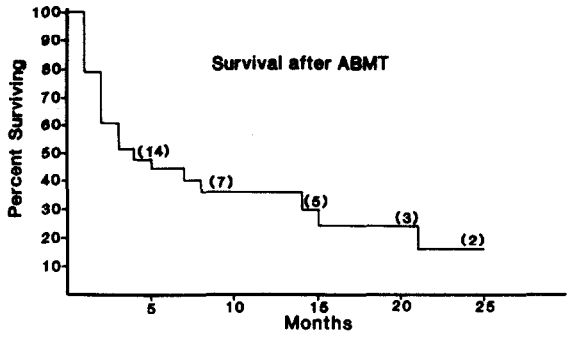

Fig. 1. The curve represents a Life Table plot of survival of the entire group of 29 patients. The numbers in parenthesis indicate patients surviving to that interval.

Table 1. Patient characteristics

Characteristic		Result
Number of patients		29
Age by decade	10–19	3
	20–29	11
	30-39	6
	40–49	5
	50–59	2
	60–69	2
Male : female		13 : 16
Karnofsky performance score:		
	⩾ 80	16
	⩽ 70	13
Frequent sites of disease		
	Mediastinum	13
	Abdominal mass	6
	Lung	5
	Stomach	3
Previous documentation of marrow Involvement by lymphoma		1
Previous documentation of CNS Involvement by lymphoma		0
Number of previous chemotherapy		
	Regimens 1	7
	2	15
	3	6
	4	1
Previous treatment with:		
	Cyclophosphamide	29
	Adriamycin	29
	Etoposide	14
	Radiotherapy	12
Best response to previous chemotherapy:		
	Complete remission	18
	Never complete remission	11
Status at high dose therapy:		
	Primarily refractory to 'standard' chemotherapy	11
	Relapsed, failed salvage therapy, active disease	16
	Treated at relapse from initial complete remission	2

after marrow infusion. The disease-free survival curve for the patients achieving a complete response and leaving the hospital well is presented in Fig. 2. There were 11 patients who combined the favourable prognostic factors of being fully ambulatory (i.e. Karnofsky ⩾ 80), having achieved a complete remission with earlier therapy, and receiving total body irradiation in the preparative regimen. These formed a particularly favourable sub-group with nine (82%) have a complete response and six (55%) continuing alive without evidence of recurrence. All the patients currently surviving in continuous remission came from this sub-group.

The myelosuppression associated with the high dose therapy was severe. All patients had $< 0.1 \times 10^9/l$ granulocytes and all required platelet and red cell transfusions. Six patients died

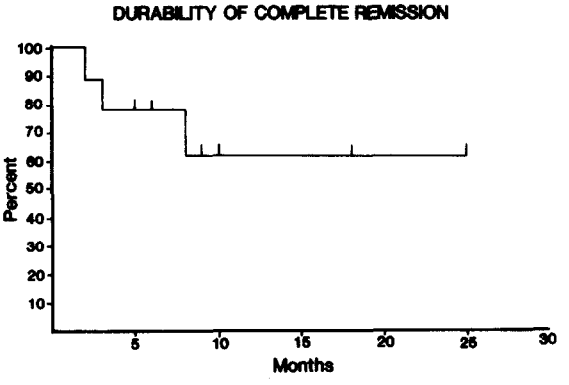

Fig. 2. The curve represents a Life Table plot of complete remission duration after high dose therapy and autologous marrow transplantation. The deflections on the curve indicate a patient currently alive and in remission at that interval.

early before peripheral blood counts had recovered. The remaining patients reached $0.5 \times 10^9/l$ granulocytes in a median of 23 days (range 9–43) and a platelet count of $20 \times 10^9/l$ in a median of 20 days (range 8–39) following marrow infusion. Two patients were not totally independent of platelet transfusions at the time of their deaths 4 and 5 months after marrow infusion. All patients had fever and required antibiotics. Fourteen patients had documented serious infections and four patients died from sepsis. Mucositis was frequent and more severe with a total body irradiation containing regimen. Interstitial pneumonia was not seen in any patient. In three patients who had never had bone marrow involvement by lymphoma, the initial site of progressive disease after treatment was in the marrow. This was associated with circulating lymphoma cells and occurred coincident with the reappearance of normal hematopoiesis suggesting possible, unrecognized marrow contamination by lymphoma.

Table 2. Tumor response by clinical characteristics

Characteristic	Number of patients	Tumor response to high dose therapy: Complete response (%)	Partial response (%)	No response (%)
Overall	29	11 (38)	13 (45)	5 (17)
Preparative regimen:				
Cytarabine + cyclophosphamide + TBI	11	8 (73)	3 (27)	0 (0)
Melphalan + TBI	6	3 (50)	3 (50)	0 (0)
Cyclophosphamide + TBI	4	0 (0)	1 (25)	3 (75)
Carmustine + etoposide + cyclophosphamide *or* amsacrine	8	0 (0)	6 (75)	2 (25)
Performance status:				
≥ 80	16	9 (56)	5 (31)	2 (13)
≤ 70	13	2 (15)	8 (62)	3 (23)
Response to previous therapy:				
Primarily refractory	11	1 (9)	9 (82)	0 (9)
Relapsed from CR, failed salvage	16	8 (50)	4 (25)	4 (25)
Treated at relapse from CR	2	2 (100)	0 (0)	0 (0)
Age:				
10–19	3	1 (33)	2 (67)	0 (0)
20–29	11	4 (36)	6 (55)	1 (9)
30–39	6	1 (17)	2 (33)	3 (50)
40–49	5	3 (60)	2 (40)	0 (0)
50–59	2	1 (50)	0 (0)	1 (50)
60–69	2	1 (50)	1 (50)	0 (0)
Bulky tumor:				
Yes	19	4 (21)	11 (58)	4 (21)
No	10	7 (70)	2 (20)	1 (10)
Sites of disease:				
Mediastinum	13	4 (31)	6 (46)	3 (23)
Abdominal mass	6	2 (33)	3 (50)	1 (17)
Lung	5	1 (20)	3 (60)	1 (20)
Stomach	3	0 (0)	3 (100)	0 (0)

DISCUSSION

These 29 patients represent the largest reported series of patients with relapsed and refractory diffuse large cell lymphoma treated with high dose therapy and autologous marrow transplantation. This approach yielded a high total response rate (83%) and frequent complete responses (38%) in these adult patients who had failed standard chemotherapy. Six patients continue alive and well without relapse of their lymphoma for 5+ to 25+ months.

Several other patients with diffuse large cell lymphoma have been included in previously published series of high dose therapy and autologous marrow transplantation. Table 3 summarizes the results in 41 previously reported patients with relapsed diffuse large cell lymphoma and Table 4 presents the results of high dose therapy and autologous marrow transplantation in 11 patients who received this treatment as their first therapy for diffuse large cell lymphoma, and nine patients treated in completed remission. In addition to these reports, Appelbaum *et al.* reported one patient treated with high dose cyclophosphamide and total body radiotherapy followed by allogeneic bone marrow transplantation while in relapse and 1 patient in second complete remission from diffuse large cell lymphoma (25]. It is apparent from our results and these studies that high dose chemotherapy with or without total body irradiation is very active in diffuse large cell lymphoma. However, this treatment requires long hospitalizations and is associated with a considerable number of treatment related deaths in these relatively older patients. It would be preferable to salvage patients with easier to administer, conventional outpatient chemotherapy regimens. Unfortunately, patients who have failed to be cured with front-line che-

Table 3. Previous reports of high dose therapy and autologous marrow rescue in relapsed diffuse large cell lymphoma

Reference	Number of patients	Treatment regimen	Complete response	Follow-up
6	13	Cyclophosphamide + TBI	6 (46%)	4 relapsed 2 in continuous CR 19+ and 38+ months
24	11	Cyclophosphamide + TBI	7 (64%)*	5 continue well for 3+ to 24+ months
7	6	Chemotherapy alone	5 (100% of evaluable patients)	All relapsed
7	1	BACT + TBI	1	In CR 40+ months
13	4	Cyclophosphamide + TBI	4 (100%)	2 relapsed, 2 in CR 19+ and 5+ months
12	3	BACT	—	All progressed
11	1	Mitomycin	0	—
23	1	Cyclophosphamide + TBI	1	Relapsed at 6 months
15	1	Cyclophosphamide + busulfan	1	Died at 2 months

* Might be an underestimate due to difficulty in restaging patients with mediastinal disease.

Table 4. Reports of high dose therapy and autologous marrow rescue as initial treatment for diffuse large cell lymphoma or as 'consolidation therapy' for patients in complete remission (CR)

Reference	Number of patients	Setting	Treatment regimen	Response follow-up
8	10	Initial treatment	BACV followed by 2 courses of 'consolidation' with conventional therapy	6 CR (1 relapsed others in CR 6+, 13+, 16+, 21+, 22+ months
24	9	Immediately following initial chemotherapy	Cyclophosphamide + TBI	8 continue well for 5+ to 31+ months
7	5	3 1st CR, 2 2nd CR	2 chemotherapy alone, 3 chemotherapy + TBI	2 in continuous CR 24+ and 25+ months
9	3	1st CR	TACC	2 in continuous CR 6+ and 30+ months
13	1	2nd CR	Cyclophosphamide + TBI	Continuous CR 10+ months
9	1	Initial treatment	TACC + local radiotherapy	CR, relapsed at 21 months

motherapy regimens have proven particularly refractory to salvage with further chemotherapy in conventional doses. Only an occasional report has described any long-term, disease-free survivors [1].

The three patients in our series who had tumor progression in the bone marrow despite having histologically negative marrows reinfused raise the issue of inapparent marrow contamination and the potential benefit of marrow 'purging'. This might be accomplished by removing or destroying unseen lymphoma cells using immunologic or pharmacologic techniques [26], or by concentrating marrow stem cells and leaving the tumor cells behind. At the present time, our inability to cause complete responses in the majority of patients with refractory diffuse large cell lymphoma is the major factor limiting successful treatment and not the reinfusion of lymphoma cells. However, as treatment regimens improve, or patients are treated earlier in the course of their disease where the present regim-

ens are more effective, this consideration is likely to become more important. Most of the patients in this series had their marrow stored immediately before high dose therapy at a time of active disease. One potential alternative to 'purging' for some patients would be to store marrows during complete remission. In sub-groups of patients at high risk to relapse this might be practical and cost-effective. Perhaps the recently described technique used to detect morphologically inapparent circulating lymphoma cells will help select patients in whom marrow 'purging' will be necessary [27].

Lymphomas are a diverse group of diseases with varying natural history and response to therapy. The most common aggressive lymphoma is diffuse large cell lymphoma. This tumor is predominantly a disease of adults. Because available chemotherapeutic regimens cure at best half of the patients with advanced, large cell lymphoma, better treatment approaches are necessary. We studied very high dose therapy with autologous marrow transplantation in 29 patients with advanced, relapsed diffuse large cell lymphoma who had failed to be cured with traditional chemotherapy. Even in this very poor risk group, high dose therapy produced a high total response rate (83%) and incidence of complete response (38%). This treatment approach was more likely to be beneficial to patients with a good performance status, less advanced disease, and a history of response to chemotherapy at traditional dose levels. High dose therapy and autologous marrow transplantation should be considered in patients without bone marrow involvement who fail to be cured with their initial chemotherapy regimen.

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