Leukemia Research xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Allogeneic hematopoietic cell transplantation without total body irradiation from unrelated donor in adult patients with idiopathic aplastic anemia: Fludarabine versus cyclophosphamide-ATG☆

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ARTICLE INFO

Article history:
Received 12 November 2013
Received in revised form
23 December 2013
Accepted 2 January 2014
Available online xxx

Keywords:
Unrelated donor
Total body irradiation
Aplastic anemia
Allogeneic hematopoietic stem cell transplantation
Fludarabine

ABSTRACT

Total body irradiation (TBI) has traditionally been used in the conditioning regimen for allogenetic hematopoietic stem cell transplantation (alloHCT) from an unrelated donor (u-HCT). However, patients are increasingly receiving a fludarabine-based conditioning regimen without TBI, as it seemed less toxic than TBI. We need to know the clinical results of non-TBI u-HCT treatments. We retrospectively investigated the clinical outcomes of allogenetic hematopoietic cell transplantation (alloHCT) from an unrelated donor without TBI (non-TBI u-HCT) and compared the clinical outcomes of fludarabine-based (FLU group) and cyclophosphamide-ATG (Cy-ATG group) conditioning regimens. Sixty-one patients received the non-TBI conditioning regimen for u-HCT (32 in the FLU group and 29 in the Cy-ATG group). The cumulative incidence of neutrophil engraftment at 30 days, platelet > 20 K/μL at 30 days, acute graft-versus host disease (aGvHD) at 100 days, and chronic GvHD (cGvHD) at 2 years were 87.01%, 65.57%, 35.20%, and 26.64%, respectively. However, transplantation outcomes and overall survival rates did not differ between the FLU and Cy-ATG groups. Only infused CD34+ cells $>3 \times 10^6$ kg^{-1} was identified as a favorable factor

Abbreviations: AA, aplastic anemia; aGvHD, Acute graft-versus host disease; ALG, anti-lymphocyte globulin; alloHCT, allogeneic hematopoietic stem cell transplantation; ANC, absolute neutrophil count; ATG, anti-thymocyte globulin; BM, bone marrow; cGvHD, chronic graft-versus host disease; Cy-ATG group, cyclophosphamide-ATG conditioning regimen; Cy, cyclophosphamide; Dx, diagnosis; FLU group, fludarabine-based conditioning regimen; IST, immune suppression therapy; MSD, matched sibling donor; non-TBI u-HCT, allogenetic hematopoietic cell transplantation from unrelated donor without total body irradiation; PC, platelet concentrate; PRC, packed red cell; SOS, hepatic sinusoidal obstruction syndrome; TBI, total body irradiation; u-HCT, allogenetic hematopoietic cell transplantation from unrelated donor; UD, unrelated donor.

☆ H. K. H.-J. Kim and J.-H. P. developed the study concept. H. K., K.-H. L., S.-K. S., C.-W. J., Y.-D. J., S.-H. K., B.-S. K., J.-H. C., J.-Y. K., M.-S. H., S.-H. B., H.-J. S., J.-H. W., S. O., W.-S. L., J.-H P., S.-S. Y. performed study. H. K. wrote the manuscript. H.-J. Kim and J.-H. P. critically reviewed the manuscript.

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0145-2126/$ – see front matter © 2014 Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.leukres.2014.01.002

for survival in the multivariate analysis. In conclusion, non-TBI u-HCT was feasible and there was no difference between the FLU and Cy-ATG groups in terms of transplantation outcomes.

1. Introduction

Allogeneic hematopoietic stem cell transplantation (alloHCT) is the treatment of choice for severe idiopathic aplastic anemia (AA) when the patient has a matched sibling donor (MSD). Allo-HCT from an unrelated donor (UD) is only attempted if immune suppression therapy is unsuccessful, as transplantation outcomes from UD are thought to be inferior to those of MSD [1,2]. However, our previous research suggested that the poor outcomes of alloHCT from UD (u-HCT) might be the result of negative clinical factors in the pre-transplantation conditions [3]. Advances in supportive care and transplantation conditioning regimens have widened the indication of alloHCT and a variety of patients who previously did not meet the criteria for alloHCT due to age, donor type, or pre-transplantation conditions, are now overcoming these limitations.

Although traditionally total body irradiation (TBI) was the standard conditioning regimen for alloHCT from UD in AA, our experience suggested the feasibility of u-HCT without TBI conditioning, as TBI caused inconvenience and therapy-related toxicities [4]. A reduced TBI dose was analyzed retrospectively and the results indicated that u-HCT with TBI-800 cGy/cyclophosphamide (Cy)-120 might be suitable for patients with severe aplastic anemia [5]. Recently, conditioning regimens without TBI have been applied to u-HCT with great success. Therefore, we need an up-to-date and large-scale review of transplantation outcome data for u-HCT without TBI.

Fludarabine is increasingly incorporated into conditioning regimens, not only for u-HCT but also for MSD [6–8], due to its immunosuppressive effect without the Cy toxicities. Our study showed that the beneficial effect of fludarabine in alloHCT from MSD was not obvious in the subgroup analysis of u-HCT. Therefore, the real benefit of fludarabine, which is used for most u-HCT without TBI, is uncertain. The aim of this retrospective study was to define the general transplantation outcomes of u-HCT without TBI, and search for the effect of fludarabine on u-HCT without TBI.

2. Patients and methods

2.1. Patient eligibility

Patients were included if transfusion dependent severe/very severe acquired aplastic anemia (AA) had been diagnosed, if patients were over 15 years of age at the time of alloHCT treatment, and if patients had undergone alloHCT from an HLA-matched related donor (MRD) or alternative donor (AD), regardless of prior IST history. The exclusion criteria were the presence of congenital aplasia, including Fanconi anemia, Diamond-Blackfan syndrome, or congenital dyskeratosis; and hypoplastic myelodysplastic syndrome.

2.2. Data collection

The original protocol for retrospective comparison between MRD and AD was approved by the Korean Society of Blood and Marrow Transplantation (KSBMT) Clinical Study Committee (approval no. KSBMT07-02). The Cooperative Study Group A for Hematology (C-006A study) approved a phase III prospective trial comparing Cy-ATG and Cy-fludarabine-ATG [3,9]. The above two study populations were combined for this analysis. Data were also collected from patients with pure red cell aplasia and paroxysmal nocturnal hemoglobinuria in the KSBMT07-02 study, and from patients with hypoplatic myelodysplastic syndrome in the COSAH (C-006A) study, but these data were not included in this analysis. The final data set analyzed in this study was alloHCT from unrelated donors who had not received TBI as a conditioning regimen (non-TBI u-HCT).

2.3. Evaluation criteria

The principal objective of the study was to define the general outcomes after u-HCT in patients who had not received TBI conditioning. We also tried to define whether a fludarabine conditioning regimen could affect transplantation outcomes. Hepatic sinusoidal obstruction syndrome (SOS) was diagnosed using McDonald's guidelines and modified according to the Seattle criteria [10,11]. Two out of the following three criteria had to be present within 30 days of transplantation to fit the diagnosis of SOS: weight gain >5% from baseline body weight; hepatomegaly with right upper quadrant pain; or hyperbilirubinemia (serum bilirubin >2 mg/dL). No other explanation for these signs and symptoms could be present at the time of the diagnosis.

Performance status was graded using ECOG performance scoring. A relapse was defined as reacquisition of transfusion-dependence or fulfillment of severe/very severe criteria after full engraftment. Other evaluation criteria were the same as in our previous study [3].

Patients were categorized as belonging to the fludarabine group (patients who had received fludarabine as a conditioning regimen) and the non-fludarabine group (patients who had not received fludarabine as a conditioning regimen) to evaluate the effect of fludarabine-containing conditioning on alloHCT outcomes.

2.4. Statistical analysis

All of the analyses were performed on an intention-to-treat basis. The patients were divided into two groups; the fludarabine (FLU) group who had received fludarabine as a conditioning regimen and the Cy-ATG (non-fludarabine) group who had received Cy-ATG as a conditioning regimen. The Chi-square test was used to compare categorical variables and Student's *t*-test was employed to compare continuous variables between any two groups. The starting point for the determination of time-dependent parameters was the first day of stem cell infusion. The time to engraftment, time to acute graft versus host disease (aGvHD), and chronic graft versus host disease (cGvHD) were estimated using the cumulative incidence function, and differences were compared using Gray's test [12]. The competing factors for the cumulative incidence function were engraftment and death by any cause. Overall survival was measured from the time of stem cell infusion to the date of death, or the last date on which the patient was known to be alive. (This constituted censoring.) Survival curves were computed according to the Kaplan–Meier method, and differences in survival were compared by the log-rank test. A Cox's proportional hazard model was used to determine the effects on survival of various prognostic factors, including age, donor/recipient gender matching, number of cells transfused, time from diagnosis to alloHCT, stem cell source, dose of irradiation, HLA matching, prior IST history, use of ATG conditioning, and fludarabine conditioning. All of these variables were dichotomized and converted into categorical classes. All of the prognostic factors with p-values <0.15 in the univariate analysis were used as variables in the multivariate analysis. Differences were assessed using a two-sided test at the $p = 0.05$ level of significance. We used the R package (cmprsk) to analyze cumulative incidence, and SPSS version 17 for all of the other statistical analyses.

3. Results

3.1. Patients

Patients' data were collected from the KSBMT2007-02 study ($n = 225$) and the C-004A study ($n = 83$). All of the 61 patients who had received non-TBI u-HCT were selected for this analysis. The median follow-up period for surviving patients was 22.3 (1.4–97.3) months. Most patients ($n = 55$, 91.2%) were severe ($n = 50$, 82.0%) or very severe ($n = 5$, 8.2%) AA. Fifty patients (82.0%) received anti-thymocyte globulin (ATG) and/or cyclosporine in immune suppression therapy (IST). Thirty-one (50.8%) patients had HLA full-matched donors. HLA were mismatched by 1/6 in 20 patients (32.8%), 2/6 in 7 patients (11.5%), 3/6 in 2 patients (3.3%), and even 4/6 in 1 patient (1.6%) patients. Low resolution (2 digits) HLA typing and serologic HLA typing test were done in 14 (23.0%) and 12 (19.7%) patients, respectively. Donor-recipient sex-matching was same-sex in 32 patients (52.5%), male to female in 22 (36.1%), and female to male in 7 (11.5%). There were no positive HBs antigens in donor/recipient ($n = 49/61$) or positive anti-HCV antibodies ($n = 49/47$). The most common drugs used for the conditioning regimen were cyclophosphamide ($n = 59$, 96.7%), ATG ($n = 55$, 90.2%), and fludarabine ($n = 32$, 52.5%). Cyclophosphamide-ATG

Please cite this article in press as: Kim H, et al. Allogeneic hematopoietic cell transplantation without total body irradiation from unrelated donor in adult patients with idiopathic aplastic anemia: Fludarabine versus cyclophosphamide-ATG. Leuk Res (2014), http://dx.doi.org/10.1016/j.leukres.2014.01.002