Biol Blood Marrow Transplant 21 (2015) 1746–1753

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Clinical Research: Adult

The Impact of Graft-versus-Host Disease on the Relapse Rate in Patients with Lymphoma Depends on the Histological Subtype and the Intensity of the Conditioning Regimen

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Financial disclosure: See Acknowledgments on page 1752.

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http://dx.doi.org/10.1016/j.bbmt.2015.05.010

Article history:
Received 6 November 2014
Accepted 11 May 2015

Key Words:
Graft-versus-host disease
Lymphoma

A B S T R A C T

The purpose of this study was to analyze the impact of graft-versus-host disease (GVHD) on the relapse rate of different lymphoma subtypes after allogeneic hematopoietic cell transplantation (allo-HCT). Adult patients with a diagnosis of Hodgkin lymphoma, diffuse large B cell lymphoma, follicular lymphoma (FL), peripheral T cell lymphoma, or mantle cell lymphoma (MCL) undergoing HLA-identical sibling or unrelated donor hematopoietic cell transplantation between 1997 and 2009 were included. Two thousand six hundred eleven cases were included. A reduced-intensity conditioning (RIC) regimen was used in 62.8% of the transplantations. In a multivariate analysis of myeloablative cases (n = 970), neither acute (aGVHD) nor chronic GVHD (cGVHD) were significantly associated with a lower incidence of relapse/progression in any lymphoma subtype. In contrast, the analysis of RIC cases (n = 1641) showed that cGVHD was associated with a lower incidence of relapse/progression in FL (risk ratio [RR], .51; $P = .049$) and in MCL (RR, .41; $P = .019$). Patients with FL or MCL developing both aGVHD and cGVHD had the lowest risk of relapse (RR, .14; $P = .007$; and RR, .15; $P = .0019$, respectively). Of interest, the effect of GVHD on decreasing relapse was similar in patients with sensitive disease and chemoresistant disease. Unfortunately, both aGVHD and cGVHD had a deleterious effect on treatment-related mortality and overall survival (OS) in FL cases but did not affect treatment-related mortality, OS or PFS in MCL. This study reinforces the use of RIC allo-HCT as a platform for immunotherapy in FL and MCL patients.

INTRODUCTION

A significant number of patients with lymphoma are not cured with conventional treatment or after high-dose therapy and autologous transplantation. Allogeneic hematopoietic cell transplantation (allo-HCT) is a potential curative procedure for these patients because of the antilymphoma effect of both the cytotoxic drugs in the conditioning regimen and the immune attack mediated by the donor's T cells. Unfortunately, the conventional myeloablative conditioning regimen (MAB) of allo-HCT is associated with high nonrelapse mortality (NRM) and, as a result, its role in the therapeutic algorithm for lymphoma remains controversial [1]. Furthermore, the average age of patients with the most frequent subtypes of lymphoma is 60 to 65 years, an age when MAB transplantations have prohibitive NRM. Allo-HCT with a reduced-intensity conditioning (RIC) regimen is associated with a lower rate of mortality and now represents 80% of all allo-HCT in some types of lymphoma [2]. RIC allo-HCT transplantations would be an immunotherapy platform for different subtypes of lymphoma, if a potent graft-versus-lymphoma (GVLy) effect were demonstrated. The reported clinical evidence of a GVLy effect is less robust than that published for a graft-versus-leukemia effect. This may be because of the relatively limited number of allo-HCT lymphoma cases reported in most series, as well as the fact that different types of lymphoma are often analyzed together. The main objectives of this study were to determine if graft-versus-host disease (GVHD) was associated with a lower relapse rate in specific subtypes of lymphomas and to analyze whether this effect differs in MAB and RIC transplantations. We hypothesized that the different biological characteristics and growth kinetics between histological subtypes might have a different impact of GVHD on relapse rate. We also wanted to identify whether a potential decreased relapse rate in patients developing GVHD would result in an overall improved clinical outcome.

PATIENTS AND METHODS

Data Source

The Center for International Blood and Marrow Transplant Research (CIBMTR) (formerly IBMTR) is a combined research program of the Medical College of Wisconsin and the National Marrow Donor Program. The CIBMTR comprises a voluntary network of more than 450 transplantation centers worldwide that contribute detailed data on consecutive allogeneic and autologous hematopoietic cell transplantations (HCT) to a centralized statistical center. Observational studies conducted by the CIBMTR are performed in compliance with all applicable US federal regulations pertaining to the protection of human research participants. Protected health information used in the performance of such research is collected and maintained in the CIBMTR capacity as a public health authority under the Health Insurance Portability and Accountability Act Privacy rule. Additional details regarding the data source are described elsewhere [3].

Patients

We analyzed 2611 cases of patients older than 18 years old who were undergoing HLA-identical sibling or unrelated-donor HCT for lymphoma reported to the CIBMTR between 1997 and 2009. Lymphoma types were categorized as Hodgkin lymphoma (HL) (n = 466), diffuse large B cell lymphoma (DLBCL) (n = 579), follicular lymphoma (FL) (n = 871), peripheral T cell lymphoma (PTCL) (n = 195), and mantle cell lymphoma (MCL) (n = 500). Patients who received cord blood and ex vivo T cell–depleted grafts were excluded.

Study Endpoints

The main goal of this study was to compare the association of GVHD with relapse rates in patients with different lymphoma subtypes and to analyze whether this association differs in MAB and RIC/nonmyeloablative (NMA) [4]. We also analyzed the impact of GVHD on NRM, overall survival (OS), and progression-free survival (PFS). *Acute* and *chronic GVHD* (aGVHD and cGVHD, respectively) were defined as the occurrence of grade II, III, or IV skin, gastrointestinal, or liver abnormalities that fulfill the consensus criteria of aGVHD [5] and limited and extensive cGVHD [6], respectively. *NRM* was defined as death after transplantation without relapse or progression, where relapse and progression were competing risks. Those patients who survived without recurrence or progression were censored at the time of last contact. *OS* was defined as time from transplantation to death. Death from any cause was considered an event. *PFS* was defined as survival after transplantation without recurrence or lymphoma progression. Recurrence or progression of the disease and death were counted as events. Those patients receiving donor lymphocyte infusions (DLI) were censored when receiving the first dose. Those patients who survived without recurrence or progression were censored at the time of last contact.

Statistical Analysis

Multivariate analyses were performed using Cox proportional hazards models. A stepwise model building approach was used to identify the significant risk factors associated with the outcomes of relapse/progression, NRM, PFS, and OS. The assumption of proportional hazards for each factor in the Cox model was tested using time-dependent covariates. When the test indicated differential effects over time (nonproportional hazards), models were constructed breaking the post-transplantation time course into 2 periods, using the maximized partial likelihood method to find the most appropriate breakpoint. The proportionality assumptions were further tested. A backward stepwise model selection approach was used to identify all significant risk factors. The main-effect variable was defined as the time-dependent occurrence of aGVHD only versus aGVHD + cGVHD versus cGVHD only versus neither. Each step of model building included the main "treatment" effect. Factors that were significant at a level of 5%