Tandem Autologous Hematopoietic Cell Transplantation for Patients with Primary Progressive or Recurrent Hodgkin Lymphoma: A SWOG and Blood and Marrow Transplant Clinical Trials Network Phase II Trial (SWOG S0410/BMT CTN 0703)


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Article history:
Received 6 April 2017
Accepted 21 December 2017

Key Words:
Hodgkin lymphoma
Tandem transplant
Autologous stem cell transplant

ABSTRACT
Based on promising pilot data a phase II tandem autologous hematopoietic stem cell transplant (AH SCT) trial for relapsed/refractory Hodgkin lymphoma (HL) was performed in the US intergroup setting to determine if long-term progression-free survival (PFS) could be improved. Patients were enrolled after salvage therapy and stem cell collection. Sensitivity to salvage was defined by 1999 Standardized Response Criteria and did not include fluorodeoxyglucose-positron emission tomography. Cycle 1 consisted of melphalan 150 mg/m2 with half of the stem cells. For stable disease or better, patients received cycle 2 consisting of single doses of etoposide 60 mg/kg and cyclophosphamide 100 mg/kg and either total body radiation 12 Gy in 8 fractions over 4 days or BCNU 150 mg/m2/day for 3 days with the remaining stem cells. Of 98 enrolled patients, 89 were eligible and treated: 82 completed both cycles of AHSCT, 47 (53%) had primary refractory HL, and 72 (81%) were resistant to salvage therapy. There were no treatment-related deaths in the first year after AHSCT. With a median follow-up of 6.2 years (range, 2 to 7.7) for eligible patients who remained alive, the 2-year and 5-year PFS were 63% (95% CI, 52% to 72%) and 55% (95% CI, 44% to 64%), respectively; the 2-year and 5-year overall survival were 91% (95% CI, 83% to 95%) and 84% (95% CI, 74% to 90%), respectively. Univariate Cox regression analysis showed Zubrod performance status and lactate dehydrogenase levels >1 times upper limit of normal at the time of enrollment were significantly associated with PFS. The observed 5-year PFS of 55% suggests the tandem approach appears to be effective in treating HL patients demonstrated to have poor prognosis in prior single AHSCT trials. This trial was registered at www.clinicaltrials.gov as NCT00233987.

INTRODUCTION
Autologous hematopoietic stem cell transplantation (AH SCT) has been established as the standard of care for primary refractory or relapsed Hodgkin lymphoma (HL) on the basis of 2 randomized controlled trials and phase II trials that collectively demonstrated AH SCT was curative in approximately 50% of patients with chemotherapy-sensitive disease pre-AH SCT [1-5]. Adverse prognostic factors for post-AH SCT outcome consistent across many reported trials included primary induction failure; initial remission duration of <3 months; relapse within 12 months of induction therapy; extranodal disease; B symptoms, or advanced stage.
at relapse; resistance to salvage chemotherapy; and persistent disease at the time of transplant [6-12]. The prognostic scoring system used by the GELA/SFGM Study Group in the H96 Trial to risk-stratify patients with relapsed and refractory HL to single or tandem AH SCT defined poor-risk HL as primary refractory disease or ≥2 of the following risk factors at first relapse: time to relapse or progression <12 months after the end of first-line treatment, stage III or IV at relapse, or relapse in a previously irradiated site after combined modality therapy [8]. For poor-risk patients the 5-year progression-free survival (PFS) drops to <30%.

To improve AH SCT outcome, SWOG investigated intensifying the transplant preparative regimen [13]. Patients with relapsed or refractory HL received etoposide 60 mg/kg, cyclophosphamide 100 mg/kg, and either 12 Gy total body irradiation (TBI) or, in previously irradiated patients, a single dose of carbamustine (BCNU) 15 mg/kg before an autologous bone marrow transplant (ABMT). The 5-year PCS was 41% and 5-year overall survival (OS) was 54% in 74 treated patients with relapse as the primary cause for failure. There was no significant difference in PCS or OS by preparative regimen (TBI versus BCNU-based). Importantly, the 5-year PCS and OS for the 9 patients who underwent ABMT in complete remission (CR) were both 67%, whereas those with 2 to 3 high-risk factors (relapse in an irradiated field, extranodal disease at relapse, ≥2 prior regimens) had a 5-year OS of only 38%.

Because HL relapse after AH SCT is the major cause of treatment failure and patients in CR pre-AH SCT appear to have better long-term PCS, several groups explored a tandem transplant approach to improve outcomes [14-17]. This strategy was also investigated in a pilot protocol developed by City of Hope and Loyola University in which preselected patients with adverse risk factors were treated initially with high-dose melphalan plus AH SCT, followed by a planned cycle 2 AH SCT if they had stable disease or better, using 1 of the 2 AH SCT intensified preparative regimens [18]. Promising 5-year OS, event-free survival, and freedom from progression of 54%, 49%, and 55%, respectively, were seen, and 100 day treatment-related mortality of only 4% was reported in that trial. The SWOG-led intergroup trial in this report was designed to evaluate in the multicenter prospective setting this tandem AH SCT approach for patients with primary progressive or high-risk recurrent HL. The goal was to improve the 2-year PCS in this unfavorable risk population from 45% in the earlier SWOG transplant study to >60%.

**METHODS**

**Study Design and Patients**

SWOG trial S0410 was a phase II, prospective, single-arm trial conducted at 10 institutions, including the Blood and Marrow Transplant Clinical Trials Network (BMT CTN trial 0703). Eligible patients were between 15 and 70 years with HL that relapsed after, or was refractory to, multagent chemotherapy. Salvage therapy before transplant was at the discretion of the treating physician. Sensitivity to salvage therapy was defined in accordance with the 1999 Standardized Response Criteria for Lymphoma and did not include fluorodeoxyglucose-positron emission tomography (FDG-PET) scan [19]. Patients who relapsed after a prior CR had to be treated with a minimum of 2 cycles of salvage chemotherapy or a minimum of 25 Gy involved field radiation therapy to determine disease sensitivity. Patients with ≥5 cm bulk disease after salvage had to agree to pretransplant treatment with 18 Gy involved field radiation therapy.

Central pathology review of the diagnosis of HL was required. Patients with a clonal cytogenetic abnormality in the prephersis bone marrow aspirate were excluded. Zubrod performance status of 0, 1, or 2 was required. Eligibility included cardiac ejection fraction ≥ 45%, corrected DLCO or FEV1 > 60%, creatinine clearance ≥ 60 mL/min or ≤2 times the upper limit of normal, and serum bilirubin ≤ 1.5 times the upper limit of normal (unless due to liver involvement with HL). Exclusion criteria included relapse more than 12 months after first CR with response to salvage therapy; active bacterial, fungal, or viral infection; known HIV or AIDS; and therapy for coronary artery disease, cardiomyopathy, congestive heart failure, or arrhythmia.

Patients were enrolled after salvage therapy and collection of a minimum of 3.5 × 10^6 CD34 cells/kg autologous peripheral blood progenitor cells. The mobilization regimen, stem cell apheresis procedures, and stem cell cryopreservation were done in accordance with institutional standard practice.

This study was designed by leadership of the SWOG Lymphoma and BMT Committees, approved by the National Cancer Institute, conducted in SWOG-approved BMT centers, and activated in the BMT CTN. Participating sites for the TBI-based cycle 2 AH SCT preparative regimen had to have an approved TBI-benchmark with SWOG Quality Assurance Review Center. The protocol was reviewed and approved by the local institutional review boards at the participating sites, was conducted in accord with Good Clinical Practice guidelines, and was registered at www.clinicaltrials.gov as NCT00233987. This study was activated on October 15, 2005 and closed to enrollment on February 1, 2009 after achieving its accrual goal. The study data were gathered and analyzed by the SWOG Statistical Center and reviewed by all authors.

**Treatment Plan**

Table 1 shows the study tandem AH SCT regimen. Cycle 1 high-dose chemotherapy consisted of melphalan 150 mg/m² administered intravenously on day –1. On day zero of each AH SCT cycle, approximately 50% of the previously collected cryopreserved autologous peripheral blood progenitor cells was administered. Post-AH SCT supportive care for both AH SCT cycles was administered in accordance with the standard institutional practice at the participating sites. After patient recovery from cycle 1 AH SCT, response assessment of all areas of measurable disease with computed tomography (CT) scans was performed within a time frame that ensured the interval between day zero of cycle 1 AH SCT and day zero of cycle 2 AH SCT was ≥28 and ≤60 days. Repeat bone marrow biopsy was required if the initial biopsy was positive. Patients with stable disease or better proceeded to cycle 2 AH SCT. Patients with progressive disease or an interval between transplant cycles of >60 days were removed from study.

Each center selected 1 of the 2 study-prepared cycle 2 AH SCT preparative regimens for use in all patients younger than age 61. Centers that selected the TBI-based regimen were required to use the nonradiation preparative regimen for use in all patients younger than age 61. Centers that selected the nonradiation preparative regimen were required to use the TBI-based regimen for use in all patients younger than age 61. Centers that selected the TBI-based regimen were required to use the nonradiation preparative regimen for use in all patients younger than age 61. Centers that selected the TBI-based regimen were required to use the nonradiation preparative regimen for use in all patients younger than age 61. Centers that selected the TBI-based regimen were required to use the nonradiation preparative regimen for use in all patients younger than age 61.

Sixty days after cycle 2 AH SCT, patients were required to undergo disease response assessment with repeat CT scans of all areas of previously measurable disease. Functional scanning with FDG-PET or gallium was recommended but not required for patients with persistent CT abnormalities. Follow-up CT scans were required every 6 months for 2 years and then annually thereafter or until disease progression. Patients were followed for a maximum of 7 years or until death, whichever occurred first.

**Statistical Considerations**

The 1999 Standardized Response Criteria for Lymphoma reported by Cheson et al. [19] were used. The trial used the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 for serious adverse events reporting and version 3.0 for routine toxicity reporting.

The analysis of PCS and OS included patients who were eligible and started protocol treatment. Patients who progressed after enrollment and before receiving any protocol treatment were excluded from all analyses because evaluation of untreated patients would contribute no information about the safety and efficacy of the trial regimen. PCS was measured from the date of enrollment to date of first observation of progressive disease or death due to any cause. OS was measured from the time of enrollment to death due to any cause. Patients lost to be alive were censored at the date of last contact. Estimates of PCS and OS were calculated using the method of Kaplan and Meier and were compared using the log-rank test. The primary study endpoint was the 2-year PCS. A designed sample size of 85 treated patients over 2 years with 18 months of follow-up was chosen to have 86% power by 0.025 one-sided alpha test to detect a 15% increase in 2-year PCS as compared with the historical PCS of 45% in the prior SWOG ABMT trial. In a sample size of 85 patients, any adverse event with at least a 5% probability would be seen at least once (98% chance).

Factors with a biologically protective value for PCS in prior AH SCT trials were evaluated by Cox regression analysis to explore if a risk model could be developed to identify a very high-risk group who should be considered for early autologous HCT. Factors with statistically significant or marginally significant (P ≤ 0.10) effect on PCS in the univariate setting were analyzed by forward stepwise Cox proportional hazards models to identify factors that retained significance in the multivariate setting and to calculate the hazard risk ratios with nominal 95% confidence limits.
RESULTS

A total of 98 patients were registered from 10 centers between January 4, 2006 and January 30, 2009. The BMT CTN activated this clinical trial in 2007, and with their participation, the study completed accrual ahead of schedule. As shown in Figure 1, 6 patients were ineligible at entry. Central pathology review excluded 1 patient with inadequate tissue to confirm HL and 1 patient who had a different diagnosis. Three eligible patients did not receive any protocol therapy after enrollment due to HL progression before the start of therapy. Eighty-nine of 92 eligible patients began cycle 1 treatment, and 82 patients completed both transplants. Cycle 2 AHSCT was with the TBI-based regimen in 19 patients and the BCNU-based regimen in 63 patients. After cycle 1 AHSCT 7 patients did not proceed to cycle 2 AHSCT for reasons shown in Figure 1.

Table 1
Tandem Transplant Regimen

<table>
<thead>
<tr>
<th>Involved Field Radiation for Residual Tumor &gt; 5 cm after Salvage Chemotherapy</th>
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<td><strong>Drugs</strong></td>
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<td>Cycle 1 high-dose therapy</td>
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<td>Melphalan</td>
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<td>Peripheral blood progenitor cell reinfusion</td>
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<td>Cycle 2 high-dose therapy (4-8 weeks after cycle 1)</td>
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<td>Peripheral blood progenitor cell reinfusion</td>
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<td>Cycle 2 high-dose therapy (4-8 weeks after cycle 1)</td>
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<td>BCNU‡</td>
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<td>Cyclophosphamide</td>
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<td>Peripheral blood progenitor cell reinfusion</td>
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For patients below ideal body weight (IBW), use actual body weight (ABW).

* Based on adjusted ideal body weight = IBW + 0.4 (ABW – IBW).
† Lungs shielded after first 750 cGy.
‡ Based on IBW or ABW, whichever is less.

Patient Characteristics

Diagnoses as confirmed by central pathology review were 81 nodular sclerosis classical HL (cHL), 7 mixed cellularity cHL, 1 lymphocyte-rich cHL, and 2 nodular lymphocyte predominant HL. Of 89 eligible and treated patients, 47 (53%) had induction failure, 15 (18%) had initial response of ≤12 months, 74 (83%) were stage III or IV at the time of trial enrollment, and 14 of 29 (48%) previously irradiated patients relapsed in an irradiated site. The median time from diagnosis of HL to date of first stem cell transplant was 13.97 months (1.17 years), range 2.82-111.02 months or 0.24-9.27 years. There were 72 patients (81%) who were resistant to first salvage therapy, defined as disease that was stable or progressed by CT scan criteria after first salvage. First salvage therapy was ICE (ifosfamide, carboplatin and etoposide) in 62 patients, rituximab-ICE (ifosfamide, carboplatin and etoposide) in 8 patients, ESHAP (etoposide, solumedrol, cytarabine and cisplatin) in 7 patients, DHAP (dexamethasone, cytarabine and cisplatin) in 2 patients, and navelbine plus gemcitabine in 2 patients. The first salvage for 2 patients is unknown, and the remaining 6 patients were treated with a variety of first salvage regimens that were each used in only 1 patient. Additional information about patient prognostic factors is shown in Tables 2 and 3.

Response

Response assessment did not include functional imaging by FDG-PET. Of 84 patients assessed for response by CT scan, the overall response was 36% (95% confidence interval [CI], 25.6% to 46.9%), and 5 patients (6%) had progressive disease. The analysis of PFS and OS included the 89 patients who were eligible and started protocol treatment. The 3 patients who progressed after registration and before the start of protocol treatment were excluded from the survival analyses.

With a median follow-up of 6.2 years (range, 2 to 7.7) in the evaluable patients who remained alive, the Kaplan-Meier estimate of 2-year and 5-year PFS was 63% (95% CI, 52% to 72%) and 55% (95% CI, 44% to 64%), respectively, as shown in Figure 2A. There was no significant difference in PFS based on chemosensitivity to first salvage therapy by CT criteria as
shown in Figure 2B. There was no significant difference in PFS based on GELA/SFGM risk group as shown in Figure 2C.

The 2-year and 5-year OS were 91% (95% CI, 83% to 95%) and 84% (95% CI, 74% to 90%), respectively, as shown in Figure 3A. There was no significant difference in OS based on sensitivity to first salvage therapy by CT criteria as shown in Figure 3B. There was no significant difference in OS based on GELA/SFGM risk group as shown in Figure 3C.

There were 15 deaths in eligible patients, 2 deaths in ineligible patients, and 3 deaths in non-evaluable patients who did not receive protocol therapy. Forty patients have either progressed or died. The causes of death in the 15 eligible and evaluable patients were 11 deaths due to progressive HL, 1 treatment-related death due to respiratory failure at 1141 days (3.1 years) after second AHSCT in a patient who had the BCNU-based regimen and no prior involved field radiation for HL, 1 death due to disseminated cytomegalovirus infection at 1455 days (4 years) after second AHSCT in a patient who underwent subsequent allogeneic HCT, and 2 deaths with cause not reported at 1763 days (4.8 years) and 300 days after second AHSCT respectively, considered treatment related in the absence of other known etiology.

As per a database check in September 2017, reported late malignancies were myelodysplasia in 3 patients, thyroid cancer in 1 patient, and 2 patients with nonmelanoma skin cancer. The 6 patients who developed secondary malignancies were not in the cohort of 19 patients who had TBI; all received the BCNU-based conditioning regimen for cycle 2 AHSCT.

Toxicities

There were no treatment-related deaths in the first year post-AHSCT. Among the 89 patients assessed for toxicities, 70 had treatment-related grade 4 adverse events that were primarily hematologic (69/70). One patient had no grade 4 hematologic toxicities but experienced grade 4 hypotension. Fourteen of 69 patients with grade 4 hematologic adverse events also experienced the following grade 4 nonhematologic adverse events: febrile neutropenia (3), hypophosphatemia (3), hypokalemia (2), oral cavity mucositis (2), esophagitis (1), fatigue (1), hyperuricemia (1), hypotension (1), hypoxia (1), bloodstream infection (1), catheter-related infection (1), foreign body infection (1), and upper airway infection (1). There were no cases of grade 4 pneumonitis or cardiac toxicity. Grade 3 adverse events included the following: hemorrhage other (1), nose hemorrhage (2), febrile neutropenia (44), fever (3), lung infection (3) blood infection (5), gastrointestinal infection (3), infection other (5), opportunistic infection (1) skin infection (2), esophagitis (4), diarrhea (8), mucositis (29), anorexia (20), nausea (32), vomiting (12), rash (4), aspartate or alanine aminotransferases (10), biliru-
bin (1), pneumonitis (3; including 1 patient diagnosed with pulmonary hypertension at 61 days after second AHSCT who died of respiratory failure 3.1 years after second AHSCT), hypoxia (3), hypotension (9), hypophosphatemia (22), hypokalemia (11), hyponatremia (11), hyperglycemia (6), and supraventricular tachycardia (1).

**Multivariate Analysis**

Eleven factors with possible prognostic significance for AHSCT outcome in relapsed and refractory HL were analyzed by Cox regression analysis, as shown in Table 3. In the univariate analysis only SWOG performance status (2-sided \( P = .04 \)) and baseline lactate dehydrogenase (2-sided \( P = .03 \)) at the time of enrollment were significant in predicting PFS.

Both factors retained marginal significance in the multivariate setting with a hazard ratio of 1.87 (95% CI, .97 to 3.59) and adjusted 2-sided \( P = .06 \) for SWOG performance status of 1 versus 0 and a hazard ratio of 1.86 (95% CI, .97 to 3.57) and adjusted 2-sided \( P = .06 \) for lactate dehydrogenase level of greater than 1 times normal versus normal.

**DISCUSSION**

By design, this study excluded good-risk HL patients who relapsed > 12 months after first CR and were sensitive to salvage therapy. The study population included HL patients with known risk factors for poor outcome after AHSCT. The cohort included 47 of 89 patients (53%) with primary refractory HL, defined as induction failure or progression during initial chemotherapy, and 72 of 89 patients (81%) with stable or progressive disease with first salvage by CT criteria, who were defined as chemotherapy-resistant. One could argue that some patients categorized as chemotherapy-resistant based on stable disease on CT after first salvage therapy in this trial would have been classified as responders if functional imaging with FDG-PET scan was used to evaluate their response. This is 1 possible explanation for the high number of patients who were classified as chemotherapy-refractory pre-AHSCT. This is a study limitation that cannot be resolved in absence of FDG-PET data. Because of the intensity of the study regimen, there may also have been a selection bias with centers enrolling only high-risk patients on this trial. Patients in the poor-risk group as defined by the GELA/SFGM Study Group in the H96 Trial included the 47 patients with primary refractory disease plus 17 of 42 patients with first relapse HL who had ≥2 of the risk factors used in the GELA/SFGM prognostic scoring system [8].

Although AHSCT leads to cure in approximately 50% of HL patients, the outcomes for HL patients with multiple adverse risk factors reported in other studies is inferior, with only 25% to 30% long-term PFS. With a 2-year PFS of 63%, this trial met the predicted study endpoint of at least 15% improvement from the historical 2-year PFS of 45% in the prior SWOG ABMT trial [13]. With a median follow-up time of 6.2 years, this trial’s PFS and OS curves show benefit in a cohort of patients with multiple recognized poor prognostic features, outcomes better than any previously reported from a multicenter prospective AHSCT trial in high-risk patients. Because the cycle 2 AHSCT regimens were the same as the prior SWOG ABMT study, it appears the increase in 2-year PFS from 45% to 63% is likely attributable to the addition of cycle 1 high-dose melphalan. This conclusion is supported by the report of Castagna et al. [20], who investigated high-dose melphalan 200 mg/m² with autologous stem cell support as a bridge to second transplant in 41 patients, albeit with a higher dose than the 150 mg/m² used in this trial. The Castagna study incorporated disease assessment by FDG-PET imaging, and at trial entry all patients were FDG-PET positive. FDG-PET after high-dose melphalan showed an overall response rate of 78%, with 17 of 22 patients in stable disease or partial response converted to partial response or CR after high-dose melphalan, suggesting high-dose melphalan is an effective regimen in refractory HL. Of note, the 2-year PFS of 63% in the SWOG tandem AHSCT trial matches the 2-year PFS of 63% in the reported AETHERA regimen of post-AHSCT maintenance brentuximab vedotin (BV) in a similar population of high-risk patients [21].

Unlike prior AHSCT reported studies, analysis of prognostic factors in our study did not identify the usual adverse risk factors for outcome including primary refractory disease and...
relapse within 90 days of first therapy. The PFS curves showed no difference based on sensitivity to first salvage therapy, which is consistent with the result seen in the prior SWOG ABMT trial using an augmented preparative regimen before single transplant in a similar cohort of patients with high-risk refractory/relapsed HL. The authors acknowledge the likelihood this study overestimates the number of patients refractory to first salvage due to absence of FDG-PET response assessment data, rendering the analysis of sensitivity to first salvage as a prognostic factor in this study irrelevant. More significant is the fact that primary refractory disease in 53% (47/89 patients) of this cohort was not identified as a poor prognostic factor, although this unexpected result may be explained by the small sample size in a phase II trial. Only Zubrod performance status of 1 versus 0 and lactate dehydrogenase level > 1 times normal versus normal at the time of study enrollment retained marginal significance as prognostic factors in the multivariate analysis. These results appear to be similar to the AETHERA trial in that patients with the most adverse risk factors benefited the most. This conclusion would have to be confirmed in a larger, multicenter, randomized controlled trial. The 5-year PFS of 55% in the patient cohort suggests the tandem AHSCt approach may overcome the negative prognostic impact of recognized adverse risk features in HL, particularly the factor of primary refractory disease.

The apparent discrepancy between the 2-year PFS of 63% and low overall response rate of 36% is explained by the inclusion of 24 patients (29%) in the denominator as nonresponders because their post-AHSCt status was inadequately assessed for various reasons. Slow resolution of bulky adenopathy in treated HL makes response assessment difficult without the use of FDG-PET to determine if metabolically active disease persists. In the absence of functional imaging, the response rate by CT assessment likely underestimated the true response rate after 2 cycles of AHSCt; thus, PFS and OS must be viewed as the relevant outcomes for assessing the effectiveness of the study regimen. The absence of FDG-PET scans, which were not standard for HL response assessment when the trial was designed and conducted, is a trial limitation. However, given the 5-year PFS of 55%, it is likely that FDG-PET scan data would reduce the percentage of patients who were considered nonresponders. The better-than-expected 2-year and 5-year OS likely reflects improved therapeutic strategies for management of HL relapse after AHSCt, including use of newer agents like bendamustine and BV as a bridge to subsequent curative allogeneic HCT with reduced-intensity conditioning [22-26].

The tandem AHSCt regimen reported herein was designed to improve AHSCt outcome in poor-risk HL by achieving a minimal disease state before a conventional second AHSCt. Alternative approaches have also been explored. Nieto et al. [27] explored the intensification of a single AHSCt regimen as an alternative approach, finding that patients with primary refractory or poor prognosis relapsed HL conditioned with gemcitabine-busulfan-melphalan,
busulfan-melphalan, or BEAM between 2005 and 2010 had EFS rates of 57%, 33%, and 39%, respectively, with median follow-up of 36 months for the entire population, which is analogous to the result of the prior SWOG ABMT trial [13] and showed regimen intensification could improve AHSCST outcome. The AETHERA multinational randomized trial investigated the alternative approach of post-AHSCST BV in BV naïve patients as maintenance therapy to decrease post-transplant relapse [21]. The estimated 2-year PFS in the BV group was 63%, higher than the PFS of 51% in the placebo group. The AETHERA trial update at 3 years reported a 3-year PFS of 61% in the BV arm versus 43% in the placebo arm and comparable secondary malignancies in both arms (4 in BV arm, 2 in placebo arm) [28]. With long-term follow-up on S0410, 1 late death due to treatment-related respiratory failure and 2 late deaths of unknown cause, assumed to be treatment related in the absence of other known etiology, were reported. There were also 6 cases of secondary malignancy, all in patients not treated with TBI. Inclusion of the TBI-based cycle 2 AHSCST preparative regimen in this tandem trial was based on data from the SWOG 9011 transplant study of augmented preparative regimens, which showed no decrement in outcome for TBI-treated patients [13]. On SWOG 9011 5-year OS was 61% for the TBI-based augmented preparative regimen but only 50% for the BCNU-based regimen, so TBI was considered standard of care at the time S0410 was designed. However, only some patients were treated with the TBI regimen (n = 19) on S0410, likely based on evolving data in the field about toxicities with TBI. Concerns about toxicities associated with the approach of tandem AHSCST were addressed in the German Hodgkin Lymphoma Study Group report of the randomized HD-R2 trial of single AHSCST with BEAM versus a sequential high-dose chemotherapy regimen of cyclophosphamide, methotrexate, and etoposide followed by BEAM, which concluded the sequential high-dose chemotherapy arm did not improve outcome and was associated with higher adverse events, although not higher mortality [29]. With a median observation time of 42 months, there was 1 secondary neoplasia in the sequential high-dose chemotherapy arm on HD-R2. An important caveat in comparing HD-R2 with S0410 was the exclusion of primary progressive HL on HD-R2, whereas half of the patients enrolled on S0410 had primary refractory HL, a group with uniformly poor prognosis across multiple trials.

As concluded by Perales et al. [30] in the guidelines from the American Society for Blood and Marrow Transplantation, post-transplant relapse remains a significant cause of treatment failure in HL. Although PFS appears to be improved for both AETHERA and S0410, approximately one-third of young patients are still not cured. Further research is needed to develop a risk-adapted treatment strategy to improve outcomes in the subset of patients with advanced HL who had disease progression in both AHSCST trials.

ACKNOWLEDGMENTS

The authors thank the patients who participated in this clinical trial; the physicians, nurses, research coordinators, and data managers at the SWOG and BMT CTN participating sites who care for enrolled patients; and Jeri Jardine, SWOG Data Operations Center CRA, for their contributions to this study.

Financial disclosure: This investigation was supported in part by the following United States Public Health Service/Department of Health and Human Services grant numbers awarded by the National Cancer Institute (NCI), National Clinical Trials Network: CA180888, CA180819, and CA180846; by the NCI Community Oncology Research Program: CA189953; CA189808, and CA189957; National Heart, Lung, and Blood Institute and the NCI National Clinical Trials Network through the National Institutes of Health (NIH) grant U10HL069294; and by NIH/NCI CA46368, CA46282, and CA76132.


REFERENCES


