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Autologous Peripheral Blood Stem Cell Transplantation in Children with Refractory or Relapsed Lymphoma: Results of Children's Oncology Group Study A5962

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This prospective study was designed to determine the safety and efficacy of cyclophosphamide, BCNU, and etoposide (CBV) conditioning and autologous peripheral blood stem cell transplant (PBSCT) in children with relapsed or refractory Hodgkin and non-Hodgkin lymphoma (HL and NHL). Patients achieving complete remission (CR) or partial remission (PR) after 2 to 4 courses of reinduction underwent a granulocyte-colony stimulating factor (G-CSF) mobilized PBSC apheresis with a target collection dose of 5×10^6 $CD34^+$/kg. Those eligible to proceed received autologous PBSCT after CBV (7200 mg/m^2, 450-300 mg/m^2, 2400 mg/m^2). Forty-three of 69 patients (30/39 HL, 13/30 NHL) achieved a CR/PR after reinduction. Thirty-eight patients (28 HL, 10 NHL) underwent PBSCT. All initial 6 patients who received BCNU at 450 mg/m^2 experienced grade III or IV pulmonary toxicity compared to none of the subsequent 32 receiving 300 mg/m^2 ($P < .0001$). The probability of overall survival (OS) at 3 years for all patients is 51% and for transplanted patients is 64%. The 3-year event-free survival (EFS) is 38% (45% for HL; 30% NHL). The 3-year EFS in transplanted patients is 66% (65% HL; 70% NHL). Initial duration of remission of $\geq$12 versus $<$12 months was associated with a significant increase in OS (3 years OS 70% versus 34%) ($P = .003$). BCNU at 300 mg/m^2 in a CBV regimen prior to PBSCT is well tolerated in relapsed or refractory pediatric lymphoma patients. A short duration ($<$12 months) of initial remission is associated with a poorer prognosis. Last, a high percentage of patients achieving a CR/PR after reinduction therapy can be salvaged with CBV and autologlous PBSCT.

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KEY WORDS: Autologous transplant, PBSCT, CBV, Lymphoma, NHL, HL

INTRODUCTION

The prognosis for children with newly diagnosed lymphomas has significantly improved over the last 25 years. The survival rate for patients with localized and disseminated non-Hodgkin lymphoma (NHL) is over 95% and over 80%, respectively, for most subtypes [1-11]. However, the prognosis for refractory or recurrent NHL in children and adolescents remains poor. Patients enrolled in the Children's Cancer Group (CCG) 551 that subsequently relapsed had a 12% 5-year overall survival (OS) [12]. The 5-year OS for relapsed NHL patients using dexamethasone, etoposide, cisplatin, high-dose cytarabine, and L-asparaginase (DECAL) was 30% [13]. Children diagnosed with Stage I or II HL experience a long-term event-free survival (EFS) >90% [14,15]. Patients with advanced stage or "B" symptoms at presentation have long-term EFS rates of over 80% [16]. As in NHL, children with relapsed or refractory Hodgkin lymphoma (HL) have a poor prognosis [17,18]. The 5-year OS is 31% for children with HL reinduced with

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DECAL [13]. The 8-year OS and EFS are 34% and 23%, respectively, with cytosine arabinoside, cisplatin, and etoposide (APE) [17].

In adults with lymphoma, autologous stem cell transplant (autoSCT) results in 4 to 10 year OS rates of 42% to 70% [19-22]. Factors associated with a poor prognosis in adults with lymphoma following autoSCT include chemoresistance, large tumor burden, short remission duration, poor performance status, and extranodal relapse [23,24]. Studies of children with lymphoma treated with high-dose chemotherapy and autologous stem cell rescue are limited by small numbers, and wide variety of pretransplant chemotherapy, and conditioning regimens. Overall, they demonstrate OS rates similar to adults [18,25].

Bone marrow transplant (BMT) conditioning regimens including cyclophosphamide, carmustine (BCNU), and etoposide (CBV), either as separate agents or together are effective in adults with recurrent NHL and HL [21,26-30]. This report describes the results of a prospective study assessing the toxicity and efficacy of CBV and autologous peripheral blood stem cell transplantation (PBSCT) in pediatric patients with relapsed or refractory lymphoma who achieve a complete remission/partial remission (CR/PR) after reinduction.

PATIENTS AND METHODS

Study Eligibility for Entry onto Protocol

This prospective study enrolled children, initially diagnosed between the ages of 12 months and 21 years, at time of their first relapse or induction failure (defined as failure to achieve a CR with a reinduction chemotherapy for HL, 2 cycles of a reinduction chemotherapy for NHL, or 4 cycles for large cell lymphoma patients). The study excluded patients with low-stage HL treated with radiation only or with chemotherapy only, and human immunodeficiency virus (HIV) positive patients. Local institutional review boards approved the study at each institution, and the patient or legal guardians signed an informed consent.

Pathology

Study pathologists centrally reviewed patient materials from initial diagnosis and relapse to confirm diagnosis utilizing the Revised European American Lymphoma (REAL) classification. Six cases of large-cell lymphoma had additional immunoperoxidase staining using an automated immunostainer (Ventana, Tucson, AZ) and heat-induced epitope retrieval with a microwave. Lineage-specific stains included: anti-CD-20 (DAKO, Carpenterial, CA) for B cell lineage, CD3 or CD45RO (DAKO) for T cell lineage, and CD30 (DAKO) and ALK-1 (DAKO) for anaplastic large-cell lymphoma (ALCL).

Criteria for Response and Relapse

No evidence of disease by physical exam and imaging studies (computed tomography [CT] scan), including negative BM and cerebrospinal fluid (CSF), constituted a CR. A reduction in the total volume of all measured lesions by at least 50% with no single lesion increasing by >25% and no new lesions constituted a PR. Stable disease (SD) was defined as a reduction in the total volume of all measured lesions of <50% with no single measured tumor lesion increasing in volume by >25% and no new lesions. Failure to achieve a CR with growth in any measured lesion by >25% in volume, or development of new lesions or new sites of tumor constituted progressive disease (PD). Recurrence was defined as redevelopment of tumor at any site after achievement of a CR.

Reinduction Chemotherapy

The protocol did not prescribe the reinduction chemotherapy regimen. Among the HL (N = 39) patients, 13 received ifosfamide, carboplatin, etoposide (ICE) and 11 received vinorelbine and ifosfamide (VI). Among the NHL patients (N = 30), 17 received ICE.

Eligibility for Stem Cell Collection

Patients completing 2 courses of reinduction chemotherapy with at least SD and no evidence of BM involvement proceeded to PBSC collection. Patients were mobilized following chemotherapy and granulocyte-colony stimulating factor (G-CSF) therapy and collected after hematologic recovery. Patients not meeting response criteria after 2 courses received 2 additional courses of reinduction therapy. Patients with persistent BM involvement after 4 cycles of reinduction therapy came off study.

PBSC Collection

Mobilization consisted of G-CSF 10 μg/kg daily for at least 3 days prior to and on the days of apheresis. The minimum goal of collection was 2×10^6 $CD34^+$ cells/kg and the target was 5×10^6 $CD34^+$ cells/kg. PBSC harvesting used standard procedures on either a COBE Spectra or Fenwall CS-3000 Plus apheresis machine.

Eligibility for Autologous PBSCT

Patients in PR or CR after no more than 4 cycles of reinduction chemotherapy and with adequate PBSC stored proceeded to CBV conditioning and autologous PBSCT. Patients with PD or SD were ineligible to proceed. Patients going to transplant met the following criteria of organ function: liver transaminsase <2.5× normal, total bilirubin <1.5 mg/dL, a glomerular filtration rate (GFR) of >60 mL/min/1.73 m^2, and a serum creatinine ≤1.5 mg/dL, a shortening fraction