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Very high dose chemotherapy with autologous bone marrow rescue in adult patients with resistant relapsed lymphoma

C. C. Anderson[1], A. H. Goldstone[1], R. L. Souhami[1], D. C. Linch[2], P. G. Harper[3], K. A. McLennan[2], M. Jones[1], S. J. Machin[2], A. M Jelliffe[2], J. C. Cawley[1], and J. D. M. Richards[1]

[1] University College Hospital, Gower St., London, Wl.
[2] Middlesex Hospital, Mortimer St., London, Wl.
[3] Guy's Hospital, St. Thomas' St., London, SEl, England

Summary. Seventeen patients with advanced lymphoma were treated with high-dose chemotherapy with autologous bone marrow rescue. In 11 patients with non-Hodgkin's lymphoma (NHL) there were 2 complete remissions (CRs) and 2 partial remissions (PRs), and in 6 patients with Hodgkin's disease there were 5 CRs. Three patients remain well in unmaintained remission (days 874, 446 and 351), and a further 2 are alive and still receiving treatment (days 650 and 558). This type of therapy appears useful and should now be considered earlier in the course of the disease.

Introduction

Recent combination chemotherapy regimens have resulted in improved rates of complete remission and probably of cure in patients with non-Hodgkins's lymphoma (NHL) of high-grade histology [2, 5, 13]. The outlook for patients who have relapsed, however, remains poor [1, 3]. The overall survival in Hodgkin's disease (HD) is better than in high-grade NHL, but some patients relapse and fail to respond to second-line therapy [4].

We have therefore investigated the effects of very high dose chemotherapy in patients with relapsed NHL and HD resistant to conventional dosage chemotherapy. Autologous bone marrow transplantation was used to ameliorate the severe myelotoxicity associated with such therapy. The aim of this study was to determine whether dose escalation of cytotoxic drugs could produce significant and lasting clinical responses in these patients.

Patients and methods

Patient characteristics. The 17 patients reported on in this paper are detailed in Table 1. They were all adult (14 male, 3 female), with a median age of 38 years (range 19–55). All patients had received more than one chemotherapy regimen and 15 had received anthracycline-containing combinations; 10 had also received radiotherapy. Eleven patients had non-Hodgkin's lymphoma (NHL) and 6 had Hodgkin's disease (HD). For the purposes of classification of status of disease at the time of grafting, 'resistant relapse' indicates progressive disease in spite of conventional chemotherapy, whilst 'nonresistant relapse' indicates response to second-, third- or fourth-line therapy despite relapse. The NCI-sponsored working formulation (1982) [10] was used for histological classification.

Bone marrow harvesting, cryopreservation and reinfusion. Bone marrow was harvested from patients at relapse in 16 cases and during remission in 1 case. In every case the marrow was clear of lymphoma as judged by morphological examination of bone marrow aspirates and trephine biopsies under the light microscope. The harvested bone marrow was processed and cryopreserved as previously described [6]. The mean number of nucleated cells frozen per kilogram of body weight was 1.6×10^8 (range 0.7×10^8/kg to 2.4×10^8/kg). Marrow was stored in liquid nitrogen for a median of 19 days (range 5–603 days) between harvesting and reinfusion of the first marrow aliquot. The marrow was reinfused into a central line as previously described [6].

Very high dose chemotherapy regimens. Two separate chemotherapy regimens were used, UCH I + II and BEAM (see Fig. 1).

UCH I+II was a two-course regimen designed to introduce as many new, potentially non-cross-resistant drugs as possible. Only one marrow harvest was performed, and providing that more than 1.2×10^8 nucleated cells/kg were obtained, after processing the harvested marrow was divided and half given after each course. UCH II was given immediatly on haematological recovery from UCH I. Twelve patients received UCH I, but only 5 received UCH I and II. UCH II was not given in 7 cases because of septicaemic death following UCH I (3 cases) or rapid progression of the disease (2 cases). In 2 cases the patients attained CR after UCH I and UCH II had been declined. No procedural deaths occurred in the 5 patients who received UCH II.

The BEAM regimen was used as a single therapeutic procedure. BCNU 300 mg/m^2 and cytosine arabinoside 800 mg/m^2 were common to UCH I. Melphalan 140 mg/m^2 was used in BEAM instead of the cyclophosphamide 4.5 g/m^2 in UCH I. BEAM also contains VPI6 400 mg/m^2.

All patients receiving very high dose chemotherapy were nursed in single rooms without filtered air precautions. Routine antifungal prophylaxis with oral nystatin or amphotericin was given. All patients had Hickman central catheters inserted prior to starting therapy.

Offprint requests to: C. Anderson

Table 1. Characteristics of patients included in the study

UPN	Age	Sex	Histopathology[a]	Interval (months) diagnosis to ABMT	Previous therapy[b]	Status at time of ABMT[c]	Chemotherapy protocol	Status after graft[d]		
								Immediate	→	Present
non-Hodgkin's lymphoma										
34	38	M	Int Gd Diff[1]	28	CHOP[1] M. BACOD[2]	Resist relapse[1]	UCH I + II	CR[1]	Relapsed Died of disease	Day 231 Day 250
65	39	M	Int Gd Diff	10	CHOP × 7 BACOP[3] M-BACOP[4]	Resist relapse	UCH I + II	PR[2]	Well	Day 874
75	49	M	High Gd[2] Lymphoblastic	11	CHOP Highdose MTX[5] DXT[6]	Resist relapse	UCH I	NE[3]	Died of septicaemia	Day 9
94	50	M	Int Gd Diff	21	Orchidectomy CHOP × 6	Nonresist[2] relapse	UCH I	CR	Relapsed Died of disease	Day 275 Day 316
101	47	M	Int Gd Diff	46	CHOP × 6 DXT	Nonresist[2] relapse	UCH I + II	PR	Relapsed	Day 263 Day 558
102	28	F	Int Gd Diff	10	CHOP × 3 HD MTX × 4 DXT	Resist relapse	UCH I	NR[4]	Died of disease	Day 33
114	29	M	Int Gd Diff	6	CHOP × 4 EVAP × 1[7]	Resist relapse	UCH I	NR	Died of disease	Day 44
126	21	M	High Gd Lymphoblastic	10	CHOP × 4 CYT/THIO/CYCLO × 1[8] Cranial DXT + IT MTX[9]	Resist relapse	BEAM	NR	Well	Day 351
133	41	M	Int Gd Diff	4	CHOP × 2	Resist relapse	BEAM	NR	Died of disease	Day 87
136	19	M	High Gd	10	M BACOD × 4	Resist relapse	BEAM	NR	Died of disease	Day 50
137	45	F	Int Gd Diff	39	DXT × 2 CHOP × 6 M-BACOD × 4	Resist relapse	BEAM	NR	Died of disease	Day 67

Table 1. Continued

UPN	Age	Sex	Histopathology[a]	Interval (months) diagnosis to ABMT	Previous therapy[b]	Status at time of ABMT[c]	Chemotherapy protocol	Status after graft[d]		
								Immediate	→	Present
Hodgkin's disease										
61	55	M	NS[3]	52	MOPP × 6[10] BACOP × 5	Resist relapse	UCH I & II	CR	Died of cardiac failure (no clinical evidence of disease at time of death)	Day 231
88	28	M	NS	47	MOPP × 6 CCNU/BLEO/Vbl/PN[11] DXT	Resist relapse	UCH I & II	CR	Relapsed	Day 143 Day 650
99	37	M	NS	65	LOPP[12] ABVD[13] DXT × 2	Resist relapse	UCH I	NE	Died of septicaemia	Day 14
113	46	M	NS	15	MOPP × 3 AVD × 5[14]	Resist relapse	UCH I	CR	Well	Day 446
116	24	F	NS	22	MOPP × 3 CCNU/BLEO/Vbl/PN × 6	Resist relapse	UCH I	CR	Died of septicaemia; tumour necrotic at autopsy	Day 40
124	29	M	Atypical	7	CHOP × 1 HD ARA C × 1[15]	Resist relapse	BEAM	CR	Died of aspergillus pneumonia, tumour necrotic at autopsy	Day 51

[a] *Histopathology:* [1] Intermediate grade diffuse; [2] High grade diffuse; [3] Nodular sclerosing

[b] *Previous therapy:* [1] Cyclophosphamide; adriamycin; vincristine; prednisolone; [2] Methotrexate; bleomycin; adriamycin; cyclophosphamide; vincristine; dexamethasone; [3] Bleomycin; adriamycin; cyclophosphamide; vincristine; prednisolone; [4] Methotrexate; bleomycin; adriamycin; cyclophosphamide; vincristine; prednisolone; [5] Methotrexate; [6] Radiotherapy; [7] VP16; vinblastine; adriamycin; prednisolone; [8] Cytosine arabinoside; thioguanine; cyclophosphamide; [9] Intrathecal methotrexate; [10] Nitrogen mustard; vincristine; procarbazine; prednisolone; [11] Lomustine (CCNU); bleomycin; vinblastine; prednisolone; [12] Chlorambucil; vincristine; procarbacine; prednisolone; [13] Adriamycin; bleomycin; vinblastine; imidazole carboximide; [14] Adriamycin; vinblastine; imidazole carboximide; [15] High-dose cytosine arabinoside

[c] *Status at time of ABMT:* [1] Resistant relapse; [2] Nonresistant relapse

[d] *Status after graft:* [1] Complete remission; [2] Partial remission; [3] Not evaluable; [4] No response

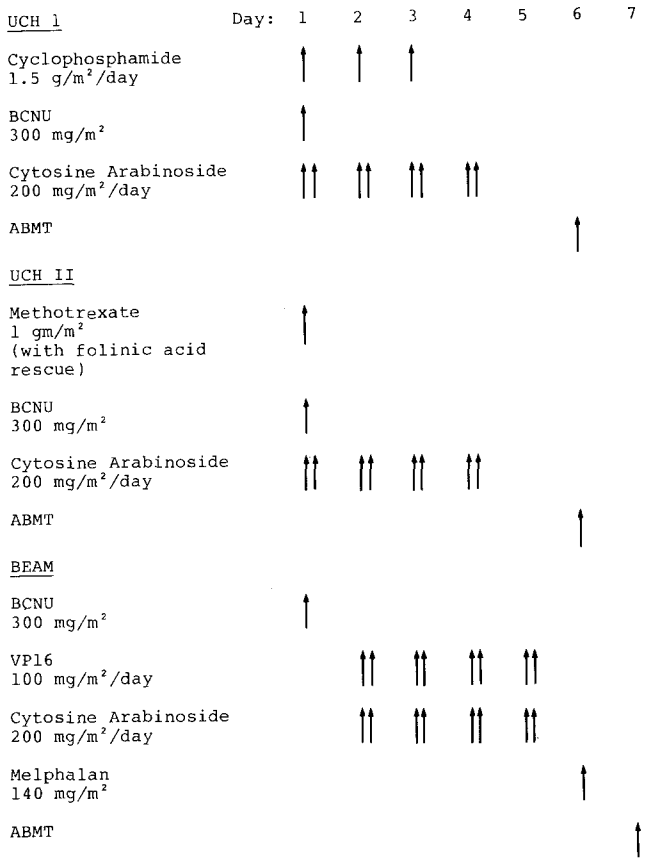

Fig. 1. Chemotherapy protocols

Results

Response to very high dose therapy

Response to therapy was evaluated both clinically and by repeat computed axial tomography (CAT) scanning where previously abnormal. A complete remission was defined as the complete resolution of all signs and abnormal investigations in patients surviving beyond 30 days.

Non-Hodgkin's lymphoma

Of 11 patients with NHL, 2 achieved CR and 2 PR. In both patients with PR there was a clinical CR but the repeat CAT scans showed a residual mass in the abdomen. One of these patients (with the unique patient number [UPN] 65) was given 29.80 Gy DXT to the abdominal mass, which had no effect as judged by further CT scanning. This patient, however, remains alive and well at day 874. The other patient (UPN 101) was given no further treatment at this stage. At day 263 laparotomy and cholecystectomy were performed following an episode of cholecystitis. Splenectomy and multiple para-aortic and mesenteric node biopsies showed no disease. A biopsy from retroperitoneal tissue near the base of the left ureter showed a lymphocytic infiltration strongly suggestive of lymphoma. The patient was then treated with para-aortic irradiation and further chemotherapy. There was no response in 6 patients. One patient was nonevaluable (UPN 75) because of death from septicaemia at day 9. Of the 4 responding patients, 2 are still alive at days 874 and 558.

A further patient (UPN 126) was treated with autologous bone marrow transplant (ABMT) when thought to have failed induction treatment with CHOP × 4, because a CAT scan showed a residual mass in the mediastinum. A repeat CAT scan after ABMT showed no change. He was therefore given boost DXT to the mediastinum. Over the next few months the mass shrank. He has therefore been classified as a nonresponder, but he remains well with no other evidence of disease and no treatment at day 351.

Hodgkin's disease

Of the six patients with HD, five achieved CR. In two of these patients marrow regeneration was delayed and these two patients died in aplasia on days 40 and 51 (UPN 116 and 124, respectively). Post-mortem examination showed foci of necrosis without evidence of viable lymphoma. One patient (UPN 61) died in CR of acute cardiac failure of uncertain cause. A further patient (UPN 88) has relapsed and only one patient (UPN 113) remains alive and well at 446 days. The sixth patient with HD was nonevaluable because of septicaemic death at day 14.

Haematological recovery

Of the 17 patients, 15 survived beyond 30 days and were evaluable for haematological recovery. Two patients had not shown haematological recovery at the time of their deaths at days 40 and 51. In the 13 remaining patients the mean time from the day of ABMT to achieving a neutrophil count of $> 0.5 \times 10^9$/l was 20 days (range 13–34 days) and that to a platelet count $> 50 \times 10^9$/l was 22 days (range 12–44 days). Among these patients there was no relationship between the number of nucleated bone marrow cells infused and the time of recovery of the neutrophil and platelet counts. In the two patients surviving beyond 30 days who did not regenerate, the numbers of nucleated cells infused were 0.85×10^8/kg and 0.7×10^8/kg, which were well below the mean of 1.6×10^8/kg (range $0.65–2.4 \times 10^8$/kg). These two patients both had Hodgkin's disease and had been heavily pretreated.

Morbidity

Infective complications. Four patients (24%) died of sepsis before engraftment. Three patients had clinical septicaemia; organisms were isolated in two cases (acinetobacter, *Staphylococcus aureus*) but not in the third. A fourth died of aspergillus pneumonia. There were other nonfatal infections with pyrexias occurring in 12 of the remaining 13 patients (92%) and organisms were isolated from the blood in 6 (46%) (4 gram-negative: 2 acinetobacter, 1 *Klebsiella aerogenes*, 1 *E. coli;* 2 gram-positive: 1 *Staph. albus* B1 haemolytic streptococcus). Candida was isolated from multiple sites in 8 patients (62%) despite antifungal prophylaxis. Infection along the line of the catheter necessitated its removal in 2 patients. *Staph. albus* was isolated from skin sites in 9 patients (53%), but only one episode of septicaemia was documented.

Noninfective complications. One patient died a cardiac death (day 231) whilst in CR. This patient had HD and his death may reflect cumulative toxicity from drugs and irradiation. One patient had his Hickman catheter removed because of a subclavian vein thrombosis. One patient suffered haemorrhagic cystitis in spite of adequate hydration and mesnum administration.

Discussion

This study demonstrates that in patients with lymphoma resistant to conventional therapy, very high dose chemotherapy may still produce significant responses and even complete remission in some cases. This was particularly noticeable in the patients with relapsed resistant Hodgkin's disease, in whom 5 of 6 achieved a CR. The overall response rate of 53% is similar to the value of 63% recently reported by Phillips et al., who used cyclophosphamide and total body irradiation as the therapeutic modalities [12].

These responses have not in general been sustained. In patients with NHL the two who achieved CR both relapsed (at day 213 and day 275) and both are now dead. Of the two patients for whom PR was recorded because of apparent residual abdominal disease on CT scanning (UPN 65 and 101), one remains alive and well at 874 days and the other has had a laparotomy at which residual disease was detected, but is alive at 558 days. With abdominal CT scanning it is sometimes difficult to determine whether a residual mass is a tumour or inflammatory and fibrotic tissue.

Of the five HD patients who achieved CR, only 1 is alive and disease-free (UPN 113) at day 446. One patient has relapsed but is still alive with further chemotherapy at day 650 (UPN 88), and three patients have died of procedure-related complications, infection in two and cardiac failure in one.

The morbidity in this series of patients has been high, with sepsis the major complication and procedure-related deaths occurring in 4/17 patients. This is perhaps not surprising in view of the poor clinical condition of many of these patients with end-stage disease.

Similarly, high numbers of treatment-related deaths have been reported in two other series with high-dose therapy and ABMT in patients with lymphoma who have received extensive previous therapy [11, 12].

To improve upon these results it will be necessary to contemplate very high dose chemotherapy and ABMT at an earlier stage in the disease process, when the patients are in better clinical condition and have less resistant disease. In addition, the marrow is more likely to be cellular at this time, thus avoiding the low cell yields obtained at marrow harvest which may have contributed to two of the deaths in this series. This strategy of bringing forward high-dose therapy to an earlier stage of the disease has been successful for allogeneic bone marrow transplantation in acute myeloid leukaemia (AML) [11], but the situation is more complex for the lymphomas. Unlike AML patients, most patients with HD, and many with NHL, can be cured by much safer initial therapy. In Hodgkin's disease it may be possible to define a very poor prognostic group at presentation based on the histology, haemoglobin, lymphocyte count and ESR [7, 8], and these patients may be suitable candidates for high-dose therapy and ABMT as early therapy. In disseminated stage III/IV NHL with aggressive histology, those patients not in CR after three courses of CHOP have a very poor prognosis, with $< 10\%$ long-term survivors (BNLI CHOP study unpublished data), and such patients should be considered for alternative therapy, such as ABMT, at this stage. In the study reported by Philip et al. [11] it should be noted that whereas all four patients treated with resistant relapsed disease died within 90 days, five of nine patients given grafts because of early failure to obtain CR or in second complete remission are alive at 100–900 days.

High-dose chemo/radiotherapy with autologous bone marrow transplantation has the advantage over allogeneic bone marrow transplantation that the approach is applicable to a large number of patients (no HLA-matched siblings required), the problems of graft-versus-host disease are not encountered, and therapy can be offered to much older patients. It has the major disadvantage, however, that lymphoma contaminating the marrow may be reinfused. In this and other studies of autologous bone marrow transplantation in lymphoma [11, 12] the marrows were not infiltrated as far as could be determined by morphological criteria, but clearly the presence of occult disease cannot be excluded. This anxiety has prompted some groups to 'purge' the harvested bone marrow of potentially malignant B cells in cases of B cell NHL [9]. In this study and that of Phillips et al. [12], however, the main cause of failure was primary resistance to the high-dose therapy used, and in those responding patients who relapsed the relapses were mainly localized to a site of previous lymphomatous involvement.

This study thus shows that in patients with relapsed Hodgkin's disease and non-Hodgkin's lymphoma resistant to conventional dosage chemotherapy very high dose chemotherapy and ABMT may still produce a significant antitumour response. The morbidity and relapse rate have been high, and it is clear that future studies of very high dose chemotherapy must be directed at poor prognosis patients at an earlier stage of their disease.

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