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High-Dose Chemotherapy Plus Non-Cryopreserved Autologous Peripheral Blood Stem Cell Transplantation Rescue for Patients With Refractory or Relapsed Hodgkin Disease

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ABSTRACT

A simplified schedule of high-dose chemotherapy consisting of cyclophosphamide (60 mg · kg^{-1} · d^{-1} for 2 days), etoposide (15 mg · kg^{-1} · d^{-1} for 2 days), and carboplatin (400 mg/m^2 per day for 2 days) plus autologous non-cryopreserved peripheral blood stem cells (PBSCs) was used for treatment of patients with relapsed (n = 25) and refractory (n = 3) Hodgkin disease. The use of such PBSCs mobilized by granulocyte colony-stimulating factor after high-dose myeloablative therapy resulted in a rapid, complete, and sustained hematopoietic recovery. The median time to achieve an absolute neutrophil count >0.5 × 10^9/L was 13 days (range, 7-18 days). The median time to a self-sustained platelet count >20 × 10^9/L was 15 days (range, 7-20 days). Twelve of the 28 patients (43%) were alive and without disease at a median follow-up of 16 months (range, 9-86 months) for all surviving patients. The estimated 2-year overall survival and disease-free survival for all patients were 45% and 42%, respectively. Thirteen patients died of relapse or progressive disease, 2 died of infection, and 1 was still surviving in relapse by the time of the analysis. The median time to relapse was 10 months (range, 3-28 months) from PBSC infusion. High-dose chemotherapy with short-duration chemotherapy and non-cryopreserved bone marrow is an effective and safe treatment modality for patients with relapsed or resistant Hodgkin lymphoma.

KEY WORDS

High-dose chemotherapy • Resistant Hodgkin disease • Relapsed Hodgkin disease • Non-cryopreserved peripheral blood stem cells • Peripheral blood stem cell transplantation

INTRODUCTION

Approximately 60% to 70% of patients with advanced Hodgkin disease (HD) can be cured with combination chemotherapy [1,2]. However patients who relapse after attaining a complete remission (CR) with chemotherapy or who do not respond to induction chemotherapy and have primary refractory disease are rarely cured with conventional salvage chemotherapy or salvage radiotherapy [3,4]

High-dose therapy followed by autologous stem cell transplantation has been shown to produce long-term disease-free survival (DFS) in selected patients with advanced refractory HD [5,6]. However, the conventional procedures for collection and freezing of peripheral blood stem cells (PBSCs) are time-consuming and expensive [7] and methods to simplify bone marrow transplantation procedures are needed mainly in developing countries

Hematopoietic stem cells appear to maintain viability for several days after collection if carefully stored. Preti et al [8], in a nonrandomized retrospective analysis, compared the engraftment kinetics of 54 patients who received cryopreserved marrow cells with those of 45 patients who received refrigerated cells. The refrigerated cells were stored for a median of 4 days (range, 3-9 days). The cryopreserved cells were stored a median of 69 days (range, 5-981 days) at

−80°C using a cryopreserving mixture of dimethylsulfoxide and hydroxyethyl starch. No significant difference in engraftment kinetics was found between the 2 groups [8].

Refrigerated storage was supplanted by cryopreservation because most transplantation centers develop multiday conditioning regimens. There is limited experience with autologous transplantation of non-cryopreserved hematopoietic stem cells. We present the results of 28 patients with Hodgkin lymphoma who were preconditioned with cyclophosphamide, etoposide, and carboplatin and received non-cryopreserved unmanipulated PBSC transplantation (PBSCT) for their advanced or refractory disease.

METHODS

Between 1996 and 2004, 28 patients with relapsed or refractory HD underwent high-dose therapy and autologous PBSCT at the Bone Marrow Transplant Unit of the Faculty of Medicine, Mansoura University (Mansoura, Egypt). The diagnosis and histologic subtype of HD were based on biopsy results.

Study Definitions and Evaluation

Patients were defined to have induction failure if they had received induction chemotherapy with or without salvage therapy and were never documented to be in a CR. A sensitive relapse was defined as ≥50% reduction in the bidimensional measurements of the disease with the use of conventional salvage chemotherapy or radiotherapy. A resistant relapse was defined as <50% reduction in the size of the tumor with the use of conventional salvage chemotherapy or radiotherapy. The duration of initial remission was calculated from time of documented CR to time of relapse.

Patients were clinically restaged at the time of entry into the study. Restaging procedures were repeated at day +30, day +90 after transplantation, or as clinically indicated. Follow-up tumor restaging was performed every 3 to 6 months for 2 years and then yearly unless recurrence was suspected. Patients who survived to at least day +30 and had no evidence of tumor by clinical and radiologic evaluation for ≥1 month were classified as having a CR. Patients who were received transplants in CR without evidence of disease were considered to be in continuous CR after transplantation. Partial remission (PR) was defined as a reduction ≥50% of measurable disease for ≥1 month.

Patient Selection

Patients were eligible for PBSCT if they did not achieve CR after first-line chemotherapy (induction failure) or if they had relapsed after a standard chemotherapy regimen. Patients whose first relapse occurred >12 months after completion of induction chemotherapy were not candidates for transplantation unless they did not respond to standard salvage chemotherapy or had relapse at extranodal sites. Additional eligibility criteria included age <60 years, Karnofsky Performance Status score ≥70, left ventricular ejection fraction >50%, forced expiratory volume in 1 second >50%, and no major organ dysfunction unrelated to their underlying lymphoma.

Table 1. *Patient Characteristics*

Item	Frequency (%)
Patients, n	**28**
Age, median (range)	**30 (16-50)**
Sex	
Male	**19 (68)**
Female	**9 (32)**
Stage at diagnosis	
II	**5 (18)**
III	**15 (54)**
IV	**8 (28)**
B symptoms at diagnosis	**12 (43)**
Extranodal disease at diagnosis	
Yes	**9 (32)**
No	**19 (68)**
Histology	
Lymphocyte predominance	**2 (7)**
Nodular sclerosis	**5 (18)**
Mixed cellularity	**13 (46)**
Lymphocyte depletion	**8 (29)**
Bone marrow involvement	
Yes	**7 (25)**
No	**21 (75)**

The patient characteristics at time of diagnosis are listed in Table 1. The median age was 30 years (range, 16-50 years). There were 19 males and 9 females. Fifteen patients (54%) had stage III disease, 8 patients (28%) had stage IV disease, and 12 patients (43%) had "B" symptoms at time of diagnosis. Nine patients (32%) had extranodal involvement at diagnosis. The pathologic examination revealed lymphocytic predominance in 2 patients (7%), nodular sclerosis in 5 patients (18%), mixed cellularity in 13 patients (46%), and lymphocyte depletion in 8 patients (29%). Bone marrow involvement was detected in 7 patients (25%).

Details of prior therapy are presented in Table 2. All patients were treated with induction chemotherapy for a minimum of 3 cycles or until they had achieved a CR or minimal disease state. The median number of prior chemotherapy regimens was 4 (range, 3-8). Four patients (14%) had received prior radiotherapy at initial presentation or as salvage therapy for relapse. Conventional salvage chemotherapy was given to all relapsed patients (20 patients [71%] received dexamethasone, cytarabine, and cisplatin and 8 patients [29%] received etoposide, methylprednisone, cytarabine, and cisplatin). Most patients received 2-3 cycles

Table 2. *Chemotherapy Regimen Before Transplantation*

Regimen	Frequency (%)
No. of chemotherapy regimens, median (range)	**4 (3-8)**
Induction chemotherapy	
MOPP/ABV	**17 (61)**
ABVD	**6 (21)**
C-MOPP	**5 (18)**
Salvage chemotherapy	
DHAP	**20 (71)**
ESHAP	**8 (29)**
Radiation therapy	
Yes	**4 (14)**
No	**24 (86)**

MOPP/ABV indicates cyclophosphamide, vincristine, procarbazine, prednisone, doxorubicin, bleomycin, and vinblastine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; C-MOPP, cyclophosphamide, vincristine, procarbazine, and prednisone; DHAP, dexamethazone, cytarabine, and cisplatin; and ESHAP, etoposide, methylprednisone, cytarabine, and cisplatin.

of salvage therapy to achieve maximal response before transplantation.

The patient characteristics at time of transplantation are presented in Table 3. Eight patients (28%) received transplants in second CR. Seventeen patients (61%) received transplants after second or subsequent relapse. The median duration of first CR to first relapse was 10 months (range, 5-16 months). The median time from diagnosis to transplantation was 13 months (range, 5-20 months). Twelve of relapsed patients (43%) had sensitive relapse. Three patients (11%) underwent transplantation after induction with or without salvage chemotherapy or chemoradiotherapy failure. The median Karnofsky Performance Status score was 90% (range, 80%-100%). Seven patients (25%) had extranodal diseases at time of transplantation. The median time from diagnosis to transplantation was 13 months (range, 5-20 months).

Mobilization of Progenitor Cells (Figure 1)

Patients received a single dose of cyclophosphamide (1.5 g/m^2) followed after 5 days by 5 $\mu g \cdot kg^{-1} \cdot d^{-1}$ recombinant human granulocyte colony-stimulating factor (G-CSF). Recombinant human G-CSF was continued until the end of leukapheresis.

Collection and Preservation of PBSCs (Figure 1)

After administration of cyclophosphamide, patients had complete blood cell counts measured daily and began leukapheresis when the total white blood counts recovered to 3×10^9/L, usually at the ninth to the eleventh day from the start of mobilization. Leukapheresis was performed daily until the collection of $>2 \times 10^8$ mononuclear cells/kg and $>3 \times 10^6$ $CD34^+$ cells/kg patient weight. The apheresis solution was acid citrate dextrose and the final product was stored at 4°C for a maximum of 72 hours without special additives. Viability was assessed by trypan blue dye exclusion test 24, 48, and 72 hours from harvesting.

Conditioning Regimen (Figure 1)

The conditioning regimen for transplantation was started after the end of leukapheresis and given over 2 days. It contained cyclophosphamide (60 $mg \cdot kg^{-1} \cdot d^{-1}$ for 2 days), etoposide (15 $mg \cdot kg^{-1} \cdot d^{-1}$ for 2 days), and carboplatin (400 mg/m^2 per day for 2 days). Twenty-four hours after the end of chemotherapy, the non-cryopreserved stem cells were reinfused.

Statistical Analysis

Neutrophil recovery was defined as the first of 2 consecutive days of neutrophil counts $>0.5 \times 10^9$/L. Platelet recovery was defined as the first of 7 consecutive days with a platelet count $>20 \times 10^9$/L unsupported by transfusion. DFS was defined as the time from PBSC reinfusion to the time of disease progression or last follow-up. Overall survival (OS) was defined as the time from reinfusion of PBSCs to death or date of last follow-up. Survival distributions were assessed with Kaplan-Meier estimates [9].

RESULTS

Viability Assessment (Table 4)

Trypan blue dye exclusion showed >90% viability in all samples tested 24, 48, or 72 hours from harvesting.

Table 3. *Patient Characteristics at Time of Transplantation*

Item	Frequency (%)
Status at transplantation	
Second CR	**8 (28)**
Relapse	
Sensitive relapse	**12 (43)**
Resistant relapse	**5 (18)**
Refractory disease	**3 (11)**
Duration of first CR, median (range)	**10 (5-16 months)**
Time from diagnosis to transplant, median (range)	**13 (5-20 months)**
KPS score	
80	**7 (25)**
90	**15 (54)**
100	**6 (21)**
Extranodal disease	
Yes	**7 (25)**
No	**21 (75)**

CR indicates complete remission; KPS, Karnofsky Performance Status.

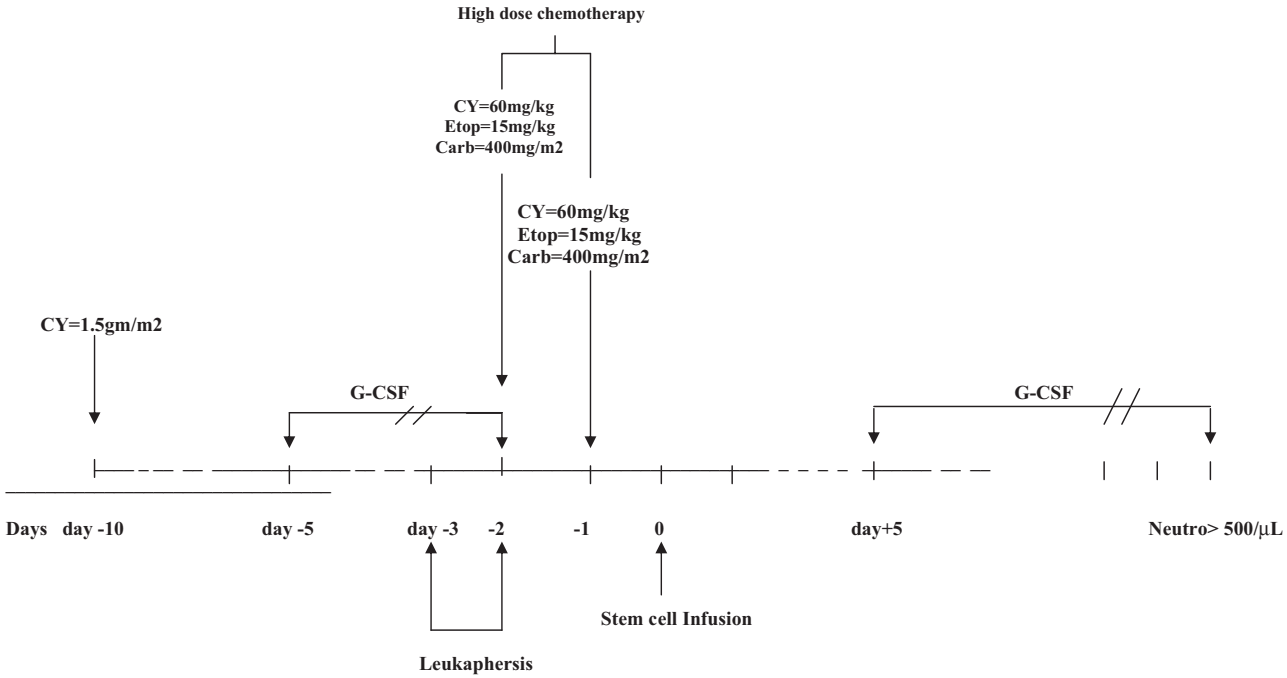

Figure 1. Schema of procedure. Carb indicates carboplatin; CY, cyclophosphamide; Etop, etoposide; G-CSF, granulocyte colony-stimulating factor; Neutro, neutrophil count.

Hematopoietic Recovery (Table 4)

Successful PBSC collection was achieved in all patients. The median number of $CD34^+$ cells collected from patients was 6.4×10^6/kg (range, 3.8-24.6 $\times 10^6$/kg). The use of such G-CSF mobilized PBSCs after high-dose myeloablative therapy resulted in a rapid, complete, and sustained hematopoietic recovery in all patients. The median time to achieve an absolute neutrophil count $>0.5 \times 10^9$/L was 13 days (range, 7-18 days). The median time to a self-sustained platelet count $>20 \times 10^9$/L was 15 days (range, 7-20 days).

Assessment of Response

All patients were assessable for response. No early deaths had occurred. At 30 days, 19 patients (68%), including the 8 patients who underwent transplantation in CR, were in CR. Five patients (19%) achieved PR. Two patients (7%) had stable disease and 2 patients (7%) did not respond. Without additional treatment, restaging at 3 months showed 22 patients (78%) in CR, 1 patient (4%) in PR, 1 patient (4%) with stable disease, and 4 patients (14%) with disease progression.

OS and DFS

Twelve of the 28 patients (43%) were alive and disease free at a median follow-up of 16 months (range, 9-86 months) for all surviving patients. The estimated 2-year OS and DFS for all patients were 45% and 42%, respectively (Figure 2). Thirteen patients died of relapse or progressive disease, 2 patients died of infection, and 1 patient was still surviving in relapse by the time of analysis. No evidence of graft failure was present by the time of death of any patient. The median time to relapse was 10 months (range, 3-28 months) from PBSC infusion.

DISCUSSION

High-dose therapy followed by autologous stem cell transplantation has been shown to produce long-term DFS in selected patients with advanced refrac-

Table 4. *Viability Data*

	Viability %			CD34 Cells × 10^6/kg	Time to Platelets Recovery (days)	Time to Neutrophiles Recovery (days)	No. of RBCs Transfusions	No. of Platelets Transfusions
	24 hrs	48 hrs	72 hrs					
Median	97.6	96	95	6.4	15	13	5	7
Range	92.4-99.4	91.6–98	91–96	3.8–24.6	7–20	7–18	4–7	5–9

RBC indicates red blood cell.

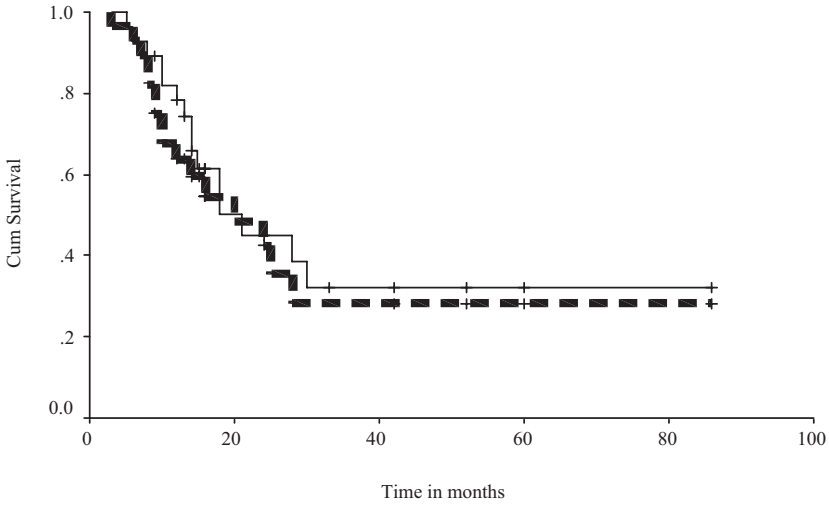

Figure 2: kaplan-Meier product estimate of the

cumulative probability of DFS and OS

Figure 2. Kaplan-Meier product estimate of the cumulative probability of DFS (dashed line) and OS (solid line).

tory or relapsed HD. Approximately 40% to 72% long-term DFS has been reported from several series [10]. However, the conventional procedures for collection and freezing of PBSCs are time-consuming and expensive. Methods to simplify bone marrow transplantation procedures are needed mainly in developing countries.

Refrigerated storage for short-term preservation of bone marrow is an alternative to cryopreservation. In an in vitro analysis, the stem cell population was concentrated and the nucleated cell recovery, viability, and colony-forming potential were compared after refrigerated storage of whole bone marrow and buffy coat with cryopreserved bone marrow stored for the same interval. Although the nucleated cell recovery for cryopreserved marrow was significantly greater than that for refrigerated storage, the viability and colony-forming potential of the refrigerated storage were superior or equivalent, independent of prior processing [8]. Conversely, no clinically meaningful variation in post-transplantation course and engraftment kinetics between refrigerated storage and cryopreserved stem cells was found [8,11,12].

A simplified schedule of high-dose chemotherapy consisting of melphalan plus VP16 given over 12-18 hours in addition to autologous non-cryopreserved autologous bone marrow transplant was used for treatment of patients with relapsed and refractory disease and as first-line treatment for poor-prognosis HD. This high-dose chemotherapy with short-duration chemotherapy regimen and non-cryopreserved bone marrow was an effective and safe treatment modality for patients with relapsed and poor-prognosis HD [13]. Our study confirms that non-frozen stem cells are useful to support patients with HD that is treated with myeloablative therapies.

One potential advantage to refrigerated storage is that it may provide an opportunity for extended exposure to growth factors and/or purging agents in vitro before transplantation [8]. Storage of PBSCs overnight at 4°C allows pooling of consecutive-day collections, resulting in decreased costs and processing time without compromising neutrophil and platelet engraftment after infusion of $CD34^+$-selected progenitor cells [14].

The use of such non-cryopreserved stem cells may yield cost savings when performing autologous stem cell transplantation. In our institution, the cost of the entire transplantation was approximately 12% less when using non-cryopreserved cells than when using a comparable treatment regimen with cryopreserved cells. The difference is mostly attributed to the lower cost of storing and infusing the non-cryopreserved cells. Over a 10-year period, Ruiz-Arguelles et al [15,16] performed autotransplantations using non-cryopreserved and unmanipulated PBSCs mobilized from the bone marrow to the peripheral blood by means of filgrastim and using a single-day conditioning regimen with high-dose (200 mg/m^2) melphalan. Their simplified method to perform autografting in patients and avoid cryopreservation of cells also resulted in a decrease in the cost of the autologous hematopoietic stem cell transplantation methods [15,16]. Therefore, it may represent a suitable approach in the management of patients requiring an autologous stem cell transplant in developing countries.

Most studies have used a high-dose combination

chemotherapy regimen. The most commonly used combinations are cyclophosphamide, carmustine, and etoposide [17,18] or bis-chloroethyl-nitrosourea, carmustine (BCNU), etoposide, cytarabine, and melphalan [19,20]. Excellent results were reported with the addition of cisplatin to a modified regimen of cyclophosphamide, carmustine, and etoposide [21,22]. Total body irradiation in combination with high-dose cyclophosphamide was used especially for those who had not received previous radiotherapy [23,24]. Hyperfractionated total lymphoid irradiation in combination with high-dose etoposide and cyclophosphamide has been shown to be efficacious in previously unirradiated patients with relapsing or chemotherapy-resistant HD [5]. At present, there is no evidence to suggest the superiority of 1 regimen over another.

In this study, we used the combination of cyclophosphamide, etoposide, and carboplatin followed by PBSCT.

Cyclophosphamide is a member of the oxazaphosphorine group of nitrogen mustard derivatives and is the most widely used alkylating agent in bone marrow transplantation, based in part on its broad range of antineoplastic activity and immunomodulatory properties [25]. The pharmacokinetics of unchanged cyclophosphamide in the plasma have shown considerable interpatient variability, with a terminal half-life of 3-9 hours [26]. Etoposide (VP16) is the podophyllotoxin derivative most commonly used in standard clinical oncologic practice and as a component of many high-dose chemotherapy regimens for hematopoietic malignancies [27]. Caution must be exercised when high-dose etoposide is delivered immediately after high-dose cisplatin, because acute cisplatin exposure can reduce the systemic clearance of etoposide by approximately 25%, leading to a substantially greater than expected etoposide area under the curve and toxicity level [28]. In contrast, high-dose carboplatin exposure may not alter the disposition of high-dose etoposide [29]. The pharmacokinetics of etoposide have been studied over the entire range of intravenous regimens, from 0.1 to 3 g/m^2. Etoposide, which is highly protein bound, has a biexponential decay with a mean terminal half-life ($t_{1/2}$)of 4-8 hours after high-dose therapy [30]. Carboplatin is an analog of cisplatin in which the 2 chloride ligands are replaced by the carboxylate moiety. Carboplatin disappearance is caused, almost exclusively, by renal excretion [31]. The disappearance of carboplatin from plasma is characterized by a triexponential decay, with a $t_{1/2\alpha}$ of approximately 20 min, a $t_{1/2\beta}$ of about 1.5 hours, and a $t_{1/2\gamma}$ of approximately 7.5-20 hours. Essentially, all unbound platinum species have been cleared from the plasma within 24 hours after completion of a high-dose carboplatin infusion [32].

The combination was beneficial in the treatment of relapsed or refractory HD. DFS over 2 years can be achieved in some patients. The results are at least equivalent to other published regimens including those based on total body irradiation and to other studies with nearly the same follow-up time [33]. The regimen appears to be a particularly attractive alternative for patients who have received dose-limiting radiotherapy and it should be evaluated further in prospective, randomized trials. Being short term, it allows the use of non-cryopreserved stem cell transplantation.

In conclusion, this simplified approach for performing autografting in patients, avoiding purging procedures, and cryopreservation of the cells is feasible and results in a substantial decrease of the cost of autologous hematopoietic stem cell transplantation methods. On the other hand, the results of the study are encouraging in so far that the DFS and OS are comparable to other protocols of high dose chemotherapy and PBSCT.

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