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Reduced-Intensity Conditioning with Fludarabine, Cyclophosphamide, and High-Dose Rituximab for Allogeneic Hematopoietic Cell Transplantation for Follicular Lymphoma: A Phase Two Multicenter Trial from the Blood and Marrow Transplant Clinical Trials Network

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A B S T R A C T

Allogeneic (allo) hematopoietic cell transplantation (HCT) can induce long-term remissions in chemosensitive relapsed follicular lymphoma (FL). The Blood and Marrow Transplant Clinical Trials Network conducted a multicenter phase 2 trial to examine the efficacy of alloHCT using reduced-intensity conditioning with rituximab (RTX) in multiply relapsed, chemosensitive FL. The primary endpoint was 2-year progression-free survival (PFS). The conditioning regimen consisted of fludarabine, cyclophosphamide, and high-dose RTX (FCR), in which 3 of the 4 doses of RTX were administered at a dose of 1 gm/m^2. Graft-versus-host disease (GVHD) prophylaxis was with tacrolimus and methotrexate. Sixty-five patients were enrolled and 62 were evaluable. Median age was 55 years (range, 29 to 74). This group was heavily pretreated: 77% had received $\geq$ 3 prior regimens, 32% had received $\geq$ 5 prior regimens, and 11% had received prior autologous HCT. Donors were HLA-matched siblings (n = 33) or HLA-matched unrelated adults (n = 29). No graft failures occurred. The overall response rate after HCT was 94% with 90% in complete remission (CR), including 24 patients not in CR before alloHCT. With a median follow-up of 47 months (range, 30 to 73), 3-year PFS and overall survival rates were 71% (95% confidence interval, 58% to 81%) and 82% (95% confidence interval, 70% to 90%), respectively. Three-year cumulative incidences of relapse/progression and nonrelapse mortality were 13% and 16%, respectively. Two-year cumulative incidences of grades 2 to 4 and grades 3 or 4 acute GVHD were 27% and 10%, respectively, and extensive chronic GVHD incidence was 55%. Serum RTX concentrations peaked at day +28 and remained detectable as late as 1 year in 59% of patients with available data. In conclusion, alloHCT with FCR conditioning confers high CR rates, a low incidence of relapse/progression, and excellent survival probabilities in heavily pretreated FL patients.

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INTRODUCTION

Follicular lymphoma (FL) affects approximately 15,000 patients per year in the United States. The median age at diagnosis is 60 years, with incidence increasing with age [1].

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When treatment is indicated, rituximab (RTX)-based regimens are the standard of care and many achieve remission [2-4]. The disease course is typically indolent and the median survival is 14 to 15 years from diagnosis. However, FL is incurable with standard therapy. Patients with poor-risk features, such as short remission duration after initial chemotherapy (<2 to 3 years), have a dramatically shorter expected survival [4]. High-dose chemotherapy with autologous (auto) hematopoietic stem cell transplantation (HCT) can confer long-term remissions, especially if a patient is not heavily pretreated before HCT [5-7]. However, allogeneic (allo) HCT is the only known curative modality for FL.

Earlier studies offering alloHCT with a myeloablative-conditioning regimen demonstrated a significantly lower risk of relapse compared with autologous HCT, but high treatment-related mortality (TRM) mitigated the benefit of this approach [8,9]. AlloHCT using a reduced-intensity conditioning (RIC) regimen became widely utilized in FL patients. RIC affords a moderate degree of cytoreduction but also relies on potent immune-mediated graft-versus-lymphoma effects to eradicate minimal residual disease. Results from several retrospective and prospective RIC alloHCT trials have yielded event-free survivals ranging from 43% to 75% and all demonstrate plateaus in relapse/progression [5,6,10-15].

Previously, the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) conducted a prospective "biologic assignment" trial in which chemosensitive FL patients beyond first response underwent either autoHCT or RIC alloHCT [16]. Patients with an available matched sibling donor were allocated to alloHCT and those without were allocated to autoHCT, followed by maintenance therapy with RTX. Unfortunately, the trial closed prematurely because of slow accrual, with only 30 patients enrolled; 22 patients underwent autoHCT and 8 patients underwent alloHCT. With a median follow-up of 36 months, the progression-free survival (PFS) and overall survival (OS) for the autoHCT recipients were 63% and 73%, respectively, and 86% versus 100% in the alloHCT group. Although this study's sample size was small, results were encouraging, as only 3 relapses were seen in the autoHCT arm versus 1 relapse in the alloHCT arm. The preparative regimen for alloHCT in that trial was modeled after the fludarabine, cyclophosphamide, and RTX (FCR) conditioning regimen introduced by investigators at the MD Anderson Cancer Center. Using this regimen, the most encouraging results to date were reported in this single institution trial in 2012. The 11-year event-free and OS rates in 47 patients were 72% and 78%, respectively, with only 3 relapses reported [17]. Based on this experience, the BMT CTN embarked on a prospective phase 2 trial in the multicenter setting utilizing the same FCR regimen.

METHODS

Patients

Individuals 75 years of age and younger with histologically confirmed (grade I or II REAL or World Health Organization [WHO] grades 1, 2, or 3a) FL in first or subsequent partial remission (PR) or second or subsequent complete remission (CR) were eligible for enrollment [18-20]. If not in CR, response criteria compared to the most recent regimen required either (1) *stable disease* if all lymph node masses were ≤ 3 cm and unchanged (or smaller); or (2) *chemotherapy sensitivity*, defined as reduction of all lymph node masses to ≤ 3 cm in axial diameter or, if larger than 3 cm, a minimum of 50% reduction in estimated nodal diameters. Patients with documented evidence of transformation were excluded. There was no restriction on number of lines of prior therapy except that patients could not have received prior alloHCT. Prior autoHCT was permitted.

Other eligibility criteria included *adequate organ function*, defined as a cardiac ejection fraction of 45% or greater; total bilirubin less than twice the upper limit of normal; aspartate and alanine serum transaminases less than thrice upper limit of normal; a creatinine clearance of at least 40 mL/minute; and diffusion capacity of carbon monoxide, forced expiratory volume in 1 minute, and forced vital capacity all more than 50% of normal after adjustment for hemoglobin. Patients were seronegative for human immunodeficiency virus and could not have evidence of active hepatitis B or hepatitis C by serology and/or viremia. Patients with *uncontrolled infections*, defined as progressing on appropriate antimicrobial therapy, were ineligible. Patients with prior malignancy, except resected basal cell carcinoma or treated cervical carcinoma in situ, or those women pregnant or breast-feeding were excluded.

Donor eligibility included either (1) fully matched (6/6 allele) related donors based on high-resolution typing at HLA-DRβ1 and intermediate-resolution typing at HLA-A and -B typing; or (2) fully matched (8/8 allele) unrelated donors based on high-resolution typing at HLA-A, -B, -C, and -DRβ1. Donors met medical eligibility of the transplantation center (related) or National Marrow Donor Program. Related donors were excluded if they had evidence of infection with human immunodeficiency virus, hepatitis B virus, hepatitis C virus, or had prior malignancy other than treated basal cell or carcinoma in situ of the cervix. Identical twins were not permitted.

Study Design and Treatment

Design

This multicenter, single-arm, phase 2 trial was designed to confirm the efficacy of a previously published RIC regimen followed by alloHCT [17]. The protocol and informed consents were approved by the Protocol Review Committee and Data and Safety Monitoring Board, each independently appointed by the National Heart Lung and Blood Institute and the institutional review boards of all participating institutions. The study was led by the National Heart Lung and Blood Institute Blood and Marrow Transplant Clinical Trials Network in collaboration with the Eastern Cooperative Oncology Group and the Southwest Oncology Group. All patients signed informed consents in accordance with the Declaration of Helsinki. The study is registered at http://www.clinicaltrials.gov as NCT00912223.

Conditioning

All patients received pretransplantation conditioning with RTX (Genentech, San Francisco, CA) at 375 mg/m^2 on day −13 and at 1000 mg/m^2 on day −6, day +1, and day +8. Patients received fludarabine i.v. at 30 mg/m^2/day and cyclophosphamide i.v. 750 mg/m^2/day on day −5, −4, and −3. Peripheral blood progenitor cells were infused on day 0. All donor cells were mobilized with granulocyte colony−stimulating factor per institutional or National Marrow Donor Program guidelines to obtain a minimum peripheral blood progenitor cells graft of 2.0 × 10^6 CD34$^+$ cells/kg with a goal collection of at least 5.0 × 10^6 CD34$^+$ cells/kg. If less than 1.0 × 10^6 CD34+ cells/kg were collected after 3 leukapheresis, the patient was managed at the discretion of the treating physician.

Graft-versus-host disease prophylaxis

Oral tacrolimus (target trough, 5 to 15 ng/mL) and i.v. methotrexate 5 mg/m^2/day on days +1, +3, and +6 were administered for all patients receiving a related donor transplant. Unrelated donor (URD) recipients received an additional dose of methotrexate of 5 mg/m^2 on day +11. No patients received antithymocyte globulin. Tacrolimus taper was to start at day +180 in the absence of graft-versus-host disease (GVHD) and the rate of taper was determined by the treating physician.

Supportive care

All patients received antimicrobial prophylaxis and blood product support in concordance with the BMT CTN Manual of Procedures. Use of hematopoietic growth factors after HCT and immunizations were administered per institutional guidelines.

Follow-up and Disease Response

Disease response was assessed based on standard criteria [20]. Within 4 weeks before the initiation of the conditioning regimen, all patients had disease staging including a bone marrow biopsy and aspirate, quantitative PCR for assessment of t(14;18) in the peripheral blood, and imaging. Imaging included computed tomography of the chest, abdomen, and pelvis and a computed tomography of the neck if prior evidence of neck disease. ^{18}F-FDG positron emission tomography was recommended only if patients had known FDG-avid disease previously. All patients were restaged at 3 months, 12 months, and 24 months after HCT. Restaging included the same studies as before HCT with the exception that bone marrow biopsy was only required if patients had prior marrow involvement and peripheral blood quantitative PCR was only necessary in those patients with documented prior t(14;18).