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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

*Richard E. Harris,[1] Amanda M. Termuhlen,[2] Lynette M. Smith,[3] James Lynch,[3] Michael M. Henry,[4] Sherrie L. Perkins,[5] Thomas G. Gross,[2] Phyllis Warkentin,[6] Adrianna Vlachos,[7] Lauren Harrison,[8] Mitchell S. Cairo[8]*

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 $5 \times 10^6$ $CD34^+$/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.

*Biol Blood Marrow Transplant 17: 249-258 (2011) © 2011 American Society for Blood and Marrow Transplantation*

**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

From the [1]Division of Bone Marrow Transplant and Immune Deficiency, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; [2]Division of Hematology/Oncology, Nationwide Children's Hospital, Department of Pediatrics, The Ohio State University College of Medicine, Columbus, Ohio; [3]Data Center, Children's Oncology Group Data Center, Omaha, Nebraska; [4]Center for Cancer and Blood Disorders, Phoenix Children's Hospital, Phoenix, Arizona; [5]Pathology Department, University of Utah Health Sciences Center, Salt Lake City, Utah; [6]Pediatric Hematology/Oncology, University of Nebraska Medical Center, Omaha, Nebraska; [7]Schneider Children's Hospital, Long Island Jewish, Long Island, New York; and [8]Department of Pediatrics, Medicine, Pathology and Cell Biology, New York Presbyterian Morgan Stanley Children's Hospital, Columbia University Medical Center, New York, New York.

*Financial disclosure:* See Acknowledgments on page 257.

Correspondence and reprint requests: Richard E. Harris, MD, Division of BMT/Immunology, Cincinnati Children's Hospital Medical Center, Room R2.2055, 3333 Burnet Avenue, Cincinnati, OH 45229-3039 (e-mail: Richard.Harris@CCHMC.org).

Received May 12, 2010; accepted July 6, 2010



1083-8791/$36.00
doi:10.1016/j.bbmt.2010.07.002

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 $2 \times 10^6$ $CD34^+$ cells/kg and the target was $5 \times 10^6$ $CD34^+$ 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

≥28% on heart echocardiogram, or an ejection fraction >50% of normal, and on pulmonary function testing (PFTs) a vital capacity (VC) ≥65% and a total lung capacity (TLC) ≥50% of normal.

### Transplant Conditioning Regimen

All patients received cyclophosphamide 1800 mg/m$^2$/day over 1 hour on days −5, −4, −3, −2, and etoposide 800 mg/m$^2$/day over 24 hours on days −8, −7, and −6. The first 6 patients received BCNU at 150 mg/m$^2$/day for 3 days and the remaining 32 patients received 100 mg/m$^2$/day for 3 days on days −8, −7, and −6, following the amendment in February 2000 reducing the BCNU dose. Protocol treatment included Mesna to prevent hemorrhagic cystitis. Patients received methylprednisolone as a protective agent to reduce the risk of pulmonary toxicity as follows: 1 mg/kg days −9 to −2, then tapered off by day +6. All other supportive care was per local institutional guidelines.

### Hematopoietic Growth Factor Support

Patients received 5 μg/kg G-CSF over 2 hours after the infusion of the stem cells daily until the absolute neutrophil count (ANC) was >2000/mm$^3$ for 3 days.

### Engraftment

The first of 3 days of an ANC of >500/mm$^3$ and a platelet count of >50,000/mm$^3$ without platelet transfusion defined neutrophil and platelet engraftment.

### Follow-up After Transplant

Imaging at sites of disease occurred on days +28, +100, 6 months, and 1, 2, 3, and 5 years after transplant. Patients underwent PFTs at 3, 6, and 12 months posttransplant. If PFTs were abnormal, patients repeated them at 6 month intervals until normalization or stabilization.

### Statistical Analysis

SAS software, Version 9.1 (SAS Institute, Cary, NC) was used for statistical analysis. OS is the time on study or transplant to death or last follow-up. Relapse, progression, or death defined the events in the EFS determination. EFS is the time from on study or transplant to an event or last follow-up for those who did not have an event. Toxicity was graded according to the NCI CTCAE v. 2.0 common toxicity scale. Descriptive statistics summarized demographic and clinical variables. Chi-square tests were used to compare response rates for HL and NHL. Fisher's exact test compared toxicity rates by BCNU dose. The days to myeloid and platelet recovery, EFS, OS, and time to relapse were determined by the method of Kaplan-Meier. Patients who did not obtain recovery were censored at first event or last follow-up following transplant. The log-rank test compared time to event distributions between groups. Statistically significant *P*-values were <.05. The above outcomes measures were tested in the following subgroups: NHL versus HL, nodular sclerosing HL versus other HL patients, Burkitt's (BL)/Burkitt like versus lymphoblastic NHL, CR versus PR just prior to transplant, length of CR1 >1 year versus <1year, HL age >15years versus <15 years, relapse on or off therapy, failed induction versus relapse, and the dose of BCNU. The effect of length of CR1 was also separately tested in HL and NHL patients.

## RESULTS

### Patient Entry

Sixty-nine patients enrolled, 39 with HL and 30 with NHL. Thirty-eight patients received CBV conditioning and autologous PBSCT; 28 with HL and 10 with NHL. Study investigators amended the protocol on February 11, 2000, to reduce the dose of the BCNU from 450 mg/m$^2$ to 300 mg/m$^2$.

### Pretreatment Characteristics

The study entry patient characteristics for the HL patients and the NHL patients are in Table 1. Four HL patients entered for failed induction and 35 at time of first relapse. Four NHL patients entered for failed induction and 26 at time of first relapse.

### Central Pathology Review

Forty-one patients (15 NHL, 26 HL) had pathology material available for central classification of histologic subtypes. The histologic subtypes of the 39 cases of HL and the 30 NHL are shown in Table 1.

### Reinduction Efficacy

Of the 39 HL patients, 30 achieved a CR/PR. Four failed because of PD, 4 achieved only an SD status, and 1 was unevaluable. Among the 30 NHL patients, 13 achieved a CR/PR among the 26 patients evaluable (4/8 with lymphoblastic lymphoma [LBL], 2/5 with diffuse large B-cell lymphoma [DLCL], 4/5 with ALCL, and 3/8 with BL). Ten NHL patients failed because of PD, 3 achieved only an SD status, and 4 were inevaluable. The NHL patients were less likely to achieve CR/PR than the HL patients (45% versus 77%, $P = .007$). Overall, 43 of the 69 patients (62%) achieved a CR/PR, and 38 (28 HL, 10 NHL) proceeded to transplant. Four patients refused to proceed to CBV conditioning and autoSCT (Figure 1).

### Autologous Collection and Hematopoietic Recovery

Fifty-one patients underwent PBSC apheresis; 40 successfully obtained adequate stem cells for transplant

**Table 1. Characteristics of the Patients**

| Characteristic | HL Patients N = 39 | NHL Patients N = 30 |
|---|---|---|
| Age at diagnosis, median (range), years | 14.5 (5.3-20.4) | 12.8 (4.2-19.9) |
| Male sex, no. (%) | 19 (49%) | 21 (70%) |
| Race, no. (%) | | |
| White, non-Hispanic | 29 (74%) | 24 (80%) |
| Black, non-Hispanic | 2 (5%) | 4 (13%) |
| Hispanic | 6 (15%) | |
| Filipino/Asian | 1 (3%) | 1 (3%) |
| Unknown | 1 (3%) | 1 (3%) |
| HL histologic subtype, no. (%) | | |
| Mixed Cellularity, NOS | 1 (3%) | N/A |
| Nodular sclerosis (NS) | 34 (87%) | N/A |
| NOS | 4 (10%) | N/A |
| NHL histologic subtype, no. (%) | | |
| Large cell lymphoma | N/A | 5 (17%) |
| Anaplastic large cell lymphoma | N/A | 5 (17%) |
| Lymphoblastic lymphoma | N/A | 8 (27%) |
| Burkitt's | N/A | 7 (23%) |
| Burkitt-like (non-Burkitt's) | N/A | 4 (13%) |
| Unknown | N/A | 2 (7%) |
| Months from diagnosis to relapse, median (range) | 12.0 (1.9-63.8) | 7.9 (1.6-52.6) |
| Age at relapse, median (range), years | 16.1 (5.7-22.4) | 13.5 (5.1-20.2) |
| Stage at relapse, no. (%) | | |
| I | 3 (8%) | 3 (10%) |
| III | 23 (59%) | 20 (67%) |
| IV | 13 (33%) | 6 (20%) |
| Unknown | | 1 (3%) |
| Mediastinum involvement at relapse, no. (%) | 23 (59%) | N/A |
| Reinduction therapy, no. (%) | | |
| ICE | 13 (33%) | 17 (57%) |
| VI | 11 (28%) | N/A |
| Other | 15 (38%) | 12 (40%) |
| Unknown | | 1 (3%) |

NS indicates nodular sclerosing; MC, mixed cellularity; LD, lymphocyte depleted; NOS, not otherwise specified; ICE, ifosfamide, carboplatin, etoposide; VI, vinorelbine, ifosfamide; HL, hodgkin lymphoma; NHL, non-hodgkin lymphoma.

($2 \times 10^6$ $CD34^+$/kg). The median $CD34^+$ dose/kg stored was $6.2 \times 10^6$/kg (range $0.2 \times 10^6$ to $94.7 \times 10^6$/kg). The median cell dose infused was $6 \times 10^6 CD34^+$/kg. The myelogenous engraftment rates for an ANC of 500/mm$^3$ or 1000/mm$^3$ were not significantly different based on $CD34^+$/kg cell dose. However, the median time to recover the platelet count of 50,000/mm$^3$ was significantly improved with a higher CD $34^+$/kg cell dose ([$>4 \times 10^6$/kg versus $\leq 4 \times 10^6 CD34^+$/kg] {20 [4-48 days] versus 41 [39-480 days]}). There was no significant difference in the engraftment kinetics between the HL versus the NHL patients.

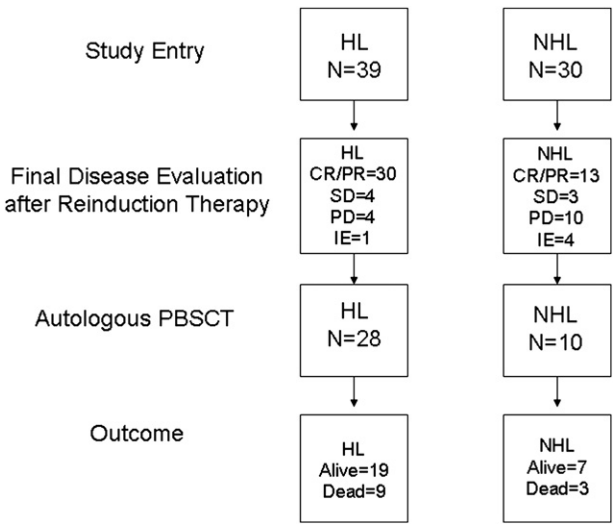


**Figure 1.** Flow diagram of patients from diagnosis and study entry, following reinduction, autologous PBSCT, and final outome.

## Toxicity and Treatment-Related Mortality (TRM) Following CBV Conditioning and Autologous Transplantation

All 6 patients receiving 450 mg/m$^2$ of BCNU developed grade III or IV pulmonary toxicity with onset between 30 to 60 days posttransplant. Four of the 6 required supplemental oxygen (duration 5 days to 9 months) and 5 received steroids. All but 2 came off supplemental oxygen therapy after a few days. One patient developed persistent abnormal PFTs, but came off oxygen after 9 months. The other patient relapsed 6 months after transplant while still on steroids and oxygen. None of the subsequent 32 patients treated with 300 mg/m$^2$ of BCNU developed grade III or IV pulmonary toxicity ($P < .0001$).

## EFS and OS

The median follow-up from date of study entry of the survivors is 3.2 years (maximum 6.3 years).

The 3-year OS in all 69 patients from study entry is 51% (95% confidence interval [CI], 38%-62%) (Figure 2A). The 3-year OS from date of study entry for HL patients is 63% (95% CI, 46%-76%) and for NHL patients is 34% (95% CI, 17%-52%) (Figure 2B) (HL versus NHL: $P = .0087$). The 3-year EFS of all 69 patients from study entry is 38% (95% CI, 27%-50%) (Figure 3A). The 3-year EFS from study entry for HL patients is 45% (95% CI, 29%-60%) and for NHL patients is 30% (95% CI, 15%-46%) (HL versus NHL: $P = .015$) (Figure 3B).

### *EFS and OS by response to reinduction chemotherapy*

Patients achieving a CR/PR versus SD/PD had significantly better OS and EFS at 3 years: OS 73% versus 6%, $P < .001$ (Figure 4A); EFS 54% versus 10%, $P < .001$ (Figure 4B). This analysis excludes 5 patients inevaluable for response because of early death from toxicity or infection. EFS and OS were similar in those patients who achieved a CR versus PR following reinduction chemotherapy.

### *Outcome after transplant*

Overall, 26 of the 38 patients who underwent CBV conditioning and autologous PBSCT survived: 20 of 26 are progression free (14 HL, 6 NHL). The 3-year OS from transplant is 64% (95% CI, 45%-78%) (HL 64%, 95% CI, 41%-80%; NHL 70%, 95% CI, 33%-89%). The 3-year EFS from transplant is 66% (95% CI, 48%-79%) (HL 65%, 95% CI, 43%-80%; NHL 70%, 95% CI, 33%-80%) (HL versus NHL: $P$ = NS).

The median time to relapse after CBV conditioning and autologous PBSCT for HL patients was 0.6

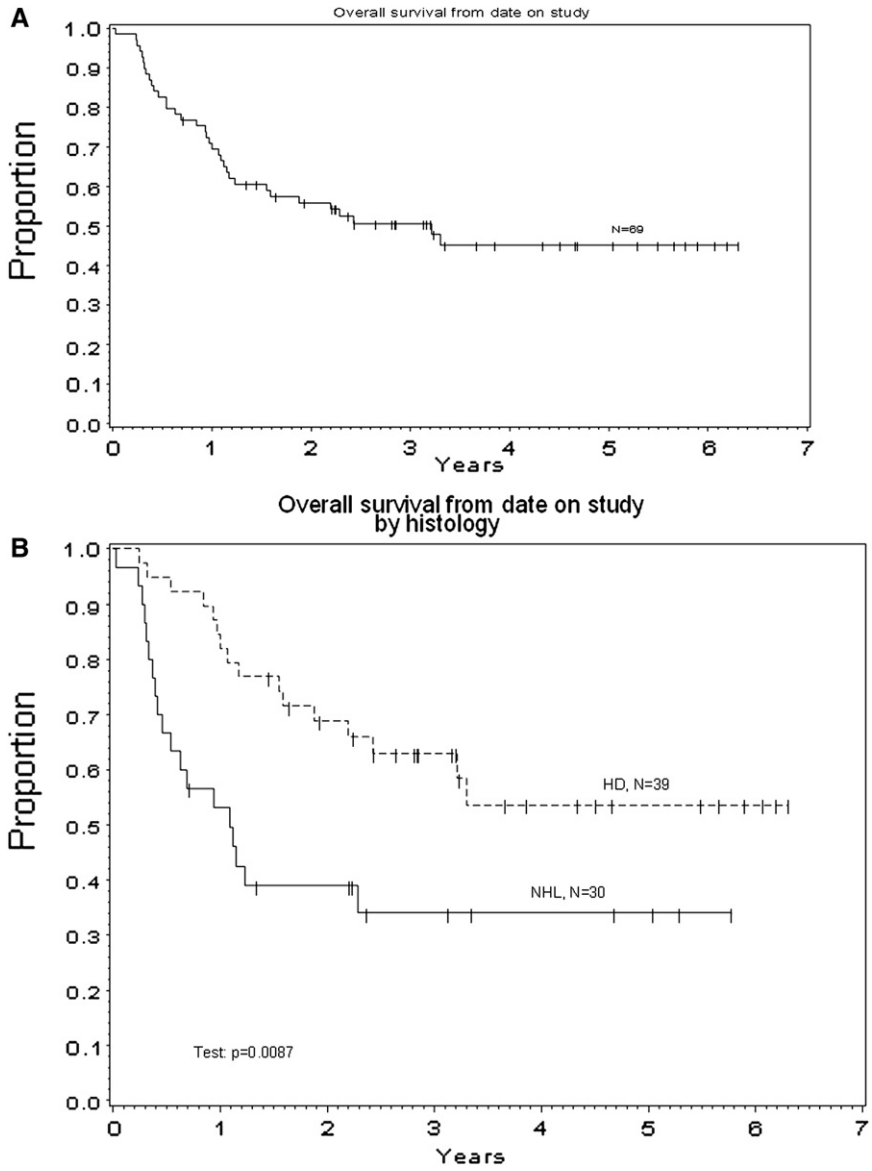


**Figure 2.** (A) OS of all patients from date of relapse or progressive disease calculated by the method of Kaplan-Meier. (B) Comparison of OS from time of relapse or progressive disease in HL versus NHL patients calculated by the method of Kaplan-Meier.

years (range: 0.2 to 2.0 years), and for NHL patients was 0.1 year (0.1-0.2 years). Twelve patients died after PBSCT: 7 from PD, 4 from infection, and 1 from toxicity. There was no difference in efficacy between the 450 mg/m$^2$ BCNU dose and the 300 mg/m$^2$ BCNU dose.

### *EFS and OS by Length of First Remission*

The median length of first remission was 11.7 months. EFS and OS were determined for all patients from study entry and from the date of PBSCT for those with a short (<12 months) versus a longer first remission (≥12 months). From study entry, there was a significant increase in OS in patients with an initial CR ≥ 12 versus <12 months (3 years OS 70% versus 34%, $P = .003$) (Figure 5). EFS was only marginally better with length of CR ≥12 months versus shorter ($P = .05$). This difference was only evident in HL patients (OS: $P < .001$, EFS: $P = .007$) (NHL patients (OS: $P = .37$, EFS: $P = .71$).

## DISCUSSION

The major finding of this study is that 300 mg/m$^2$ of BCNU within a CBV conditioning regimen prior to autologous PBSCT is well tolerated by children with

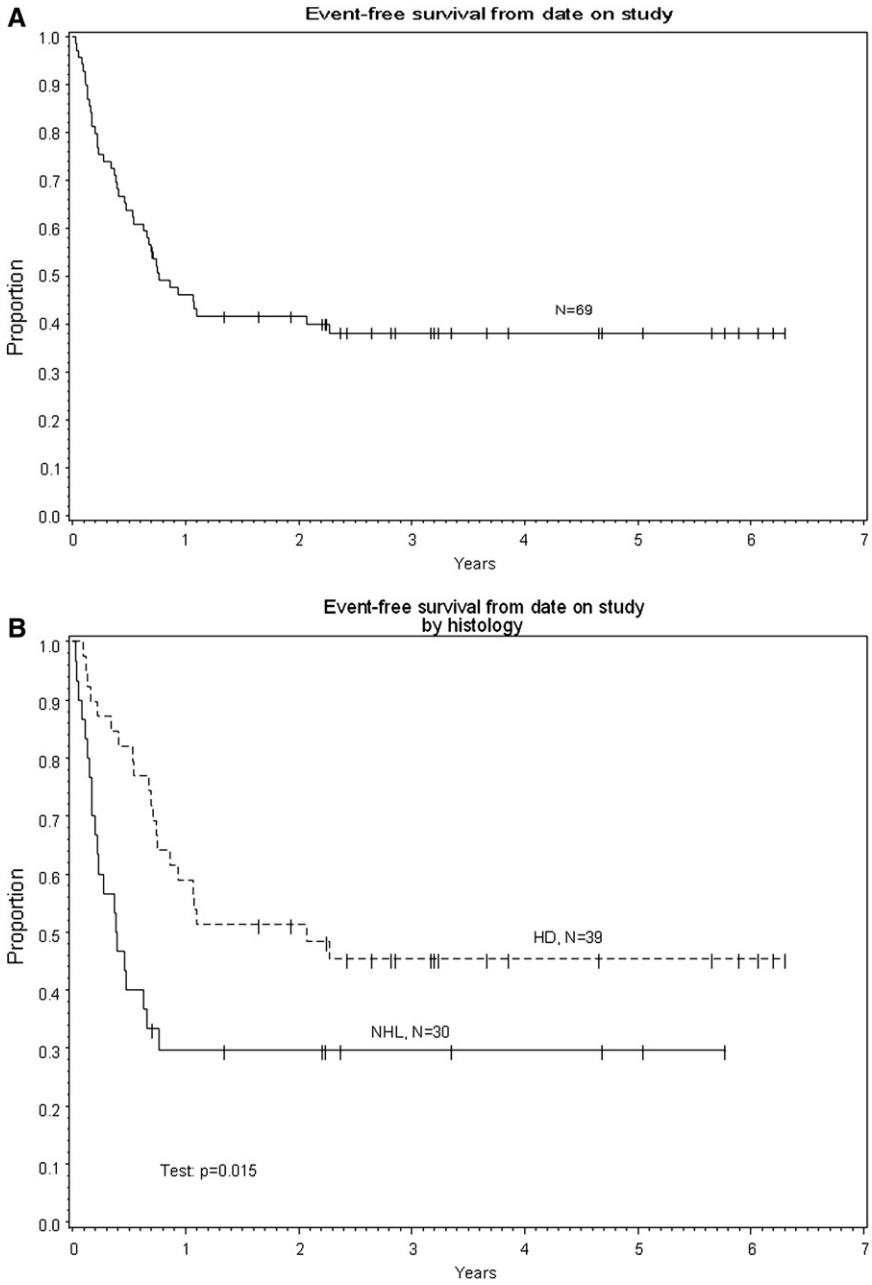


**Figure 3.** (A) EFS of all patients from date of relapse or progressive disease calculated by the method of Kaplan-Meier. (B) Comparison of EFS from time of relapse or progressive disease in HL versus NHL patients calculated by the method of Kaplan-Meier.

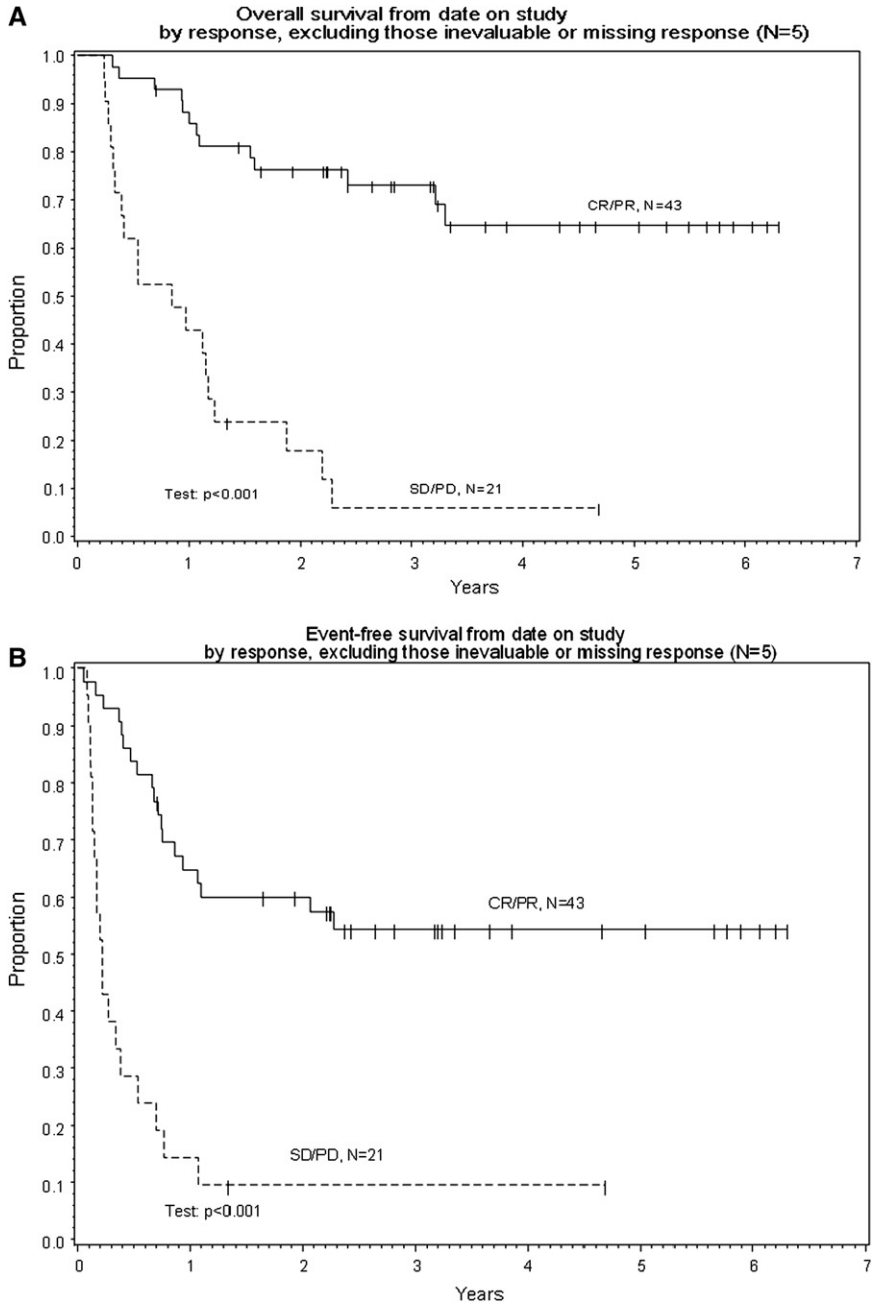


**Figure 4.** (A) Comparison of OS from date of relapse or progressive disease in patients achieving a CR/PR versus SD/PD following reinduction calculated by the method of Kaplan-Meier. All patients were included except those who were inevaluable for response because of early toxic or infectious death (n = 5). (B) Comparison of EFS from date of relapse or progressive disease in patients achieving a CR/PR versus SD/PD following reinduction calculated by the method of Kaplan-Meier. All patients were included except those who were inevaluable for response because of early toxic or infectious death (n = 5).

relapsed/refractory lymphoma. A dose of 450 mg/m$^2$ of BCNU was associated with unacceptable pulmonary toxicity. Five of the 6 patients who developed pulmonary toxicity in this study also received mantle irradiation around the time of CBV conditioning and autologous PBSCT. Reece and others [28,30-32] first described pulmonary toxicity in patients receiving 600 mg/m$^2$ of BCNU and irradiation. Subsequent studies in adults using either 450 mg/m$^2$ or 300 mg/m$^2$ of BCNU reported less pulmonary toxicity [20,31,32]. The BCNU dose of 300 mg/m$^2$ was not associated with any reduction in efficacy.

The efficacy of CBV conditioning in this pediatric study is comparable to that demonstrated in studies of adults. Reece et al. [28] reported 5-year OS and EFS rates of 53% and 47% using a BCNU dose of 600 mg/m$^2$ in CBV and autologous PBSCT in 56 relapsed HL patients. Using 300 mg/m$^2$ BCNU in a CBV conditioning regimen resulted in 5-year OS and failure free rates of 51% and 40%, respectively [28]. Brice

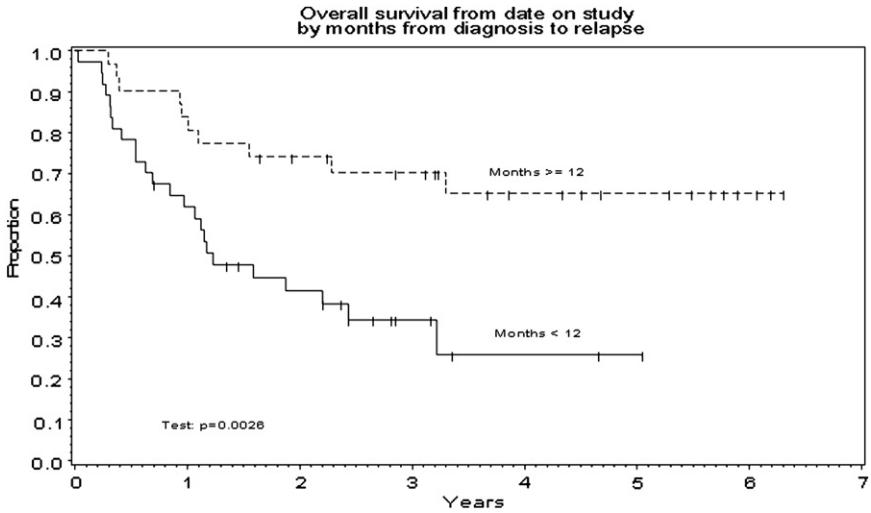


**Figure 5.** Comparison of OS from date on study (all patients) in patients with first remission <12 months versus patients with first remission ≥12 months calculated by the method of Kaplan-Meier.

et al. [33] reported OS and progression-free survival (PFS) rates at 4 years of 66% and 60%, respectively, in 280 patients undergoing myeloablative conditioning and autologous BMT for relapsed HL. The largest series of autoSCT in adult NHL patients with aggressive histologies demonstrated a 43% 5-year OS and relapse-free survival (RFS) [19]. Poor prognostic factors in adults include "B" symptoms, extranodal disease, duration of first remission, and chemosensitivity [28,30,33]. We confirmed that chemosensitivity in children and adolescents with relapsed NHL and HL following reinduction therapy was associated with a better outcome for children with both HL and NHL, but a duration of first remission was only significant in predicting outcome in children with recurrent HL.

Studies in pediatric patients are confounded by small numbers and a mixture of patients receiving autologous transplant and allogeneic transplant [25]. However, this is the first pediatric prospective autologous SCT study reported that follows the outcome of patients from the time of relapse, induction failure, or progression and not just at the time of conditioning and autologous SCT. This is of critical importance because most autoSCT results only report outcomes from the time conditioning starts and not the time from disease relapse/progression. Our study notes that only 62% of patients achieved a CR/PR after reinduction therapy and were eligible for CBV conditioning and autologous PBSCT and 90% of those patients proceeded to autoSCT. For recurrent HL in pediatric patients, a report by Verdeguer et al. [34] from the Spanish Pediatric BMT Group reported on 20 children with relapsed or refractory HL who underwent autologous BMT; 18 with CBV (cyclophosphamide 6000 mg/m$^2$, BCNU 300 mg/m$^2$, and etoposide of 1000 mg/m$^2$). Most were in CR2 or greater and 14 of 18 had prior irradiation. Among all 20 children, the 5-year OS and EFS was 95% and 62%, respectively [34]. Four of 5 children who relapsed posttransplant were successfully salvaged. Only 1 death occurred from transplant related causes. The only pulmonary toxicity was pneumonia and the transplant regimens were well tolerated [34]. For recurrent NHL in pediatric patients, Bureo et al. [35] reported on 46 children with relapsed NHL who underwent a transplant (14 allogeneic, 32 autologous) including 21 children with LBL, 19 with BL, and 6 with large cell lymphoma (LCL). In this study where all patients were at least a CR2, 13 of the children received transplant in first CR, 9 because of prolonged time to achieve CR or failure of frontline therapy. Overall EFS was 58% with a median follow-up of 33 months. EFS was similar for autologous and allogeneic recipients. The only factor which predicted outcome was disease status at BMT (CR1 versus CR2 versus CR3 versus more advanced disease) [35]. Brugieres et al. [36] reported that myeloablative therapy and autologous SCT for children with relapsed ALCL is dismal in patients with early relapse (28% 3 year EFS).

Of patients achieving a CR/PR, autologous PBSC apheresis was successful in 89% of the children and adolescents on this trial in achieving an adequate CD34$^+$/kg cell yield. Engraftment results in the current study is consistent with other reported studies involving myeloablaitve conditioning and autologous PBSCT [34].

The weaknesses of this study include a lack of consistent reinduction regimen and small numbers of patients with NHL who were eligible to proceed to CBV conditioning and autologous PBSCT either from lack of response to reinduction therapy or refusal. Most HL patients received either ICE or a combination of VI. Most NHL patients received ICE. Surprisingly, our reinduction efficacy in patients with LBL is higher than expected but the numbers are quite small [37].

The high rate of posttransplant relapse in this study is potentially because of 2 mechanisms: tumor

cells in the PBSC product, and/or inadequate disease control using cytotoxic agents. It is generally accepted that autologous PBSC are less likely to be contaminated with tumor cells than BM. PBSC were not collected until patients achieved a CR/PR/SD with negative BM disease, which potentially reduced the risk of tumor cell contamination.

New approaches are needed to improve the EFS reported in our study. Reinduction therapy, especially for NHL patients, is not adequate. Salvage therapy might be improved by the addition of rituximab (anti-CD20 monoclonal antibody) in patients with B cell disease (COG ANHL0121) [38]. The addition of anti-T cell or anti CD-30 monoclonal antibodies or other targeted therapy in patients with T-lymphoblastic lymphoma, ALCL, or HL may improve the reinduction rate. The use of monoclonal antibodies or other therapies post-BMT might also reduce the relapse rate [39,40]. Improved conditioning regimens using conventional chemotherapy agents prior to autologous transplant are unlikely to significantly affect outcome [34]. However, there is considerable emerging evidence of a graft-versus-lymphoma effect following allogeneic SCT [41-46]. There may be benefit from combining autologous PBSCT with reduced intensity allogeneic transplantation to add graft-versus-lymphoma effects after cytoreduction [47]. Pilot studies using CBV and autologous PBSCT followed by reduced intensity allogeneic BMT show promise in children with high-risk lymphoma [25,48]. A larger cohort with a longer follow-up is required to determine the feasibility of these approaches.

## ACKNOWLEDGMENTS

This work was presented in part at the Second International Childhood, Adolescent and Young Adult Non Hodgkin's Lymphoma Symposium New York, May 2006, and at the American Society of Hematology Annual Meeting, San Diego, CA, December 2004.

*Financial disclosure:* This was supported by Chair's Grant, U10 CA98543, Statistics and Data Center Grant, U10 CA98413 from the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Department of Health and Human Services (COG), as well as from CureSearch National Childhood Cancer Foundation. A complete listing of grant support for research conducted by CCG and POG before initiation of the COG grant in 2003 is available online at: http://www.childrensoncologygroup.org/admin/grantinfo.htm.

The authors thank Amber Quiltan from the COG publications office for her assistance in the preparation of this manuscript.

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