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Clofarabine Plus Busulfan is an Effective Conditioning Regimen for Allogeneic Hematopoietic Stem Cell Transplantation in Patients with Acute Lymphoblastic Leukemia: Long-Term Study Results

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A B S T R A C T

We investigated the long-term safety and disease control data obtained with i.v. busulfan (Bu) combined with clofarabine (Clo) in patients with acute lymphoblastic leukemia (ALL) undergoing allogeneic hematopoietic stem cell transplantation (HSCT). A total of 107 patients, median age 38 years (range, 19 to 64 years) received a matched sibling donor (n = 52) or matched unrelated donor (n = 55) transplant for ALL in first complete remission (n = 62), second complete remission (n = 28), or more advanced disease (n = 17). Nearly one-half of the patients had a high-risk cytogenetic profile as defined by the presence of t(9;22) (n = 34), t(4;11) (n = 4), or complex cytogenetics (n = 7). Clo 40 mg/m^2 was given once daily, with each dose followed by pharmacokinetically dosed Bu infused over 3 hours daily for 4 days, followed by hematopoietic cell infusion after 2 days of rest. The Bu dose was based on the drug clearance as determined by a test Bu dose of 32 mg/m^2. The target daily area under the curve was 5500 μmol/min for patients aged <60 years and 4000 μmol/min for patients aged >59 years. With a median follow-up of 3.3 years among surviving patients (range, 1 to 5.8 years), the 2-year progression-free survival (PFS) for patients undergoing HSCT in first complete remission (CR1), second complete remission (CR2), or more advanced disease was 62%, 34%, and 35%, respectively. The regimen was well tolerated, with nonrelapse mortality (NRM) of 10% at 100 days and 31% at 2 years post-HSCT. The incidence of grade II-IV and III-IV acute graft-versus-host disease (GVHD) was 35% and 10%, respectively; 18% patients developed extensive chronic GVHD. The 2-year overall survival (OS) for patients undergoing HSCT in CR1, CR2, or more advanced disease was 70%, 57%, and 35%, respectively. Among 11 patients aged >59 years treated with reduced-dose Bu in CR1 (n = 7) or CR2 (n = 4), 4 remain alive and disease-free, with a median follow-up of 2.6 years (range, 2 to 4.7 years). Only the presence of minimal residual disease at the time of transplantation was associated with significantly worse PFS and OS in multivariate analysis. Our data indicate that the Clo-Bu combination provides effective disease control while maintaining a favorable safety profile. OS and NRM rates compare favorably with those for traditional myeloablative total body irradiation-based conditioning regimens.

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HSCT) is an effective, potentially curative treatment option for adults with acute lymphoblastic leukemia (ALL), but may be associated with significant morbidity. Nonrelapse mortality (NRM) of 20% to 45% has been reported in patients receiving a standard total body irradiation (TBI)-based myeloablative preparative regimen [1-3]. In an effort to improve NRM,

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reduced-intensity conditioning (RIC) regimens have been investigated; these RIC regimens have been associated with improvement in acute NRM, but with an increased risk of relapse, especially in patients beyond first complete remission [4-6]. In an attempt to limit the toxicities associated with TBI-based myeloablative regimens, we replaced radiation with a chemotherapy-only double-alkylator regimen consisting of i.v. pharmacokinetically dosed busulfan (Bu) and melphalan (Mel) [7]. We found comparable disease control to radiation-based regimens with decreased acute regimen-related toxicities; however, long-term NRM, related primarily to graft-versus-host disease (GVHD), remained substantial at 55% at 2 years for patients aged >40 years [7].

We and others have shown good disease control and decreased toxicity when a second alykylator (Mel or cyclophosphamide [Cy]) was replaced with the nucleoside analog (NA) fludarabine (Flu) in the transplantation conditioning regimen in children and adults with leukemia [8-15]. We further hypothesized that replacing the NA Flu with the second-generation NA clofarabine (Clo), which has single-agent activity in refractory relapsed ALL [16,17], would provide particularly good disease control in patients with ALL. The i.v. Clo-Bu combination was used in patients undergoing allogeneic HSCT for ALL, and the early published results in 51 patients were encouraging, showing a low 100-day transplantation-related mortality of 6% and a projected 1-year disease-free survival rate of 64% in patients undergoing HSCT in first complete remission (CR1) [18].

We have completed the trial and accrued 107 patients. This report presents the long-term follow-up results of this trial.

PATIENTS AND METHODS

Patient eligibility and study treatment

This was a prospective, phase II single-arm study investigating the combination of Bu and Clo in patients with ALL. Enrollment began in October 2009 and completed in July 2015, and we are reporting the outcomes for adult patients treated consecutively during this time period. Patient eligibility and study methods were detailed in a previous report [18]. In brief, patients were between 18 and 65 years of age, with an available HLA-matched related donor or 8/8 matched unrelated donor undergoing first allogeneic HSCT. Additional eligibility criteria included a Zubrod performance status of 0 or 1, adequate organ function, and absence of active infection. Patients with active central nervous system (CNS) disease were excluded.

The transplantation conditioning regimen consisted of Clo 40 mg/m^2 infused over 1 hour, followed by pharmacokinetically dosed Bu infused over 3 hours once daily for 4 days, followed by hematopoietic cell infusion after 2 rest days. The therapeutic dose was determined by the drug clearance, as determined from a pharmacokinetic Bu test dose of 32 mg/m^2 infused i.v. over 45 minutes. The therapeutic i.v. Bu dose targeted an average daily area under the curve (AUC) of 5500 μmol/minute for patients aged <60 years and 4000 μmol/minute for patients aged >59 years. Blood collection and pharmacokinetic analyses were performed as reported previously [7,19].

Phenytoin 600 mg orally was administered during and at 1 day after completion of i.v. Bu therapy, starting the evening before the first dose [20]. GVHD prophylaxis consisted of a combination of tacrolimus and mini-dose methotrexate. Patients who received unrelated donor products also received rabbit antithymocyte globulin, for a total of 4 mg/kg infused over 3 days beginning 3 days before HSCT. Institutional transplantation guidelines for antimicrobial, antifungal, and antiviral prophylaxis were followed as reported previously [21]. Patients with a previous history of CNS involvement received craniospinal radiation therapy immediately before transplantation conditioning or post-transplantation intrathecal preemptive therapy, as feasible; patients without a history of CNS involvement of leukemia did not receive any CNS therapy beyond their recommended primary treatment [22]. Finally, patients positive for the Philadelphia chromosome were started on maintenance therapy with tyrosine kinase inhibitor (TKI) on normalization of blood counts after HSCT, to be continued for up to 5 years.

Definitions and clinical outcome variables

The disease stage at transplantation was defined using established criteria based on bone marrow morphology. Criteria for complete response included normal cytogenetics, absence of circulating blasts, <5% marrow blasts, and normalization of complete blood count. Response was documented as best response occurring by day 30 post-HSCT. Standard morphologic criteria were used to diagnose recurrent disease. Molecular response, measured by quantitative PCR analysis for BCR-ABL rearrangement, was assessed when possible. Multiparameter flow cytometry, with a sensitivity of 0.01%, was used to further assess for minimal residual disease (MRD). MRD and PCR analyses were not used to assign disease stage or to document relapse. Hematologic recovery was defined as the first day on which the patient had an absolute neutrophil count of $\geq 0.5 \times 10^9$/L for 3 consecutive days. Platelet recovery was defined as the first of 7 consecutive days with a platelet count of $\geq 20 \times 10^9$/L without transfusion support. Failure to engraft by day +30 was considered primary engraftment failure. Hematopoietic chimerism was evaluated in peripheral blood (with myeloid and T lineage cell sorting) by restriction fragment length polymorphisms using PCR methods to determine donor engraftment. Mixed chimerism was defined as the presence of any detectable (≥1%) recipient DNA in addition to donor-derived DNA in myeloid or T lineage cells.

Overall survival (OS) was estimated from the time of HSCT until death from any cause, and patients still alive at last follow-up were administratively censored. Progression-free survival (PFS) was estimated from HSCT until the date of relapse or death from any cause. Patients alive and disease-free at last follow-up were censored. NRM was defined as death from any cause other than disease progression or relapse. Acute and chronic GVHD were graded based on standard criteria [23,24].

Statistical methods

The trial completed accrual in July 2015, and this is the final report of the 107 adult patients treated with a matched related or unrelated donor on this study. Patients undergoing transplantation with a syngeneic donor were excluded from this analysis. The primary outcomes for this single-arm trial were safety and OS. Bayesian early stopping rules, based on the observed rates of these 2 outcomes compared with historical data, were implemented [25]. The methods of Gooley, Fine, and Gray were used to compare the cumulative incidence of NRM versus the competing risk of relapse, separately by age group (<40 years versus ≥40 years) and by disease stage. OS and PFS were analyzed using the Kaplan-Meier estimator [26] and univariate and multivariate Cox proportional hazards models. The factors age (age <40 years