Successful Treatment of Refractory Hodgkin’s Disease by High-Dose Combination Chemotherapy and Autologous Bone Marrow Transplantation


Forty-four patients with refractory Hodgkin’s disease were treated with high-dose combination chemotherapy followed by autologous bone marrow rescue. Twenty-two patients (50%) entered complete remission within 6 months of the procedure and four other patients are free of disease progression. Only two patients have subsequently relapsed from complete remission (CR). Bone marrow suppression was the predictable major toxicity of this procedure, and two patients (4.5%) died of sepsis during the aplastic phase. High-dose therapy with autologous bone marrow transplantation (ABMT) appears to be an effective salvage regimen for patients with refractory Hodgkin’s disease.

MOST PATIENTS with Hodgkin’s disease may now be cured using combination chemotherapy or local or extended field radiotherapy. Chemotherapy is the optimum treatment for patients with advanced disease, although the best regimen remains a matter of contention. Alternating, non-crossresistant regimens, or hybrids thereof, may give improved results although this has been demonstrated in only one randomised controlled trial. Despite these advances, some patients fail to respond to first-line therapy and have a very poor prognosis. The prognosis of patients who relapse after first-line therapy is not necessarily unfavorable because durable second remissions can be achieved in some patients using alternative chemotherapeutic regimens. In contrast, patients who fail to achieve a second complete remission (CR) or who have a further relapse have a very poor prognosis. Patients with primary resistance and patients who fail conventional salvage regimens are therefore candidates for high-dose therapy in view of clinical evidence of a dose-dependent response rate of Hodgkin’s disease to chemotherapy. We report a single-center experience of high-dose chemotherapy and autologous bone marrow transplantation (ABMT) in the treatment of 44 patients with refractory Hodgkin’s disease.

PATIENTS AND METHODS

Patients. Forty-four patients with Hodgkin’s disease were treated with high-dose chemotherapy and ABMT by the Bloomsbury Transplant Group. All patients had active disease at the time of ABMT despite receiving standard regimen treatments at standard dosage with at least two modalities/regimens or following "hybrid" therapy. These patients are hereafter referred to as refractory. All patients who met these criteria who were deemed fit to undergo high-dose chemotherapy and ABMT received this treatment after giving informed consent in accordance with institutional guidelines. The median age of these patients (28 men and 16 women) was 29 years (range 18 to 40 years). The stage and histology as defined by the British National Lymphoma Investigation (BNLI) at diagnosis are shown in Table 1. This classification divides the nodular sclerosis subtype into grade 1 and grade 2, where grade 2 indicates easily recognized areas of lymphocyte depletion or numerous pleomorphic Hodgkin’s cells. This revised classification has significant prognostic value. The histologic diagnosis of each patient was reviewed prior to ABMT by an expert histopathologist. Twenty-three patients had extranodal disease during their clinical course. Three patients had previous bone marrow involvement. At the time of ABMT, extranodal disease was identified in 21 patients; 12 of them had Hodgkin’s disease infiltrating the lung. The size of the largest residual tumor mass at the time of ABMT is shown in Table 1.

Previous therapy. Two patients (UPN 225 and 291) had failed to respond to front-line alternating chemotherapy and progressed immediately to ABMT at 7 and 8 months from diagnosis. All other patients had received at least two regimens of chemotherapy, and 28 patients (64%) had also received radiotherapy. Nine of these patients initially had localized disease and received radiotherapy as first-line treatment but subsequently relapsed and received at least two chemotherapy regimens. Twenty-two patients (50%) had never achieved CR. Twenty-two patients had achieved CR in response to first-line therapy and subsequently relapsed. The median time from diagnosis to ABMT was 20 months (range 7 to 195 months).

Bone marrow harvest. At the time of bone marrow harvest no patient had evidence of bone marrow involvement by histologic examination of bilateral iliac crest trephine biopsies. Bone marrow was harvested under general anaesthesia and cryopreserved as previously described. All patients had a Hickman central venous catheter inserted at the time of bone marrow harvest.

High-dose therapy regimen. Patients received combination chemotherapy using BCU 300 mg/m² on day −6, etoposide 100 or 200 mg/m² and cytosine arabinoside 200 or 400 mg/m² on days −5 to −2 inclusive, and melphalan 140 mg/m² on day −1 (BEAM protocol). The cryopreserved bone marrow was reinfused on day 0, 24 hours after completion of BEAM. Eighteen patients received etoposide and cytosine arabinoside at the lower dose, and all subsequent patients received the higher dose regimen.

Statistical analysis. Statistical analyses were performed by Student’s t test, Mann Whitney rank-sum test, and chi-square analysis. Multivariate analysis was performed by stepwise regression. Survival curves were drawn by the Kaplan-Meier life-table method and compared by the log-rank test.

RESULTS

Patients were reviewed clinically and radiologically for response to the high-dose therapy by computerized axial tomography (CT) 3 months after ABMT. Fifteen patients (34%) achieved CR within 3 months of ABMT. These patients received no further therapy as consolidation or maintenance. Twenty-three patients (52%) achieved a partial response (PR) as defined by a ≥50% reduction in tumor mass at the time of assessment. Two patients who had a
residual mediastinal mass at 3 months had slow resolution of this mass and had entered CR without further therapy by 6 months after ABMT. Four more patients have shown a progressive decrease in the size of a residual mediastinal mass over 10 to 33 months without having received further therapy; indeed they may no longer have active disease. These four patients have been defined as partial responders for the purposes of further analysis.

Seven patients have received postgraft radiotherapy to sites of residual disease (six to mediastinum and one to paraaortic nodes; five of these patients have subsequently entered CR. In all, therefore, 22 patients (50%) were in CR 6 months after ABMT and four other patients are free of disease progression. Two patients relapsed from CR at 7 and 9 months after ABMT and subsequently died of progressive disease; both relapsed at sites of previous disease. The remaining patients continue in remission and all have a Karnovsky score of 100%. The disease-free survival of these patients is shown in Fig 1 with a plateau at 9 months of >80%.

Four patients (7%) showed no response to high-dose therapy. Three of these patients had very large mediastinal masses, and the fourth patient had multiple pulmonary nodules at the time of ABMT. Three died of progressive disease within 6 months of the procedure and the fourth received palliative radiotherapy which achieved a PR.
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Fig 3. Overall survival after ABMT of 44 patients stratified by the size of the largest residual mass at the time of high-dose therapy.

Table 2. Hematologic Recovery after ABMT

<table>
<thead>
<tr>
<th>Cells</th>
<th>Days Post ABMT</th>
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<tbody>
<tr>
<td>Neutrophils &gt;0.5 x 10^9/L</td>
<td>24 (range 11-68)</td>
</tr>
<tr>
<td>Leukocytes &gt;1.0 x 10^9/L</td>
<td>18 (range 9-48)</td>
</tr>
<tr>
<td>Platelets &gt;50 x 10^9/L</td>
<td>32 (range 13-54)</td>
</tr>
</tbody>
</table>

Although he subsequently developed rapidly progressive disease.

New sites of disease involvement were not seen after ABMT, and progressive disease that occurred did so at previously involved sites. In particular, no patients developed bone marrow involvement after ABMT. The median survival of all patients after ABMT is 22 months; overall survival is shown in Fig 2. Patients who achieved CR have significantly better survival than patients who do not achieve CR.

Toxicity. The major procedure-related toxicities were significant neutropenia and thrombocytopenia. Febrile episodes occurred in 88% of patients during the period of neutropenia, and two patients (4.5%) died of sepsis during their aplastic phase. The hematologic recovery of the 42 evaluable patients is shown in Table 2. There was no significant difference in the times to recovery in patients who received the higher or lower doses of etoposide or cytosine arabinoside as detailed above. No patient had failure of marrow engraftment. Mucositis was frequently severe, and 35% of patients required parenteral nutrition.

Analysis of prognostic factors. Univariate and multivariate methods were performed on the following factors to determine their prognostic value: age, sex, stage and histology at diagnosis; size of largest tumor mass at diagnosis and at the time of ABMT; presence of extranodal disease; amount of previous chemotherapy; exposure to previous radiotherapy; and whether the patients had ever previously entered CR. The size of tumor mass at ABMT (chi-square = 12.48) was the only significant factor identified by these analyses. The survival of patients by size of largest tumor mass at ABMT is shown in Fig 3. The presence of extranodal disease or of infiltrative lung disease did not adversely affect outcome. Those patients who had received third-line or further therapy did not have a significantly different response rate to ABMT (chi-squared = 2.28). The histologic subtype at diagnosis had no significant effect on response rate or survival after ABMT; in particular, there was no difference between nodular sclerosing grades 1 and 2 disease, which were the predominant histologic types.

DISCUSSION

High-dose combination chemotherapy with adjuvant radiotherapy when necessary achieved a CR rate of 50% in a group of heavily pretreated patients with active Hodgkin's disease. Only two patients who achieved a CR have relapsed at the time this article was written. Although reports from other groups have given comparable results, our study has the merit of being a relatively uniform series of patients who received their high-dose therapy in a single institution. The prognosis of patients with primary resistant disease or of patients who have relapsed after salvage therapy is poor, with a 5-year survival of <20%; high-dose therapy with ABMT may represent an advance over conventional salvage therapy. In view of the well-recognized radiosensitivity of Hodgkin's disease, a high-dose therapy regimen based on total body irradiation (TBI) may have a theoretical advantage over regimens containing combination chemotherapy.
alone. However, the prior exposure of patients to full doses of localized radiotherapy, particularly to the mediastinum, has been associated with an unacceptably high morbidity and mortality from TBI. On the other hand, an advantage of a chemotherapy-based high-dose regimen is the feasibility of using adjuvant radiotherapy to sites of residual disease. Such an approach has achieved durable complete remissions in 22% of patients who achieved PR in this study with follow-up of >2 years in two patients. The use of adjuvant radiotherapy was restricted to 27% of patients with residual disease after ABMT because the remaining patients had already received maximum doses of radiotherapy to that area. Six patients initially assessed as partial responders remain free of disease progression despite not having received further therapy because they had already received full doses of radiotherapy to sites of residual disease. Two of these patients had delayed shrinkage of the tumor mass and are now in CR. More of these patients may be disease-free despite the persistence of a mass on the CT scan. Confirmation by biopsy of the mediastinum was not undertaken because we did not believe it was in the patients' interest.

These studies have been performed with unpurged autologous bone marrow, which may result in reinfection of residual disease, contaminating the harvested bone marrow but not detected by routine histology. However, there is a low incidence of overt bone marrow involvement in Hodgkin's disease, and the pattern of disease progression in our patients is clearly owing to failure of eradication of existing disease rather than reinfection of tumor cells at the time of ABMT. To date we have no evidence to suggest that purging of autologous bone marrow is necessary in treatment of Hodgkin's disease. Furthermore it would be difficult to demonstrate any benefit from this procedure until there are advances in eradication of existing disease.

The identification of patients who would benefit from intensive treatment of this nature at an earlier stage in their disease is difficult. Patients who have primary resistant disease or who have failed any two modalities of therapy should be considered candidates for this approach. We believe that this study demonstrates the potential value of ABMT in treatment of refractory Hodgkin's disease. All patients in this study had active Hodgkin's disease resistant to standard-regimen therapy at standard dosage at the time of ABMT. However, this is not an unselected group of patients: These patients had clearly been selected by their referring physician. Instead this is a problem of all nonrandomized studies undertaken in referral centers for bone marrow transplantation. A randomized study has now been started in the United Kingdom by the BNLI to establish whether high-dose therapy with ABMT is superior to other salvage therapy in these groups of patients with Hodgkin's disease.

ACKNOWLEDGMENT

We thank members of the BNLI who referred patients reported in this study.

Appendix: Treatment regimens used

<table>
<thead>
<tr>
<th>ABVD</th>
<th>Adriamycin, bleomycin, vinblastine, dacarbazine</th>
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</thead>
<tbody>
<tr>
<td>BACOP-OPEC</td>
<td>Bleomycin, Adriamycin, cyclophosphamide, vinblastine, prednisolone-vincristine, prednisolone, etoposide, chlorambucil</td>
</tr>
<tr>
<td>BEAM</td>
<td>BCNU, etoposide, cytarabine, melphalan (for dosage see text)</td>
</tr>
<tr>
<td>beam</td>
<td>BCNU 60 mg/m²; etoposide 75 mg/m²; cytarabine 200 mg/m²; melphalan 30 mg/m²</td>
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<tr>
<td>CC-Vb-Bl</td>
<td>CCN, vinblastine, bleomycin</td>
</tr>
<tr>
<td>CCNU-P</td>
<td>CCNU, prednisolone</td>
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<tr>
<td>DXT</td>
<td>Extended field radiotherapy</td>
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<tr>
<td>EVAP</td>
<td>Etoposide, vinblastine, adriamycin, prednisolone</td>
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<tr>
<td>IMVP-16</td>
<td>Ifosfamide, methotrexate, etoposide</td>
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<tr>
<td>LOPP</td>
<td>Chlorambucil, vincristine, procarbazine, prednisolone</td>
</tr>
<tr>
<td>MOPP</td>
<td>Mustine, vincristine, prednisolone, procarbazine</td>
</tr>
<tr>
<td>TN1</td>
<td>Total nodal irradiation</td>
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</tbody>
</table>

REFERENCES


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JG Gribben, DC Linch, CR Singer, AK McMillan, M Jarrett and AH Goldstone