A 2-step comprehensive high-dose chemoradiotherapy second-line program for relapsed and refractory Hodgkin disease: analysis by intent to treat and development of a prognostic model

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Salvage of patients with relapsed and refractory Hodgkin disease (HD) with high-dose chemoradiotherapy (HDT) and autologous stem cell transplantation (ASCT) results in event-free survival (EFS) rates from 30% to 50%. Unfortunately, the reduction in toxicity associated with modern supportive care has improved EFS by only 5% to 10% and has not reduced the relapse rate. Results of a comprehensive 2-step protocol encompassing dose-dense and dose-intense second-line chemotherapy, followed by HDT and ASCT, are reported. Sixty-five consecutive patients, 22 with primary refractory HD and 43 with relapsed HD, were treated with 2 biweekly cycles of ifosfamide, carboplatin, and etoposide (ICE). Peripheral blood progenitor cells from responding patients were collected, and the patients were given accelerated fractionation involved field radiotherapy (IFRT) followed by cyclophosphamide-etoposide and either intensive accelerated fractionation total lymphoid irradiation or carmustine and ASCT. The EFS rate at a median follow-up of 43 months, as analyzed by intent to treat, was 58%. The response rate to ICE was 88%, and the EFS rate for patients who underwent transplantation was 68%. Cox regression analysis identified 3 factors before the initiation of ICE that predicted for outcome: B symptoms, extranodal disease, and complete remission duration of less than 1 year. EFS rates were 83% for patients with 0 to 1 adverse factors, 27% for patients with 2 factors, and 10% for patients with 3 factors (P < .001). These results compare favorably with other series and document the feasibility and efficacy of giving uniform dose-dense and dose-intense cytoreductive chemotherapy and integrating accelerated fractionation radiotherapy into an ASCT treatment program. This prognostic model provides a basis for risk-adapted HDT. (Blood. 2001; 97:616-623)

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Introduction

Most patients with Hodgkin disease (HD) are cured with radiation therapy, combination chemotherapy, or both. However, patients who have relapses after attaining complete remission with chemotherapy or combined modality programs and those who have primary disease refractory to such therapy have poor outcomes with conventional dose salvage chemoradiotherapy regimens. In the past 15 years, several clinical trials using high-dose chemotherapy or chemoradiotherapy with autologous stem cell transplantation (ASCT) have been reported, and 30% to 50% of patients appear to have been cured using this approach. Two randomized studies comparing standard-dose, second-line chemotherapy with high-dose therapy (HDT) and ASCT have been reported. Each study demonstrated a statistically significant improvement in event-free and progression-free survival for patients treated on the HDT arms, but neither was powered to show an overall survival advantage. Both trials were limited to patients with chemosensitive disease.

The most commonly used transplant-conditioning regimens are CBV (cyclophosphamide, carmustine, and etoposide) and BEAM (carmustine, etoposide cytarabine, and melphalan). Six-year event-free survival (EFS) rates for patients who underwent transplantation with these regimens range from 25% to 45%; further dose escalation or the addition of other chemotherapeutic agents has resulted in increased toxicity without improving outcomes. Others and we have determined that chemosensitive disease is a critical factor in predicting survival after ASCT, and many patients receive some type of salvage chemotherapy before HDT. However, because only the results of the HDT are reported, the benefit of cytoreduction before HDT is unclear from the current literature. Minimal data evaluate the impact of HDT as a comprehensive treatment strategy in which failure can occur at multiple time points, including failure of cytoreduction or HDT itself or because of death from toxicity or secondary malignancy.

The pattern of relapse after HDT is similar to relapse after chemotherapy for early-stage HD; namely, it occurs at sites of initial involvement. These sites are, therefore, amenable to radiotherapy. In 1985, we tested a treatment program and have recently updated our results using high-dose combined modality...
therapy in patients with relapsed and primary refractory HD. The program used accelerated fractionation radiotherapy either as total lymphoid irradiation (TLI) or as an involved field followed by high-dose chemotherapy and bone marrow infusion. One hundred fifty-six patients were treated from 1985 to 1994. At a median follow-up of 7 years, the EPS rate is 42%, and no relapses have occurred later than 36 months after transplantation. After the introduction of granulocyte colony-stimulating factor (G-CSF), overall mortality rates of the program decreased from 18% to 6%.

These results demonstrated the feasibility of incorporating dose-intense radiotherapy into HDT for HD and contributed to the design of our current study.

We now report the results of a comprehensive program for relapsed and primary refractory HD that includes cytoreductive chemotherapy and is analyzed by intent to treat. The planned accrual of 65 patients for this 2-step program was completed in February 1998. Patients underwent cytoreduction with 2 cycles of ifosfamide, carboplatin and etoposide (ICE) administered on a biweekly dose-dense schedule. Peripheral blood progenitor cells (PBPCs) were collected from responders, and this was followed by the administration of involved-field radiotherapy and either CBV or intensive accelerated fractionation TLI, cyclophosphamide, and etoposide.

Patients, materials, and methods

Patients

Sixty-five consecutive transplantation-eligible patients with relapsed or primary refractory HD after chemotherapy/combined modality therapy were treated from October 1994 to February 1998 on an institutional review board–approved 2-step, second-line protocol after providing written, informed consent. All patients were presented at the weekly lymphoma staging conference, at which time the clinical features, radiology pathology findings, and protocol eligibility were reviewed. All patients were staged according to the Cotswolds modification of the Ann Arbor system. They were required to have a repeat biopsy confirming HD before ICE chemotherapy was initiated (no patient was allowed to enter the protocol based on abnormal findings on imaging studies alone). Histologic review of the original diagnosis and of pre-ICE biopsy specimens was performed by one of 2 expert hematopathologists. In addition, each patient failed at least one chemotherapy program.

Baseline cardiac function was normal in each patient (left ventricular ejection fraction greater than 50%), diffusion capacity on pulmonary function tests was greater than 50% predicted, and serum creatinine levels were 1.5 mg/dL or lower (or creatinine clearance levels were 60 mL/min or greater).

Treatment program: step 1

ICE second-line chemotherapy treatment program. It was planned that 2 cycles of ICE chemotherapy would be administered, with a 2-week interval between cycles. The ICE regimen was administered as previously described: etoposide, 100 mg/m² per day intravenously on days 1 to 3; carboplatin, administered on day 2 and dosed to an area under the curve (AUC) of 5 (the maximum dose of carboplatin was 800 mg, which corresponds to a creatinine clearance level of 135 mg/dL); and ifosfamide, 5 g/m² mixed with an equal dose of MESNA, administered by continuous infusion for 24 hours beginning on day 2. G-CSF was administered at 5 µg/kg on days 5 to 12 (except during PBPC mobilization; see below). There were no dose reductions; instead treatment was delayed until the absolute neutrophil count was greater than 1000/µL and the platelet count was greater than 50 000/µL. Computed tomography (CT) imaging of the chest, abdomen, and pelvis was performed before the initiation of ICE and 2 to 4 weeks after the second cycle of ICE to evaluate the extent of disease and the response to chemotherapy. Gallium imaging and bone marrow biopsies were conducted before the initiation of ICE and repeated after the second cycle of ICE if the initial study results were positive.

Stem cell collection mobilization. PBPCs were mobilized after the second cycle of ICE chemotherapy using G-CSF (10 µg/kg per day) beginning on day 5 and continuing until the completion of leukaapheresis). Leukapheresis was initiated when the white blood cell count was greater than 5000/µL. For the first 30 patients leukaapheresis was performed daily until more than 2 × 10⁶ CD3⁴ cells/kg were collected; a back-up bone marrow harvest was also taken for each patient. For the remaining 35 patients, bone marrow harvest was performed only if apheresis yielded less than 2 × 10⁶ CD3⁴ cells/kg. Each patient underwent a maximum of 5 apheresis procedures. The mobilization procedure was considered to have failed if less than 2 × 10⁶ CD3⁴ cells/kg were collected in a patient after 5 apheresis procedures; bone marrow and PBPCs were then reinfused for ASCT. Apheresis, storage procedures, and CD34 analysis have been previously described.

Treatment program: step 2

High-dose therapy and ASCT: eligibility for high-dose therapy and ASCT. Patients were eligible for HDT if they achieved a complete response (CR), partial response (PR), or minor response (MR, defined as at least a 25% reduction in tumor bulk with normalization of gallium imaging) to ICE. Bone marrow involvement by HD had to have resolved by the end of the second cycle of ICE. Furthermore, patients had to have adequate liver function defined as a serum bilirubin level less than 2 mg/dL. Previously irradiated patients were ineligible to receive accelerated fractionation TLI, but they could receive accelerated fractionation involved field radiotherapy (IFRT).

Accelerated fractionation involved field radiotherapy. Accelerated fractionation IFRT was administered to patients who had nodal sites of disease that measured 5 cm or more on entering the program or who had residual disease after step 1. IFRT started within 2 weeks of the successful collection of stem cells. Patients who underwent prior radiotherapy to a dose above standard tolerance for a specific site had reduced-dose IFRT or no radiotherapy (based on consensus discussion of the principal investigators). The IFRT dose was 1800 to 3600 cGy, administered in 10 to 20 × 180 cGy twice daily fractions within a period of 5 to 10 days. The minimal interval between the 2 daily fractions was 7 hours, and all planned fields were delivered at each treatment session. IFRT was given as an outpatient treatment.

High-dose therapy for previously unirradiated patients. Accelerated fractionation TLI was started on the completion of accelerated fractionation IFRT and was administered as an in-patient treatment. The TLI dose was 1800 cGy, administered in 10 × 180 cGy twice daily fractions within a period of 5 days (days 10 through −6). The minimal interval between the 2 daily fractions was 7 hours, and all planned fields were delivered at each treatment. The day after the completion of TLI, chemotherapy was begun as follows: cyclophosphamide, total dose 4.5 g/m² intravenous (IV), daily dose 2.25 g/m² administered on days −5 and −4; etoposide, total dose 1 g/m² IV continuous infusion over 4 days, daily dose 250 mg/m² continuous infusion on days −5 through −2. PBPCs were infused 48 hours after HDT was concluded. G-CSF was started on day +1 and was administered until the absolute neutrophil count (ANC) was greater than 1000/µL for 3 consecutive days.

HDT for previously irradiated patients. High-dose CBV chemotherapy began 1 to 3 days after IFRT was completed: cyclophosphamide, total dose 6 g/m² IV, daily dose 3 g/m² administered on days −6 and −5; etoposide (VP-16), total dose 1.6 g/m² IV continuous infusion over 4 days, daily dose 400 mg/m² continuous infusion on days −7 through −4; carbamustine, total dose 300 mg/m² IV on day −2. PBPCs were infused approximately 48 hours after HDT was concluded. G-CSF was administered until the ANC was greater than 1000/µL for 3 consecutive days.
Supportive measures for transplantation phase

On admission, patients received prophylactic antimicrobial treatment containing ciprofloxacin, fluconazole, acyclovir, and trimethoprim-sulfamethoxazole. All blood products were irradiated to prevent transfusion-associated graft-versus-host disease. Platelet counts were checked daily, and prophylactic transfusion of platelets was given with either random-donor or single-donor platelets if a patient’s platelet count fell below 20,000/µL. Platelet counts were checked twice daily in patients who received accelerated fractionation IFRT to the mediastinum or who had previous mantle radiotherapy with their original chemotherapy program; they underwent transfusion if the platelet count fell below 50,000/µL as prophylaxis against diffuse hemorrhagic alveolitis. Red blood cells were transfused to maintain a hemoglobin level of 8 g/dL or more. If clinically indicated, additional transfusions were administered.

Posttreatment evaluation

Patients were examined at least weekly until they became transfusion independent. Initial staging re-evaluation occurred 90 days after stem cell infusion. CT imaging of the chest, abdomen, and pelvis was performed on all patients. Bone marrow studies and gallium imaging were performed when clinically indicated or if relapse was suspected. Pulmonary function testing and echocardiography were repeated 1 year after stem cell infusion. In patients who were event free, CT imaging was repeated every 6 months for 3 years and then according to institutional guidelines.

Statistical considerations

All patients were analyzed by intent to treat, but only patients who had at least a minor response to ICE second-line chemotherapy were eligible for HDT and ASCT. Because it was difficult to ascertain the significance of residual masses in HD, EFS was the main response parameter evaluated. EFS and overall survival (OS) were assessed from the first day of ICE chemotherapy. An event was defined as treatment failure (ICE-failure, ICE toxicity precluding ASCT, or residual disease following ASCT), relapse after ASCT, or death from any cause. If relapse or other cause of treatment failure occurred before a patient’s death, the former date was used for the calculation of EFS. Survival curves were generated using the method of Kaplan and Meier and compared using the log-rank test.

Sixty-five consecutive patients with primary refractory HD and HD in relapse were evaluated for ICE response, EFS, and OS. The intent was that all patients would receive potentially curative HDT and ASCT; however, only patients who had at least a minor response to ICE were eligible for the HDT phase of the program. All 65 patients were included in the EFS and OS analyses.

Patient characteristics

Patient characteristics before the initiation of ICE chemotherapy are listed in Table 1. There were 39 male patients and 26 female patients. The median age was 27 years (range, 12-59 years); 4 patients were younger than 20. Twenty-two patients had refractory disease (primary refractory HD, 20 patients; refractory to their most recent chemotherapy program, 2 patients). Forty-three patients had previously achieved CR (duration was more than 1 year in 30 patients and less than 1 year in 13 patients). Initial treatment varied according to the stage and date at diagnosis. Thirty-nine patients received radiotherapy as part of their previous treatment program for HD. All patients previously received chemotherapy, and the most common chemotherapy program administered was adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) (48% of patients).

Table 1. Patient characteristics before ifosfamide, carboplatin, and etoposide chemotherapy

| Patient characteristics before ifosfamide, carboplatin, and etoposide chemotherapy | No. patients |
|---|---|
| Age | Median (range) |
| | 27 (12-59) |
| Response to primary therapy | 22 |
| Primary refractory | 22 |
| Relapsed disease | 43 |
| Histology (WHO classification) | 56 |
| Nodular sclerosis | 56 |
| Mixed cellularity | 7 |
| Lymphocyte predominant | 2 |
| Prior radiotherapy | 39 |
| Yes | 39 |
| No | 26 |
| B symptoms pre-ICE | 16 |
| Yes | 16 |
| No | 49 |
| Extramedial sites of disease prior to ICE | 32 |
| Yes | 32 |
| No | 33 |
| Relapsed disease | 30 |
| CR < 1 y | 13 |
| CR > 1 y | 30 |
| Prior chemotherapy | 32 |
| ABVD | 32 |
| MOPP/ABVD | 11 |
| MOPP/ABV | 3 |
| MOPP | 3 |
| Other or multiple | 16 |
| Median no. prior regimens (range) | 1 |
| (1-6) | 1 |
| Prognostic model | 10 |
| 0-1 factor | 40 |
| 2 factors | 15 |
| 3 factors | 10 |

WHO indicates the World Health Organization; ICE, ifosfamide, carboplatin, and etoposide; CR, complete response; ABVD, adriamycin, bleomycin, vinblastine, and dacarbazine; MOPP, mechlorethamine, vincristine, procarbazine, and prednisone.
ICE response

Sixty-three of the 65 patients received both cycles of ICE chemotherapy, whereas 2 patients had progressive disease after the first cycle. Fifty-seven of the 65 patients responded (CR, 17; PR, 38; MR, 2), resulting in an 88% overall response rate. The median interval between the first and second cycles of ICE was 16 days (range, 13-28 days). Twenty-three patients received therapy on time. Two patients did not receive the second cycle because of disease progression. The administration of ICE was delayed beyond the planned 14-day interval in 40 patients because of scheduling difficulty or patient preference (21 patients), thrombocytopenia (17 patients), and infection (2 patients). The planned dose intensity of ICE was as follows: ifosfamide, 2500 mg/m² per week, carboplatin AUC, 2.5 per week; and etoposide, 50 mg/m² per week. Median dose intensities were 2187 mg/m² per week ifosfamide, carboplatin AUC 2.187 per week, and etoposide 43.5 mg/m² per week (87.5%). Patients who underwent transplantation and achieved CR to ICE had better outcomes after HDT than patients who achieved less than CR. The percentages of patients who were event free at a median follow-up of 43 months were 82% for those in CR after ICE and 59% for those in PR or MR after ICE; this trend has not reached statistical significance (P = .10). Those in whom ICE therapy failed had a median survival of only 5 months.

PBPC analysis

PBPCs were collected from 63 patients after cycle 2 of ICE and G-CSF (10 μg/kg per day). Collection began in 50 of the 63 patients on day 12 or 13 after cycle 2 of ICE. The median number of CD34+ cells collected was 7.0 × 10⁹/kg (range, 0.1-80.0 × 10⁹/kg) in a median of 3 (range, 1 to 5) apheresis procedures. We collected more than 5 × 10⁶ CD34+ cells/kg in 42 patients (67.1%), 2-5 × 10⁶ CD34+ cells/kg in 12 patients (19%), and less than 2 × 10⁶ CD34+ cells/kg in 9 patients (14%; mobilization failure). These 9 patients received bone marrow in addition to peripheral blood as the stem cell source for their HDT.

Accelerated fractionation involved field radiotherapy

Forty-one of the 57 patients with chemosensitive disease received IFRT to one site (24 patients) or multiple sites (17 patients) of which 7 received IFRT to the mediastinum. Single sites of IFRT included the mediastinum (12 patients), para-aortic field (4 patients), inverted Y (3 patients), axilla or pelvis (2 patients each), and peripancreatic area (1 patient). IFRT was well tolerated and administered on time, and no patient was admitted to the hospital for radiation-induced toxicity during the boost. Of the 19 patients who received boost radiotherapy to the mediastinum as part of single-site or multiple-site radiation, 4 patients required pulmonary consultation during their hospital stay for suspected pneumonitis. As described below, one patient with documented aspiration pneumonia died of adult respiratory distress syndrome complicated by pulmonary hemorrhage. The 3 other patients responded to brief courses of corticosteroids.

Outcome for patients undergoing transplantation

Fifty-six of the 57 patients with chemosensitive disease underwent HDT/ASCT. The choice of HDT regimen was dependent on a history of radiotherapy; hence, patients were selected to receive either a TLI-based HDT regimen (22 patients) or CBV (34 patients). At the median follow-up of 43 months, the EFS and OS rates for patients with chemosensitive disease were 68% and 83%, respectively (Figure 1).

Seventeen patients had disease progression or relapse after transplantation. Ten (59%) of these treatment failures occurred in extranodal sites (lungs, 6; liver, 2; liver and lungs, 1; chest wall, 1) that were not irradiated originally or during the high-dose program. Four (24%) treatment failures occurred in nodal areas (mediastinum, 4; neck, 1) that were fully irradiated before enrollment in the salvage program and were not further irradiated. Only 3 (18%) treatment failures occurred in a site (mediastinum) irradiated during the salvage program.

The EFS and OS rates were 68% and 81% for patients who received TLI-cyclophosphamide and etoposide and 68% and 84% for patients who received CBV. The number of days to ANC of 500/μL was 9 and to a platelet count greater than 20,000, 14; the median hospital stay was 23 days. The median number of red blood cell transfusions was 4, and the median number of platelet transfusions was 9.

Intent-to-treat analysis of the 2-step program

The median follow-up time for patients still alive is 43 months. The Kaplan-Meier estimates of the proportion of patients alive, event free and analyzed by intent to treat are 73% and 58%, respectively (Figure 2). As stated above, patients who underwent transplantation had OS and EFS rates of 83% and 68%, respectively.

Nonhematologic toxicity

No toxicity-related deaths resulted from ICE therapy. One patient with primary refractory HD who achieved PR to ICE did not undergo transplantation because of prior chronic radiation pneumonitis and progressive pulmonary dysfunction from massive HD. This patient eventually died of progressive HD and is included among the patients for whom the overall program failed. Another patient required admission to the intensive care unit for Gram-negative sepsis and neutropenia after cycle 2 of ICE chemotherapy but recovered fully.

Two of the 56 (3.6%) patients who received HDT died before the 90-day posttreatment re-evaluation. The first patient was thought to have pneumonitis and eventually died of aspiration pneumonia and acute respiratory distress syndrome. The second patient, who had a history of inferior wall myocardial infarction and paroxysmal atrial fibrillation, developed marantic endocarditis.
with cerebral emboli and subsequent multisystem organ failure. These 2 patients had no evidence of HD, but they are included as failures in the analysis of the entire program. Another patient had a short stay in the intensive care unit because of upper airway bleeding from a tracheal tear that resolved spontaneously without ventilatory support.

**Prognostic factor analyses for EFS and OS**

Prognostic factors associated with EFS, according to a univariate analysis, were entered into a multivariable logistic regression model (Table 2). The factors associated with poor outcome were ENS (P < .001), CR duration less than 1 year or primary refractory disease (P = .001), and B symptoms (P < .001) (Table 3).

A model that was highly predictive of both EFS and OS was developed based on these 3 adverse factors. Forty patients had 0 to 1 adverse factor (group 1), 15 patients had 2 adverse factors (group 2), and 10 patients had all 3 adverse factors (group 3). The EFS and OS rates were 83% and 90% for group 1, 27% and 57% for group 2, and 10% and 25% for group 3 (P < .001) (Table 3). This 3-factor model also predicted survival in the cohort of 57 patient who received transplants (P = .04).

### Discussion

We report the results of a comprehensive program for the treatment of patients with primary refractory and relapsed HD. All patients received uniform cytoreductive chemotherapy with ICE, and only responders were subsequently offered high-dose combined modality therapy and ASCT. Previous studies reported the results of only those patients who received HDT, which is a subset of all patients entered in second-line programs. All patients in this trial had biopsy-proven relapsed or refractory disease, and our data were analyzed by intent to treat; therefore, we could determine the true benefit of HDT in this cohort. The Kaplan-Meier estimate of the proportion of patients alive, event free, and analyzed by intent to treat at 43 months is 58%. In the subset of patients with chemo-sensitive disease who received HDT and ASCT, the EFS rate is 68%. These results compare favorably with the most commonly used transplant-conditioning regimens, CBV and BEAM.19,20 Our program documents the feasibility and efficacy of ICE chemotherapy as a highly effective dose-dense and dose-intensive cytoreductive regimen in HD, as part of a comprehensive program to treat patients with primary refractory HD. It also demonstrates the efficacy and feasibility of integrating higher-dose radiotherapy into an ASCT treatment program. The results of this trial also compare well with our historical results.10

In nearly all reported series of autotransplantation in relapsed HD, patients received some cytoreductive therapy before HDT and ASCT. Patients who relapse after chemotherapy but who respond to standard-dose salvage chemotherapy constitute the bulk of long-term survivors in previous transplantation studies.21,22 Unfortunately, the design of these studies does not allow an accurate assessment of the role of cytoreduction. There are limited data, analyzed by intent to treat, that describe the use of uniform standard-dose salvage chemotherapy followed by HDT and ASCT. Recently, Rodriguez et al23 reported on the use of the ASHAP regimen (doxorubicin, methylprednisolone, high-dose cytarabine, and cisplatin) as cytoreductive therapy before HDT in HD. The initial response to ASHAP was highly predictive of survival with ASCT. All 17 patients in whom ASHAP failed died of progressive HD, regardless of whether they received HDT. Although patients received additional mobilization chemotherapy before HDT, this program does partially address the impact of salvage chemotherapy before HDT. It supports the concept commonly used in intermediate-grade non-Hodgkin lymphoma: patients with disease refractory to cytoreduction achieve minimal benefit from HDT and ASCT. The response rate to ICE in our study was 88%. Seven of the 8 patients who did not respond to ICE died of HD; the median survival time of ICE failures was 5 months.

The ability to mobilize PBPCs is a critical requirement for a

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**Table 2. Univariate analysis of survival**

| Prognostic factors | No. patients | EFS | P    |
|-------------------|-------------|-----|------|
| Age               |             |     |      |
| < 40              | 53          | 0.618 |     |
| ≥ 40              | 12          | 0.583 | 0.812 |
| < 40 vs ≥ 40      |             |     |      |
| Gender            |             |     |      |
| Male              | 39          | 0.629 |     |
| Female            | 26          | 0.577 |     |
| Male vs female    |             |     | 0.959 |
| Histology         |             |     |      |
| NS/LP             | 58          | 0.614 |     |
| MC                | 7           | 0.571 |     |
| NS/LP vs MC       |             |     | 0.714 |
| Relapse vs refractory |         |     |      |
| Rel               | 43          | 0.653 |     |
| Ref               | 22          | 0.524 |     |
| Rel vs ref        |             |     | 0.051 |
| Ref/rel < 1 y     | 35          | 0.428 |     |
| Rel > 1 y         | 30          | 0.807 |     |
| Ref/rel < 1 y vs rel > 1 y | | 0.001 |      |
| Radiation treatment |             |     |      |
| No prior RT       | 26          | 0.559 |     |
| Prior RT          | 39          | 0.641 |     |
| No prior RT vs prior RT | | 0.756 |      |
| B symptoms pre-ICE |             |     |      |
| − B symp          | 49          | 0.729 |     |
| + B symp          | 16          | 0.225 |     |
| − B symp vs + B symp |             |     | <.001 |
| Extranodal disease pre-ICE | |     |      |
| + ENS             | 33          | 0.818 |     |
| − ENS             | 32          | 0.392 |     |
| + ENS vs − ENS    |             |     | <.001 |

EFS indicates event-free survival; NS/LP, nodular sclerosis/lymphocytic predominance; MC, mixed cellularity; rel, relapse; ref, refractory; RT, radiation treatment; ICE, ifosfamide, carboplatin, and etoposide; symp, symptoms; ENS, extranodal disease.
Infusion is often not uniform.27,28 In 1985 we began examining the setting because patients are often not treated uniformly and the use of IFRT is not specifically mandated in these protocols. Thus, the rationale is based on the observation that disease progression after ICE and G-CSF has a 1.68-fold risk for treatment failure compared to patients without B symptoms. The 95% CI is (1.164, 2.526). Patients who have had a complete remission lasting more than 1 year have a 0.587-fold risk for treatment failure compared to patients who have had a remission duration less than 1 year and those with primary refractory disease. The 95% CI is (0.369, 0.934). Patients with extranodal disease have a 1.87-fold risk for treatment failure compared to patients without extranodal disease. The 95% CI is (1.164, 3.005).

SE indicates standard error; for other abbreviations, see Table 2.

Pre-ASCT cytoductive chemotherapy regimen. Although the optimal number of CD34+ cells per kilogram needed for marrow reconstitution is undetermined, most studies have demonstrated that at least $2 \times 10^6$ CD34+ cells/kg are needed to achieve platelet engraftment by day 14 after infusion, to reduce the number of platelet transfusions, and to shorten the length of hospital stay.24 The median number of CD34+ cells per kilogram collected after ICE and G-CSF was $7.03 \times 10^6$ CD34+ cells/kg. This compares favorably with other salvage regimens such as DHAP (ESHAP) or dexamethasone (mini-BEAM) regimens, where the median numbers of CD34+ cells per kilogram collected were $3.6 \times 10^6$ and $1.6 \times 10^6$, respectively.25,26 In only 9 patients was PBPC mobilization inadequate after ICE and G-CSF.

An important component of this comprehensive program is the incorporation of accelerated fractionation IFRT before ASCT. The rationale is based on the observation that disease progression after HDT tends to occur at sites of prior nodal involvement. However, there is a lack of prospective data evaluating radiotherapy in this setting because patients are often not treated uniformly and the use of IFRT is not specifically mandated in these protocols. Thus, the amount and the timing of radiotherapy before or after stem cell infusion is often not uniform.27,28 In 1985 we began examining the feasibility and efficacy of incorporating accelerated fractionation TLI (20 Gy, with an additional 15 Gy to selected sites) with high-dose chemotherapy into an ASCT strategy for HD. The use of an accelerated TLI schedule permitted the delivery of radiation within a short period of time, before ASCT, thus decreasing the risk for tumor repopulation during radiotherapy and minimizing the period of marrow aplasia before engraftment.10 In an earlier study, 68 consecutive patients with unirradiated refractory and relapsed HD were treated from 1985 to 1994. At a median follow-up of 8 years, the EFS and OS rates were 47% ± 6% and 54% ± 7%, respectively. In our current program, we modified the radiotherapy using twice-daily fractions. This modification, in addition to using mobilized PBPCs and administering epotoposide as 96-hour continuous infusion, probably helped to decrease morbidity rates in the entire program. Importantly, IFRT and TLI were well tolerated and resulted in minimal extramedullary toxicity.

Most failures in this transplantation program occurred in either unirradiated extranodal sites (59%) or in nodal sites that could not be further irradiated (24%). Although the pattern of failure may suggest that the extensive use of nodal irradiation in our program contributed to its overall success, the study has not been designed to examine directly the contribution of radiotherapy. It is of interest that although there was no difference in EFS rates between TLI-treated patients and non–TLI-treated patients (both 68%), the TLI group included more patients with poor-risk disease. Forty-three percent of the patients in the TLI group had more than one adverse prognostic factor (according to our model) compared to only 22% in the non-TLI group. The similar outcome of prognostically different groups may also indirectly imply a benefit from radiotherapy. Still, randomized cooperative group studies would be needed to determine whether integrating radiotherapy, such as TLI and/or IFRT, into a transplant-conditioning regimen would contribute to the excellent long-term EFS in this study.

Response to second-line chemotherapy (chemosensitive disease) has been used as the major selection criterion to proceed to ASCT, but other prognostic factors may also predict for long-term EFS in patients with relapsed and refractory HD. Several reports describe prognostic factors identifiable before transplantation that

### Table 3. Multivariate survival analysis for event-free survival

| Prognostic factor                        | Coefficient | SE    | P     | Hazard ratio |
|------------------------------------------|-------------|-------|-------|--------------|
| B symptoms pre-ICE (baseline = no)       | 0.519       | 0.208 | .012  | 1.680        |
| Ref/ref < 1 y vs > 1 y (baseline < 1 y)  | −0.533      | 0.237 | .025  | 0.587        |
| Extranodal disease (baseline = no)       | 0.626       | 0.242 | .009  | 1.870        |

Patients with B symptoms have a 1.68-fold risk for treatment failure compared to patients without B symptoms. The 95% CI is (1.164, 2.526). Patients who have had a complete remission lasting more than 1 year have a 0.587-fold risk for treatment failure compared to patients who have had a remission duration less than 1 year and those with primary refractory disease. The 95% CI is (0.369, 0.934). Patients with extranodal disease have a 1.87-fold risk for treatment failure compared to patients without extranodal disease. The 95% CI is (1.164, 3.005).

### Table 4. Three-factor model

| Group | No. patients | EFS | OS  | P     |
|-------|--------------|-----|-----|-------|
| A     | 40           | 0.83| .90 |       |
| B     | 15           | 0.27| .57 |       |
| C     | 10           | 0.10| .25 |       |

EFS indicates event-free survival; OS, overall survival; CR, complete response.

EFS A vs B vs C < .001
OS A vs B vs C < .001

Prognostic factors: B symptoms, extranodal disease, and CR duration less than 1 year. Group A, 0-1 factor; group B, 2 factors; group C, 3 factors.

EFS indicates event-free survival; OS, overall survival; CR, complete response.
predict for a poor outcome with this approach. In a series of 128 patients treated with CBV and reported by Bierman et al,29 poor performance status, 2 or more failed chemotherapy regimens, and mediastinal disease were associated with poor failure-free survival (FFS). The 4-year FFS for patients who failed more than 2 prior regimens was only 10%. In patients treated with 2 or fewer regimens, only poor performance status was predictive of survival. Similarly, a study from the City of Hope identified more 2 prior chemotherapy regimens (relative risk, 2.5), prior radiation (relative risk, 2.1), and extranodal disease at the time of ASCT (relative risk, 1.8) as associated with poor survival after CBV or TBI-cyclophosphamide and etoposide.30 A study from Stanford University that included 119 patients with relapsed and refractory HD who received either TBI, cyclophosphamide and etoposide, or CBV identified B symptoms at relapse, bone marrow or pulmonary involvement with HD, and greater than 2-cm involvement of HD at the time of ASCT as poor prognostic factors. Patients with none of these factors had 4-year EFS rates of 85% compared to 41% in patients with any one factor.31

Brice et al32 reviewed 280 patients with relapsed HD, reported to the French lymphoma registry, and developed a 2-factor model incorporating CR duration of less than 1 year and extranodal disease at relapse. Patients with zero, one, or 2 factors had progression-free survival rates of 93%, 59%, and 43%, respectively. Reece et al8 reported the results of 58 patients with relapsed HD treated with CBV plus or minus cisplatin and ASCT. Their analysis identified the same independent prognostic factors that emerged from our study and were used in our prognostic model: B symptoms at relapse, extranodal disease at relapse, and initial remission duration of less than 1 year. Patients with no risk factors had 3-year progression-free survival rates of 100% versus 81% for patients with one factor, 40% for patients with 2 factors, and 0% for patients with all 3 factors. However, in that study conventional-dose cytotherapy was not mandated in the protocol, patients were not formally restaged before high-dose therapy, and patients with primary refractory disease were excluded. Our prognostic model was developed for patients who were transplant eligible and included patients with relapsed and primary refractory HD. In our intent-to-treat analysis, patients with 0 to 1 adverse factor had an OS rate of 90%, patients with 2 factors had an OS rate of 57%, and patients with all 3 factors had an OS rate of 25%.

Because of the lack of comparable intent-to-treat data in the literature, we applied the 3-factor prognostic model to the subgroup of 57 patients in the current study who received transplants, and it remained significant ($P = .008$). We also applied our prognostic factor model to 85 consecutive patients who underwent transplantation from 1990 to 1994. These patients all received modern supportive care (including hematopoietic growth factors) and either IFRT-CBV or IFRT-TLI-cyclophosphamide-etoposide as the conditioning regimen with bone marrow support. Our 3-factor model predicted overall survival in that data set as well ($P = .04$). Our prognostic model is, therefore, also applicable to non-intent-to-treat studies, and it indicates that an initial remission duration of less than 1 year, B symptoms before cytotherapy, and extranodal or stage IV disease predict survival in patients with relapsed and primary refractory HD who undergo ASCT.

The impact of modern supportive care that includes hematopoietic growth factor support, PBPCs (vs bone marrow) as the primary stem cell source, single-donor platelet transfusions, and newer antibiotics and antifungal agents have markedly decreased transplantation-related toxicity in the past 7 years. However, this has not translated into major improvements in overall survival. Therefore, critical issues such as response to salvage chemotherapy before HDT, the transplant-conditioning regimen, and prognostic factors at the time of relapse must have an impact on survival. The application of a treatment strategy combining ICE cytotherapy followed by HDT provided an EFS rate of 58% in patients with relapsed or primary refractory HD undergoing ASCT.

The identification of 3 prognostic groups has influenced the design of our new protocol. This is a risk-adapted, comprehensive, intent-to-treat, second-line program for patients with relapsed or refractory Hodgkin disease. Although we have not modified the program for patients in our most favorable group, those with 2 risk factors receive augmented ICE for cytotherapy and an intensified HDT therapy regimen. Patients with all 3 factors receive a tandem autotransplant.

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A 2-step comprehensive high-dose chemoradiotherapy second-line program for relapsed and refractory Hodgkin disease: analysis by intent to treat and development of a prognostic model

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