Tandem Autologous Stem Cell Transplantation for Patients with Primary Refractory or Poor Risk Recurrent Hodgkin Lymphoma

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ABSTRACT

Although autologous stem cell transplantation (ASCT) for patients with relapsed/refractory Hodgkin lymphoma (HL) appears to offer a survival advantage over conventional therapy, only approximately 25% to 35% of patients with primary progressive or poor-risk recurrent HL can achieve durable remission after ASCT, with disease progressive after transplant accounting for most of the treatment failures. We conducted a pilot study to evaluate the toxicities and efficacy of a tandem transplant approach in this subgroup of patients. Between April 1998 and March 2000, 46 patients were enrolled in the study. Eligibility criteria: primary progressive (n = 28) or recurrent HL (n = 18) with at least 1 of the following poor prognostic factors: first complete remission (CR) <12 months (n = 15) or extra-nodal disease (n = 4) or B symptoms at relapse (n = 4). The first cycle consisted of melphalan (150 mg/m^2) alone. The second cycle consisted of fractionated total body irradiation (FTBI) 1200 cGy or BCNU (450 mg/m^2) in combination with etoposide (60 mg/kg) and cyclophosphamide (100 mg/kg). Of the 46 patients, 5 (11%) did not receive the planned tandem transplants because of inadequate stem cell collection for 2 ASCT. After a median of 64 days (25-105), 41 patients received the second ASCT. With a median follow-up of 5.3 years (1.6-8.1), the 5-year estimate of overall survival, progression-free survival, and freedom from progression were 54% (95% confidence interval [CI] 40%-69%), 49% (95% CI, 34%-63%), and 55% (95%CI, 40%-70%), respectively. Our mature results from this study suggest that in patients with primary progressive or poor risk recurrent HL, this tandem ASCT program is effective and well tolerated and compares favorably with the conventional single transplant.

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KEY WORDS

Hodgkin lymphoma • Tandem transplant

INTRODUCTION

Combination chemotherapy with or without radiation can cure 60% to 70% of patients with advanced stage Hodgkin lymphoma (HL) [1]. For patients who develop disease progression during induction or within 12 months after completion of treatment, the prognosis is poor. In a long-term follow-up report from Milan Cancer Institute, the 8-year overall survival (OS) rate was 8% for patients who failed to achieve complete remission after nitrogen mustard, vincristine, procarbazine, prednisone, adriamycin, bleomycin, vinblastine and dacarbazine (MOPP-ABVD) [2]. Relapses after longer initial remissions (ie, 12 months or greater) are more amenable to conventional dose salvage treatment [2]. However, in a long-term follow-up report from the National Cancer Institute, the OS was only 24% among patients with long initial remission after retreatment with MOPP chemotherapy [3]. Based on the evolving maturing data from multiple phase II studies and 2 prospective phase III studies, autologous stem cell transplantation (ASCT) is becoming the preferred treatment for patients who fail to achieve a remission with conventional therapy or who relapse after achieving an initial remission. The results from single institution studies

[4-6], as well as cooperative group trials [7], have indicated that various high-dose regimens can result in disease-free survival rates of 30% to 65% in patients who failed their initial treatment. Although these results represent a significant improvement over those obtained with conventional therapy, up to 50% of patients still relapse after ASCT.

Multiple transplant studies have attempted to identify prognostic factors to predict transplant outcomes [4-8]. Failure to achieve an initial clinical remission or a short initial remission is the most commonly reported unfavorable prognostic factors. The estimated probability of long-term progression-free survival after transplant was approximately 25% to 35% for patients with primary refractory or poor risk recurrent HL. Conversely, the best results after autografts are seen in patents with a complete remission to salvage therapy [6,7,9]. Based on these studies, we hypothesized that transplant outcome could be improved if a minimal disease state can be achieved in a higher number of patients before the "conventional" transplant. We designed a tandem transplant program using high-dose melphalan with stem cell support (cycle I) followed by a planned second high dose therapy with stem cell rescue (cycle 2) [5,7].

PATIENTS AND METHODS

Between April 1998 and March 2000, 46 patients participated in this pilot study through the collaboration between City of Hope Comprehensive Cancer Center and Loyola University Medical Center. Both participating institutions' review boards approved the protocol. Eligibility criteria: patients with the following characteristics were eligible for the study: biopsy-proved Hodgkin lymphoma; aged 15-65 years, with primary refractory disease defined as progressive disease while on therapy, relapse within 3 months after completion of treatment or less than a partial response to initial therapy; or relapsed disease associated with 1 or more of the following poor risk features: extranodal disease or B symptoms at relapse, chemorefractory disease, and duration of first response of <12 months. Specifically, patients who relapsed >12 months after the completion of initial chemotherapy and who responded to salvage therapy were excluded. Eligible patients needed to have a normal cardiac ejection fraction of >50%, FEV1 >60% or DLCO >50% predicted, creatinine clearance >60 mL/min, normal bone marrow examination by morphology, and a normal cytogenetic study, negative HIV testing, and no evidence of active hepatitis infection with SGOT and SGPT <2 times of upper limit of normal.

Treatment Plan

Patients who fulfilled the criteria for entry received high-dose etoposide 1 gm/m^2 in combination with cyclophosphamide 1.5 gm/m^2 for cytoreduction and stem cell mobilization. Granulocyte-colony stimulating factor (G-CSF) was started after chemotherapy followed by stem cell collection. In patients who already had good response to salvage chemotherapy, stem cells were collected after last cycles of salvage therapy. The minimum target number of CD 34$^+$ cells was 5×10^6/kg. Restaging with CT and if possible PET or gallium scans were performed before each transplant. The first cycle of high-dose therapy consisted of a single 1-hour infusion of melphalan (150 mg/m^2) and stem cells were infused 24-48 hours later. After recovery, the second high dose cycle was given (minimum 28 days between cycles). The second cycle consisted of total body irradiation (TBI) 1200 cGy in 8-10 divided doses given over 4 days in combination with high-dose etoposide (60 mg/kg, adjusted body weight) and cyclophosphamide (100 mg/kg, ideal body weight). For patients who had received prior dose-limiting radiation, we substituted BCNU (450 mg/m^2) for TBI. A minimum of 2×10^6 CD 34-positive autologous stem cells were reinfused after each cycle of therapy. All patients received growth factor support, G-CSF after ASCT. All blood product transfusions were irradiated and filtered. Platelet and red blood cells transfusions were given to maintain platelets above 20,000 per μL and hematocrit above 25%. All patients received standard antibiotics prophylaxis with a quinolone and fluconazole for antifungal prophylaxis. Patients who were seropositive for herpes simplex also received acyclovir prophylaxis.

Statistical Analyses

Demographic and disease characteristics were summarized for all patients using descriptive statistics. Survival estimates were calculated based on the product-limit method, and 95% confidence intervals were calculated using the logit transformation with Greenwood's variance estimate. Factors possibly associated with overall survival, event-free survival, and freedom from progression were examined by univariate Cox regression analysis. The assumption of proportionality of the hazard ratio was tested for each variable. The variables tested included age, sex, stage at diagnosis (I/II versus III versus IV), "B" symptoms or extranodal disease at diagnosis and relapse, number of prior chemotherapy regimens, prior radiation therapy, disease status (primary refractory versus relapsed), chemosensitivity, interval between cycle 1 and cycle 2 high-dose therapy, and conditioning regimen (TBI versus BCNU). The risk ratio was calculated for each variable, along with the 95% confidence limits. Multivariate analyses were not performed because of the small number of patients in the study.

In this study, disease progression and death from any cause defined events in the calculation of event

free survival. Progression of Hodgkin lymphoma was the only event defined in freedom from progression: toxic death and second malignancies were censored.

RESULTS

The patient characteristics are shown in Table 1. The median age at transplant was 37 (range: 17-65) and 27 patients (59%) were male. The initial staging were stage I/II in 18 (39%), III in 21 (46%), and IV in 7 (15%). Twenty-four (52%) patients had "B" symptoms at diagnosis. Induction chemotherapy consisted of ABVD in 30 (65%), MOPP/ABVD in 7 (15%), MOPP/ABV hybrid in 2 (4%), Stanford V in 3 (7%), and others in 4 (9%). Twenty-eight patients (61%) had primary refractory disease and 18 (39%) had poor risk recurrent HL. Among the 28 patients with primary refractory HL, 11 progressed while receiving their initial induction chemotherapy, 15 achieved a transient complete/partial remission but progressed within 90 days after the end of treatment, and 2 had achieved partial remission with residual disease documented by CAT scan and FDG PET scan. Among the 18 relapsed patients, 15 had the duration of first remission <12 months, 4 had extra-nodal disease at relapse, 4 had B symptoms at relapse, and 3 had chemorefractory disease. Seven of the 18 had more than 1 poor risk features.

Salvage Therapy

Although it was not our intention to test for the chemosensitivity before transplant, 29 patients received some form of salvage therapy before transplant and 7 patients were found to have chemorefractory disease. The other 17 patients received high-dose etoposide and cyclophosphamide for cytoreduction and stem cell mobilization as per protocol. None of the patients received salvage radiotherapy before transplant.

Transplantation

Five patients (11%) who consented and were enrolled in the study did not receive the planned tandem transplant. Four had inadequate stem cell collections for 2 ASCT and 1 withdrew consent before the first cycle of high-dose therapy. Of these 5 patients, 3 went on to receive a single cycle conventional ASCT, 1 received an allogeneic stem cell transplant, and the other received conventional salvage treatment. Currently, 3 of these 5 patients are alive and progression free at last follow-up, whereas the other 2 patients developed disease progression.

Of the 41 patients who received the planned first cycle of high-dose therapy, 5 developed disease progression before receiving the second high-dose therapy. Four proceeded to receive the second cycle of high-dose as planned, but all developed disease progression after the second ASCT. One patient who elected to receive an allogeneic stem cell transplant also relapsed after that transplant. The other 36 patients, all responded to high-dose melphalan based on CT scan; 18 of these had gallium or FDG PET before the second transplant and 5 continued to have positive gallium scans or FDG PET.

At a median of 64 days (range: 25-105), 41 patients received the second high-dose therapy and ASCT. Twenty-five patients received FTBI-based regimen and 16 received BCNU-based regimen. Seven pa-

Table 1. *Patient Characteristics (n = 46)*

Age at transplant (years)	
Median (range)	37 (17–65)
Sex	
Male	27 (59%)
Female	19 (41%)
Stage at Dx	
I/II	18 (39%)
III	20 (46%)
IV	8 (15%)
"B" Symptoms at Dx	
Yes	24 (52%)
No	22 (48%)
Induction chemotherapy	
ABVD	30 (65%)
MOPP/ABVD, MOPP/ABV	9 (19%)
Stanford V	3 (7%)
Other	4 (9%)
Induction radiotherapy	
Yes	19 (41%)
Reason for tandem transplant	
Primary refractory	28 (61%)
Poor risk recurrent	18 (39%)
Disease status at ASCT	
Relapsed	16 (35%)
Induction failure	30 (65%)
Chemosensitivity	
Chemoresistant	7 (15%)
Chemosensitive	22 (48%)
Not tested	17 (37%)
Salvage chemotherapy	
Yes	29 (63%)
High-dose etoposide + cyclophosphamide	17 (37%)
Extranodal involvement at ASCT	
Yes	17 (37%)
No	29 (63%)
Stage at ASCT	
I/II	20 (43%)
III/IV	20 (44%)
Remission	6 (13%)
"B" Symptoms at ASCT	
Yes	9 (19%)
No	37 (81%)
Involved Radiation Posttransplant	
Yes	7 (15%)

ABVD indicates adriamycin, bleomycin, vinblastine, dacarbazine; MOPP, nitrogen mustard, vincristine, procarbazine, and prednisone; MOPP/ABV, nitrogen mustard, vincristine, procarbazine, prednisone, adriamycin, bleomycin, and vinblastine; ASCT, autologous stem cell transplant.

tients received involved radiotherapy 24-36 Gy to residual bulky mass >5 cm at 4-6 weeks after recovery from second high-dose except 1 who received before the second transplant. For the 5 patients with positive gallium/FDG PET before second SCT, 4 are still alive in remission and 1 died from adenocarcinoma of liver at 1 year after transplant. Two received involved-field radiation to residual bulky mass (neck/media-stimun 1, and minimantle 1) posttransplant.

Hematopoietic Recovery

All patients had achieved hematopoietic recovery post the first and the second high-dose treatment. The median day to reach absolute neutrophil count of 500 and platelet count of 20,000/μL were 10 days (range: 8-14), and 11 days (range: 10-13), respectively, after high-dose melphalan, and 12 days (range: 10-14) and 14 days (range: 10-19), respectively, after the second high-dose therapy. There was no statistically significant difference between the engraftment following the first and the second high-dose treatment.

Survival

With a median follow-up of 5.3 years (range: 1.6-8.1 years), 21 (46%) patients are alive and progression-free at last follow-up. Of the 41 patients who received both cycles of high-dose therapy, 18 are alive and disease free. Eighteen had disease progression at a median of 4 months (range: 1-64) posttransplant and all but 1 died from progressive disease. Five died from nonrelapse mortality.

Using an intent-to-treat analysis for all 46 patients included in the study, the 5-year estimate of OS, progression-free survival (PFS), and freedom from progression (FFP) were 54% (95%CI 40%-69%), 49% (95%CI 34%-63%), and 55% (95% CI 40%-70%), respectively (Figure 1). In an analysis limited to patients (n = 41) who received the planned treatment program according to the protocol, the estimated
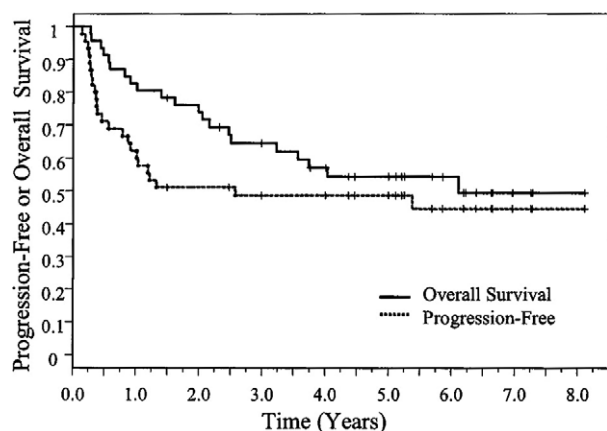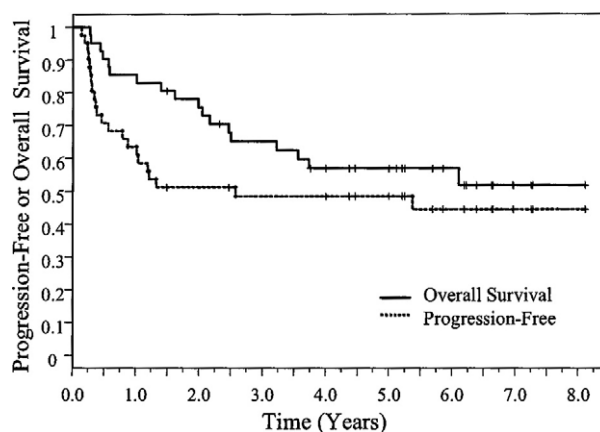

Figure 2. OS and PFS for the 41 patients who underwent transplant as planned.

5-year OS, PFS, and FFP were 57% (95%CI 41%-73%), 49% (95%CI 33%-64%), and 55% (95%CI 39%-71%), respectively (Figure 2). In a univariate analysis, we failed to identify any prognostic factors that predicted for transplant outcomes (Table 2).

Death/Toxicity

There were 2 early deaths resulting from regimen-related toxicities with 100-day mortality of 4%. One patient died from sepsis at day 30 postsecond transplant and the other patient who had received 2500 cGy of mediastinal irradiation before the second high-dose TBI regimen died of interstitial pneumonitis. Three other patients died of nonrelapse causes while in remission because of adenocarcinoma (1), ruptured aneurysm (1), and cardiac event (1). Adenocarcinoma was diagnosed at 7 months posttransplant in a 55-year-old patient with history of documented liver involvement by HL. Another 58-year-old with prior history of hypertension died from a ruptured aortic aneurysm at 6 months posttransplant and a 40-year-old male with prior mediastinal radiation died from cardiac arrest at 2 years posttransplant.

The transplant-related toxicities were similar to historic control patients who received single high-dose therapy [5]. There were no cases of veno-occlusive disease. Secondary malignancies occurred in 3 patients. One patient who relapsed 7 months after tandem transplant was subsequently found to have therapy-induced myelodysplasia (MDS) at 28 months after transplant. He received TBI-based regimen followed by IFRT to minimantle field posttransplant. He underwent matched unrelated donor transplant for both HD and MDS. There were 2 cases of solid tumors. One patient developed endometrial carcinoma 4 years after ASCT and is currently in remission after total abdominal hysterectomy and bilateral salpingo-oophorectomy. One patient who had liver involvement by HL developed adenocarcinoma of the

Figure 1. OS and PFS for the 46 patients who were enrolled in the study as intent to treat.

Table 2. *Univariate* P-*Values for PFS*

Variable [relative to]	Hazard Ratio and 95% CI	P Value
Sex [female]	0.95 (0.62, 1.43)	.7999
Age	1.02 (0.98, 1.06)	.3523
B Symptoms at diagnosis	0.84 (0.54, 1.27)	.4082
B Symptoms at BMT	0.73 (0.48, 1.18)	.1910
TBI vs. BCNU	0.94 (0.63, 1.46)	.7917
Stage at Dx (I/II vs. III vs. IV)	I/II vs. IV 1.36 (0.76, 2.46)	.8580
	III vs. IV 0.58 (0.29, 1.11)	.2313
Extra-nodal disease at Dx	0.83 (0.55, 1.29)	.3938
Extra-nodal disease at relapse	1.17 (0.64, 2.20)	.6062
Number of prior chemotherapy regimens	1.41 (0.72, 2.68)	.3146
Chemosensitivity [resistant]	1.04 (0.55, 1.76)	.8872
Radiation at induction [NO]	0.68 (0.43, 1.03)	.0707
Primary refractory vs. relapsed	1.36 (0.89, 2.19)	.1653

CI indicates confidence interval; TBI, total body irridiation; BMT, blood and marrow transplant.

liver at 7 months after transplant. He received TBI based high-dose regimen.

DISCUSSION

The experiences from City of Hope [5] and Southwest Oncology Group [7] have demonstrated that augmented BCV (BCNU 450 mg/m^2, cyclophosphamide 100 mg/kg, and etoposide (VP-16) 60 mg/kg) or FTBI (1200 cGy) + VP-16 (60 mg/kg) + cyclophosphamide (100 mg/kg) are highly effective preparative regimens for patients with advanced HL undergoing ASCT. Approximately 40% to 50% of unselected patients can achieve durable remission after transplant with very low transplant-related mortality (TRM). Progressive disease after transplant accounts for most of the treatment failures, in particular, for patients with poor risk features before ASCT. Multiple transplant studies have identified adverse prognostic factors that predict transplant outcome such as early relapse after CR1, B symptoms at relapse, extra-nodal involvement of lung or bone marrow at relapse, multiple relapses, and more than minimal disease at the time of transplantation [4-8]. The estimated probability of long-term PFS after transplant for these patients was approximately 25% to 35%; therefore, an alternative strategy is needed.

One possible approach to decrease the relapse rates is to further intensify the conditioning regimens, either by increasing the dose of the individual drugs or to add a fourth agent. Wheeler et al [10] performed a phase I study using escalating doses of the drugs in the CBV combination. They concluded that the maximum cumulative doses of Cytoxan, BCNU, and VP-16 that can be tolerated were 7200 mg/m^2 of cyclophosphamide, 450 mg/m^2 of carmustine, and 2000 mg/m^2 of etoposide. Further dose intensification was limited by toxicities and had not been shown to improve efficacy. Reece et al [11] added cisplatin as a fourth agent to their intensified high-dose CBV

regimen (VP-16 2400 mg/m^2, BCNU 500 mg/m^2, Cyclophosphamide 7200 mg/m^2, and cisplatin 150 mg/m^2). Although the toxicities remained acceptable, there was no evidence that this regimen was more effective than CBV alone. Different dose-intense regimens had been tested but none of them has shown an advantage over the commonly used regimens such as CBV or BEAM (carmustine, etoposide, cytarabine, and melphalan). Minimal disease state before transplant has been shown to be an important prognostic factor for transplant outcomes [6,9]. However, repeat cycles of conventional dose salvage chemotherapy may increase drug resistance and increase transplant related toxicity. Melphalan is widely used as a component of conventional salvage chemotherapy (MVP or mini-BEAM) and as a preparatory regimen in stem cell transplant (BEAM or BEM). Russell et al [12] treated 20 HL patients with single high-dose melphalan (140-200 mg/m^2) and stem cell support. All 20 patients had relapsed/refractory HL and were heavily pretreated by multiple chemotherapeutic regimens. The overall response rate was 86%, with complete remission and partial remission rate of 33% and 56%, respectively. Twenty percent of patients achieved a durable complete remission and the regimen was well tolerated.

Given the above background and the unfavorable outcomes of patients with poor risk disease, we conducted this pilot study to evaluate the safety and efficacy of a tandem ASCT program for patients with primary progressive or poor risk recurrent HL. With a median follow-up of 5 years, the 5-year Kaplan-Meier estimate of OS and FFP were 57% and 55%, respectively. The results reported in our study are promising and compare favorably to historic controls where the EFS were approximately 25% to 35% in these unfavorable patients. Because most relapses after transplant occurred within the first 2 years of ASCT, our median follow-up of 5 years suggests that tandem transplant may induce long-term disease control and

possibly "cure" in some patients despite the presence of poor risk factors. Although many reported transplant series had excluded patients who failed stem cell collection or progressed before transplant, we included all enrolled patients in our analysis to avoid selection bias. In this study, all patients who progressed after cycle 1 of high-dose melphalan developed disease progression shortly after cycle II high-dose therapy. These subgroups of patients with highly chemoresistant disease do not benefit from high-dose therapy and ASCT, and alternative treatment strategy will need to be developed for these patients.

The experiences of tandem high-dose therapy and ASCT have been previously reported by other investigators using different approaches. Ahmed et al [13] reported results of tandem ASCT in 45 patients with refractory HL. With a median follow-up of 4 years, the median survival was 45 months. However, it is worth noting that only 55% of the patients received both planned cycles. Patients were ineligible for second cycle because of toxicity or disease progression. In our present trial, 83% of patients completed the planned 2 cycles of high-dose therapy and none of the patients were excluded from the second high dose therapy because of transplant related toxicity. In another study reported by Brice et al [14,15], 72 patients with very unfavorable HL received 2 cycles of high-dose therapy with stem cell rescue. The first cycle consisted of CBV + mitoxantrone (30 mg/m^2) and the second cycle consisted of cytarabine (6 gm/m^2), melphalan (140 mg/m^2) and TBI (12 Gy) or busulfan (12 mg/m^2). Seventy-two percent of patients received both transplants with a response rate of 91%. There were 2 toxic deaths from veno-occlusion disease and acute respiratory distress syndrome.

The Intergruppo Italiano Linfomi used a high-dose sequential chemotherapy approach in 102 patients with refractory/relapsed HL [16]. At a median follow-up of 5 years, the 5-year event-free survival and OS for all patients were 53% and 64%, respectively. A similar approach was conducted by the German HL study group for 102 patients with relapsed and refractory HL. With a median follow-up of 30 months, freedom from second failure and OS for patients with early relapse were 59% and 78%, respectively [17].

The results of these studies suggest that patients with primary refractory HL or poor-risk relapsed HL may benefit from a more intensive approach such as high-dose sequential therapy or tandem ASCT with stem cell support with low toxicities. Nevertheless, the favorable results from our study and similar studies could result from patient selection. In our study, we selected patients with primary progressive HL and patients with recurrent disease associated with 1 of the following poor risk factors: extra-nodal disease or symptoms at relapse or duration of initial response <12 months. Although, they are often reported as adverse prognostic factors, most of these studies include a heterogeneous patient population and small number of patients may complicate the interpretation. A large-scale phase II study followed by a phase III randomized study will be required to confirm the results.

Taken together, our data suggest that for patients with primary refractory or poor risk recurrent HL, a tandem AHCT is effective and well tolerated without excessive toxicities. The results compare favorably with the historic control of conventional single transplant. To confirm the encouraging results from this pilot study, the Southwest Oncology Group is currently testing this approach in the cooperative group setting.

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