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Impact of Postgrafting Immunosuppressive Regimens on Nonrelapse Mortality and Survival after Nonmyeloablative Allogeneic Hematopoietic Stem Cell Transplant Using the Fludarabine and Low-Dose Total-Body Irradiation 200-cGy

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ABSTRACT

The development of nonmyeloablative (NM) hematopoietic cell transplantation (HCT) has extended the potential curative treatment option of allografting to patients in whom it was previously contraindicated because of advanced age or comorbidity. Acute and chronic graft versus host disease (GVHD) and its consequent nonrelapse mortality (NRM), remains the major limitation of NM HCT. In this report, we analyzed the outcome of 67 patients (median age, 45 years) with hematologic diseases receiving NM conditioning with fludarabine 90 mg/m^2 and total body irradiation (TBI) 200-cGy, followed by filgrastim-mobilized peripheral blood stem cell transplant from HLA identical (n = 61), 5/6 antigen-matched related (n = 1), 6/6 antigen-matched unrelated (n = 3), and 5/6 antigen-matched unrelated (n = 2) donors. The first cohort of 21 patients were given cyclosporine (CSP) and mycophenolate mofetil (MMF) as postgrafting immunosuppression, whereas the subsequent cohort was given additional methotrexate (MTX) and extended duration of CSP/MMF prophylaxis in an attempt to reduce graft-versus-host disease (GVHD). Sixty-four (95%) patients engrafted and 3 (5%) had secondary graft failure. Myelosuppression was moderate with neutrophil counts not declining below 500/μL in approximately 25% of patients, and with more than half of the patients not requiring any blood or platelet transfusion. The 2-year cumulative interval (CI) of grade II-IV, grade III-IV acute GVHD and chronic GVHD were 49%, 30%, and 34%, respectively. The 2-year probability of NRM, overall (OS), and progression-free (PFS) survival were 27%, 43%, and 28%, respectively. GVHD-related death accounted for 85% of NRM. Compared with patients receiving CSP/MMF, patients receiving extended duration of CSP/MMF with additional MTX in postgrafting immunosuppression had a significantly lower risk of grade III-IV acute GVHD (CI 20% versus 52%; $P = .009$) and NRM (CI at 2 years: 11% versus 62%; $P < .001$), without any significant adverse impact on the risk of relapse (CI at 2 years: 59% versus 33%; $P = .174$) Subgroup analysis of a cohort of patients given MTX/CSP/MMF showed that patients with "standard risk" diseases (n = 21) had a 3-year OS and PFS of 85% and 65%, respectively. This compares favorably to the 41% ($P = .02$) and 23% ($P = .03$) OS and PFS, respectively, in patients with "high-risk" diseases (n = 25). In conclusion, the addition of MTX onto the current postgrafting immunosuppression regimen with extended CSP/MMF prophylaxis duration provides more effective protection against severe GVHD, and is associated with more favorable

outcome in patients receiving NM fludarabine/TBI conditioning than in patients receiving fludarabine/TBI conditioning with CSP and MMF without MTX.

KEY WORDS
Nonmyleloablative • Allogeneic transplant • GVHD prophylaxis • Methotrexate • Fludarabine • Low-dose TBI

INTRODUCTION

Allogeneic hematopoietic cell transplantation (HCT) after myeloablative conditioning regimens has been an effective treatment for many patients with hematologic malignancies or inherited blood disorders. Unfortunately, such regimens have been associated with significant toxicities, limiting their use to otherwise healthy, relatively young patients. To extend allogeneic HCT to older patients and those with comorbid conditions, reduced-intensity or truly nonmyeloablative (NM) conditioning regimens lacking such toxicities [1-4] have been developed. These regimens have relied more on graft-versus-tumor effects than on chemoradiation therapy to facilitate engraftment and eradicate malignant cells. Although NM HCT has been associated with reduced regimen-related toxicities and has been curative for a number of patients with hematologic malignancies, challenges have remained with regard to graft-versus-host disease (GVHD), infections, and disease progression. Acute GVHD (aGVHD) (grade II or higher), which developed in 20% to 65% of patients in single or multicenter clinical trials [4-6], remains a major limitation to success of NM HCT. Furthermore, recent analysis suggests that aGVHD, particularly early-onset GVHD, is associated with increased transplant-related mortality (TRM) [7], but not with improved disease control, for which chronic GVHD (cGVHD) appears more important [8].

In an attempt to reduce GVHD-related death, various approaches have been employed. In vivo T cell depletion, such as incorporating alemtuzumab into the conditioning regimen, has been shown to reduce the incidence of GVHD [9-13]. However, this type of intervention, although reducing GVHD, may have an adverse impact on disease response. This is because of the inverse relationship between GVHD and relapse of malignancies [14-16] and the fact that NM HCTs exhibit their antitumor activity by relying on a graft-versus-malignancy effect [2,3,17-19]. In fact, several nonrandomized studies have demonstrated that such strategies have resulted in a reduction in risk for GVHD without any survival benefit [20-23]. Clearly, optimizing GVHD control without reducing graft-versus-malignancy effects after NM conditioning remains a critical research objective.

Different immunosuppressive drug combinations have also been evaluated in efforts to decrease the incidence and severity of GVHD [24-35]. However, the most effective combination and the optimal duration of immunosuppressive therapy to protect against GVHD have not been defined.

Here we report the results of a prospective pilot trial evaluating the feasibility and efficacy of allogeneic HCT after 2 Gy total body irradiation (TBI) and fludarabine NM conditioning developed in Seattle [3,4,36], followed by postgrafting immunosuppression with mycophenolate mofetil (MMF) and cyclosporine (CSP) in 67 patients with various hematologic diseases. In this study, a second patient cohort was accrued based on the modification of postgrafting immunosuppression, which was made following the observation of a considerably high incidence of severe GVHD in the first patient cohort. These 2 sequential patient cohorts, which differed only by GVHD prophylaxis regimen, allow us to compare the efficacy of 2 different immunosuppressive combination regimens on transplantation outcome.

PATIENTS, MATERIALS, AND METHODS

Patient Eligibility and Donors

Included in the study were results from 67 consecutive patients with hematologic diseases treated at 2 tertiary centers in Singapore between November 1999 and October 2005. Treatment protocols were approved by the ethics committee or institution review board at each institution. Informed consent was obtained from all patients and donors before treatment initiation. Patients with lymphoma, aplastic anemia, acute leukemia, myelodysplasia, multiple myeloma, chronic myelogenous leukemia (CML), and chronic lymphocytic leukemia, between ages 45 and 70 years were considered eligible. Patients were also eligible if they were younger than 45, but deemed poor candidates for conventional conditioning because of (1) medical comorbidities (eg, renal dysfunction, liver cirrhosis, existing fungal infections); (2) extensive prior therapy resulting in poor performance status; or (3) failed prior autologous transplantation. Exclusion criteria were cardiac ejection fraction $<35\%$; diffusion capacity of carbon monoxide $<35\%$ predicted; bilirubin >2 times and/or transaminase >4 times the upper limit of normal, and Karnofsky performance score <50.

HLA typing of patients and their donors were