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The Value of Augmented Preparative Regimens Combined with an Autologous Bone Marrow Transplant for the Management of Relapsed or Refractory Hodgkin Disease: A Southwest Oncology Group Phase II Trial

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ABSTRACT

Several single-institution pilot studies have suggested that augmented preparative regimens, including those containing total body irradiation combined with an autologous bone marrow transplantation, are superior to standard regimens for the treatment of relapsed or refractory Hodgkin disease. On the basis of these data, we undertook, in the cooperative group setting, a phase II trial of augmented preparative regimens for patients experiencing treatment failure with conventional chemotherapy. Eighty-one patients with either sensitive or refractory (induction failures or chemoresistant) relapse received etoposide (60 mg/kg), cyclophosphamide (100 mg/kg), and either total body irradiation (12 Gy) or, if previously irradiated, carmustine (15 mg/kg), followed by an autologous bone marrow transplantation. Progression-free (PFS) and overall (OS) survival were estimated, and a Cox regression model was used to assess potential prognostic variables. The 5-year PFS and OS for the 74 eligible patients treated at 20 Southwest Oncology Group centers were 41% (95% confidence interval [CI], 29%-53%) and 54% (95% CI, 43%-65%), respectively, despite a median remission after initial chemotherapy of only 6 months. The 3-year OS for those whose induction therapy failed was 72% (95% CI, 52%-93%). There was 1 (1.4%) early treatment-related death, 2 late deaths due to lung toxicity, and only 1 death due to myelodysplasia. There were no differences in PFS or OS on the basis of regimen or chemosensitivity. A Cox prognostic factor analysis determined that >2 prior regimens, relapse in a radiated field, and extranodal disease were adverse prognostic factors. Among the 46 patients who received prior radiotherapy, the 5-year OS was 38% (95% CI, 14%-61%) for patients with 2 or 3 adverse factors, versus 60% (95% CI, 42%-78%) for those with 0 factors or 1 adverse factor. Augmented preparative regimens seem promising for the treatment of relapsed or refractory Hodgkin disease, without an increase in regimen-related mortality. A poor-prognosis group was identified that should be treated with novel therapies.

KEY WORDS

Hodgkin disease • Autologous bone marrow transplantation • Augmented preparative regimens

INTRODUCTION

Although patients who experience disease progression or relapse after combination chemotherapy for Hodgkin disease frequently respond to conventional salvage chemotherapy, few are long-term disease-free survivors [1-7]. However, high-dose therapy combined with an autologous hematopoietic stem cell transplantation after salvage chemotherapy seems to increase the proportion of those who survive disease-free [8-15]. This is especially true for patients whose induction therapy fails. These patients have little pros-

pect for long-term progression-free survival (PFS) with conventional chemotherapy alone [2,5-7,16], but they have approximately a 40% 5-year overall survival (OS) after transplantation [17,18].

Less convincing is the potential benefit of transplantation for those who undergo transplantation at the time of the first chemotherapy relapse. These patients have a 5-year OS of approximately 50% [19-21]. Although 2 phase III trials comparing conventional chemotherapy versus transplantation for patients who relapse after a chemotherapy-induced complete remission (CR) have shown an improved PFS for those undergoing transplantation [9,10], a short-term OS benefit for transplant therapy has not yet been shown. Long-term data from these trials are lacking. It is indeed possible that longer follow-up may show a survival advantage for transplantation (given the higher PFS and long survival after subsequent relapse, including those whose autograft fails). Because of the potential for longer survival with transplantation and because of the increased risk of treatment-related myelodysplasia (MDS) and acute myeloid leukemia (AML) after repeated cycles of conventional chemotherapy/radiotherapy [22-25], it is generally agreed that a transplantation is appropriate for patients whose front-line combination chemotherapy fails. Patients likely to be offered a transplant are those in poor-risk groups, defined by a short initial remission duration, chemoresistance at relapse, poor performance status, B symptoms, >1 extranodal site at relapse, and increased lactic dehydrogenase [1-15,17-21].

Given that 60% of patients still relapse after an autotransplantation, several groups have explored intensifying the preparative regimens. Horning et al. [26] reported a PFS of 55% at 3 years for patients who received total body irradiation (TBI) along with both high-dose etoposide and cyclophosphamide. Nademanee et al. [27] reported 85 patients who received either the same TBI-based regimen or the same doses of etoposide and cyclophosphamide with high-dose carmustine (BCNU; 450 mg/m^2) for those who had received prior radiotherapy. At 28 months, the PFS rate after transplantation was 52%. Because most relapses after autotransplantations for Hodgkin disease occur before 2 years, these collective data suggested that increasing the intensity of preparative regimens for this disease could improve PFS by 10% to 15% compared with less-aggressive regimens.

On the basis of these results, a phase II study was undertaken in the Southwest Oncology Group (SWOG) for patients who progressed during induction chemotherapy or relapsed after at least 1 chemotherapy-induced remission. This study was modeled on a similar SWOG study of augmented regimens for the treatment of relapsed or refractory diffuse aggressive non-Hodgkin lymphoma (NHL) [28]. Given that chemotherapy sensitivity was identified as an important prognostic factor in phase II trials, patients were stratified before transplantation on the basis of chemotherapy sensitivity. In addition, a multivariate analysis was undertaken to explore factors associated with long-term OS.

PATIENTS AND METHODS

Patient Selection

Patients aged 15 to 56 years with relapsed or refractory Hodgkin disease and who had experienced treatment failure with at least 1 combination chemotherapy regimen were eligible. Those who relapsed after a previous CR were required to undergo either 2 cycles of salvage chemotherapy or radiotherapy of localized disease. Salvage therapy was not required for those whose induction therapy failed, but it was permitted.

Patients were required to have adequate renal (creatinine clearance >60 mL/min), hepatic (serum transaminases <3 times the upper limit of normal and serum bilirubin <2.0 mg/dL), pulmonary (forced expiratory volume in 1 second or diffusion capacity of carbon monoxide >60% of predicted), and hematologic (white blood cell count >3500/μL, hemoglobin level >10 g/dL, and platelets >100,000/μL) function and histologically normal bone marrow examinations. In addition, patients must have had a normal cardiac history and a SWOG performance status of 0 or 1. Criteria for exclusion included prior hemorrhagic cystitis and active infections. All patients were required to sign a written, informed consent for this trial. The trial was required to have local institutional review board approval before implementation.

Patients who had relapsed and responded to salvage chemotherapy were considered to have sensitive disease, whereas those who either did not enter a CR with induction chemotherapy or did not have at least a partial response (PR) to salvage therapy were considered to have resistant disease. However, patients who achieved a PR with induction therapy and subsequently responded to salvage chemotherapy were considered to have chemosensitive disease. Patients were also classified by their response to induction therapy (CR versus less than a CR) and by whether they received salvage or subsequent therapy. Patients were further defined retrospectively as having primary refractory disease if they progressed, had less than a CR, or relapsed within 6 months after completing the initial chemotherapy.

Treatment Regimen

Treatment details were essentially identical to those of our previously reported transplant trial in diffuse aggressive NHL [28]. Before entry, patients

underwent a bone marrow harvest under general anesthesia. A minimum of 2.0×10^8 nucleated cells per kilogram of actual body weight was required to proceed. Once this was completed, patients underwent their preparative regimen, as shown in Table 1. Briefly, patients who had not received a minimum of 2500 cGy of radiation to any field were required to receive the TBI-based transplantation regimen. Patients received 150 cGy twice a day, separated by a minimum of 5 hours, for 4 days in the anterior and posterior positions or by opposing lateral fields from days −8 to −5. The dose rate was 5 to 20 cGy/min, and the fractions were separated by a minimum of 5 hours. The lungs were shielded anterior/posterior and posterior/anterior for the final 600 cGy in all patients by using standard (5 half-value layer) lung blocks. The dose was calculated at the midplane and central axis. Thermoluminescent dosimeters were used at the first dose, and compensators were allowed to keep the dose in homogeneity at ≤10%. Corrections for lung inhomogeneity were not performed.

On day −4, patients received etoposide as a single 4-hour infusion at a dose of 60 mg/kg based on actual body weight. No adjustments were made on the basis of actual body weight. Each patient received 25 mg of diphenhydramine and hydrocortisone 100 mg intravenously before the infusion and 2 hours into the 4-hour infusion for prophylaxis against allergic reactions. On day −2, patients received cyclophosphamide at a dose of 100 mg/kg intravenously over 1 to 2 hours based on ideal body weight. No adjustment was made on the basis of body weight over ideal weight calculations. To prevent hemorrhagic cystitis, patients underwent continuous bladder irrigation during and for 24 hours after the cyclophosphamide infusion. On day 0, patients received their cryopreserved marrow stem cells. Hematopoietic growth factors were permitted.

For those not eligible to receive TBI, the same doses of etoposide (day −4) and cyclophosphamide (day −2) as used in the TBI-based regimen were administered along with high-dose BCNU. The dose of BCNU was 15 mg/kg, based on ideal body weight, and it was administered as a single dose on day −6 in 500 mL of saline over 2 hours. The dose was adjusted, however, to account for obese patients: 40% of the patient's weight that was 15 kg above the ideal body weight was added to the ideal body weight.

Table 1. *Transplantation Regimens*

TBI/cyclophosphamide/etoposide
TBI* 150 cGy twice daily, days −8, −7, −6, −5
Etoposide† 60 mg/kg IV over 4 h, day −4
Cyclophosphamide‡ 100 mg/kg IV over 1 h, day −2
ABMT day 0
BCNU/cyclophosphamide/etoposide
BCNU† 15 mg/kg IV over 1 h, day −6
Etoposide† 60 mg/kg IV over 4 h, day −4
Cyclophosphamide‡ 100 mg/kg IV over 1 h, day −2
ABMT day 0

IV indicates intravenous; ABMT, autologous bone marrow transplantation.

*Lungs shielded after first 600 cGy.

†Based on actual body weight.

‡Based on ideal body weight.

Statistical Considerations

A CR was defined as the disappearance of all clinical evidence of active tumor for a minimum of 4 weeks. A PR was defined as a ≥50% decrease in the sum of the product of diameters of all measurable lesions for a minimum of 4 weeks. For both CR and PR, a confirmation assessment was required at least 4 weeks after the first determination of response. Progression was defined as (1) an increase of at least 50% or 10 cm^2 (whichever was smaller) in the sum of the products of measurable lesions over the smallest sum observed or (2) the appearance of any new disease. Patients were considered to be nonresponders if they did not have a PR or CR. Responses were determined by examinations, radiographs, and computed tomographic scans. Gallium scans were not used for response measurement. Early mortality was defined as deaths that occurred within the first 50 days after transplantation (infusion of bone marrow) or approximately 60 days after the preparative regimen began. Standard SWOG toxicity criteria were used to define the toxicities in this trial.

The anticipated accrual goal was 45 patients with sensitive disease and 45 with resistant disease. Forty-five patients is sufficient to estimate response probabilities and survival estimates to within ±15%. Among 90 total patients, any toxicity occurring with at least 5% probability is likely to be seen once (99% chance). All eligible patients were included in the analysis of PFS and OS. PFS was measured from the date of registration until progression, relapse, or death. OS was measured from the date of registration until death from any cause. PFS and OS were estimated by the method of Kaplan and Meier [29] and were compared by using the log-rank test statistic [30]. Hazard ratios for PFS and OS were estimated with the Cox regression model [31]. All significance values reported for PFS and OS are 2 sided.

Multivariate Analysis

Because a significant number of patients relapse after a transplantation for Hodgkin disease, we undertook a prognostic factor analysis to develop a prognostic factor scale for use in designing future studies. We analyzed 14 factors with possible predictive value, including those suggested by the results of previous studies (Table 2). Factors with a statistically significant or marginally significant ($P \leq .10$) effect on OS in

Table 2. *Factors Considered for Multivariate Analysis*

Sex
SWOG performance status
Duration of initial chemotherapy process
Number of extranodal sites
Sensitivities
B symptoms
Disease bulk >5 cm
No. of prior chemotherapy regimens
LDH at the hospital
Parenchymal lung disease
Relapse in prior RT field
Induction failures
CR to induction therapy
Preparative regimen

LDH indicates lactic dehydrogenase; RT, radiation.

univariate analysis were considered for inclusion in a risk model. A forward stepwise Cox regression analysis identified factors that remained significant predictors of OS in a multivariate setting. For each patient, the number of adverse factors was counted, and the number was subsequently analyzed in Cox regression as an independent variable.

RESULTS

This study opened in 20 SWOG institutions in April 1990. A total of 81 patients were enrolled before the trial was closed in December 1995. Seven patients were ineligible: 1 began protocol therapy before enrollment, 1 had NHL, 1 did not receive the required salvage therapy before transplantation, and 4 had insufficient prestudy documentation. Of the remaining 74 eligible patients, 47 had sensitive disease and 27 had resistant disease. The study was closed after the sensitive-disease cohort met its accrual goal.

All 74 eligible patients completed protocol therapy. There were 5 regimen-related protocol deviations: 2 patients received TBI despite prior thoracic radiotherapy, 1 received the BCNU-based regimen despite no prior radiotherapy, and 2 received post-transplantation radiotherapy as consolidation therapy. All eligible patients were assessable for efficacy and toxicity.

Patient Characteristics

Patient characteristics are shown in Tables 3 and 4. The median age was 28 years (range, 17-53 years). Among the 74 eligible patients, the TBI-based preparative regimen was administered to 28 (38%) patients (15 in the sensitive-disease group and 13 in the resistant-disease group), whereas the BCNU-based preparative regimen was administered to 48 (62%) patients. Forty-seven eligible patients (64%) had sensitive disease, and 27 (36%) had resistant disease. Eighteen patients (24%) had treatment failure with their initial induction therapy. The median duration of initial remission was only 6 months; only 33% had an initial remission >1 year, and only 7% had an initial remission >2 years. Thirty-five percent had increased lactic dehydrogenase, 63% had B symptoms, and 28% had pulmonary parenchymal lung disease. Most patients (59%) received 2 prior chemotherapy regimens, with 19% receiving 3 and 14% receiving 4 more. The largest-diameter mass at transplantation was >5 cm in 23% of patients. Among the 46 patients who received prior radiotherapy, 70% relapsed in at least 1 of the fields before transplantation.

Prior Treatment Experience

Among the 74 eligible patients, 7 (9%) received radiotherapy alone as initial therapy for low-stage disease (and received chemotherapy only after relapse), whereas 19 (26%) received combined-modality therapy at diagnosis and 48 (65%) received chemotherapy alone. Fifty-three patients (72%) received methotrexate, vincristine, procarbazine, and prednisone (MOPP), MOPP with doxorubicin, bleomycin, and vinblastine, or similar treatment as induction chemotherapy, whereas 10 (14%) received doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) alone and 11 (15%) received other regimens. (An additional 8 patients [11%] received MOPP as second- or third-line therapy.) Approximately half received a platinum-based regimen as their pretransplantation salvage chemotherapy. In the entire cohort, 19 (26%) had treatment failure with induction therapy (disease progression or less than a CR); among the 55 patients (74%) who had a CR to induction therapy, 24 (44%) relapsed within 6 months of completing induction chemotherapy. The 43 patients (19 induction failures plus 24 induction CRs relapsing within 6 months) in these 2 categories (58%) were considered to have primary refractory disease.

Patient Outcome

All 74 patients completed their transplantation. There was only 1 (1.4%) early treatment-related death, which was due to sepsis. This patient was in the

Table 3. *Patient Characteristics*

Variable	Sensitive	Resistant	Total
No. registered	**53**	**28**	**81**
Ineligible	**6**	**1**	**7**
Insufficient documentation	**3**	**1**	**4**
Eligible	**47**	**27**	**74**
Median age (y)	**30**	**27**	**28**
Male sex	**19 (40%)**	**14 (52%)**	**33 (45%)**
CR to induction therapy	**41 (87%)**	**15 (56%)**	**55 (74%)**
Induction failure	**6 (13%)**	**12 (44%)**	**18 (24%)**
Salvage therapy	**47 (100%)**	**25 (93%)**	**72 (97%)**
TBI preparation	**15 (32%)**	**13 (48%)**	**28 (38%)**

Table 4. *Potential Prognostic Factors for Overall Survival*

Variable	n	%	Univariate *P* Value
Sex			.39
Male	33	45	
Female	41	55	
SWOG performance status			.63
0	56	76	
1	18	24	
Duration of initial remission (mo)			.88
<12	49	67	
≥12	24	33	
Median (range)	6 (0.5-102)		
No. of extranodal sites*			.03
0	58	78	
≥1	14	22	
Disease type			.84
Sensitive	47	64	
Resistant	27	36	
Symptoms			.80
A	27	37	
B	46	63	
Disease bulk >5 cm			.20
Yes	17	23	
No	56	77	
Number of prior chemotherapy regimens*			.007
1	6	8	
2	44	59	
3	14	19	
≥4	10	14	
LDH			.99
Normal	48	65	
>1 normal	26	35	
Parenchymal lung disease			.71
Yes	16	28	
No	42	72	
Relapse in a prior RT field (in patients with prior RT only)			.09
Yes	32	70	
No	14	30	
No RT	26		
True induction failure			.36
Yes	18	24	
No	56	76	
Response to induction therapy			.10
CR	55	74	
Less than CR	19	26	
Type of preparative regimen			.52
TBI	28	38	
BCNU	46	62	

LDH indicates lactic dehydrogenase; RT, radiation.
*Analyzed on an ordinal scale.

sensitive-disease group and received the BCNU-based preparative regimen. There were 3 (4.2%) other late treatment-related deaths, all after engraftment and all in the BCNU group. Two patients died of pulmonary fibrosis/pneumonitis. One of these patients, who received 5 prior chemotherapy regimens (including nitrosoureas and bleomycin) and mantle radiotherapy, died 90 days after transplantation; the other patient, who received 6 prior regimens and mantle radiotherapy, died on day 68. The third patient died of treatment-related MDS 25 months after his transplantation. This patient had received combined-modality therapy with an alkylating agent–based induction chemotherapy regimen. To date, there have been no reports of MDS in the TBI arm and no others in the BCNU arm.

Twelve patients had no evidence of disease at transplantation and were therefore not assessable for response. Of the remainder, 9 had insufficient follow-up data to accurately determine response. These patients were assumed to be nonresponders. Among the 39 patients with sensitive disease who were available for response assessment, the CR rate was 23% (95% confidence interval [CI], 11%-39%). Among the 23 patients with resistant disease who were available for response assessment, the CR rate was only 9% (95% CI, 1%-28%). The most common response in each group was stable disease (41% and 26%, respectively).

The 5-year PFS and OS values for the entire group were 41% (95% CI, 29%-53%) and 54% (95% CI, 43%-65%), respectively. As shown in Figure 1, the 5-year PFS values for the sensitive and resistant cohorts were 40% (95% CI: 26%-54%) and 41% (95% CI: 22%-59%), respectively. As shown in Figure 2, the 5-year OS values for the sensitive and resistant cohorts were 55% (95% CI, 41%-70%) and 52% (95% CI, 33%-71%), respectively. Of note, for the 18 patients whose induction chemotherapy failed, the 3-year and 5-year PFS values were 56% (95% CI, 33%-79%) and 44% (95% CI, 21%-67%), respectively, whereas the 3-year and 5-year OS values were 72% (95% CI, 52%-93%) and 61% (95% CI, 39%-84%), respectively. The 5-year PFS and OS values for the 9 patients who underwent transplantation in CR were both 67% (95% CI, 36%-97%). As shown, estimates of 8-year survival continue to show no differences between the 2 groups. The 5-year PFS for the TBI-based regimen was 43% (95% CI, 25%-61%), versus 39% (95% CI, 25%-53%) for the BCNU-based regimen, whereas the 5-year OS rates were 61%

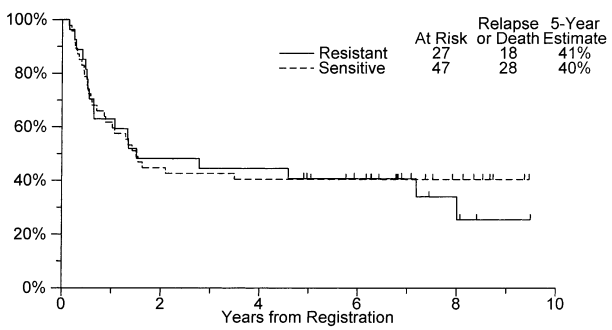

Figure 1. Progression-free survival based on disease sensitivity.

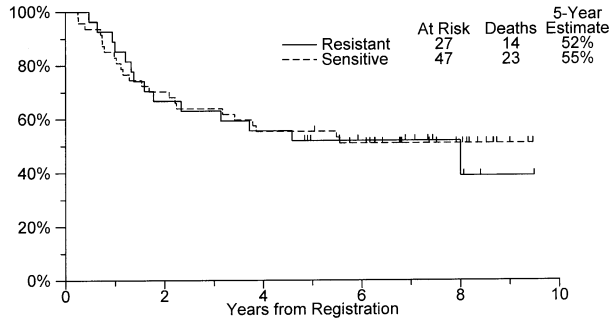

Figure 2. Overall survival based on disease sensitivity.

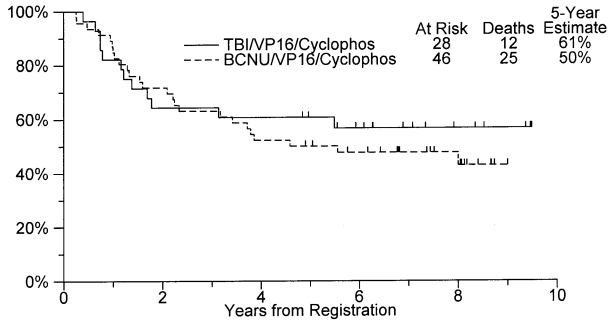

Figure 4. Overall survival based on preparative regimen.

(95% CI, 43%-79%) and 50% (95% CI, 36%-64%), respectively (Figures 3 and 4). The small numbers prevent statistical comparisons.

Toxicities

The median time to absolutely neutrophil count recovery after transplantation to >500/μL was day 12 and to platelet recovery >20,000/μL was day 15. Similar to the NHL study previously reported, a substantial amount of mucositis was seen; however, overall, only 5 cases (6.8%) of grade 4 mucositis, pharyngitis, or esophagitis were reported. The overall incidence of grade 3/4 mucositis was higher in those who received the TBI regimen (64% versus 15%). The only other difference in toxicity between the 2 regimens was a higher incidence of grade 3/4 bilirubin increases in the BCNU arm (17% versus 7%), but no cases of fatal veno-occlusion were seen in either group. Apparent differences in these toxicities may be due to patient selection. In addition to the single death due to sepsis reported previously, there was only a single case of grade 4 infection, which resolved with appropriate antibiotic therapy. There were no cases of grade 4 pneumonitis, and there was only 1 case of grade 4 skin toxicity, presumably due to etoposide.

Multivariate Analysis

Of the 14 factors analyzed for OS in univariate analysis, the number of extranodal sites at transplantation (P = .03) and the number of prior chemotherapy regimens (P = .007) were significant, whereas relapse in a prior radiation field (P = .09) and response to initial or induction therapy (P = .10) were borderline significant (Table 4). Of note, the duration of initial remission did not predict OS. The 4 significant or borderline significant factors were analyzed in a forward stepwise Cox regression procedure. Two of the 74 patients had incomplete prognostic data. In the remaining 72 patients, the number of prior chemotherapy regimens, number of extranodal sites, and relapse in a prior radiation field retained at least marginal significance in the multivariate setting (Table 5).

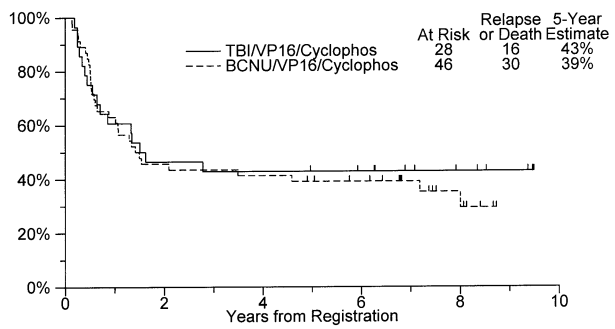

Figure 3. Progression-free survival based on preparative regimen.

Relapse in a prior radiation field was defined only for the subset of 46 patients who received prior radiation and so was not considered as a risk factor for the entire cohort of 72 patients. For the entire cohort of 72 patients, only the number of prior chemotherapy regimens and the number of extranodal sites had predictive value. Predetermined cutoffs for these 2 factors (≥3 prior chemotherapy regimens and ≥1 extranodal site) were chosen to define the adverse risk factors. Thirty-eight patients (53%) had no risk factors, 29 had 1 risk factor, and 5 had 2 risk factors. The number of risk factors (0-2) was a significant predictor of survival in a Cox regression model (P = .02). To summarize the effect, in terms of prognostic groups, patients with 2 factors were grouped with patients with 1 risk factor (P = .11). The hazard ratio was 1.76 (95% CI, 0.90-3.43).

A second analysis was performed in the 46 patients who received prior radiotherapy, in whom relapse in a prior radiation field was also associated with OS. Six patients (13%) had no factors, 24 (52%) had 1 risk factor, 13 (28%) had 2 risk factors, and 3 (7%) had all 3 adverse risk factors. The number of risk factors (0-3) was a significant predictor of OS in a Cox regression model (P = .01). As before, to summarize the effect in terms of prognostic groups, patients with 0 factors or 1 risk factor were grouped together, as were those with 2 and 3 risk factors (P = .05). The hazard ratio was 2.26 (95% CI, 1.01-5.07). Five-year OS estimates are shown in Figure 5. The 5-year OS for patients with 0 factors or 1 risk factor was 60% (95% CI,

Table 5. *Results of the Forward Stepwise Cox Regression Procedure (P Values) (N = 72 Patients with Complete Data)*

Step	Prognostic Factor			
	No. Prior Chemotherapy Regimens	No. Extranodal Sites	Relapse in a Prior RT Field*	Response to Induction Therapy
Step 1: add number of prior chemotherapy regimens (P = .007)	**.009**			
Step 2: add number of extranodal sites (P = .03)	**.02**	**.05**		
Step 3: add relapse in prior RT field (P = .09)	**.06**	**.03**	**.07**	
Step 4: add response to induction therapy (P = .10)	**.05**	**.02**	**.07**	**.12**

RT indicates radiation.

*In patients with prior RT only.

42%-78%), versus 38% (95% CI, 14%-61%) for those with 2 or 3 risk factors.

DISCUSSION

This SWOG study was based on 2 pilot studies that suggested that augmented regimens could be administered safely and that survival might be enhanced by 15% to 20% as compared with conventional preparative regimens [26,27]. This first US multicenter study of transplant therapy in Hodgkin disease found only a 1.4% early-death rate and a survival and toxicity similar to those in the pilot studies. Our 3-year OS of 72% (95% CI, 52%-93%) for those whose induction chemotherapy failed represents the best reported survival for this group to date and compares favorably to the 50% rate (95% CI, 39%-60%) recently reported by the Autologous Blood and Marrow Transplant Registry (ABMTR) [17]. At 5 years, this group had a survival of 61% (95% CI, 39%-84%), indicating that the remissions induced by these regimens are durable. In addition, similar to the results for the NHL trial [28], all resistant-disease patients seemed to benefit from these augmented regimens, with a 52% (95% CI, 33%-71%) 5-year OS. Because gallium scans were not used for disease responsiveness after salvage chemotherapy and because positron emission tomographic scans were not available at most centers during the study, it is possible that some patients we considered resistant were actually in remission at the time of transplantation. We believe, however, that this is unlikely, considering that the median relapse-free survival after initial chemotherapy for the entire group was only 6 months. Together, these results suggest that augmented preparative regimens are indicated in this patient group, although this conclusion requires a phase III trial for validation.

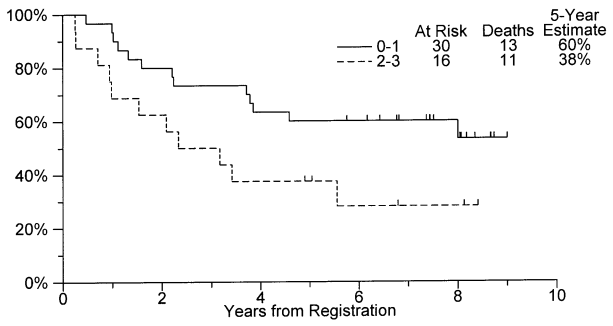

Figure 5. Overall survival by number of risk factors: >2 prior chemotherapy regimens, extranodal disease, and relapse in prior radiation field. Hazard ratio: 2.26 (95% CI, 1.01- 5.07).

We considered these regimens to be augmented from both a dose and schedule standpoint. For the TBI regimen, the maximum-tolerated dose of etoposide combined with TBI [32] was added to the equivalent of the maximum-tolerated dose of cyclophosphamide (100 mg/kg) combined with TBI in a standard cyclophosphamide/TBI regimen. In addition, compared with the first studies of high-dose BCNU, cyclophosphamide, and etoposide (VP16; BCV), the BCV regimen tested here used a higher dose of both BCNU and etoposide [33,34], and all chemotherapy agents were given as single-bolus doses rather than as prolonged infusions or repeated daily doses. The schedule, along with the total dose, of alkylating agents may be important in antitumor responses [35-37], as validated by in vitro data of cyclophosphamide analogs suggesting that single large doses may be superior to multiple smaller doses given over a prolonged period. This benefit is possibly due to a progressive shortening of the area under the curve of the active metabolites of cyclophosphamide seen with a multiple dosing schedule [35].

Long-term follow-up for this study is out to nearly 10 years, allowing us for the first time in this disease to describe the risk of late relapse. As shown, no late relapses have been seen in the chemotherapy-sensitive subgroup after 3.5 years, with only a single relapse more than 2 years after transplantation. Although late relapses did occur in the chemotherapy-resistant group (with 2 relapses beyond 7 years), in general these data extend results from numerous pilot studies that found that most relapses occur in the first 18 months after transplantation [8-15,17-21,38]. This suggests that novel transplantation therapies intended to reduce relapses could be evaluated quickly in phase

II trials and pursued or discarded on the basis of 2-year PFS.

Our results seem to verify the utility and safety of TBI-based preparative regimens for this disease. Although TBI has been suggested in the past as an etiologic factor in posttransplantation AML and MDS [39-41], none of the 28 patients who received this preparative regimen and only 1 patient overall developed MDS with posttransplantation follow-up times nearing 10 years, despite the use of MOPP or MOPP/ABVD before transplantation in all but 13 of the patients treated here and the use of radiotherapy in half of our patients. The low rate may be related to the young age of our patients, although the median age of our group (28 years) is virtually identical to recent registry reports for this treatment in this disease from the ABMTR and the European Bone Marrow Transplantation Group [17,18]. That TBI may not be a causative factor in the genesis of posttransplantation AML/MDS is further supported by the recent ABMTR/National Cancer Institute analysis of posttransplantation MDS/AML in patients who underwent autotransplantation for lymphoma, including Hodgkin disease [42], and fluorescence in situ hybridization data indicating that post–autologous stem cell transplantation AML/MDS results from clones detected before transplantation [43]. However, single-institution studies do indicate the possibility that TBI might be a contributing factor to the development of AML/MDS [43-45]. This is certainly plausible given that involved field radiotherapy with chemotherapy does increase the risk of AML/MDS when used in standard doses for the treatment of lymphoma, either alone [46] or followed by an autotransplantation [47].

The adverse prognostic factors identified in the multivariate analysis indicate that patients with multiple relapses and with extranodal disease at transplantation have an inferior transplantation outcome. These are similar to other multivariate analyses reported in the literature [13,14,17,18,20,21,27,39,48,49]. Not previously described is the finding that relapse in a prior radiation field, likely a new measure of resistant disease, was also an independent risk factor. Unlike other studies, we did not find chemoresistance at transplantation to be an adverse risk factor. This may be explained by the intensity of the preparative regimens, as described previously, but the determination of chemosensitivity was made only several weeks after a second and final cycle of salvage chemotherapy; this was potentially too early to determine a favorable response to the salvage regimen. In an attempt to identify a poor-prognostic group in whom to test novel therapies, we identified a subgroup of patients with 2 or all 3 of these adverse factors, who had a 5-year OS of only 38%, indicating that novel approaches should be targeted for this patient subgroup. This is similar to other reports that also divided patients into groups on the basis of the number of adverse prognostic factors [48,49]. Wheeler et al. [49] described 3 prognostic groups based on the number of extranodal sites and additional significant prognostic factors not found to be significant in our analysis: nodular sclerosis histology, abnormal performance status, short time from diagnosis to transplantation, and presence of B symptoms at relapse. Survival for the 3 groups ranged from 82% to 19% and again suggests that the high-risk patients should be offered innovative therapies rather than a standard transplantation [49].

Options for improving transplantation outcome have been limited. In most studies, patients with the best posttransplantation survival were those who underwent transplantation in CR (67% long-term survival in our study) [14,38,39]. It is appropriate, then, to investigate whether increasing the CR rate before transplantation would improve the outcome for patients with adverse factors. Multicycle high-dose therapy has recently been tested in this disease on the basis of this strategy [50-52]. In a recently completed 2-institution pilot study, 47 patients with poor prognostic factors (induction failures, relapse <1 year, B symptoms, or extranodal disease) received a cycle of high-dose melphalan at 150 mg/m^2 with an autotransplantation before one of the ablative transplantation regimens used in this study [50]. After a follow-up of 2 years, the PFS and OS rates for the 47 eligible patients were 64% (95% CI, 48%-79%) and 73% (95% CI, 38%-68%), respectively; these are higher than the estimates obtained in this study and other studies in the literature. On the basis of these favorable data and those of other tandem approaches [51-53], SWOG plans to initiate a groupwide phase II study of this tandem transplantation approach.

Another strategy for the poor-prognosis group would be to explore allogeneic transplantation. Although there seems to be a graft-versus–Hodgkin disease effect, studies performed in the late 1980s and 1990s that used ablative preparative regimens had a dismal outcome, with a 70% incidence of treatment-related mortality [54-57]. With the early success of submyeloablative approaches in reducing regimen-related toxicities in low-grade leukemia and lymphoma, Cooney et al. [58] tested BCNU, etoposide, cytarabine, and melphalan chemotherapy with either a related or an unrelated allograft in 10 patients who had experienced treatment failure with a previous autograft for Hodgkin disease. They recently reported a 0% 100-day mortality and an estimated 2-year PFS of 65% [58]. These preliminary data will need to be verified, ideally in a multicenter setting. If PFS is favorable, other trials will need to determine the exact timing of this therapy. However, the favorable pilot data on tandem transplantations for patients with high-risk disease and these preliminary allograft data

suggest that allografts should be reserved currently for patients who relapse after an autograft.

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