# Intensive Therapy With Cyclophosphamide, Carmustine, Etoposide ± Cisplatin, and Autologous Bone Marrow Transplantation for Hodgkin's Disease in First Relapse After Combination Chemotherapy

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**The optimal timing in which to use intensive chemotherapy and autologous bone marrow transplantation (BMT) in Hodgkin's disease (HD) is uncertain. In 1985, we initiated a program in which this modality was used as the initial salvage therapy in patients relapsing after combination chemotherapy. Fifty-eight patients with HD in first relapse after primary chemotherapy received conditioning with high-dose cyclophosphamide, carmustine, etoposide (VP16-213) ± cisplatin (CBV ± P) followed by autologous BMT. All but six of these patients were given a median of two cycles of conventional chemotherapy ± involved field radiation therapy before CBV ± P and autologous BMT. These measures were not used as a means for patient selection; all patients receiving such therapy ultimately were transplanted. The probability of nonrelapse mortality, progression of HD, and progression-free survival post-BMT were calculated, and prognostic factors for progression-free survival were evaluated using the Cox proportional hazards method. Treatment-related deaths occurred in only three patients. Thirteen patients have relapsed at a median 0.7 years (range 0.1 to 3.5) post-BMT. At a median follow-up of 2.3 years (range 0.4 to 7.2), the actuarial progression-free survival is 64% (95% confidence interval, 46% to 78%). In the statistical analysis, three similarly weighted but independent prognostic factors were identified: "B" symptoms at relapse, extranodal disease at relapse, and initial remission duration of less than 1 year. Patients with no risk factors had a 3-year progression-free survival of 100%, compared with 81% in patients with one factor, 40% in those with two factors, and 0% in patients with all three factors. CBV ± P and autologous BMT is highly effective salvage therapy for HD patients in a first relapse, particularly in the subset of patients with less than two adverse factors. Therapy must be improved in the future for patients with ≥2 adverse factors.**


ALTHOUGH THE MAJORITY of patients with Hodgkin's disease (HD) achieve durable remissions and cure with conventional chemotherapy and/or radiation therapy, a proportion either fail to enter remission with primary chemotherapy or relapse after such therapy.[1] High-dose chemotherapy plus autologous bone marrow transplantation (BMT) has been applied to such HD patients for over a decade; numerous reports indicate that a significant proportion enter prolonged remission, although many relapse or succumb to regimen-related toxicity.[2]

The optimal time in the course of the patient's disease in which to apply this treatment has been the subject of considerable debate, particularly for patients relapsing after an initial complete remission (CR). In this setting, further conventional therapy can achieve subsequent CR that may be of long duration in some patients,[3,4] although a high percentage eventually die of their malignancy.[5] Since 1985, we have recommended the use of intensive therapy and autologous BMT at the first evidence of failure of primary chemotherapy. Of our first 100 patients treated with high-dose cyclophosphamide, carmustine (BCNU), etoposide (VP16-213) ± cisplatin (CBV±P), and autologous BMT for progressive HD, 58 were transplanted at the time of their first relapse after CR induced by primary multiagent chemotherapy. This report describes the outcome of patients receiving an autologous BMT regimen as their first salvage therapy.

## PATIENTS AND METHODS

### *Eligibility Criteria*

Patients were required to have progression of HD proven by biopsy or unequivocal radiologic progression after a CR induced by primary chemotherapy; patients with residual nonprogressive radiographic masses of uncertain origin were not treated with this transplant protocol. Patients were considered to have a low likelihood of cure with further conventional therapy; those with localized nodal recurrences considered curable with radiotherapy were specifically excluded.[3] Patients were required to be ≤60 years old and have major organ function ≥75% of normal. All patients who received autologous BM as the source of hematopoietic stem cell rescue were required to have a normal BM histology within 4 weeks of marrow harvest. Patients were treated according to institutional review board-approved studies at the University of British Columbia (BC), Vancouver General Hospital and BC Cancer Agency. All patients provided informed consent.

### *Patients*

The characteristics of the 58 patients are summarized in Table 1. Most had initial stage III or IV disease and 33 had "B" symptoms at diagnosis. All but seven patients had received initial therapy with seven- or eight-drug combinations such as mechlorethamine, vincristine, prednisone, and procarbazine (MOPP) alternating with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD),[6]

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**Table 1. Patient Characteristics**

| | |
|---|---|
| Age in yrs, median (range) | 29 (13-51) |
| Sex, male:female | 35:23 |
| Histology | |
| Nodular sclerosis | 49 |
| Mixed cellularity | 9 |
| Initial stage | |
| II | 18 |
| III | 27 |
| IV | 13 |
| A:B | 25:33 |
| Extranodal disease at diagnosis | 19 |
| Initial chemotherapy | |
| MOPP/ABVD | 16 |
| MOPP/ABV hybrid | 17 |
| VECABOP | 18 |
| MOPP | 3 |
| ABVD | 3 |
| Other | 1 |
| Prior radiotherapy | 20 |
| Mediastinal | 18 |
| Relapse in field | 16 |
| History of BM involvement | 6 |
| Duration of initial CR | |
| <1 yr | 35 |
| ≥1 yr | 23 |
| "B" symptoms at relapse | 16 |
| KPS ≤ 80% at relapse | 21 |
| Extranodal disease at relapse | 21 |

MOPP/ABV hybrid[7] or VECABOP, a regimen of vinblastine 6 mg/m$^2$ intravenously on day 1; procarbazine 100 mg/m$^2$ per os (po) on days 1 to 7 in cycles 1, 3, 5, and 7; etoposide 100 mg/m$^2$ intravenously on days 1 and 5, and 100 mg/m$^2$ po on days 4, 5, and 6 in cycles 2, 4, 6, and 8; cyclophosphamide 400 mg/m$^2$ intravenously on day 1; doxorubicin 35 mg/m$^2$ on day 5; bleomycin 10 U/m$^2$ intravenously on day 5; vincristine 1.2 mg/m$^2$ intravenously on day 5; and prednisone 40 mg/m$^2$ on days 1 to 10 given every 21 days for 8 cycles. Twenty patients had received prior radiotherapy that included the mediastinum in 18. Sixteen had "B" symptoms at the time of relapse. Twenty-one had an abnormal (≤80%) Karnofsky performance status (KPS),[8] including all those with constitutional symptoms. Forty had relapse in nodal areas only, whereas 21 had extranodal (± nodal) tumor involvement. Detailed information regarding number of disease sites or maximal tumor size at relapse was not usually sought. The majority of patients had an initial CR duration of less than 12 months, with a median duration of 9 months (range 1 to 68). Forty-three of our patients had received all of their therapy within BC, where lymphoma care is centralized[3,9]; in 15 patients, initial chemotherapy had commenced in other provinces.

### *Exclusions*

To examine the potential influence of patient selection on our results, we examined the records of all BC patients with HD who relapsed after a CR induced by multiagent chemotherapy during the study period. Fifty-nine such patients were seen during this period; 43 were autotransplanted and 16 were not. (The additional 15 autotransplanted patients included in this report were referred from other Canadian provinces.) Alternative therapy for BC patients not autografted included radiation therapy given for curative intent in 8 patients,[3,10,11] intensive therapy plus allogeneic BMT in one patient with active marrow disease, and conventional therapy in 4 patients, 3 of whom had had a long initial CR (ie, 1.5 to 9 years). Three patients refused any therapy for their relapsed disease. Seven of the patients not autografted, including four who had received radiotherapy only and three treated with further chemotherapy, are currently alive and progression free.

### *Treatment*

After documentation of a negative BM aspirate and biopsy, patients underwent BM harvesting using previously described techniques,[12] along with placement of an indwelling silastic central venous catheter. In patients with a greater than 3-month interval since prior chemotherapy, a median of two cycles of mechlorethamine, vinblastine, procarbazine, and prednisone (MVPP)[13] in conventional doses was administered. One patient with active marrow involvement at first relapse underwent a total of nine leukaphereses for collection of peripheral blood (PB) stem cells after each cycle of MVPP. During the second half of the second cycle of MVPP, patients with bulky disease or disease easily encompassed within a previously untreated radiotherapy field received 3,000 cGy in 10 fractions or 3,500 cGy in 20 fractions of local radiation therapy, as previously described.[14] Patients with a ≤3-month interval since prior chemotherapy and in whom systemic disease was not rapidly progressing were not given MVPP but were candidates for local radiation alone. It should be emphasized that conventional cytoreduction with MVPP and/or radiotherapy was not used as a test for chemosensitivity and patients were not formally restaged after this phase of treatment. All patients treated with conventional cytoreduction later underwent autologous BMT.

Drug dosages were calculated on the basis of the lower value of ideal or actual body weight. The first 13 patients transplanted between 1985 and 1988 received CBV (cyclophosphamide 1.8 g/m$^2$ intravenously over 2 hours on days −7, −6, −5, and −4; VP16-213 0.4 g/m$^2$ intravenously over 1 hour every 12 hours on days −7, −6, and −5; BCNU 0.6 g/m$^2$ day −3).[14] One patient received the same regimen except that VP16-213 was given as a 34-hour continuous infusion. Beginning in 1988, the conditioning regimen was modified, mainly because of toxicity considerations. In the new regimen, the same total dose of VP16-213 was given as a 34-hour infusion on day −7, followed by the identical cyclophosphamide dose on days −6, −5, −4, and −3; cisplatin 50 mg/m$^2$ was added on days −7, −6, and −5 followed by a reduced dose of BCNU 0.5 g/m$^2$ on day −2. Forty-four patients received this regimen (CBVP). BM was thawed and infused on day 0 in both studies; in the single patient receiving PB stem cells, the cells were administered on 2 consecutive days because of the large volume of fluid infused. The median nucleated cell count infused was $3.36 \times 10^8$ cells/kg (range 1.12 to 12.70).

All patients were hospitalized in single rooms on specialized units with high-efficiency particulate air filtration using approximately 20 exchanges per hour at either the BC Cancer Agency or the Vancouver General Hospital. All blood products were irradiated and administered to keep the hemoglobin greater than 90 g/L and the platelet count greater than $20 \times 10^9$/L. Therapeutic acyclovir was used until 1988 when prophylactic therapy was introduced for herpes simplex virus. Total parenteral nutrition, broad-spectrum antibiotics and amphotericin B were given when needed. Beginning in 1989, all patients seronegative for cytomegalovirus (CMV) received CMV-seronegative blood products. Hematopoietic growth factors were given post-BMT in 18 patients.[15] The details of protocol therapy given to these patients are summarized in Table 2.

### *Statistical Methods*

Because of the difficulty in interpreting the significance of residual radiographic masses in HD,[16,17] progression-free survival was

**Table 2. Summary of Treatment**

| | |
|---|---|
| Conventional cytoreduction | |
| None | 6 |
| Any | 52 |
| Involved-field radiotherapy | 3 |
| MVPP | 24 |
| MVPP + involved-field radiotherapy | 25 |
| Conditioning regimen | |
| CBV | 14 |
| CBVP | 44 |
| Source of hematopoietic stem cells | |
| BM | 57 |
| PB | 1 |
| Post-BMT hematopoietic growth factors | |
| GM-CSF | |
| 2-h infusion | 7 |
| 24-h infusion | 9 |
| G-CSF | 1 |
| PIXY-321 (GM-CSF/IL-3) | 1 |

Abbreviations: GM-CSF, granulocyte-macrophage colony-stimulating factor; IL-3, interleukin-3.

the main parameter of outcome assessed. The probability of progression-free survival was calculated from the date of BMT using the method of Kaplan and Meier.[18] Patients were censored at the time of last follow-up without evidence of progressive HD and all patients were evaluable. The times to disease progression, nonrelapse mortality, death from any cause, neutrophil engraftment, and platelet engraftment post-BMT were also examined using this method.

The following parameters were evaluated as potential prognostic factors for progression-free survival: age; sex; histology; initial stage; "B" symptoms at diagnosis; extranodal disease initially; history of BM involvement with HD; prior radiation therapy; relapse in the radiation field; initial chemotherapy regimen (MOPP/ABVD, MOPP/ABV hybrid or VECABOP versus other regimens); number of prior drugs and regimens; length of initial CR; province in which initial therapy was given (BC versus other); presence of "B" symptoms, KPS, and extranodal disease at time of first relapse; conventional cytoreduction therapy before conditioning (none versus MVPP only versus local radiotherapy only versus both MVPP and radiotherapy); history of chest irradiation (none versus during initial therapy versus pre-BMT versus at both times); conditioning regimen (CBV versus CBVP); marrow cell dose; and use of hematopoietic growth factor post-BMT. Prognostic factors were evaluated using the Cox proportional hazards model.[19]

## RESULTS

### *Overall Outcome*

Currently 47 patients are alive, including 42 continuously free of malignancy post-BMT. Thirteen patients have had progressive HD after transplantation; 2 of these are in a third CR, induced by local radiotherapy, which has been sustained for more than 3.5 years. Three patients died of nonrelapse causes, as described below. The actuarial overall survival of all 58 patients is 72% (95% confidence interval [CI] 52% to 85%) with a median follow-up of 2.3 years (range 0.4 to 7.2).

### *Toxicity*

*Hematologic.* The median time for absolute neutrophil count (ANC) recovery to $\geq 0.5 \times 10^9$/L was 16 days (range 9 to 33) in the 56 evaluable patients. In the 56 patients evaluable for platelet recovery, the median day of the last platelet transfusion given to maintain a count of $\geq 20 \times 10^9$/L was 19 (range 6 to 192). For the patients receiving post-BMT hematopoietic growth factors, the median time for ANC recovery and platelet transfusion independence were 11 days (range 9 to 27) and 18 days (range 10 to 33), compared with 17 days (range 6 to 103) and 19 days (range 8 to 72), respectively, for those receiving no growth factor. The ANC recovery was statistically significantly more rapid in the growth factor group ($P = .003$, log rank).

*Nonhematologic.* Three treatment-related deaths occurred, for a cumulative incidence of 6.6% (95% CI 2.0% to 20%). One patient died of pulmonary fibrosis (day +739), another of clinical acute myopericarditis (day 0) and a third of pulmonary hemorrhage after gram-negative septicemia (day +16). The major nonhematologic toxicity was idiopathic interstitial pneumonitis,[20] which occurred in nine patients at a median of 57 days (range 32 to 160) after BMT. Late recognition and therapy of this complication, which is presumably related to high-dose BCNU,[21] likely contributed to the single pulmonary death that occurred early in our experience. With a policy of prompt evaluation of respiratory symptoms and immediate treatment with corticosteroids, no further deaths caused by interstitial pneumonitis were seen in patients autografted in first relapse.

### *Progression*

Progressive HD occurred at a median of 0.7 years (range 0.1 to 3.5) post-BMT in 13 patients (Fig 1). Progression occurred in sites of previous disease in all except one patient. Five patients had additional new sites of HD, including one with marrow involvement. Relapses were nodal only in six patients and involved extranodal sites, with or without concomitant nodal disease, in seven patients. The probability of disease progression was 31% (95% CI 18% to 51%). Only three patients have progressed after 1 year post-BMT, at 2.2, 2.2, and 3.5 years. All patients with late relapses had nodular

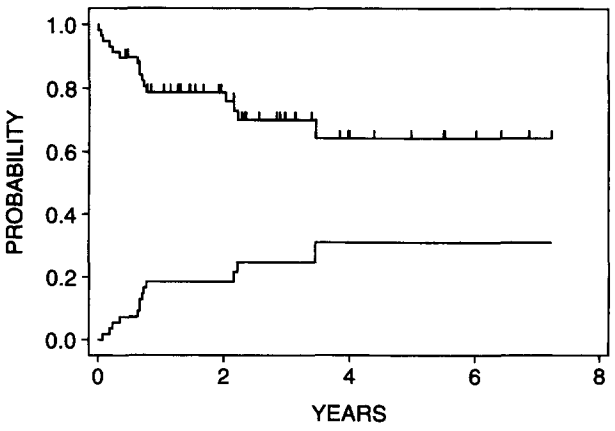


**Fig 1. Actuarial progression-free survival (upper curve) and probability of disease progression (lower curve) after intensive chemotherapy and autologous BMT in 58 patients treated at the time of first relapse.**

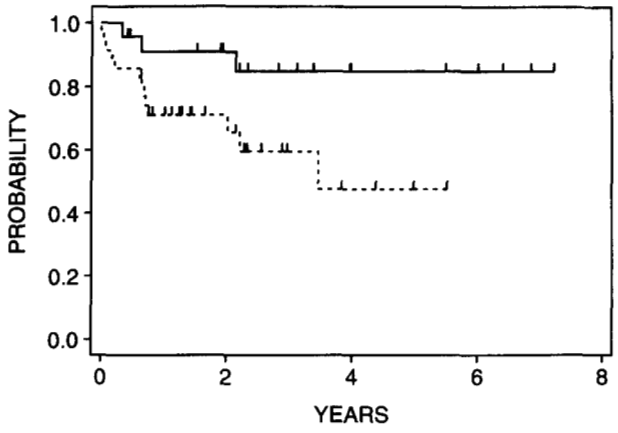


**Fig 2. Actuarial progression-free survival curves in patients with length of initial complete remission ≥1 year (———) (n = 23) or < 1 year (– – –) (n = 35).**

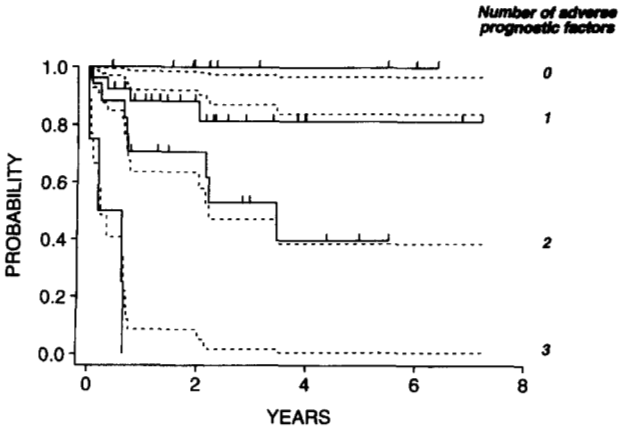


**Fig 3. The observed (———) and expected (– – –) progression-free survival curves according to the number of adverse prognostic factors present at the time of first relapse.**

sclerosing histology.[22] Two of these patients remain in a third remission of 3.6 and 6.4 years after further salvage radiation therapy.

*Progression-Free Survival*

The actuarial progression-free survival of the 58 patients is 64% (95% CI 46% to 78%) with a median follow-up of 2.3 years (range 0.4 to 7.2) (Fig 1). One patient received an 18-month course of intravenous gammaglobulin for hypogammaglobulinemia and recurrent infections post-BMT; Ig levels subsequently normalized. A second patient has required intermittent small doses of corticosteroids for control of dyspnea after post-BMT pneumonitis. All patients surviving without progression have a KPS of 90% or 100%.

Univariate analysis identified the following variables that were associated with a reduced progression-free survival: "B" symptoms at diagnosis ($P = .038$); "B" symptoms at first relapse ($P < .001$); KPS ≤ 80% at first relapse ($P = .011$); extranodal disease at relapse ($P = .02$); and length of initial CR less than 1 year ($P = .032$). Progression-free survival curves by initial CR duration are shown in Fig 2. The actuarial progression-free survival was 85% (95% CI 59% to 95%) in the group with an initial CR length ≥1 year, compared with 48% (95% CI 21% to 70%) in the group with a shorter first CR. The actuarial overall survival of the patients with longer initial remissions was 95% (95% CI 70% to 99%).

The final Cox model identified "B" symptoms at relapse, extranodal disease at relapse, and short initial CR interval as independent determinants of outcome (Table 3). Because the relative risk of each of these factors was similar, a prognostic system for any one, two, or three of these factors was evaluated. A model with a separate relative risk estimate for each factor did not offer significant improvement over the model with a single risk estimate ($P = .36$). The observed and predicted progression-free survival curves for patients with 0, 1, 2, or 3 adverse factors are shown in Fig 3. The 11 patients with no adverse factors had a predicted 3-year progression-free survival of 97%, compared with 87% in the 26 patients with one adverse factor, 47% in the 17 patients with two factors and 1.5% in the 4 patients with all three factors. The predicted progression-free survivals are very close to the observed curves, indicating the adequacy of this simple model. The observed progression-free survivals were 100%, 81% (95% CI 56% to 92%), 40% (95% CI 12% to 67%), and 0% for patients with 0, 1, 2, or 3 adverse factors, respectively.

**Table 3. Multivariate Analysis of Risk Factors for Progression-Free Survival**

| Variable | *P* Value | Relative Risk | 95% CI |
|---|---|---|---|
| "B" symptoms at relapse | <.001 | 6.26 | 2.1-18.7 |
| Length of CR < 1 yr | .016 | 4.71 | 1.4-20.5 |
| Extranodal disease at relapse | .006 | 5.46 | 1.6-13.8 |

*Resource Utilization*

The median duration of hospitalization for autologous BMT was 37 days (range 18 to 84). Unanticipated invasive procedures performed during the BMT hospitalization included thoracentesis (1 patient) and pericardiocentesis (2 patients). One of the latter patients succumbed to acute myopericarditis and the other had progressive HD in the chest post-BMT. Two patients were transferred to the intensive care unit with a stay of 5 days each.

Eighteen patients had at least one readmission within the first 6 months post-BMT. The median number of hospitalized days for these patients was 8 days (range 1 to 70); one readmitted patient was later transferred to the intensive care unit for 18 days for respiratory failure that was found at autopsy to be caused by widespread recurrent HD.

## DISCUSSION

Dose-intensive chemotherapy requiring hematopoietic stem cell support has been increasingly used in HD patients for whom combination chemotherapy is not curative.[14,22-28]

Whereas BMT is widely accepted in patients who fail to enter an initial CR, its role in relapsed patients has been less clearly defined because some series indicate that a significant number of patients—particularly those with a long first remission[3,4]—may have prolonged survival after further combination chemotherapy. One recent publication using decision analytic methods concluded that autologous BMT in second relapse was the optimal strategy[29]; a possible exception to this recommendation involved patients relapsing after the use of seven- or eight-drug regimens, for whom minimal data on salvage therapy are available. Such patients appeared to have a small survival advantage when immediate autologous BMT was performed at the time of first relapse. However, this analysis was based on a series of assumptions, and is sensitive to the validity of these assumptions.

Starting in 1985, we chose to enter the majority of first relapse HD patients onto autologous BMT protocols. This approach was feasible in almost all patients; only 2 of our 59 BC patients had active marrow disease at first relapse. Patients excluded from BMT were generally those felt to be potentially curable by further radiotherapy or chemotherapy alone, or those who refused all further treatment. The transplanted patients were in an "untreated" relapse at protocol entry but most received some conventional therapy before BMT conditioning, as discussed below. Also, we used CBV-based regimens[14] containing higher doses of the agents than initially reported,[30] postulating that these doses would be better tolerated in patients transplanted relatively early in their disease course.

Conventional cytoreductive therapy before conditioning was given both in an attempt to reduce the tumor burden and to allow time to organize a bed in the transplant facility. Such therapy was generally well tolerated and did not appear to contribute to post-BMT interstitial pneumonitis.[20] Although patients were not rigorously restaged after MVPP and/or radiation therapy, most had obvious disease regression and only two clearly failed to have tumor shrinkage. It is also possible that some of the patients with nodal-only relapses may have been cured by the pre-BMT radiotherapy alone, although most of these also had a short initial CR as an unfavorable feature.[10] In any event, the patients given conventional therapy pretransplant likely started their conditioning in a favorable state of minimal disease.[31] Also, it is noteworthy that HD recurred post-BMT in the irradiated field in only three sites among 28 patients who had received local radiotherapy before conditioning. Although we considered the use of conventional cytoreduction therapy to be a key element in our strategy, our study design did not permit evaluation of this component.

Treatment-related deaths occurred infrequently in this study, a finding likely related in part to the lack of cumulative organ damage from multiple attempts at salvage chemotherapy. The incidence of therapy-related deaths was lower than that seen in our more heavily pretreated autologous BMT patients receiving CBV±P[32] and was in the range of that reported with several aggressive nontransplant salvage chemotherapy regimens.[33-38] HD patients receiving multiple courses of conventional-dose therapy are also at risk for the development of fatal late cardiac and pulmonary abnormalities and second malignancies[4,5]—particularly acute myelogenous leukemia (AML). A determination of whether similar delayed organ toxicity and second malignancies will present problems in our patients receiving intensive therapy and BMT as their initial salvage therapy will require longer follow-up.

When marrow autografting is part of the salvage approach, the complication of secondary AML is of particular concern. Secondary AML and myelodysplasia have now been reported after autologous BMT in HD patients,[39-42] and cytogenetic abnormalities detected before marrow harvest have precluded BMT in some patients.[40] Of 12 patients harvested and autografted at our center in a second or greater relapse, one has subsequently developed AML 4 years post-BMT (data not shown). In all of these cases, the marrow had been exposed to multiple chemotherapy regimens (with or without radiotherapy) before harvest. To date, none of our HD patients transplanted in first relapse have developed AML. These observations suggest the desirability of procurement of marrow for autografting before multiple attempts at salvage therapy are undertaken.

Our overall progression-free survival is higher than that usually reported with nontransplant salvage modalities in HD.[5,34,43-45] We do not feel that patient selection alone accounts for these favorable results, because the majority of our patients not transplanted were excluded because they were felt to have an excellent prognosis without BMT,[3] leaving poorer risk patients for BMT. However, our analysis of risk factors confirms the importance of several biologic features of this disease in determining outcome.[3,4] A short initial CR interval, presence of "B" symptoms at relapse and extranodal disease at relapse independently and multiplicatively predicted for a reduced post-BMT progression-free survival in our prognostic model. These factors overlap with those previously described with the use of either conventional- or high-dose salvage therapy approaches.[3-5,46] However, most of the previous reports of BMT regimens in progressive HD combine the results in patients with different disease statuses at BMT (ie, induction failure, multiple relapses, and resistant relapse). Our study was able to define three useful predictors of outcome in a less heterogenous group of patients, all of whom presented in an initial relapse after first-line chemotherapy.

Whereas it might be argued that our best-risk groups of patients (ie, those with no or one adverse factor) might have done well with salvage chemotherapy alone, our preliminary results showing low mortality and relapse rates in these groups support the further development of this approach in patients relapsing after primary chemotherapy. Future efforts will be directed at reducing the morbidity, mortality, and cost of treatment in this subset.[47,48]

Conversely, patients with two adverse factors had a significant risk of disease progression, although 40% survived free of disease progression. Finally, newer strategies are required for patients with all three risk factors, a group in which no long-term survivors were seen. Possible approaches in these unfavorable patient groups include the use of more than one course of dose-intensive therapy with

growth factor and/or hematopoietic stem cell support, or the use of post-BMT immune modulation with agents such as cyclosporine (to induce autologous graft-versus-host disease[26,49]), $\alpha$-interferon[50] and/or interleukin-2.[51]

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