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Long-Term Outcomes after Treatment with Clofarabine ± Fludarabine with Once-Daily Intravenous Busulfan as Pretransplant Conditioning Therapy for Advanced Myeloid Leukemia and Myelodysplastic Syndrome

Gheath Alatrash [1], Peter F. Thall [2], Benigno C. Valdez [1], Patricia S. Fox [2], Jing Ning [2], Haven R. Garber [1], Selma Janbey [1], Laura L. Worth [3], Uday Popat [1], Chitra Hosing [1], Amin M. Alousi [1], Partow Kebriaei [1], Elizabeth J. Shpall [1], Roy B. Jones [1], Marcos de Lima [1,4], Gabriela Rondon [1], Julianne Chen [1], Richard E. Champlin [1], Borje S. Andersson [1,*]

[1] *Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, Texas*
[2] *Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, Texas*
[3] *Department of Pediatrics, The University of Texas MD Anderson Cancer Center, Houston, Texas*
[4] *Department of Hematologic Malignancies and Stem Cell Transplant, Case Western Reserve University, Cleveland, Ohio*

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Pretransplant conditioning regimens critically determine outcomes in the setting of allogeneic stem cell transplantation (allo-SCT). The use of nucleoside analogs such as fludarabine (Flu) in combination with i.v. busulfan (Bu) has been shown to be highly effective as a pretransplant conditioning regimen in acute myeloid leukemia (AML), chronic myeloid leukemia (CML), and myelodysplastic syndrome (MDS). Because leukemia relapse remains the leading cause of death after allo-SCT, we studied whether clofarabine (Clo), a nucleoside analog with potent antileukemia activity, can be used to complement Flu. In a preliminary report, we previously showed the safety and efficacy of Clo ± Flu with i.v. Bu in 51 patients with high-risk AML, CML, and MDS. The study has now been completed, and we present long-term follow-up data on the entire 70-patient population, which included 49 (70%), 8 (11%), and 13 (19%) patients with AML, MDS, and CML, respectively. Thirteen patients (19%) were in complete remission, and 41 patients (59%) received matched unrelated donor grafts. Engraftment was achieved in all patients. Sixty-three patients (90%) achieved complete remission. There were no deaths reported at day +30, and the 100-day nonrelapse mortality rate was 4% (n = 3). Thirty-one percent of patients (n = 22) developed grades II to IV acute graft-versus-host disease, and the median overall survival and progression-free survival times were 2.4 years and .9 years, respectively. Our results confirm the safety and overall and progression-free survival advantage of the arms with higher Clo doses and lower Flu doses, which was most prominent in the AML/MDS group.

INTRODUCTION

The conditioning regimens used in the allogeneic (allo-) stem cell transplantation (SCT) setting are critical for reducing disease burden and establishing an immunosuppressed environment that allows engraftment of donor cells. Intravenous busulfan (Bu) combined with the nucleoside analog fludarabine (Flu) has become one of the principal conditioning regimens used in the allo-SCT setting [1-7]. Factors that contribute to the safety and efficacy of i.v. Bu-Flu include the nonoverlapping end-organ toxicities of Flu and Bu and the predictability of systemic Bu levels with the use of i.v. Bu [8-11].

The cytoreductive capability of the conditioning regimen has a significant bearing on long-term disease outcomes, especially in high-risk patients [12,13]. This observation underscores the critical need for conditioning regimens with potent antileukemia activity that would eradicate residual leukemia and provide ample time to establish donor immunity for the graft-versus-leukemia effect of the allo-SCT [12-15]. We introduced clofarabine (Clo) in combination with Flu and i.v. Bu as one strategy to improve the antileukemia activity

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* Correspondence and reprint requests: Borje S. Andersson, MD, PhD, Department of Stem Cell Transplantation and Cellular Therapy, University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd., Unit 0423, Houston, TX 77030.
E-mail address: bandersson@mdanderson.org (B.S. Andersson).

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of the conditioning regimen and demonstrated its safety and efficacy in 51 patients with acute myeloid leukemia (AML; n = 42) and chronic myeloid leukemia (CML; n = 9) [16]. Clo has a potent antileukemia activity and synergizes with Flu and Bu in vitro [16,17], hence providing the rationale to test it in the allo-SCT setting.

Using a Bayesian model, in our original study [16] we randomized patients adaptively to 1 of 4 arms in which Flu was complemented with Clo in different proportions; all patients received i.v. Bu. The 4 arms were as follows: arm 1, Clo/Flu 10:30 mg/m^2; arm 2, 20:20 mg/m^2; arm 3, 30:10 mg/m^2; and arm 4, single-agent Clo at 40 mg/m^2. The addition of Clo had minimal toxicities with no major organ toxicities or graft-versus-host disease (GVHD) that were attributed to this nucleoside analog. We reported rates of 2-year overall survival (OS) and progression-free survival (PFS) of 48% and 41%, respectively, with a median OS of 23 months. A multivariate analysis suggested a trend for improved OS and PFS for AML patients treated in the arms with higher Clo doses, including patients treated in arm 4 who received Clo without Flu.

In this report, we present a long-term follow-up on the entire group of 70 patients. Patient covariates were balanced between all treatment arms. Our results confirm the safety of this new double nucleoside analog + i.v. Bu regimen and demonstrate an advantage for better disease control in the patients conditioned with higher Clo doses.

METHODS

Patient Eligibility

We studied 70 patients with AML (n = 49), myelodysplastic syndrome (MDS; n = 8), or CML (n = 13) transplanted at The University of Texas MD Anderson Cancer Center between October 2006 and October 2011. Patients provided written informed consent for their treatment and were treated in accordance with the Declaration of Helsinki.

The inclusion criteria for AML patients were induction chemotherapy failure or high-risk disease in first complete remission (CR1), characterized by cytogenetics other than translocation (t) (8;21), inversion (inv) 16, or t(15;17), and/or by the need for more than 1 cycle of chemotherapy to achieve CR [18]. Patients with AML beyond CR1 were also eligible and were prioritized to include those with active leukemia at the time of transplantation. For MDS, eligibility criteria included patients with an International Prognostic Score System score ≥ 2 [19] or if they progressed after previous chemotherapy. CML patients were eligible for this trial if they failed to achieve a cytogenetic CR to tyrosine kinase inhibitor–based therapy and completed tyrosine kinase inhibitor therapy at least 10 days before the start of preparative treatment to avoid a serious hepatic interaction with Bu metabolism. The patients enrolled in this study were eligible for standard myeloablative conditioning regimens. In addition to the above-listed disease-specific criteria, eligibility criteria included acceptable renal function (creatinine ≤ 1.5 mg); adequate hepatic function (normal bilirubin and serum glutamic pyruvic transaminase ≤ 3 times the upper normal limit); ZUBROD performance status ≤ 2; absence of uncontrolled infection, including negative serology for hepatitis B and C and HIV; adequate cardiac function (left ventricular ejection fraction ≥ 45%); acceptable pulmonary function (forced expiratory volume in one second, forced vital capacity, and diffusion capacity of the lungs for carbon monoxide ≥ 50% of predicted); and no chemotherapy within 30 days of study entry.

Stem cell grafts were obtained from HLA-compatible related (fully matched or 1-antigen mismatched) donors or matched unrelated donors (MUDs). HLA matching was assessed using high-resolution DNA typing. The National Institutes of Health Common Terminology Criteria version 3.0 was used to assess clinical serious adverse events. All patients signed informed consent according to institutional guidelines. PCR-based technology was used to document engraftment and chimerism from blood and marrow [4].

Pretransplant Conditioning Program

The treatment regimens used are considered myeloablative and were based on a backbone of i.v. Bu-Flu. Regimens consisted of Flu (Fludara; Genzyme Corporation, Cambridge, MA) infused over 60 minutes daily for 4 days (days –6 to –3). Each Flu dose was followed by Clo (Clolar; Genzyme Corp.), also infused over 60 minutes daily for 4 days, and then by i.v. Bu (IV Busulfex [busulfan] Injection; Otsuka America Pharmaceuticals Inc., Princeton, NJ), over 3 hours once daily for 4 days. The Bu dose was calculated to target an average daily systemic exposure dose, represented by the area under the concentration versus time curve of 6000 μMol-min ± 10%, or total course area under the concentration versus time curve of 24,000 μMol-min over 5 days. Pharmacokinetic parameters derived from a Bu test dose of 32 mg/m^2 administered 48 hours before the start of the therapeutic conditioning program (day –8) was used to calculate the Bu dose. The clinical study was designed as an adaptively randomized 4-arm trial:

Arm 1: Flu 30 mg/m^2/day + Clo 10 mg/m^2/day
Arm 2: Flu 20 mg/m^2/day + Clo 20 mg/m^2/day
Arm 3: Flu 10 mg/m^2/day + Clo 30 mg/m^2/day
Arm 4: Clo alone at 40 mg/m^2/day

In addition to the fixed dose of i.v. Bu and the above 4 Flu-Clo chemotherapy schedules, a total dose of 4 mg/kg of rabbit antithymocyte globulin (Thymoglobulin; Genzyme Corp.) was infused to patients who had a 1-antigen-mismatched related donor or a MUD using the following schedule: .5 mg/kg on day –3, 1.5 mg/kg on day –2, and 2.0 mg/kg i.v. on day –1. The stem cell products were infused on day 0. Tacrolimus and minidose methotrexate were used for GVHD prophylaxis [2,20].

Regimen Stopping Rule

The stopping rule terminates an experimental arm for safety if, given the observed 30-day treatment-related mortality (TRM) data, it was likely that the rate of 30-day TRM in that arm was higher than the rate of 1% seen historically. Specifically, denoting the probability of TRM within 30 days in arm j = 1, 2, 3, 4 by pj and the historical probability of this event by pH, the safety rule would stop accrual to the jth arm if $\Pr(pj > \text{pH} \mid \text{data}) > .95$, where it was assumed that pH followed an informative β prior with effective sample size 120 and mean .01, and that $p1$, $p2$, $p3$, and $p4$ followed noninformative β priors with effective sample size 1 and mean .01.

Statistical Analyses

Unadjusted distributions of OS and PFS were estimated by the method of Kaplan and Meier [21]. The log rank test was used to test differences in OS or PFS between subgroups [22]. Exact tests for association were carried out using the exact Fisher-Freeman-Halton test [23]. Bayesian survival time regression was used to assess the relationship between OS, PFS, and patient covariates and treatment arms, assuming a log-normal distribution for flexibility and numerical stability [24]. In the fitted model, for each variable the posterior probability of a beneficial effect (pbe) = $\Pr(\beta > 0 \mid \text{data})$, where β denotes the coefficient of the variable in the model's linear term. Values of pbe > .99 or <.01 may be interpreted as highly significant and pbe > .95 or <.05 as significant. All statistical analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC) for Windows.

RESULTS

Patient Characteristics

Seventy patients with AML (n = 49), MDS (n = 8), or CML (n = 13) received allo-SCT between April 2006 and October 2011. The median age at the time of transplant was 46 years (range, 6 to 59); 25 patients (36%) were >50 years. Thirty-one patients (44%) were female and 39 (56%) male. Only 13 patients (19%) were in CR at the time of SCT. Forty-one patients (57%) received MUD SCTs; 19 (46%) of these MUD patients received bone marrow as the stem cell graft. Twenty-nine patients received their graft from a related donor, and of these patients, 27 (93%) were fully matched related donor (MRD), whereas 2 (7%) were 1-antigen mismatched. Of the patients who received a MRD graft, 24 (89%) received a peripheral blood progenitor cell graft. Bone marrow was used as the graft source for 2 patients who received a 1-antigen-mismatched SCT. Pretransplant characteristics for this subgroup of patients are presented in Table 1.

Patient Characteristics According to the Treatment Arm

Eighteen patients were randomized to treatment arm 1 (Flu 30 mg/m^2, Clo 10 mg/m^2), including 11 patients (61%) with AML, 2 patients (11%) with MDS, and 5 patients (28%) with CML. The median age of these patients at the time of transplant was 36.5 years (range, 6 to 59). Seven patients were randomized to treatment arm 2 (Flu 20 mg/m^2, Clo 20 mg/m^2), which included 4 patients (57%) with AML,