High-Dose Chemoradiotherapy Followed by Autologous Bone Marrow Transplantation as Consolidation Therapy During First Complete Remission in Adult Patients With Poor-Risk Aggressive Lymphoma: A Pilot Study


Twenty consecutive patients with poor-risk aggressive lymphoma who at presentation either had elevated serum lactic dehydrogenase level (LDH) and any one of the other poor-prognostic features: bulky mass >10 cm, advanced stage III or IV, and ≥2 extranodal sites, or normal LDH level and all other three features, underwent high-dose chemo/radiotherapy followed by unmanipulated autologous bone marrow transplantation (BMT) during their first complete remission. Eighteen had B-cell lymphoma and 2 had T-cell lymphoma. Eleven patients had high-grade (7 immunoblastic, 3 small noncleaved, non-Burkitt's, and 1 Burkitt's) and 9 had diffuse large cell lymphoma. All patients had achieved a complete remission following conventional chemotherapy. Four patients had also received involved field radiotherapy to areas of bulky disease. The preparative regimen consisted of high-dose etoposide 60 mg/kg and cyclophosphamide 100 mg/kg in combination with fractionated total body irradiation (FTBI) 1,200 cGy (15 patients), or single-dose TBI 750 cGy (2 patients), or carmustine 450 mg/m² (3 patients). All patients tolerated the treatment well and achieved complete hematologic recovery. Three patients have relapsed at days 79, 196, and 401 after transplantation. Seventeen patients (84%) are alive and relapse-free with a median follow-up of 34 months (range 2 to 54). We conclude that high-dose chemo/radiotherapy followed by autologous BMT can be given as consolidation therapy during first remission in these patients with minimal transplant-related toxicity.

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also reproducible when this prognostic index was applied to another set of 155 patients with diffuse mixed lymphoma, DLCL, and immunoblastic lymphoma treated on different protocols of the Nebraska Lymphoma Study Group. These also reproducible when this prognostic index was applied to considered for alternative innovative therapy.

Based on this concept, we have conducted a pilot study to determine the role of high-dose therapy followed by autologous bone marrow transplantation (BMT) as consolidation therapy during first CR in 20 patients with intermediate- and high-grade lymphoma who have poor-prognostic features at presentation. In our study, we used the poor-prognostic features described in the above studies and validated by the model described by Coiffier et al that predict for both shortened survival and increased risk of relapse.

**PATIENTS AND METHODS**

*Definition of poor-risk factors.* The poor-prognostic features at presentation in this study included: (1) elevated serum LDH level, (2) bulky mass ≥ 10 cm in greatest dimension, (3) advanced stage III or IV, and (4) two or more extranodal sites.

*Patient characteristics.* Twenty patients with DLCL, intermediate-grade lymphoma, or high-grade lymphoma who at presentation had either elevated LDH level and any one of the other three factors, or normal LDH level and all other three factors, underwent autologous BMT during first CR at the City of Hope National Medical Center. Additional criteria for entry included the absence of underlying heart, lung, kidney, and liver diseases and a pulmonary function study of greater than 75% predicted value. All patients were informed of the investigational nature of this study and informed consent was obtained from each patient in accordance with institutional guidelines.

The patient characteristics are shown in Table 1. There were 17 males and three females with a median age of 31 years (range 19 to 54). Stage at diagnosis included stage II (4 patients), stage III (5 patients), and stage IV (11 patients). Eleven patients had high-grade (7 immunoblastic; 3 small noncleaved, non-Burkitt's; and 1 Burkitt's), 8 had DLCL, and 1 had diffuse mixed cell lymphoma. Immune characterization showed 18 B-cell phenotypes and 2 T-cell phenotypes. Fifteen patients had extranodal involvement at presentation. All patients had received combination chemotherapy and were in first CR at the time of transplantation. The median number of cycles of combination chemotherapy administered was 6 (range 3 to 10). Patients receiving MACOP-B (methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin) had completed 12 weeks of treatment as described. Four patients also received involved field radiation to sites of bulky disease as part of their initial therapy including mediastinal (two patients) and abdominal radiation (two patients). The median time from diagnosis to BMT was 7 months (range 3 to 11). The median Karnofsky Performance Status at BMT was 90% (range 80% to 100%).

*Preparative regimen and supportive care.* As part of the sequential studies investigating the preparative regimen for lymphoma, three different preparative regimens were used in this study. Fifteen patients received fractionated total body irradiation (FTBI) 1.200 cGy at 200 cGy per fraction with 50% transmission lung blocks for a total of six treatments from day −6 to −6, in combination with etoposide (VP-16) 60 mg/kg on day −4 and cyclophosphamide 100 mg/kg on day −2. Two patients received single-dose TBI 750 cGy on day −6. Another three patients who had prior radiation treatment received carmustine (BCNU) 450

### Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>UPN</th>
<th>Age/Sex</th>
<th>Histology</th>
<th>Stage</th>
<th>PS ECOG</th>
<th>LDH X ml</th>
<th>Tumor Bulk</th>
<th>Extra Nodal Sites</th>
<th>Prior Rx</th>
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<tr>
<td>5018</td>
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<td>ileum, cecum</td>
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<tr>
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<td>3.2 X</td>
<td>10 X 7 cm</td>
<td>Lung</td>
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</table>

**Abbreviations:** UPN, unique patient number; PS, performance status; ECOG, Eastern Cooperative Oncology Group; SNC, small noncleaved Burkitt's; SNC, NB, small noncleaved non-Burkitt's; DM, diffuse mixed; DLC, diffuse large cell; IBS, immunoblastic lymphoma; BM, bone marrow; CSF, cerebrospinal fluid; CHOP/HDMTX, cyclophosphamide, doxorubicin, vincristine, high-dose methotrexate; M-BACOD, methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine and dexamethasone; MACOP-B, methotrexate, doxorubicin, cyclophosphamide, vincristine, bleomycin; ProMAC, prednisone, methotrexate, doxorubicin, cyclophosphamide and etoposide; VACOP-B, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin; CytaBOM, cytarabine, bleomycin, vincristine, methotrexate.

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mg/m² on day −6, VP-16 60 mg/kg on day −4, and cyclophosphamide 100 mg/kg on day −2. Three patients also received involved field radiotherapy boost of 2,000 cGy to residual bulky masses delivered over 2 weeks before BMT followed by the FTBI regimen.

Autologous marrow harvest, cryopreservation, and reinfusion. All patients had undergone bilateral iliac crest bone marrow biopsies that showed no microscopic evidence of lymphomatous involvement at the time of bone marrow harvesting and at BMT. In addition, cytogenetic studies and immunophenotyping were normal in all patients. The technique of bone marrow harvest has been previously described. Briefly, heparinized marrow was depleted of red blood cells by gravity sedimentation using 6% hydroxyethyl starch (HES). The unmanipulated bone marrow was cryopreserved in 6% HES, 5% dimethylsulfoxide without controlled-rate freezing. Patients with prior bone marrow involvement at the time of diagnosis underwent reinfusion of peripheral blood stem cells (PBSCs) collected via leukapheresis procedures that have been previously described. 13,14 Before 1989, all patients also underwent three PBSC collections and received a combination of bone marrow and PBSCs. The PBSCs were collected during the steady state of hematopoiesis without priming with chemotherapy or growth factor. The marrow and PBSCs were reinfused at 48 hours after completion of cyclophosphamide on day 0.

Four patients received bone marrow only, 14 patients received a combination of bone marrow and PBSC, and 2 patients with prior bone marrow involvement received PBSC only. The median marrow cell dose given was 1.87 × 10¹⁰ nucleated cells/kg (range 0.3 to 3.3 × 10¹⁰). The median dose of peripheral stem cells administered was 2.63 (range 1.6 to 6.6) × 10⁹/kg for patients receiving a combination of bone marrow and PBSC. For the two patients administered PBSC only, the doses were 5.5 and 11.8 × 10⁹/kg. Two patients received hematopoietic growth factor after the transplantation.

Supportive care. All patients were housed in high efficiency particulate air (HEPA)-filtered isolation rooms during the period of granulocytopenia. Nonabsorbable antibiotics (neomycin and oral vancomycin) for gastrointestinal decontamination were administered to all patients. 15 Trimethoprim-sulfamethoxazole was administered from day −13 to day −3 and prophylaxis was reinstituted at the time of discharge and continued until 6 months posttransplant. Empiric broad spectrum antibiotics and parenteral nutrition were used as clinically indicated. Low-dose amphotericin-B (0.1 to 0.2 mg/kg) was administered on day +1 and continued daily until the day of discharge. All blood components were irradiated to 2,000 cGy. Patients who were sero-negative for cytomegalovirus (CMV) were administered CMV seronegative blood supports. Intravenous Ig (500 mg/kg) was administered every 2 weeks beginning on day −11 until day +60.

Statistical methods. The probabilities of DFS and relapse were estimated using the product-limit of Kaplan and Meier. The 95% confidence limits for the cumulative probability of survival or relapse were calculated using the logit transformation and Greenwood's estimate of the variance.

RESULTS

Seventeen of the 20 patients (84%) are alive and free of disease with a median follow-up of 34 months (range 2 to 54). The estimates of DFS (shown in Fig 1) were 90% at 6 months post-BMT (95% confidence interval [CI]: 67% to 97%) and 84% at 13 months post-BMT (95% CI: 60% to 95%). The estimates of relapse (shown in Fig 1) were 10% at 6 months post-BMT (95% CI: 3% to 33%) and 16% at 13 months post-BMT (95% CI: 5% to 40%). Three patients relapsed at day +79 (unique patient number [UPN] 5090), day +196 (UPN 5036), and day +401 (UPN 5125). Of these three, two relapsed in areas of previously irradiated bulky disease.

Toxicity. The National Cancer Institute toxicity criteria for autologous BMT were used for toxicity grading. All patients developed mucositis (maximum grade II) and etoposide related erythematous skin rashes. Fever in association with neutropenia occurred in all patients and resolved after appropriate antibiotics and the resolution of granulocytopenia. The number of febrile days with temperature greater than 38.5°C ranged between 1 to 16 days, with a median of 6 days. There were no deaths from transplant-related complications. One patient (5%) developed transient veno-occlusive disease of the liver and one patient (5%) had mild idiopathic interstitial pneumonitis that resolved after treatment with corticosteroid. Both of these patients had received the BCNU-containing regimen.

Engraftment. All patients achieved a complete hematologic recovery. The median time to reach an absolute granulocyte count of > 0.5 × 10⁹/L was 14 days (range 10 to 48). The median time to a self-sustaining platelet count > 20,000/mm³ was 14 days (range 10 to 48). There was no difference in the hematopoietic recovery or the supportive care requirements between patients being administered bone marrow alone, combined bone marrow and PBSC, or PBSC alone.

DISCUSSION

Our pilot study has clearly shown that high-dose chemo/radiotherapy followed by autologous and/or peripheral stem cell reinfusion is a safe and well-tolerated procedure. It may be applied as consolidation therapy during first remission in patients with poor-risk intermediate-grade and high-grade lymphoma with acceptable transplant-related toxicity. This study also suggests that such therapy may achieve long-term control of disease in this select group of patients with poor-risk, aggressive lymphoma. Although all patients in our study achieved CR with different combina-
tion chemotherapy before transplantation, at presentation all had poor-risk factors previously described in different prognostic models, which predict for both poor survival and increased risk of relapse. Despite this, 84% of the patients are alive and free of disease at the median follow-up of almost 3 years and 15 of these 20 patients have been followed up for more than 24 months.

Several sets of prognostic factors for poor survival have been reported in patients with DLCL, but these factors remain controversial and differ in several reported series caused by variability in patient population, sample sizes, the type of analysis, and differences in treatment regimens. Nevertheless, certain factors including age, performance status, and factors that measure tumor burden such as LDH level, tumor bulk, stage, number of nodal and extranodal sites, have been consistently shown to predict poor outcome. Recent reports from two large series showed that these poor prognostic factors retain their impact on survival in patients achieving a CR. By using these prognostic factors it may be possible to identify a subset of patients with aggressive lymphomas who will do poorly despite attaining a CR with conventional chemotherapy. These patients may benefit from consolidation therapy with autologous BMT during first CR because of the high rate of relapse.

High-dose chemotherapy or chemoradiotherapy followed by autologous BMT has been reported to produce durable CR in patients with relapsed lymphoma. The outcomes are significantly better when autologous BMT is performed in CR or for chemo-sensitive disease rather than when performed during resistant relapse. However, only 10% to 50% of patients with relapsed lymphoma can achieve long-term disease control with myeloablative therapy and autologous BMT. Moreover, some patients may be excluded from autologous BMT because of overt bone marrow involvement at the time of relapse. The experience of high-dose therapy and autologous BMT during first CR in patients with poor-risk lymphoma is very limited.

Recently, one study reported the results of autologous BMT in 31 patients with DLCL who had high LDH and/or bulky mediastinal or abdominal disease at diagnosis. Fourteen patients who underwent ABMT immediately after induction of remission had 79% probability of DFS with a median follow-up of 49.2 months, compared with a median survival of 5.2 months for the 17 patients who received autologous BMT while in relapse and/or after failing conventional chemotherapy. These results support the early use of autologous BMT in patients with poor-risk aggressive lymphoma.

One of the major issues concerning the role of myeloablative therapy and autologous BMT during first CR is the transplant-related morbidity and mortality. The transplant-related toxicity reported here is also lower than previously described, which could be caused by the small numbers of patients, careful patient selection, good performance status at the time of transplantation, or limited prior exposure to cytotoxic therapy. These factors have been shown to affect the outcome of BMT in patients with lymphoma. The lack of transplant-related mortality in our study is encouraging and supports the use of transplantation in this clinical setting. The administration of granulocyte-macrophage colony-stimulating factor (GM-CSF) and granulocyte-CSF (G-CSF) following high-dose therapy with or without autologous BMT in patients with lymphoma has been shown to accelerate the hematopoietic recovery, decrease infectious complications, and shorten the overall hospital stay. Therefore, it is likely that transplantation-related morbidity can further be reduced with the use of hematopoietic growth factors.

Our results support the concept that the outcome of autologous BMT may be improved when performed early during the course of treatment while the disease is still sensitive to chemotherapy and the tumor burden is small. Using the previously described prognostic index, we identified a group of patients with aggressive lymphoma who had poor prognostic features at presentation and, therefore, were considered candidates for additional consolidation therapy. Although patients were selected among those who had achieved remission, the high relapse rate of such patients was the basis for this pilot study. Our results show that high-dose therapy and autologous BMT may be administered during first CR with minimal transplantation-related toxicity. Furthermore, it might be possible for patients with poor-risk factors to have an improved DFS with this approach. Obviously, further trials with a larger patient population and longer follow-up will be required to confirm this result. Nevertheless, our result should provide a basis for a randomized trial to determine the role of high-dose therapy followed by autologous BMT as consolidation therapy in patients with poor-risk aggressive lymphoma. In such a study, once complete remission is achieved with conventional chemotherapy, those patients with poor-risk factors can be randomized either to receive consolidation therapy with high-dose marrow-ablative therapy followed by autologous BMT, or to be observed and undergo BMT only at the time of relapse. The results obtained from such a randomized trial may further clarify the role of autologous BMT in the management of patients with aggressive lymphoma. Alternatively, new therapeutic strategies with sequential high-dose combination chemotherapy and hematopoietic growth factor support may allow increased dose intensity and offer the potential for improved treatment results for the poor-risk patient.

REFERENCES


NADEMANEE ET AL


High-dose chemoradiotherapy followed by autologous bone marrow transplantation as consolidation therapy during first complete remission in adult patients with poor-risk aggressive lymphoma: a pilot study [see comments]

A Nademanee, GM Schmidt, MR O’Donnell, DS Snyder, PA Parker, A Stein, E Smith, JA Lipsett, I Sniecinski and K Margolin