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Outcomes of autologous or allogeneic stem cell transplantation for non-Hodgkin lymphoma

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Transplant outcomes of autologous or allogeneic stem cell transplantation (SCT) have not been elucidated as a single cohort in non-Hodgkin lymphoma (NHL). We analyzed the outcomes of 270 adult recipients receiving autologous (auto) SCT (n = 198) or allogeneic (allo) SCT (n = 72) for NHL between the years 2000 and 2010. Five-year overall survival rates for B and T cell NHL were 58% and 50%, respectively (allo-SCT 51% vs. 54% for B and T-cell NHL, and auto-SCT 60% vs. 47% for B and T cell lymphoma, respectively). In multivariate analysis, the number of chemotherapy regimens and disease status pre-SCT were independently associated with long-term outcome after SCT (for both auto- and allo-SCT). We conclude that the type of transplantation offered to patients, based on patient selection and disease-related factors, can achieve long-term survival, highlighting the importance of further improvement in disease control and reducing procedure-related mortality. The role of transplantation needs to be reevaluated in the era of targeted therapy. © **2014 ISEH - Society for Hematology and Stem Cells. Published by Elsevier Inc.**

Stem cell transplantation is frequently considered for eligible patients with non-Hodgkin lymphoma (NHL) [1–6]. Autologous-SCT (auto) is recommended for patients with either relapsed NHL or in first remission as consolidative therapy. Given the high rate of relapse seen even after chemotherapy and auto-SCT, and the potential benefit of a graft-versus-lymphoma (GVL) effect after allogeneic-SCT (allo) patients with NHL are frequently considered for allo-SCT. The outcomes for these patients in large prospective studies are lacking, and current recommendations and timing of selection of auto- or allo-SCT are influenced by a variety of factors, including patient- or disease-related factors, physician preference, and intuitional practices [7–10].

Registry data from the European Society for Blood and Marrow Transplantation (EBMT) and the Center for International Blood and Marrow Transplant Research (CIBMTR) show no plateau in the relapse rates after autografting [11–13]. Furthermore, the risk of second malignancies after auto-HCT is not insignificant, ranging from 5%–15% in several studies. On the other hand, clinical evidence of a GVL effect after allo-SCT is suggested by a plateau in relapse risk that is reached 2–5 years following allo-SCT, indicating that a substantial proportion of patients with lymphoma derive long-term disease control from transplantation [10,12,14].

The only prospective comparison being conducted of auto- and allo-SCT for relapsed NHL (low-grade histology only) closed early as a result of poor accrual [15]. Moreover, it would be impossible to perform comparative studies because of varied disease courses among vast and heterogeneous NHL histologies. The comparisons based on retrospective analyses of registry data have shown a lower relapse rate and a longer progression-free survival after allo-SCT than after auto-SCT [14–17]. The high nonrelapse mortality (NRM) rate associated with myeloablative (MST) allo-SCT, however, offsets any potential survival benefits [12,14,18,19]. Reduced-intensity conditioning (RIC) and nonmyeloablative conditioning (NST) regimens are being used increasingly in patients with NHL [5,6,20]. These lower-intensity conditioning regimens (RIC or NST) reportedly have lower NRM and can be used in older patients with comorbidities. Lower-intensity

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regimens for allo-SCT use lower doses of conditioning chemotherapy and radiation and rely on an immune-mediated GVL effect for disease control [21,22]. In the era of emerging novel therapies, the actual timing, optimal conditioning regimens, and long-term effects of the type of stem cell transplantation are unclear.

The primary objective of the present analysis was to define outcomes after SCT in patients with NHL and to correlate disease and treatment-related variables with outcomes in the rituximab era. We clarify that this analysis does not attempt to compare directly the outcomes of subjects with NHL who received auto- or allo-SCT.

Methods

Two-hundred-seventy consecutive patients older than age 18 years with NHL receiving SCT between January 2000 and December 2010 at Vanderbilt University Medical Center adult transplant program, were included in this study (Table 1). All patients with B cell NHL received planned rituximab-based chemotherapy pre-SCT. Patients were required to have chemotherapy-sensitive disease (or nonbulky stable disease) documented before SCT after the induction or salvage chemotherapy. This study was approved by the Institutional Review Board of Vanderbilt University Medical Center. All patients provided informed consent in accordance with the Declaration of Helsinki. Clinical information was reviewed, and baseline characteristics were recorded, including common pretransplant and transplant variable information.

NHL: histologic subtypes

In B cell histologic subtypes, diffuse large, mantle cell, transformed lymphoma were considered aggressive lymphomas, whereas follicular lymphoma was indolent. All peripheral T cell lymphomas were considered aggressive in nature except ALK-positive anaplastic large cell lymphoma. All pathologic analyses were reviewed, and diagnosis was confirmed at our institution.

Table 1. Patient characteristics

Variable	Auto-SCT (n = 198)	Allo-SCT (n = 72)
Male sex	127 (64%)	43 (60%)
Female sex	71 (36%)	29 (40%)
Median age (y)	52 (22–71)	47 (22–65)
B cell	176 (89%)	62 (86%)
T cell	22 (11%)	10 (14%)
B cell indolent	19 (25%)	30 (48.2%)
B cell aggressive	157 (75%)	32 (51.8%)
Stage		
I/II	53 (27%)	11 (15%)
III/IV	145 (73%)	61 (85%)
Number of prior regimens		
≤2	128 (65%)	30 (42%)
>2	70 (35%)	42 (58%)
Disease status before transplant		
Complete remission	142 (70%)	40 (56%)
Partial remission or stable disease	56 (29%)	32 (44%)
Prior radiation	19 (10%)	15 (20%)
Matched related donor	—	45
Unrelated stem cell source	—	27
Reduced-intensity conditioning	—	49 (68%)
Myeloablative conditioning	—	23 (32%)

allo = allogeneic; auto = autologous; SCT = stem cell transplantation.

Definitions and response criteria

Overall survival (OS) was defined as the time from date of transplantation to date of death or last follow up. Progression-free survival (PFS), was calculated as the interval between the date of transplantation and date at relapse, progression, or death after transplantation. Patients who were alive without evidence of disease relapse or progression were censored at last follow-up, and PFS was summarized by a survival curve. NRM was defined as death from any cause without evidence of lymphoma progression or relapse.

Response criteria were based on guidelines from the International Workshop on non-Hodgkin Lymphoma [23]. *Complete remission* (CR) was defined as complete radiologic regression of all previous measurable disease or bone marrow involvement. *Partial response* (PR) was defined as a reduction of 50% or greater reduction in the sum of the products of the longest and perpendicular diameter of measurable lesions. Progression was defined as an increase of 25% or more in the sites of lymphoma or development of new sites of lymphoma at any time after transplantation. Relapse was defined as recurrence of lymphoma after a complete response. Based on these criteria, all data were verified individually regarding the best response status before SCT.

Other outcomes analyzed include acute and chronic graft-versus-host disease (GVHD) and cause of death. Acute GVHD was defined and graded based on the pattern and severity of organ involvement using established criteria [24]. *Chronic GVHD* was defined as the development of any chronic GVHD based on clinical criteria [25,26]. Both these events were summarized by the corresponding cumulative incidence estimate, with death without development of GVHD as the competing risk. The World Health Organization criteria were used to define histologic classification of NHL after 2001.

Transplantation procedures

Auto-SCT. Stem cells were mobilized using high-dose chemotherapy (cyclophosphamide) and G-CSF (with or without plerixafor). CBV (7200 mg/m^2 cyclophosphamide, 2000 mg/m^2 etoposide, and 400 mg/m^2 carmustine) was the most commonly used (87%) conditioning regimen in patients receiving auto-SCT. Patients with a histologic diagnosis of mantle cell and peripheral T cell lymphoma received auto-SCT in CR1. Patients with relapsed diffuse large B cell NHL underwent auto-SCT in CR2.

Allo-SCT. Forty-nine patients received RIC (fludarabine and busulfan, n = 39; fludarabine-cyclophosphamide-rituximab [FCR], n = 10), and 23 received an MST regimen followed by either matched-related (n = 45) or unrelated donor (n = 27) stem cell transplantation. All patients received GVHD prophylaxis with a calcineurin inhibitor and either methotrexate (myeloablative and FCR RIC regimen) or mycophenolate mofetil (fludarabine and busulfan RIC regimen).

Supportive care

All patients received standard supportive care per institutional guidelines. Standard antimicrobial prophylaxis, surveillance cultures, and treatment were administered per protocol.