High-Dose Cyclophosphamide, Carmustine (BCNU), and Etoposide (VP16-213) With or Without Cisplatin (CBV ± P) and Autologous Transplantation for Patients With Hodgkin’s Disease Who Fail to Enter a Complete Remission After Combination Chemotherapy


Patients with Hodgkin’s disease (HD) who fail to enter a complete remission after an initial course of combination chemotherapy are usually considered to have had an induction failure (IF); this subset of patients has an extremely poor outcome with further conventional therapy. Since 1985, we have entered 30 IF patients into protocols using conditioning with high-dose cyclophosphamide, carmustine (BCNU), and etoposide (VP16-213) with or without cisplatin (CBV ± P) followed by autologous stem cell transplantation (ASCT) with bone marrow (19 patients), peripheral blood stem cells (PBSCs; 8 patients), or both (3 patients). All except 2 patients had previously received chemotherapy regimens for HD that contained at least 7 drugs, and 9 had received prior radiotherapy (RT). After documentation of IF, the majority of patients received some cytoreductive therapy as specified by protocol (local RT in 9, 2 cycles of conventional chemotherapy in 2, both modalities in 2, or high-dose cyclophosphamide to enhance PBSC collection in 11) before CBV ± P. Five treatment-related deaths occurred, all before day 150 posttransplant. Eleven patients have had progressive HD at a median of 6 months (range, 0.1 to 45 months) after ASCT. The actuarial progression-free survival (PFS) at a median follow-up of 3.6 years (range, 0.2 to 8.2 years) is 42% (95% confidence intervals, 21% to 61%). The statistical analysis identified only prior clinical bleomycin lung toxicity as an adverse risk factor for PFS, mainly because of the increased nonrelapse mortality seen in these patients. CBV ± P and ASCT can produce durable remission in a substantial proportion of IF HD patients who otherwise have a poor survival, and we believe ASCT approaches represent the best therapy currently available for these patients. Additional measures are needed to reduce the primary problem of disease progression despite high-dose chemotherapy and stem cell transplantation.

© 1995 by The American Society of Hematology.

THE MAJORITY OF patients with advanced Hodgkin’s disease (HD) enter a complete remission (CR) with initial combination chemotherapy, and many are cured.1 However, despite such therapy, a proportion either do not enter a CR or have evidence of disease progression and are considered to have had an induction failure (IF). When further conventional chemotherapy or radiation therapy is administered to these patients, the prospect of prolonged disease-free survival is quite small.2,3 Given the dismal prognosis of this particular group of patients, the use of intensive therapy and autologous stem cell transplantation (ASCT) is often considered. Since 1985, we have recommended intensive therapy with high-dose cyclophosphamide, carmustine (BCNU), and etoposide (VP 16-213), with or without cisplatin (CBV ± P), followed by ASCT in such patients. This report describes the outcome of our first 30 patients with HD who were treated with CBV ± P and ASCT as salvage therapy after having an IF of initial chemotherapy.

PATIENTS AND METHODS

Eligibility Criteria

Patients were required to have persistent or progressive HD proven either by biopsy or unequivocal radiographic progression after primary chemotherapy. Patients with residual nonprogressive radiographic masses of uncertain origin after primary chemotherapy were not treated with this transplant protocol.

Patients were required to be ≥60 years of age and have adequate organ function. Patients who received ASCT using bone marrow were required to have a normal bone marrow biopsy within 4 weeks of marrow harvest, whereas an adequate peripheral blood stem cell collection was required in the remaining patients. Patients were treated according to studies approved by the institutional review boards at the University of British Columbia (BC), Vancouver Hospital and Health Sciences Centre, and Vancouver Clinic of the BC Cancer Agency. All patients provided informed consent.

Patient Characteristics

Table 1 summarizes the characteristics of the 30 patients who did not enter CR. At diagnosis, 15 had “B” symptoms and 16 had bulky disease, defined as a single mass of tumor exceeding 10 cm in the largest diameter or a mediastinal mass exceeding one third of the maximal transverse thoracic diameter. Twenty-two patients had received initial therapy with 7- or 8-drug combinations such as mechlorethamine, vincristine, prednisone, and procarbazine alternating with doxorubicin, bleomycin, and vincristine, and dacarbazine (MOPP/ABVD)4; MOPP/ABV hybrid5; VECABOP (a regimen of vinblastine, procarbazine, etoposide, cyclophosphamide, doxorubicin, bleomycin, vincristine, and prednisone)6; or CVPPABO (a hybrid regimen of cyclophosphamide, vinblastine, procarbazine, prednisone, doxorubicin, bleomycin, and vincristine). Five patients were initially treated with MOPP, whereas 1 patient initially received ABVD1. Another patient who was pregnant at the time of diagnosis received single agent vinblastine until delivery and then received 6 cycles of CVPPABO before developing progressive disease. One patient had been first treated with an MACOP-B variant for malignant lymphoma7 and in retrospect was reclassified as having HD. Eighteen

From The Leukemia/Bone Marrow Transplantation Program of British Columbia, Divisions of Hematology, Medical Oncology and Radiation Oncology, Vancouver Hospital and Health Sciences Centre, British Columbia Cancer Agency, and the University of British Columbia, Vancouver, British Columbia, Canada.

Submitted December 14, 1994; accepted February 28, 1995.

Address reprint requests to D.E. Reece, MD, University of Kentucky, Bone Marrow Transplantation Program, Markey Cancer Center, 800 Rose St, Lexington, KY 40536.

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. section 1734 solely to indicate this fact.

© 1995 by The American Society of Hematology.

0006-4971/95/8602-007$3.00/0


451
patients received all of their care in British Columbia, where lymphoma management is centralized, whereas 12 patients were referred for transplantation from other provinces. After primary chemotherapy, 10 patients received one or more additional chemotherapy regimens in an attempt to achieve CR; 1 patient received 3 regimens. Specifically, of the 5 patients initially treated with MOPP, 2 later received ABVD, 1 received MOPP/ABV hybrid, and 1 received MOPP/ABVD in which epidoxorubicin was substituted for doxorubicin. The patient who initially failed to respond to ABVD was subsequently treated with MOPP. Four patients who initially received VECABOP had their regimen changed to CVPPABO (2 patients), single-agent cyclophosphamide (1 patient), and mechlorethamine, vinblastine, procarbazine, and prednisone (MOPP) in conventional doses to doxorubicin, vinblastine, procarbazine, and prednisone (MVPP) in conventional doses. One patient had partial regression, with persistent HD confirmed on biopsy of a nonprogressive nodal lesion, whereas another patient had a PR followed by clinical progression when conventional therapy could not be adequately administered because of persistent, severe thrombocytopenia. Fifteen patients had biopsy confirmation of persistent active HD, whereas the remainder had clear-cut radiographic evidence of disease progression in prior sites of involvement. At the time the IF was documented, 11 had B symptoms and 1 had an abnormal (<80%) Karnofsky performance status (KPS; including all of those with "B" symptoms). Sites of active HD included nodal areas only in 19 and extranodal disease with or without nodal involvement in 11.

In these patients, the median interval from diagnosis to ASCT was 12 months (range, 1 to 35 months). The median interval from the time of completion of induction therapy to the documentation of persistent active HD was 2 months (range, 0.5 to 8.75 months), whereas the median interval from the time of IF to ASCT was 2.5 months (range, 0.5 to 5 months).

Exclusions

The records of all BC patients with HD who failed to enter CR during the study period were reviewed. Between 1985 and 1994, 20 IF patients were evaluated in BC. Eighteen received CBV ± P and autologous transplantation, whereas 2 did not. One of the patients not treated with CBV ± P and ASCT received a successful allogeneic BMT, whereas another was conditioned with an alternative regimen before autologous bone marrow transplantation (BMT) because of physician preference; both patients died of treatment complications.

Although the total number of IF patients from areas outside British Columbia is not known, 14 out-of-province patients who had failed to enter CR were evaluated in our center for transplantation during the study period. One patient refused autotransplantation, whereas a second received a successful allogeneic BMT and is alive and well 9 years posttransplant. The remaining 12 patients were autografted after CBV ± P conditioning.

Treatment Schema

The details of the protocol therapy administered to the 30 patients receiving CBV ± P and ASCT are shown in Table 2.

Preconditioning cytoreduction and autologous hematopoietic stem cell collection. Nineteen patients treated between 1985 and 1991 underwent bone marrow harvesting using previously described techniques shortly after documentation of IF. Six of these patients proceeded directly to CBV ± P and ASCT. However, 9 patients with bulky disease or disease easily encompassed within a previously untreated radiotherapy field first received irradiation with 3,000 cGy in 10 fractions or 3,500 cGy in 20 fractions of local RT, depending on field size, before CBV ± P, as described previously.

Four patients with ≥3 month interval since prior chemotherapy (that had produced a PR) received 2 cycles of mechlorethamine, vinblastine, procarbazine, and prednisone (MVPP) in conventional doses to allow time to arrange for a transplant bed, 2 of these patients also received local RT.

Beginning in 1991, patients failing induction therapy received
CBV ± P AND ASCT FOR INDUCTION FAILURE HD

Table 2. Treatment Features

<table>
<thead>
<tr>
<th>Conditioning cytoreduction</th>
<th>None</th>
<th>MVPP</th>
<th>Local RT</th>
<th>MVPP + local RT</th>
<th>HD-CY</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBV</td>
<td>6</td>
<td>2</td>
<td>9</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>CBVP</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBV ± P variants</td>
<td>20</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Source of stem cells</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone marrow</td>
<td>19</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral blood</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td>3*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-BMT GM-CSF</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

One patient was not reinfused because of a fatal event on day 0.

High-dose cyclophosphamide (HD-CY) at 1.15 g/m² daily for 4 days (7 g/m² total) both to accomplish pretransplant tumor cytoreduction and to enhance peripheral blood stem cell (PBSC) progenitor collection. Eleven IF patients received HD-CY. One patient received HD-CY alone, whereas 10 received hematopoietic growth factors after HD-CY, consisting of granulocyte-macrophage colony-stimulating factor (GM-CSF) in 3 and GM-CSF plus interleukin-3 (IL-3) in 7. An adequate PBSC collection was obtained in 8, whereas an additional bone marrow harvest was required in 3 individuals.

As in our previous studies, patients were not formally restedaged after preconditioning cytoreductive therapy such as local RT, MVPP, or HD-CY, and such therapy was not used as a means to select chemosensitive patients; all patients receiving such therapy later received transplants.

**Conditioning regimens.** The drug doses in the conditioning regimens were based on the lesser of ideal or actual body weight. The initial 6 patients received CBV (cyclophosphamide at 1.5 g/m² IV over 2 hours on days −7, −6, −5, and −4; VP16-213 at 0.4 g/m² IV over 1 hour every 12 hours on days −7, −6, −5, and −4; and BCNU at 0.6 g/m² on day −3). One patient received this regimen except that VP16-213 was administered as a 34-hour continuous infusion. Because of toxicity considerations, the CBV conditioning regimen was modified in 1988 so that the same total dose of VP16-213 was administered as 34-hour infusion on day −7, followed by the identical cyclophosphamide regimen on days −6, −5, −4, and −3; cisplatin (50 mg/m²) was added on days −7, −6, −5, and −4, whereas a reduced dose of BCNU (0.5 g/m²) was administered on day −2.

Twenty patients received the CBVP regimen. Three other patients received close variations of these protocols, with omission of BCNU due to marked pulmonary compromise before ASCT in 2 patients and early discontinuation of VP16-213 in another patient due to a severe allergic reaction to this drug.

**Autologous transplantation.** Bone marrow was thawed and infused on day 0 in the 19 patients receiving autologous marrow, whereas the 8 patients receiving only PBSC transplants received their cells on 2 consecutive days because of the large volume of fluid infused. One of the patients who received both marrow and PBSCs had the infusions spread over 3 days, whereas the second received both products on the same day; the third patient died on day 0 before the planned reinfusion of both marrow and PBSCs. The median nucleated cell count in the 29 patients reinfused was 4.64 × 10⁹ (range, 1.42 to 9.10 × 10⁹) cells/kg.

**Supportive care.** All patients were hospitalized in a specialized facility with HEPA-filtered single rooms with approximately 20 air exchanges per hour. Blood products were irradiated and transfused to maintain a hemoglobin level greater than 90 g/L and a platelet count greater than 20 × 10⁹/L. Therapeutic acyclovir was used until 1988, at which time prophylactic therapy was instituted for herpes simplex management. Total parenteral nutrition, broad spectrum antibiotics, and antifungal therapy were administered needed. Cytomegalovirus (CMV) prophylaxis, consisting of the use of CMV-negative blood products in seronegative patients, was initiated in 1989. Five recipients of autologous bone marrow received hematopoietic growth factor (GM-CSF) posttransplant as part of a separate institutional study of growth factor use in this setting.

**Statistical Methods**

Because of the difficulty in ascertaining the significance of residual masses in HD, and hence complete remission rates, progression-free survival (PFS) was the main response parameter evaluated. PFS was calculated from the date of autologous transplantation (day 0) until the date of progression of disease, death from nonrelapse causes, or last follow-up if still free of progression using the method of Kaplan and Meier. Patients without disease progression were censored at the time of last follow-up. Similar methods were also used to evaluate overall survival, the probability of disease progression, and nonrelapse mortality.

The following factors were evaluated as possible prognostic indicators for PFS: age, sex, histology, initial stage, and "B" symptoms at diagnosis or transplant; extranodal disease at diagnosis or transplant; presence of bulky disease at diagnosis; prior radiation therapy; relapse in the irradiated field; initial combination chemotherapy (MOPP/ABVD, MOPP/ABV hybrid, VECABOP, CVPPABO hybrid or other); number of prior drugs and regimens; history of prior clinical bleomycin lung toxicity; Karnofsky performance status at relapse; use of cytoreduction therapy (local radiotherapy, MVPP, both modalities, or HD-CY) before conditioning; history of chest irradiation; pattern of IP (progression during induction chemotherapy or other); conditioning regimen (CBV vs CBVP, excluding the 3 patients with protocol violations); dose of BCNU in the conditioning regimen (0.5 or 0.6 g/m², excluding the 2 patients in whom the drug was omitted); and interval from diagnosis to transplantation. Prognostic factors were evaluated using the Cox proportional hazards model.

**RESULTS**

**Overall Results**

Currently, 15 patients are alive and without evidence of progressive HD posttransplant at a median follow-up of 3.6 years (range, 0.2 to 8.2 years). Ten patients have progressed. Of these, 3 are alive 34, 46, and 57 months after transplantation and 19, 39, and 25 months after disease progression, respectively; all 3 have active tumor. Five patients have succumbed to nonrelapse causes. The actuarial overall survival at 5 years in all patients is 60% (95% confidence interval [CI], 39% to 77%; Fig 1). The actuarial survival curve subsequently decreases to 30% (95% CI, 2% to 69%), lower than the PFS, when one of the initial patients, who progressed at 3.7 years, died of HD 6.2 years post-ASCT.

**Toxicity**

**Hematologic.** In the 29 evaluable patients, the median time for an absolute neutrophil count recovery (ANC) to 0.5 × 10⁹/L was 15 days (range, 10 to 61 days), whereas the...
median time of the last platelet transfusion was 17 days (range, 4 to 68 days); one patient continues to receive transfusions at day +84. The hematologic recovery in 3 subgroups was also examined. In the 5 patients receiving GM-CSF after infusion of bone marrow only, the median time for ANC recovery was 13 days (range, 10 to 15 days) compared with 19 days (range, 11 to 28 days) in the 14 patients who received bone marrow without GM-CSF (P = .0005). In the 10 patients receiving peripheral blood stem transplants (plus marrow in 2) after priming with HY-CY ± growth factors, the median time to ANC recovery was 12 days (range, 10 to 61 days). Although the recovery time with peripheral blood stem cells was the most rapid, it was not statistically different from that seen with either bone marrow alone (P = .08) or with GM-CSF (P = .85). The day of last platelet transfusion was 23 days (range, 9 to 37 days), 14 days (range, 6 to 29 days), and 11 days (range, 4 to 84 days) posttransplant in the bone marrow alone, bone marrow plus GM-CSF, and primed peripheral blood stem cell groups, respectively (P = .356).

Nonhematologic. The principal nonhematologic toxicity was acute lung toxicity, which was presumably related to BCNU16,17 and which occurred in 7 patients. Four responded to steroids; 3 in whom steroid therapy was delayed succumbed to lung toxicity on days 50, 65, and 133 posttransplant. One other patient died of unexplained pulmonary hypertension on day 62; postmortem examination showed cor pulmonale and fibrotic mediastinal lymph nodes with no evidence of HD. A fourth patient died of acute pulmonary edema on day 0. No second malignancies or late nonrelapse deaths have occurred. The actuarial probability of nonrelapse mortality was 18% (95% CI, 8% to 38%; Fig 2).

Progression

In the 10 relapsing patients, disease progression occurred at a median of 6 months (range, 0.1 to 45 months) posttransplant. Disease progression occurred in previous sites of disease in 7 patients, 4 of whom had new additional sites of disease recurrence. Three others recurred only in new sites, including bone in 2. Only 3 patients have progressed more than 1 year post-BMT (at 1.2, 2.6, and 3.7 years); all had nodular sclerosing histology. The probability of developing progressive HD after ASCT was 49% (95% CI, 26% to 71%; Fig 2).

PFS

The actuarial PFS in these 30 patients is 42% (95% CI, 21% to 61%) with a median follow-up of 3.6 years (range, 0.2 to 8.2 years; Fig 1). Fourteen of the patients surviving without HD have a normal KPS; 1 has a KPS of 80% because of recurrent upper extremity venous thrombosis and an iatrogenic functional superior vena caval syndrome resulting from the placement of multiple indwelling vascular devices. One female patient conceived and delivered a normal infant 50 months posttransplant.

The univariate analysis identified two significant adverse risk factors for PFS. First, patients with a history of prior clinical bleomycin lung toxicity had a poorer PFS (P = .003). Also, patients who received no prior cytotherapy before CBV ± P had a worse outcome; this parameter was significant only when patients receiving no cytoreduction therapy were compared with patients receiving any of the protocol treatments (MVPP, RT, both, or HD-CY; P = .027). Only prior bleomycin lung toxicity was significant in the multivariate analysis. All 3 of the patients with this complication of induction chemotherapy died post-ASCT, due to BCNU lung toxicity in 2 and rapidly recurrent HD in the other; in the latter patient, BCNU had been omitted from the conditioning regimen because of severe pulmonary compromise pretransplant.

DISCUSSION

Patients with advanced-stage HD who fail to enter a first remission after multidrug chemotherapy regimens have a
poor expected survival. Although an occasional patient can achieve a durable remission with radiation therapy,\textsuperscript{18-20} one large series reported that patients who did not achieve CR with 7- or 8-drug regimens had an actuarial freedom from progression and overall survival with additional therapy of 0% and 12%, respectively, at 5 years.\textsuperscript{3} Clearly, conventional salvage therapy is inadequate in this group of patients.

It should be noted that patients who had entered a stable clinical partial remission after chemotherapy, with or without RT, were not considered candidates for ASCT until either disease progression occurred, or, in 1 case, biopsy disclosed active HD. In our institution, as in others,\textsuperscript{1} partial remitters are routinely observed. In these patients the significance of residual abnormalities, particularly radiographic abnormalities, may be uncertain,\textsuperscript{21} and some of these patients may experience prolonged PFS.\textsuperscript{22}

Our study confirms the ability of high-dose chemotherapy with ASCT support to produce prolonged PFS in a significant proportion of patients failing induction therapy despite primary treatment with at least 7 drugs (often supplemented with RT).\textsuperscript{23,24} Our analysis of potential prognostic factors identified only prior clinical toxicity from bleomycin as an adverse risk factor for PFS. In contrast to our experience in HD patients who received CBV \pm P and ASCT at the time of their first relapse after a CR induced by combination chemotherapy, biologic features such as "B" symptoms and extranodal disease at relapse were not correlated with PFS in patients who had failed to enter CR.\textsuperscript{5} It appears likely that failure of induction chemotherapy per se is such an unfavorable feature that it overrides the influence of other disease characteristics.

The majority of our patients received some cytotherapeutic measures before CBV \pm P and autologous transplantation, consisting of either conventional chemotherapy and/or local RT or more recently HD-CY as part of hematopoietic stem cell mobilization. Because of the design of our study, an accurate assessment of the contribution of such precondi-

The principal problem with CBV \pm P and ASCT in IF patients was the failure to eradicate the underlying malignancy. Disease progression occurred despite the use of higher doses of the components in the CBV regimen compared with the original reports.\textsuperscript{25} Therefore, the primary challenge in the future will be to optimize a high-dose chemotherapy approach to decrease recurrence rates in this setting. One area for future study involves the development of conditioning that might be more effective than CBV \pm P. Several other approaches are under evaluation, including sequential high-dose chemotherapy with either hematopoietic stem cell infusions\textsuperscript{26} or growth factors, as well as "double autografts".\textsuperscript{27} Exploitation of immune mechanisms by administering \(\alpha\)-interferon\textsuperscript{28} or IL-2 posttransplant\textsuperscript{29} represents another investigational strategy.

The observation that CBV \pm P can produce PFS in approximately 40% of patients with HD who have failed to respond to a 7- or 8-drug induction chemotherapy program argues strongly for its application as soon as it is apparent that the initial chemotherapy regimen has not been successful. Because ABVD induction therapy may be equivalent to MOPP alternating with ABVD in terms of response and failure-free survival rates and early ABVD failures who are subsequently treated with MOPP have failure-free survival rates of only about 30% at 5 years,\textsuperscript{1} patients who fail to respond to ABVD induction chemotherapy are also potential candidates for intensive therapy and ASCT. Accordingly, we recommend that ASCT be performed promptly in virtually all HD patients who fail to respond to induction chemotherapy. Although a phase III trial would be required to show conclusively the superiority of intensive therapy and autologous BMT over other salvage chemotherapy or radiotherapy efforts, the poor results reported with further conventional therapy dampen the enthusiasm for such an endeavor.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{Probability of nonrelapse mortality (NRM) and progression HD in 30 patients treated with CBV \pm P and ASCT after failure of induction chemotherapy.}
\end{figure}
ACKNOWLEDGMENT

The authors thank Calla Currie for data collection and Marcia Lang and Linda Williams for their assistance in preparing this manuscript.

REFERENCES


High-dose cyclophosphamide, carmustine (BCNU), and etoposide (VP16-213) with or without cisplatin (CBV +/- P) and autologous transplantation for patients with Hodgkin’s disease who fail to enter a complete remission after combination chemotherapy

DE Reece, MJ Barnett, JD Shepherd, DE Hogge, RJ Klasa, SH Nantel, HJ Sutherland, HG Klingemann, RN Fairey and NJ Voss