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Allotransplantation for Patients Age ≥40 Years with Non-Hodgkin Lymphoma: Encouraging Progression-Free Survival

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A B S T R A C T

Non-Hodgkin lymphoma (NHL) disproportionately affects older patients, who do not often undergo allogeneic hematopoietic cell transplantation (HCT). We analyzed Center for International Blood and Marrow Transplant Research data on 1248 patients age ≥40 years receiving reduced-intensity conditioning (RIC) or nonmyeloablative (NMA) conditioning HCT for aggressive (n = 668) or indolent (n = 580) NHL. Aggressive lymphoma was more frequent in the oldest cohort 49% for age 40 to 54 versus 57% for age 55 to 64 versus 67% for age ≥65; $P = .0008$). Fewer patients aged ≥65 had previous autografting (26% versus 24% versus 9%; $P = .002$). Rates of relapse, acute and chronic GVHD, and nonrelapse mortality (NRM) at 1 year post-HCT were similar in the 3 age cohorts (22% [95% confidence interval (CI), 19% to 26%] for age 40 to 54, 27% [95% CI, 23% to 31%] for age 55 to 64, and 34% [95% CI, 24% to 44%] for age ≥65. Progression-free survival (PFS) and overall survival (OS) at 3 years was slightly lower in the older cohorts (OS: 54% [95% CI, 50% to 58%] for age 40 to 54; 40% [95% CI, 36% to 44%] for age 55 to 64, and 39% [95% CI, 28% to 50%] for age ≥65; $P < .0001$). Multivariate analysis revealed no significant effect of age on the incidence of acute or chronic GVHD or relapse. Age ≥55 years, Karnofsky Performance Status <80, and HLA mismatch adversely affected NRM, PFS, and OS. Disease status at HCT, but not histological subtype, was associated with worse NRM, relapse, PFS, and OS. Even for patients age ≥55 years, OS still approached 40% at 3 years, suggesting that HCT affects long-term remission and remains underused in qualified older patients with NHL.

INTRODUCTION

The use of allogeneic hematopoietic cell transplantation (HCT) to treat non-Hodgkin lymphoma (NHL) is increasing in patients with high-risk and relapsed/refractory disease [1]. Considering that more than one-half of such NHL cases are diagnosed in individuals age >65 years, this represents a growing population of patients for whom allogeneic HCT may provide long-term disease-free survival and improve outcomes [2]. It has been postulated that conventional myeloablative conditioning before HCT is not feasible for the vast majority of older patients owing to limited physiological resilience and accompanying comorbidities. Nonmyeloablative (NMA) conditioning and reduced-intensity conditioning (RIC) strategies have made HCT available to less-fit individuals with relapsed or poor-risk hematologic malignancies amenable to allogeneic HCT. Recent studies have reported acceptable nonrelapse mortality (NRM) rates of 10% to 20% and 2- to 3-year progression-free survival rates of 25% to 75% depending on NHL subtype [3-7]; however, data specific to older patients with NHL remain limited.

We recently examined the influence of age on outcomes in older patients with acute myelogenous leukemia (AML) or myelodysplastic syndrome (MDS) in first complete remission (CR) and found similar outcomes as seen in younger patients when given an RIC HCT regimen [8]. In the present study, we examined the same question in older patients undergoing RIC or NMA allogeneic HCT for NHL of aggressive or indolent histology, with the aim of defining post-HCT outcomes in older patients and evaluating patient, disease, and treatment characteristics influencing these outcomes.

PATIENTS AND METHODS

Data for this analysis were submitted to the Center for International Blood and Transplant Research (CIBMTR), a voluntary working group of more than 450 transplant centers worldwide who contribute data on consecutive allogeneic HCTs to a statistical center housed at the Medical College of Wisconsin in Milwaukee and the National Marrow Donor Program in Minneapolis. Patients are followed longitudinally with yearly follow-up. Computerized checks for errors and onsite audits of participating centers ensure data quality. Physician review of data and additional requested information from reporting centers are included. Observational studies conducted by the CIBMTR are performed with a waiver of informed consent and in compliance with Health Insurance Portability and Accountability Act (HIPAA) regulations as determined by the Institutional Review Board and the Privacy Officer of the Medical College of Wisconsin.

Patient Selection

The study group included patients age ≥40 years undergoing RIC or NMA HCT between 2001 and 2007 for aggressive NHL (ie, diffuse large B cell [n = 202], mantle cell [n = 279], immunoblastic/anaplastic B/T cell [n = 52], peripheral T cell [n = 60], peripheral T cell lymphoma not otherwise specified [n = 25], Burkitt lymphoma [n = 4], other [n = 46]) and indolent NHL (ie, small lymphocytic lymphoma [SLL]/chronic lymphocytic leukemia [CLL] [n = 156], follicular [n = 387], marginal zone [n = 13], and other [n = 24]). Patients were classified as being in first (n = 87) or second (n = 231) complete remission (CR), in first (n = 478) or second (n = 304) partial remission (PR), or with resistant disease (RD; n = 304) as known before HCT. Grafts were from a related donor or an unrelated donor (URD); cord blood grafts were not studied. Patients who underwent previous autologous HCT were included.

A total of 1248 cases were identified, including 668 patients with aggressive NHL and 580 patients with indolent NHL treated at 165 centers. There were 1119 patients with B cell histology and 106 patients with T cell histology; 3 patients were not classifiable. Patients ranged in age from 40 to 75 years and were divided into 3 age cohorts for analysis: 40 to 54 years (n = 614); 55 to 64 years (n = 552), and ≥65 years (n = 82). Previously established criteria for donor–recipient HLA matching were used to define well-matched, partially matched, and mismatched categories [9]. Preparative regimens were classified as either RIC or NMA. RIC regimens included ≤500 cGy total body irradiation as a single fraction or ≤800 cGy if fractionated, ≤9 mg/kg busulfan oral (or i.v. equivalent), <140 mg/m2 melphalan, <10 mg/kg thiotepa, and BEAM (carmustine, etoposide, cytarabine, and melphalan) [10,11]. Other regimens were classified as NMA when hematopoietic recovery without transplantation within 28 days could be reasonably expected [12]. T cell depletion accomplished via ex vivo or in vivo methods was included.

Study Endpoints and Definitions

Primary outcomes were overall survival (OS) and progression-free survival (PFS), defined as survival from allogeneic HCT without death and without disease progression or relapse, respectively. NRM was defined as any death occurring in the first 28 days post-transplantation or any death after day +28 without documented NHL progression or relapse. All data were censored at the date of last reported follow-up. Secondary endpoints included neutrophil recovery, defined as the time to an absolute neutrophil count of ≥500 cells/μL sustained for 3 consecutive days, and the cumulative incidence of acute (grade II-IV) and chronic graft-versus-host disease (GVHD) as defined by consensus criteria [13,14].

Statistical Analysis

Patient-, disease-, and transplantation-related variables were compared in the 3 age cohorts using the chi-square test for categorical variables and the Kruskal-Wallis test for continuous variables. Univariate probabilities of PFS and OS were calculated using the Kaplan-Meier estimator, with variance estimated using Greenwood's formula. Probabilities of neutrophil recovery, acute and chronic GVHD, NRM, and relapse were calculated using cumulative incidence curves to accommodate competing risks. The 95% confidence intervals (CIs) for all probabilities and *P* values of pairwise comparisons were derived from pointwise estimates and calculated using standard techniques.