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Improved Outcomes after Autologous Bone Marrow Transplantation for Children with Relapsed or Refractory Hodgkin Lymphoma: Twenty Years Experience at a Single Institution

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A B S T R A C T

The purpose of this study is to evaluate the survival of pediatric patients undergoing autologous bone marrow transplantation (auBMT) for relapsed or refractory Hodgkin lymphoma (rrHL) and to identify factors that might contribute to their outcome. We reviewed the records and clinical course of 89 consecutive rrHL patients ≤ 21 years old who underwent auBMT at Stanford Hospitals and Clinics and the Lucile Packard Children's Hospital, Stanford between 1989 and 2012. We investigated, by multiple analyses, patient, disease, and treatment characteristics associated with outcome. Endpoints were 5-year overall and event-free survival. Our findings include that cyclophosphamide, carmustine, and etoposide (CBV) as a conditioning regimen for auBMT is effective for most patients ≤ 21 years old with rrHL (5-year overall survival, 71%). Transplantation after the year 2001 was associated with significantly improved overall survival compared with our earlier experience (80% compared with 65%). Patients with multiply relapsed disease or with disease not responsive to initial therapy fared less well compared with those with response to initial therapy or after first relapse. Administration of post-auBMT consolidative radiotherapy (cRT) also appears to contribute to improved survival. We are able to conclude that high-dose chemotherapy with CBV followed by auBMT is effective for the treatment of rrHL in children and adolescents. Survival for patients who undergo auBMT for rrHL has improved significantly. This improvement may be because of patient selection and improvements in utilization of radiotherapy rather than improvements in chemotherapy. Further investigation is needed to describe the role of auBMT across the entire spectrum of patients with rrHL and to identify the most appropriate preparative regimen with or without cRT therapy in the treatment of rrHL in young patients.

INTRODUCTION

Chemotherapy with radiation therapy cures most pediatric patients with Hodgkin lymphoma (HL). As a result of multidisciplinary risk-stratified therapy, young patients diagnosed with HL have a 5-year survival rate approaching 90% [1,2]. Nevertheless, initial therapy is unsuccessful for 10% to 15% of patients [3,4]. Treatment options for these patients include salvage chemotherapy with or without radiotherapy (RT) or high-dose chemotherapy followed by rescue with autologous stem cell transplantation (auBMT). Attempts to cure children with incompletely responsive or rapidly relapsed disease (recurrence ≤ 12 months from end of therapy) with salvage chemotherapy strategies that do not include auBMT have been less successful, with reported overall survival (OS) as low as 47% and event-free survival (EFS) as low as 27% [5]. High-dose chemotherapy followed by auBMT is effective therapy for patients with relapsed or refractory HL (rrHL) and has become a standard approach for such patients, with OS ranging from 43% to 95% [6-8].

AuBMT was first demonstrated to be effective treatment for adults with rrHL [9,10]. Similarly, studies have demonstrated auBMT to be the treatment of choice for many

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pediatric patients with rrHL with overall survival rates of 60% to 95% [11-14]. In the management of both pediatric and adult patients, the 2 most widely used chemotherapy-based preparative regimens are carmustine (BCNU), etoposide, cytarabine, and melphalan (BEAM) or cyclophosphamide, carmustine, and etoposide (CBV) [15]. At our institution, we have utilized several preparative regimens for auBMT, including CBV along with RT before or after auBMT. We previously published the results for children who underwent HSCT for rrHL between 1989 and 2001 and demonstrated that more than one half of these patients can be treated successfully with high-dose therapy followed by auBMT [14].

In this report, we have updated our results and evaluate whether outcome for children with rrHL who undergo auBMT has changed over time. We analyzed 89 consecutive patients 21 years old or younger who underwent auBMT for rrHL at Stanford Hospitals and Clinics and the Lucile Packard Children's Hospital, Stanford between 1988 and 2012.

PATIENTS AND METHODS

Study Design

We conducted a retrospective analysis of all patients 21 years old or younger who underwent auBMT for rrHL at Stanford Hospitals and Clinics or Lucile Packard Children's Hospital, Stanford. Patients were treated with 1 of several auBMT regimens available at our institution between September 1988 and April 2012. Although some patients were enrolled on clinical trials, this report is not a clinical trial and participation in another clinical trial did not affect the inclusion of their case information in the current study. All patients had histologically confirmed diagnosis of HL at initial presentation and relapse. To be eligible for transplantation, patients had to have had primary refractory HL (ie, never in remission), first relapse had to have occurred $\leq$ 12 months from the end of initial or salvage therapy, or patients had to have multiply relapsed disease. The goal of pre-auBMT therapy was to achieve minimal residual disease using salvage therapy.

Eligibility requirements for auBMT also included adequate organ function including: adequate hematologic parameters (WBC $>$ 3500/uL and platelets $>$ 100,000/uL unless there was biopsy-proven bone marrow involvement), pulmonary function (diffusion capacity $>$ 60%), cardiac function (ejection fraction greater than 50%), hepatic function (serum bilirubin $<$ 2 mg/100mL and aspartate transaminase and alanine transaminase $<$ 3 $\times$ normal, unless there was radiographic or biopsy evidence of involvement with HL), and renal function (serum creatinine $<$ 1.5 mg/100 mL). Patients and/or their parents or guardians provided informed consent for therapy and for long-term follow-up. The institutional review board approved all clinical research protocols and data collection used in this study.

Patients with rrHL first received chemotherapy and/or RT to achieve minimal disease burden before high-dose therapy. For patients registered on a research protocol, the preparative regimen was determined by protocol. For patients not enrolled on a research protocol, treatment regimen depended upon physician preference among treatment regimens available at the institution at the time. Patients were assessed for RT as consolidation after auBMT depending on prior RT.

Conditioning regimens are listed in detail in Table 1 and include CBV; cyclophoshamide, lomustine, and etoposide (CCV); fractionated total body irradiation, cyclophosphamide, and etoposide (fTCV); CBV plus gemcitabine (GVCBV); or in 2 cases, a different regimen. The use of fractionated total body irradiation as part of the high-dose therapy regimen was part of a small institutional trial and patient participation in this trial was not based upon disease severity.

Patients who underwent auBMT before 1997 did not receive consolidative RT (cRT). CRT was introduced gradually as institutional practice in the late 1990s and became standard of care by 2001. After 2001, all patients who received auBMT also were treated with cRT as allowed by tissue tolerance. Patients who already received tissue maximal doses did not receive cRT. Patients who had received reduced-dose RT during up-front therapy received cRT up to maximal tissue tolerance or 25 Gy. Thus, precise dosing varied from patient to patient but typically ranged from 5 to 25 Gy in 1.5 Gy fractions to relapsed nodal sites when sufficient recovery of blood counts permitted RT.

Tumor Response Evaluation

Patients were classified by response to upfront induction therapy as follows:

Complete response (CR) was defined as no evidence of tumor by clinical, or biochemical evaluation and no more than minimal disease by, radiographic evaluation by 30 days after completion of primary or salvage therapy (ie, second CR, third CR) [14,16,17].

Partial response (PR) was defined as persistence of tumor by clinical, biochemical, or radiographic evaluation by 30 days after therapy without further worsening of the disease [14,18].

Induction failure (IF) was defined as disease that progressed during initial therapy or attained only transient ($<$60 days) response, respectively [14,18].

We defined *relapsed disease* as histologically proven disease recurrence $\geq$ 60 days after successful primary treatment. We did not consider stage or disease extent at transplantation in our study.

We categorized patients by disease status at the time of transplantation into 3 groups according to response to treatment and number of relapses: those who never entered remission (IF or PR), those who underwent transplantation after first relapse (second CR or PR or failure of reinduction/salvage therapy), and those who underwent transplantation after 2 or more relapses ($\geq$third CR or PR).

Restaging studies (CBC, complete metabolic panel, chest x-ray, computed tomography scans [CT], and for some patients positron emission tomography [PET]) were obtained between day +30 and day +60 after transplantation.

Routine follow-up studies including regular labs, chest radiography, tomography, and nuclear medicine studies were repeated at least every 3 to 6 months for 2 years and then annually unless disease-related signs or symptoms recurred.

Statistical Methods

OS was defined as the date from stem cell infusion until the date of death from any cause.

EFS was calculated as the time from date of stem cell infusion until the date of an adverse event, including relapse or progression of HL, development of a secondary malignancy, or death from any cause. When patients suffered more than 1 event, the time to the first event was used to determine the EFS.

Lifetables were constructed using the method of Kaplan and Meier [19]. Patients not suffering adverse events were censored at the time of last follow-up.

Treatment-related mortality (TRM) was defined as death within 100 days of the date of stem cell infusion, excluding those deaths due to relapsed disease.

Table 1
Preparative Regimens and the Number of Patients who Received Each

Regimen (n)	Agent	Agent	Agent	Agent	Agent
CBV (51)			BCNU (10-15 mg/kg) Day −6	Etoposide (60 mg/kg) Day −4	Cyclophosphamide (100 mg/kg) Day −2
CCV (12)			CCNU (6 mg/kg) Day −6	Etoposide (60 mg/kg) Day −4	Cyclophosphamide (100 mg/kg) Day −2
fTCV (6)			fTBI (12 gy) Days −8 to −5	Etoposide (60 mg/kg) Day −4	Cyclophosphamide (100 mg/kg) Day −2
GVCBV (17)	Gemcitabine (1250 mg/m^2) Days −13 & −8	Vinorelbine (30 mg/m^2) Days −13 & −8	BCNU (10 mg/kg) Day −6	Etoposide (60 mg/kg) Day −4	Cyclophosphamide (100 mg/kg) Day −2
Other (3)					

CCV indicates cyclophosphamide, CCNU (lomustine), and etoposide; fTBI, fractionated total body irradiation.
Radiation received as part of regimen 3 is separate from radiation therapy received as initial therapy not associated with auBMT.