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High-dose Chemoradiotherapy and Bone Marrow Transplantation in Patients with Refractory Lymphoma*

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Abstract—*Eight adult patients with refractory Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL) were treated with high-dose combination chemotherapy (cyclophosphamide, BCNU and VP-16) or with cyclophosphamide and fractionated whole-body irradiation (TBI), followed by bone marrow transplant (BMT). Six patients received autologous and two patients allogeneic BMT. Five patients achieved complete remissions, and three of them (two with undifferentiated lymphoma, one with lymphoblastic lymphoma) are alive and free of disease* 4–18+ months *after BMT. The other two complete responders died of opportunistic infections* 2 *and* 5 months, *respectively, after BMT. One patient with HD achieved partial remission and is alive* 18+ months *after BMT. Two patients were considered failures: one developed leptomeningeal disease* 24 days *after BMT, and the other died of progressive lymphoma* 7 months *after BMT. Engraftment and prompt hematologic recovery occurred in all patients. The major toxicity included two fatal infections and one case of diffuse idiopathic interstitial pneumonitis. High-dose chemotherapy with or without TBI followed by BMT appears to produce a high response rate and, although associated with toxicity, it demonstrates the potential for salvaging patients with refractory lymphoma who otherwise would have a dismal prognosis.*

INTRODUCTION

PATIENTS with advanced Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL) are rarely cured of their disease after they fail conventional chemotherapy. However, some histological types, notably Burkitt's lymphoma (BL), may still be sensitive to intensive chemotherapy. With the help of bone marrow transplantation (BMT) as a means of hematologic support, it has been possible to administer intensive cytoreductive therapy and cure some patients with disseminated BL, and obtain long-term disease-free survivors in other types of NHL [1–4].

In the past several years we have gained experience with high-dose combination chemotherapy using cyclophosphamide, BCNU and VP-16 (CBV), and have documented its activity and acceptable toxicity against several refractory malignancies [5, 6]. Based on the fact that these drugs are active against lymphomas [7–9], we have treated selected patients with refractory HD or NHL using CBV, or cyclophosphamide plus total body irradiation (TBI), followed by autologous or allogeneic BMT.

We report here our experience in eight patients with encouraging preliminary results.

MATERIALS AND METHODS

Eight patients were treated, 4 women and 4 men. Their age ranged between 21 and 35 yr, with a median of 25 yr. Two patients had HD, 3 had undifferentiated lymphoma (UL), 2 had lymphoblastic lymphoma (LL), and 1 had diffuse histiocytic lymphoma (DHL). All patients had received extensive prior chemotherapy, radiotherapy or both, depending on the daignosis, stage and protocol used at the time. All patients

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had BMT after they relapsed, either during or off therapy. Table 1 summarizes the clinical characteristics of the patients at the time of BMT.

Five patients received high-dose combination chemotherapy with CBV and 3 patients received high-dose cyclophosphamide and fractionated TBI (CY-TBI). In each group (CBV and CY-TBI), 1 patient received an allogeneic rather than autologous BMT because of suspected contamination of the autologous marrow with tumor cells. For autologous BMT, the bone marrow was harvested and cryopreserved 2–26 months (median 9 months) prior to infusion. At the time of collection the marrow was morphologically normal and had a normal cellularity. The process of aspiration and storage has been described previously [10].

All patients were restaged clinically before treatment. Prior to the administration of chemotherapy, patients received allopurinol and vigorous hydration to ensure adequate urinary output. In the CBV group cyclophosphamide was administered at a dose of 1.5 g/m^2 i.v. daily for 3 consecutive days (days 1–3). BCNU was given i.v. as a single dose of 300 mg/m^2 on day 1, and VP-16 150 mg/m^2 daily for 4 consecutive days (days 1–4). To prevent possible hypotension the daily dose of VP-16 was divided in two, each given i.v. over 2 hr in 250 ml normal saline solution. In the CY-TBI group cyclophosphamide was given at a dose of 2.4 g/m^2 on 2 consecutive days. After 1 day of rest, fractionated TBI was started at the dose of 170 rad twice a day for 3 days. The bone marrow was infused within 24 hr after irradiation was completed and at least 24 hr after the last dose of CBV chemotherapy. The two patients given allogeneic BMT received graft-vs-host disease (GVHD) prophylaxis with methotrexate, 10 mg/m^2 i.v. on days 1, 3, 7 and 11 from the day of bone marrow infusion (day 0), and weekly thereafter for the first 100 days after BMT.

Six patients received this therapy in a laminar air-flow room. Platelet transfusions were administered routinely when platelet counts fell below 20,000/μl. Three patients received therapeutic granulocyte transfusions. All blood products were irradiated with 5000 rad prior to transfusion.

Patients were evaluated for tumor response on day 30 and monthly thereafter. Patients were considered to have complete remission (CR) if all clinical and laboratory evidence, including roentgenograms and radioisotopic scans, showed that the tumor had disappeared. Partial response (PR) indicated a diminution in measurable tumor size by more than 50%. Patients failing to achieve CR or PR were defined as having achieved no response to the therapy.

RESULTS

Tumor response

Table 2 summarizes the outcome of each patient after BMT. The overall response rate was 75%; 5 patients had CRs and 1 had a PR. Two patients with UL and 1 patient with LL are alive and in complete, unmaintained remissions 540+, 120+ and 120+ days, respectively, after BMT. One patient with HD achieved PR with >50% reduction in parenchymal lung involvement. At 540+ days after BMT she is still in PR, receiving no further therapy. An attempt to evaluate her residual lung disease by needle aspiration failed to reveal any cells suggestive of HD. One patient with UL had almost total regression of her nodal disease, but developed leptomeningeal relapse 24 days after transplantation and is currently receiving intrathecal therapy.

There were 3 deaths in our series. One patient with HD achieved CR but died 150 days after BMT of respiratory failure caused by *Pneumocystis carinii* and *Legionella pneumophilia* serogroup III. At post-mortem no evidence of residual tumor was found. One patient with DHL also achieved CR, but died 2 months after BMT of disseminated cytomegalovirus (CMV) and candida sepsis. At post-mortem microscopic lymphomatous involvement was demonstrated in the kidneys, bone marrow and lymph nodes. One patient with LL had only a transient PR of less than 2 months' duration and died of progressive lymphoma 7 months after BMT.

Hematopoietic reconstitution

Both regimens produced severe marrow aplasia. All patients had leukocyte counts of $\leqslant$100/μl for a median of 8 days (range 5–14) and platelet counts of $\leqslant$20,000/μl for a median of 10 days (range 3–13). Marrow recovery occurred in all patients. The absolute granulocyte count (AGC) was $\geqslant$500/μl at a median of 21 days (range 15–39) following transplantation for the 6 patients with autologous BMT and at 29 days for the 2 patients with allogeneic BMT. For AGC to reach $\geqslant$1000/μl, the median was 31 days (range 17–43) in the group that received autologous marrow transplants and 34 days for the 2 patients who received allogeneic transplants. For AGC to reach $\geqslant$1500, the median was 36 days (range 18–50) for those with autologous transplants and 37.5 days for the other 2 patients. We found it more difficult to define the day when the platelet count rose spontaneously to $\geqslant$20,000/μl and $\geqslant$50,000/μl, as most patients received transfusions when their platelet count dropped to or below 20,000/μl. However, platelet transfusions were no longer necessary by day 18–43 (median 21.5) after BMT.

Table 1. Clinical characteristics of patients at BMT

Patient	Age/sex (yr)	Diagnosis*	Disease duration (months)	Prior chemotherapy†	Prior irradiation	Response/ duration (months)	Disease sites‡ at BMT	Comments
1	22/M	HD-NS	24	MOPP-bleo × 9	mantle	PR/13	LN	relapse off treatment
2	35/M	LL	28	CHOP × 8 COP × 5 AIV × 7 HD-Ara-C × 4	none	CR/25	mediastinum BM, PB	CR after 1st course; relapse during treatment
3	26/F	DHL	15	CHOP-bleo-levamisole × 10 Ifos/MTX/VCR × 5 gallium nitrate	femur spine	CR/8	LN	relapse during treatment
4	22/F	LL	6	MCOP × 2 IMV × 2 HOAP-bleo × 2 MCOP × 1	none	CR/5	pelvis, BM	CR after 1st course; relapse during treatment
5	28/M	UNBL	24	CHOP × 9 AIV × 2	thigh	CR/20	jejunum	BMT done after resection of jejunal segment
6	24/F	HD-NS	60	MOPP-bleo × 4 ABVD × 8 IMV × 3 AMSA × 11 VM-26 × 3	mantle lung	PR/23	lungs	relapse off treatment
7	21/F	UNBL	8	MTX/CTX/VCR × 2 CTX/VP-16 × 1 HOAP-bleo × 2	none	PD	LN, abdomen	progressive refractory disease
8	32/M	UNBL	18	MCOP × 2 IMV × 2 HOAP-bleo × 2, then 3 courses of each combination above	brain	CR/14	BM, PB	successful treatment of prior leptomeningeal relapse

*HD-NS, Hodgkin's disease, nodular sclerosis; LL, lymphoblastic lymphoma; DHL, diffuse histiocytic lymphoma; UNBL, undifferentiated non-Burkitt's lymphoma.

†MOPP-bleo, nitrogen mustard, vincristine, prednisone, procarbazine and bleomycin; AIV, AMSA, ifosfamide and VP-16; HD-Ara-C, high-dose cytosine arabinoside; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; Ifos, ifosphamide; MTX, methotrexate; VCR, vincristine; CTX, cyclophosphamide; MCOP, methotrexate, vincristine, Ara-C and prednisone; ABVD, adriamycin, bleomycin, vinblastine and dacarbazine; COP, cyclophosphamide, vincristine and prednisone.

‡LN, generalized lymphadenopathy; BM, bone marrow; PB, peripheral blood.

Table 2. Treatment and result

Patient	Conditioning regimen	BMT	Outcome
1	CBV	autologous	died of mixed pneumocystis and legionella pneumonia at 5 months (no evidence of residual Hodgkin's disease)
2	CBV	allogeneic	alive in CR at 4+ months
3	CBV	autologous	died of disseminated CMV and candidemia at 2 months (microscopic residual lymphoma)
4	CBV	autologous	died of refractory lymphoma at 7 months
5	CY-TBI	allogeneic	alive in CR at 18+ months
6	CBV	autologous	alive in PR at 18+ months
7	CY-TBI	autologous	alive; leptomeningeal relapse at 24 days post-BMT
8	CY-TBI	autologous	alive in CR at 4+ months

CR, complete remission; PR, partial remission.

Non-hematologic toxicity

Two patients developed thrombocytopenia-related upper gastrointestinal bleeding that necessitated transfusion with blood products. Four patients with neutropenic fever responded to empiric systemic antibiotics, even though no causative organism was identified. In one patient with fever hypotension occurred, presumably due to sepsis. There were 2 fatal infections. One patient died of pneumonia caused by *Pneumocystis carinii* and *Legionella pneumopohila* serogroup III simultaneously. The other died of disseminated CMV and candidemia. Less serious infections included herpetic esophagitis in 1 patient who responded to systemic Ara-A, and *Herpes zoster* in another. All patients developed acute nausea or vomiting. A less common side-effect was mucositis (in three patients). Two patients had transient increase in liver enzymes. GVHD occurred in the 2 patients who received allogeneic BMT. Patient 2 developed acute GVHD-grade II involving the skin only, and patient 5 developed mild chronic GVHD with Sjögren-like features involving mainly the skin and mucous membranes. This patient also developed diffuse idiopathic interstitial pneumonitis, which improved with steroids.

DISCUSSION

Our results demonstrate that, using high-dose cytoreductive therapy and BMT, it is possible to achieve a high response rate in patients with advanced HD and NHL who have been extensively treated prior to progression of their disease. Using the 'BACT' regimen (BCNU, Ara-C, cyclophosphamide and 6-thioguanine) and autologous BMT for hematologic support, Applebaum and colleagues were the first to show that cures in poor-risk patients with disseminated malignant lymphoma were possible [1]. However, all of the long-term survivors in that series were patients with BL. Later, combining high-dose cyclophosphamide and TBI with identical-twin transplantation, Applebaum *et al.* reported 7 complete remissions in 8 patients with other types of NHL; 4 were long-term survivors, including 2 with diffuse poorly-differentiated lymphocytic lymphoma (DPDL), 1 with composite lymphoma (CL), and 1 with diffuse moderately well-differentiated lymphocytic lymphoma (DMWDLL) [11].

Gorin and colleagues used a regimen similar to BACT but substituted CCNU for BCNU, and reported complete remissions of short duration in 2 patients with Hodgkin's disease [12]. In their series, patients with NHL who had a long-term survival, including 1 patient with DHL, 2 with DPDL and 1 with nodular, poorly-differentiated lymphocytic lymphoma (NPDL), as well as 1 patient with HD, were treated at initial diagnosis and therefore are not considered refractory cases since they could have achieved a similar response with conventional chemotherapy alone [12]. Using high-dose cyclophosphamide with TBI and autologous BMT, Phillips *et al.* treated 18 lymphoma patients resistant to conventional therapy (8 with DHL, 6 with BL, 2 with HD and 1 with malignant histiocytosis-MH) and had a 56% CR rate. Two patients with BL, 1 with DHL and 1 with MH are alive after 14–46 months in unmaintained CR [4].

Autologous BMT has been tried more often than allogeneic BMT in patients with malignant lymphoma because of better availability and fewer complications. Using a high-dose combination of BCNU, Ara-C and cyclophosphamide plus TBI, followed by allogeneic BMT, O'Leary and colleagues treated 9 children with BL or LL.

Six of these 9 patients were treated in remission. Two patients died of acute carditis and sepsis and 1 patient died of GVHD and interstitial pneumonitis [13]. The overall survival rate in this series was 44%, with 4 patients alive, active and in complete unmaintained remission 6–51 months later.

Although allogeneic BMT is associated with more complications than autologous BMT, notably GVHD, there are situations where one prefers to use allogeneic BMT, as we did in 2 of 4 patients who had marrow involvement with lymphoma. Whether GVHD has any beneficial antitumor effect in lymphoma patients, as has been suggested in acute leukemia [14], remains to be established.

The hematologic recovery in our patients with autologous BMT was prompt and comparable with most published series, confirming again the established fact that cryopreserved autologous BMT enhances hematopoietic reconstitution [12, 15]. The toxicity of both conditioning regimens we used was acceptable. Four patients had fever during the neutropenic phase that presumably was due to infection, although no etiologic organism could be identified. There were 2 fatal infections, but in 1 patient this may have been due to the impaired host immunity known to occur in patients with HD, even during unmaintained complete remissions [16, 17]. One patient developed diffuse interstitial pneumonitis, which could have been due to radiation toxicity or be a result of immune dysregulation associated with chronic GVHD [18–20].

Although our series is small and a longer follow-up is needed, we have shown that with intensive cytoreductive therapy and BMT, patients with refractory HD and NHL can still be salvaged. The exact response rate and response duration for each disease category still need to be defined after more patients are treated.

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