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Phase II Trial of Tandem High-Dose Chemotherapy with Autologous Stem Cell Transplantation Followed by Reduced-Intensity Allogeneic Stem Cell Transplantation for Patients with High-Risk Lymphoma

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Many patients with lymphoma relapse after autologous stem cell transplantation (AutoSCT). These patients are often considered for allogeneic stem cell transplantation (AlloSCT) if remission can be achieved. If a tandem approach was organized, some cases of relapse might be prevented. We conducted a phase II trial of tandem AutoSCT followed by reduced-intensity conditioning (RIC) AlloSCT for patients with high-risk lymphoma. High-dose chemotherapy was given with busulfan, cyclophosphamide, and etoposide. AlloSCT was composed of RIC with busulfan/fludarabine and tacrolimus, sirolimus, and methotrexate as graft-versus-host disease (GVHD) prophylaxis. Donors were fully matched related or unrelated donors. AlloSCT was performed any time between 40 days and 6 months after AutoSCT. Forty-two patients were enrolled, and all patients underwent AutoSCT. RIC AlloSCT was performed in 29 patients. In the 29 patients who underwent tandem transplant, median time from AutoSCT to AlloSCT was 96 days (range, 48 to 169). The 6-month cumulative incidence of grades II to IV acute GVHD was 13.8% (90% confidence interval [CI], 5.3% to 26.3%). Cumulative incidence of chronic GVHD at 1 year was 37.9% (90% CI, 23.1% to 52.7%). Nonrelapse mortality at 2 years after AlloSCT was 11.1% (90% CI, 3.5% to 23.6%). At a median follow-up of 30 months (range, 17.1 to 51.5) for the entire group, the 2-year progression-free survival rate was 64% (90% CI, 50% to 75%) and the 2-year overall survival rate was 69% (90% CI, 43% to 85%). For the 29 patients who underwent tandem SCT, the 2-year progression-free survival rate was 72% (90% CI, 55% to 83%) and the 2-year OS rate was 89% (90% CI, 74% to 96%). Tandem AutoSCT–RIC AlloSCT appears to be safe and effective in patients with high-risk lymphoma. Prospective trials using such an approach in specific lymphoma subtypes are warranted.

INTRODUCTION

High-dose chemotherapy with autologous hematopoietic stem cell transplantation (AutoSCT) is a standard component of care for many patients with relapsed/refractory Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). Although many patients can achieve durable remissions with AutoSCT, disease relapse remains the principle cause of failure. Many well-defined risk factors are predictive of relapse after AutoSCT, including histology (eg, mantle cell lymphoma [1,2] or peripheral T cell lymphoma [3]), primary refractory disease [4], and early relapse [5].

Allogeneic hematopoietic SCT (AlloSCT) is considered in a subgroup of patients with a chemosensitive relapse after AutoSCT with the goal of achieving a durable remission through an immunologically driven graft-versus-lymphoma effect [6-9]. Increasingly, reduced-intensity conditioning (RIC) approaches have been used for such patients given the

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overall morbidity and mortality experienced with traditional myeloablative regimens in patients with lymphoma, particularly in patients who have undergone a prior AutoSCT. Yet for patients with aggressive lymphoma, the use of RIC regimens might result in early disease relapse before the emergence of an effective graft-versus-lymphoma effect [10,11]. Tandem AutoSCT–RIC AlloSCT could combine the cytotoxicity of AutoSCT with an allogeneic graft-versus-lymphoma effect while decreasing the morbidity and mortality associated with conventional myeloablative AlloSCT. We thus conducted a phase II tandem AutoSCT–RIC AlloSCT trial for patients with high-risk lymphoma.

METHODS

This study was approved by the Institutional Review Board at the Dana-Farber Harvard Cancer Center and conducted at Dana-Farber Brigham & Women's Cancer Center and Massachusetts General Hospital Cancer Center. Informed consent was obtained from all patients. This trial was registered at ClinicalTrials.gov (NCT01181271).

Participants were enrolled between October 2010 and June 2013. Patients were ≥18 years of age and had an Eastern Cooperative Oncology Group performance status score of 0 to 2, a left ventricular ejection fraction ≥ 45%, adequate pulmonary function tests (forced expiratory volume in 1 second, forced vital capacity, and diffusing capacity of the lungs for carbon monoxide all ≥50% of predicted), total serum bilirubin < 2.0 mg/dL, transaminases < 3 times the upper limit of normal, and serum creatinine < 2.0 mg/dL. Disease eligibility was as follows: (1) diffuse large B cell lymphoma (DLBCL) or transformed low-grade NHL with residual disease after at least 6 cycles of anthracycline-based chemotherapy, progressive disease after at least 2 cycles of anthracycline-based chemotherapy, or disease relapse within 12 months after completion of anthracycline-based chemotherapy; (2) indolent B cell NHL refractory to most recent therapy or relapsed within 12 months after most recent therapy; (3) any peripheral T cell NHL (excluding cutaneous T cell lymphoma); (4) mantle cell lymphoma; (5) "double-expressing" DLBCL characterized by concurrent over-expression of BCL-2 and MYC proteins; and (6) HL refractory to at least 1 standard salvage chemotherapy regimen.

The trial did not require that a suitable donor be identified before enrollment. To assess disease response before AutoSCT and AlloSCT, positron emission tomography (PET) was preferred, but standard computed tomography images were allowed.

AutoSCT

Autologous hematopoietic stem cell mobilization was carried out per physician discretion using methods such as chemotherapy with granulocyte colony-stimulating factor (G-CSF), G-CSF alone, and G-CSF with plerixafor. Leukapheresis was performed per institutional standard, and a minimum of 2×10^6 $CD34^+$ cells/kg was required to enroll. Myeloablative conditioning consisted of busulfan (.8 mg/kg i.v. every 6 hours × 14 doses for a total of 11.2 mg/kg i.v. given on days −8, −7, −6, and −5), cyclophosphamide (60 mg/kg/day i.v. on days −3 and −2), and etoposide (30 mg/kg i.v. on day −4) (BuCyE). Busulfan pharmacokinetic levels were not measured, and no dose adjustments were made. All patients were hospitalized from admission until neutrophil engraftment. G-CSF was started on day +1 and given daily until engraftment. Infectious prophylaxis was per institutional norm but included agents against bacteria when neutropenic and varicella-zoster and *Pneumocystis jirovecii* upon discharge.

RIC AlloSCT

Once patients recovered, they were allowed to proceed to RIC AlloSCT 40 to 180 days after AutoSCT. All eligibility tests and disease restaging were repeated, and participants with progressive disease were taken off trial. RIC consisted of busulfan 3.2 mg/kg i.v. (.8 mg/kg i.v. daily × 4 days) and fludarabine 120 mg/m^2 (30 mg/m^2 i.v. daily × 4 days). Donors were 8/8-matched (HLA-A, -B, -C, and -DRB1 by allele level typing) related or unrelated donors. Peripheral blood stem cell products were mobilized with G-CSF and collected by leukapheresis.

Graft-versus-host disease (GVHD) prophylaxis was composed of tacrolimus, sirolimus, and low-dose methotrexate (5 mg/m^2 i.v. given on days +1, +3, and +6). Tacrolimus and sirolimus were both started orally on day −3, and therapeutic trough levels were recommended until day +90; in the absence of active GVHD, they were tapered off by day +180. Prophylaxis against varicella-zoster virus and *P. jirovecii* was continued through at least 1 year after AlloSCT. Cytomegalovirus was monitored routinely after AlloSCT, and significant reactivation was treated pre-emptively.

Statistical Considerations

The primary objective of this study was to assess engraftment after this tandem AutoSCT–RIC AlloSCT approach. The tandem transplant approach was considered feasible if at least 65% of the eligible patients who completed AutoSCT were able to proceed to the allogeneic transplant. It was envisioned that 40 patients would enter the study and undergo AutoSCT. Of these 40, we predicted that 15 would not be eligible to proceed to AlloSCT for various reasons that would not apply toward evaluation of feasibility, including patient choice, lack of a suitable donor, or disease progression. Of these 25 patients, if at least 14 patients proceeded to undergo RIC AlloSCT, this tandem transplant design would be considered feasible.

The primary endpoint of the study was donor stem cell engraftment as measured by peripheral blood all cell chimerism before measurement at day +100 after RIC AlloSCT. Secondary endpoints included incidence of nonrelapse mortality (NRM) at 100 days and 1-year after AlloSCT, 2-year progression-free survival (PFS), 2-year overall survival (OS), cumulative incidence of grades II to IV and III to IV acute GVHD by day +200, and cumulative incidence of chronic GVHD requiring systemic immunosuppression. An early stopping rule was written in the case of excessive NRM where if 3 or more cases of NRM were observed in the first 100 days after RIC AlloSCT in the first 10 patients, the study would be terminated for safety reasons.

RESULTS

AutoSCT

Forty-two 42 patients were enrolled and underwent AutoSCT. Twenty-nine patients proceeded to RIC AlloSCT. Clinical and transplant characteristics are presented in Table 1. Median patient age was 56.5 (range, 22 to 69), and 62% of patients were men. Forty-one patients had various

Table 1
Clinical and Transplant Characteristics of all Patients (n = 42) and Patients Undergoing Tandem Transplant (n = 29)

	All Patients (n = 42)	Patients Undergoing Tandem (n = 29)
Gender (male/female)	26/16	16/13
Median age (range) in years	56.5 (22-69)	56 (22-68)
Diagnosis		
Rel/Ref DLBCL	10	5
Rel/Ref indolent NHL	6	5
Double-Expressing NHL	9	7
Transformed B-cell NHL	8	6
T-cell NHL	4	2
Mantle cell NHL	3	2
Rel/Ref Hodgkin	1	1
Heavy chain disease	1	1
Prior lines of chemotherapy, median (range)	2 (1-6)	3 (1-6)
Disease status prior to ASCT		
PR	21	15
CR	21	14
High-dose chemotherapy for ASCT	BuCyE	BuCyE
Reason for not doing AlloSCT		
Disease progression	6	
Patient choice	4	
No suitable donor	2	
Therapy-related AML	1	
Median days interval between ASCT − RIC AlloSCT (range)		96 d (48-169)
Disease status prior to AlloSCT		
PR		6
CR		23
RIC for AlloSCT		Bu/Flu
GVHD prophylaxis		Tac/Siro/MTX
Donor type		
Matched related donor		16
Matched unrelated donor		13
Median follow-up, months (range)	30.0 (17.1-51.5)	29.5 (17.1-48.0)

Rel/Ref indicates relapsed/refractory; ASCT, autologous stem cell transplant; BEAM, BCNU, etoposide, cytarabine, melphalan; AML, acute myeloid leukemia; RIC, reduced intensity conditioning; Bu/Flu, busulfan/fludarabine; Tac, tacrolimus; Siro, sirolimus; MTX, methotrexate.