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Reduced-Intensity Allografting as First Transplantation Approach in Relapsed/Refractory Grades One and Two Follicular Lymphoma Provides Improved Outcomes in Long-Term Survivors

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A B S T R A C T

This study was conducted to compare long-term outcomes in patients with refractory/relapsed grades 1 and 2 follicular lymphoma (FL) after allogeneic (allo) versus autologous (auto) hematopoietic cell transplantation (HCT) in the rituximab era. Adult patients with relapsed/refractory grades 1 and 2 FL undergoing first reduced-intensity allo-HCT or first autograft during 2000 to 2012 were evaluated. A total of 518 rituximab-treated patients were included. Allo-HCT patients were younger and more heavily pretreated, and more patients had advanced stage and chemoresistant disease. The 5-year adjusted probabilities, comparing auto-HCT versus allo-HCT groups for nonrelapse mortality (NRM) were 5% versus 26% ($P < .0001$); relapse/progression: 54% versus 20% ($P < .0001$); progression-free survival (PFS): 41% versus 58% ($P < .001$), and overall survival (OS): 74% versus 66% ($P = .05$). Auto-HCT was associated with a higher risk of relapse/progression beyond 5 months after HCT (relative risk [RR], 4.4; $P < .0001$) and worse PFS (RR, 2.9; $P < .0001$) beyond 11 months after HCT. In the first 24 months after HCT, auto-HCT was associated with improved OS (RR, .41; $P < .0001$), but beyond 24 months, it was associated with inferior OS (RR, 2.2; $P = .006$). A landmark analysis of patients alive and progression-free at 2 years after HCT confirmed these observations, showing no difference in further NRM between both groups, but there was significantly higher risk of relapse/progression (RR, 7.3; $P < .0001$) and inferior PFS (RR, 3.2; $P < .0001$) and OS (RR, 2.1; $P = .04$) after auto-HCT. The 10-year cumulative incidences of second hematological malignancies after allo-HCT and auto-HCT were 0% and 7%, respectively. Auto-HCT and reduced-intensity–conditioned allo-HCT as first transplantation approach can provide durable disease control in grades 1 and 2 FL patients. Continued disease relapse risk after auto-HCT translates into improved PFS and OS after allo-HCT in long-term survivors.

INTRODUCTION

Follicular lymphoma (FL), with its long natural history and indolent course, is a heterogeneous malignancy. Although many patients survive for decades, a significant portion have a more aggressive course and ~20% of patients die within 2 to 3 years of diagnosis. For patients with repeated relapses and short remissions, hematopoietic cell transplantation (HCT) remains a vital tool. However, there is continued debate on the optimal timing and most effective HCT modality. Autologous (auto) HCT is frequently performed in patients with relapsed/refractory FL, but therapy failure remains a challenge [1-3]. To mitigate the relapse risk, allogeneic (allo) HCT is often considered in relapsed/refractory FL [4]. Whether auto-HCT or allo-HCT represent the preferred first transplantation approach in FL remains to be determined, especially in the rituximab era. In pre-rituximab era, the EBMT (European Group for Blood and Marrow Transplantation) Chemotherapy, Unpurged or Purged auto-HCT (CUP) Trial showed a progression-free survival (PFS) and overall survival (OS) benefit for auto-HCT compared with salvage chemotherapy alone in relapsed FL [5]. Some but not all retrospective studies from the pre-rituximab era have shown durable disease control after auto-HCT, especially among FL patients in first or second complete remission (CR) [1,6,7]. Unfortunately similar randomized or retrospective data in the rituximab era are not available. The post hoc analysis of 2 successive Groupe d'Etude des Lymphomes Folliculaires (GELF-86/-94) trials suggest that in relapsed FL patients receiving rituximab-containing salvage therapies, auto-HCT does not provide a PFS or OS advantage compared with chemoimmunotherapy alone, with neither strategy resulting in apparent cures [8]. Furthermore, the risk of second malignancies after auto-HCT is not insignificant, ranging from 5% to 20% [1,2].

Allo-HCT provides a lymphoma-free graft devoid of prior chemotherapy-induced DNA damage and has the potential to mediate a graft-versus-lymphoma (GVL) effect. Allo-HCT has been shown to confer long-term remissions in patients with FL, with a plateau for PFS after 2 to 3 years from transplantation, suggesting clinical evidence of durable GVL effects and likely cure [9-12].

Historically, myeloablative allo-HCTs in FL were associated with increased nonrelapse mortality (NRM) (~30% to 40%) [12,13]. To exploit the beneficial GVL effects without high rates of NRM, reduced-intensity/nonmyeloablative conditioning (RIC/NMA) HCTs have been widely adopted [11,14-16]. However, as the toxicity of RIC allo-HCT still remains higher than that of auto-HCT, the question arises whether the potential benefit of the GVL effects associated with the allo-HCT justifies its application as the first transplantation approach in FL. The only prospective comparison between auto-HCT and allo-HCT for relapsed FL performed by Bone and Marrow Transplantation Clinical Trials Network closed early because of poor accrual [17]. A recent retrospective EBMT study did not show improved OS in FL patients after RIC allo-HCT compared to auto-HCT when either modality was applied as the first transplantation procedure [18]. However, > 50% of patients in the EBMT analysis never received rituximab before HCT, a scenario that is no longer clinically relevant.

We utilized the Center for International Blood and Marrow Transplant Research (CIBMTR) registry to assess the relative efficacy of auto-HCT against RIC/NMA allo-HCT, when either modality is used as the first transplantation procedure, in relapsed/refractory FL in the rituximab era.

PATIENTS AND METHODS

Data Sources

The CIBMTR is a working group of more than 450 transplantation centers worldwide that contribute detailed data on HCTs to a statistical center at the Medical College of Wisconsin. Centers report HCTs consecutively, with compliance monitored by on-site audits. Patients are followed longitudinally with yearly follow-up. Observational studies by the CIBMTR are performed in compliance with federal regulations with ongoing review by the institutional review board of the Medical College of Wisconsin.

Patients

Patients with a histologically proven diagnosis of relapsed/refractory grade 1 or 2 FL, undergoing a first auto-HCT or a first RIC/NMA allo-HCT, reported to the CIBMTR between 2000 and 2012 were eligible. RIC/NMA allo-HCT patients with a history of prior auto-HCT were not included. Donor source for the allo-HCT cohort was restricted to either HLA-identical siblings or at least a 7/8 (antigen or allele-level)-matched unrelated donors (URD). Pediatric patients (<18 years), those undergoing alternative donor HCT (eg, umbilical cord blood, haploidentical, mismatched URD), and patients