


RESEARCH ARTICLE

The Combination of Anti-Thymocyte Globulin and Basiliximab for Haploidentical Hematopoietic Stem Cell Transplantation

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ABSTRACT

Objectives: Identical hematopoietic stem cell transplantation (haplo-HSCT) is associated with a higher risk of graft rejection when compared to matched sibling donor transplantations. **Methods:** The study included 34 patients who were treated with a novel regimen combining basiliximab, Anti-thymocyte globulin (ATG) and conventional immunosuppressive in the recipients of haplo-HSCT. **Results:** The cumulative incidence of grade II–IV and grade III–IV aGVHD was 38.2% and 11.8%, while the rates of limited and extensive cGVHD were 17.6% and 23.5%, respectively. Laboratory evidence of CMV and EBV reactivation were found in 9 patients (26.5%) and 6 patients (18.8%), respectively. The relapse rate of haplo-HSCT was 14.7% at 1 year; and 1-year OS and DFS were achieved in 58.8% and 55.9% of the patients, respectively. **Conclusions:** The results suggested that basiliximab combined with low-dose ATG could be a promising treatment strategy in haplo-HSCT.

Keywords: Basiliximab; Anti-Thymocyte Globulin; Haploidentical Hematopoietic Stem Cell Transplantation.

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INTRODUCTION

HLA-matched allogeneic hematopoietic stem cell transplant (HSCT) is limited by the availability of matched related or unrelated donors. Haploidentical HSCT is readily available for almost all patients who need HSCT. However, this therapy is associated with high incidence of acute and chronic Graft Versus Host Disease (GVHD), delayed immune recovery, and increased transplantation-related mortality (TRM)[1-3]. Fortunately, Anti-Thymocyte Globulin (ATG) has been extensively studied as a means to prevent graft rejection as well as acute and chronic GVHD in HLA-matched transplantation[4-6]. However, its efficacy in modulating severe acute and chronic GVHD is offset by an increased risk of infectious complications including CMV and EBV reactivation [7-10] and relapse after HSCT[11]. Anti-thymocyte globulin, varying in immune source and host species, are polyclonal IgG antibodies that act mainly through direct cytotoxicity and complement dependent lysis[12]. Due to their broad spectrum of targets including T-cells, B-cells, NK-cells and monocytes as well as platelets and granulocytes, ATG

have many side effects that include allergic reactions, delayed immunological recovery and infections especially virus reactivations[13]. Alternative immunosuppressive agents with less toxicity and better outcomes are urgently needed.

Basiliximab is a nonlymphocyte-depleting monoclonal antibody targeting the interleukin-2 receptor (IL-2R), which has been found predominantly on the surface of activated cytotoxic T cells. Specific binding of monoclonal antibody to CD25 blocks the IL-2-induced proliferation and results in selective immune-suppression [14]. The prophylactic use of basiliximab has been proved as a safe and promising immunosuppressive agent for the prevention of GVHD in recipients of haploidentical HSCT [14-17].

In this retrospective analysis, we assessed the effects of basiliximab combined with ATG on the incidence of acute GVHD, chronic GVHD, relapse, overall survival (OS), disease-free survival (DFS) and infections in patients with hematologic diseases undergoing haploidentical HSCT.

MATERIALS AND METHODS

Patient characteristics

From July 2012 to December 2017, a total of 34 patients with diseases who underwent haplo-HSCT at the Second Affiliated Hospital of Chongqing Medical University (Chongqing, China) were included in this retrospective study. All study patients had failed to find suitable HLA-matched donor in their families or donor registries prior to undergoing HLA-haploidentical HSCT as a salvage treatment. All patients included in the study were followed longitudinally until death or lost to follow-up. All study patients had a Karnofsky performance score (KPS) of >60 and did not have active/untreated infection or HIV-seropositivity at baseline. Other criteria used in the pre-transplant organ function evaluation included left ventricular ejection fraction (LVEF) $\geq 45\%$ without significant pre-existing cardiac disease; pulmonary function testing (PFT) demonstrating forced expiratory volume (FEV1) $>50\%$ predicted and diffusing capacity of carbon monoxide (DLCO) >50 ; normal/stable kidney function on biochemistry, and liver functions tests showing total bilirubin <2.5 times normal with transaminases <3 times the upper limit of normal (ULN). All study patients had signed the informed consents before they underwent HLA-haploidentical HSCT.

Conditioning regimen and supportive care

Prior to transplantation, 11 patients received a conditioning regimen that included fludarabine, busulfan, and cyclophosphamide (Flu, 25 mg/m² per day intravenously from day -9 to -5, BU, 3.2mg/kg daily from day -6 to -4, Cy, 50 mg/kg daily from day -3 to -2) and 23 patients received a conditioning regimen that included busulfan, cyclophosphamide (BU, 3.2mg/kg daily from day -6 to -4, Cy, 50 mg/kg daily from day -3 to -2). Phenytoin (100 mg) was administered orally three times daily to prevent epilepsy when busulfan was administered. Mesna (80% of the cyclophosphamide dose) was administered in three divided doses to prevent urinary tract toxicity when cyclophosphamide was administered. All dosing was based on ideal body weight. Ten days before transplantation, alprostadil, danshen tablets, and low molecular weight heparin sodium was administered to prevent hepatic veno-occlusive disease (HVOD) until platelet counts were less than $20 \times 10^9/L$. EBV-PCR monitoring was performed weekly until day 100. Patients were monitored weekly until day 100 for cytomegalovirus (CMV); those who were positive for CMV received preemptive treatment with ganciclovir. The schema of the conditioning protocol is shown in Figure 1.

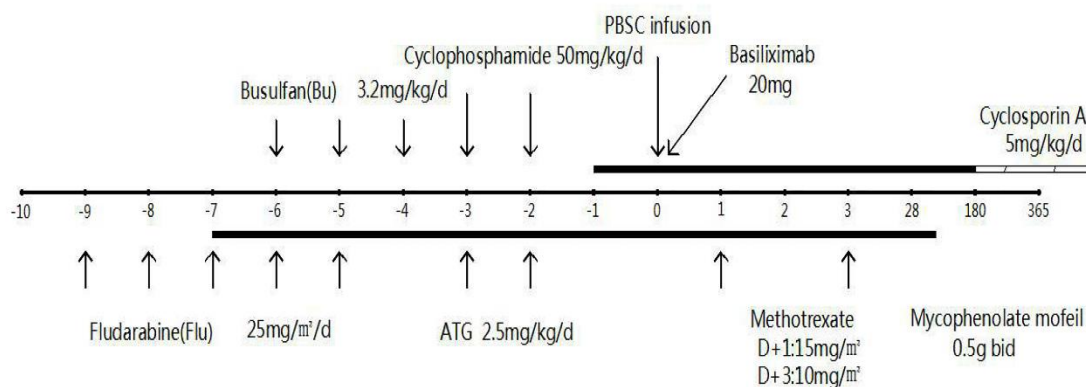


Figure 1. Haplo-HSCT conditioning and post-transplant immunosuppressive regimen.

Collection of hematopoietic cells

The donors were primed with granulocyte colony-stimulating factor (250µg bid) injected subcutaneously for five to six consecutive days. Starting on the fifth and sixth day (day 0 of HCT) of G-CSF administration, donor mononuclear cells were harvested by large-volume leukapheresis. Mononuclear cells were collected at $>4 \times 10^8/kg$ (body weight of patients), while CD34+ cells were collected at $>2 \times 10^6/kg$ (body weight of patients). Hematopoietic cells harvested from the donor were directly transfused into the recipient through a central venous catheter.

Evaluation of engraftment

Neutrophil engraftment was defined as an absolute neutrophil count of $0.5 \times 10^9/L$ or more for two consecutive days. Platelet engraftment was defined as $20 \times 10^9/L$ or more for three consecutive days without transfusion.

GVHD prophylaxis

Basiliximab was injected intravenously two hours before stem cell infusion at a dose of 20mg on first day. Rabbit ATG (Thymoglobulin; Genzyme-Sanofi) was intravenously administered at a dose of 2.5 mg/kg daily from day -3 to day -2 (total dose, 5mg/kg). Cyclosporin A (CsA) was administered from day -1 at a dose of 5 mg/kg/day, and the serum concentration was maintained

between 150 and 250 ng/ml. Starting sixth months after HSCT, the CSA dose was decreased by 10% every 2 to 4 weeks in patients with no evidence of GVHD. Methotrexate was administered intravenously at a dose of 15 mg/m² on day +1 and at 10 mg/m² on days +3. Mycophenolate mofetil was administered twice daily at a dose of 0.5g from day -8 to day +28; it was then discontinued gradually. The schema of the post-transplant immunosuppressive regimen is shown in Figure 1. Acute GVHD was assessed and graded according to the Seattle Criteria [9]. Chronic GVHD was defined per the previously published criteria [10].

Statistical analysis

Descriptive analyses (counts and percentages) were performed for demographics and patient characteristics. The distinction between aGVHD and cGVHD was based on time of onset post-transplantation. Rates of hematopoietic recovery, GVHD, virus activation, relapse were calculated using cumulative incidences. Overall survival (OS) was defined as the time from transplantation to death from any cause. Disease-free survival (DFS) was defined as the interval from transplantation to relapse of the disease or death from any cause. Patients alive without relapse were censored at the date of last contact. Incidences/rates were estimated using proportions. The

Kaplan-Meier method was used to estimate OS and DFS. Survival rates were calculated one year after haplo-HSCT. Data were analyzed using SPSS Statistics 23 and graphs were drawn with Graphpad Prism 7.0.

RESULT

Patient Characteristics

Table 1 summarizes baseline patient characteristics. The 34 patients included in the study consisted of 19 males and 15 females with a median age of 25.5 years (range, 10-59 years). All patients had been diagnosed with acute myeloid leukemia (AML) (n=15), acute lymphoblastic leukemia (ALL) (n=6), chronic myeloid leukemia (CML) (n=6), non-Hodgkin lymphoma (NHL) (n=3), severe aplastic anemia (SAA) (n=2), or myelodysplastic syndrome (MDS) (n=2). Among these patients, ten patients had failed chemotherapy; fourteen patients had an extremely poor prognosis with unfavorable cytogenetic risk factor; five patients were in complete remission (CR); and five had active disease.

Table 1. Clinical Characteristics of Haploidentical Stem Cell Transplant Patients.

| Characteristics | Number |
|-------------------------------------|--------------|
| Age/years, median (range) | 25.5 (10-59) |
| Sex | |
| Male | 19 |
| Female | 15 |
| Diagnosis | |
| AML | 15 |
| ALL | 6 |
| CML | 6 |
| NHL | 3 |
| SAA | 2 |
| MDS | 2 |
| Stage at transplant | |
| CR | 5 |
| Active disease | 5 |
| Refractory/relapsed | 10 |
| unfavorable cytogenetic risk factor | 14 |
| Donor/recipient relationship | |
| Parent donor | 17 |
| Sibling donor | 9 |
| Child donor | 6 |
| Lateral relative donor | 2 |

Abbreviations: AML, Acute Myeloid Leukemia; ALL, Acute Lymphoblastic Leukemia; CML, Chronic myeloid leukemia; NHL, Non-Hodgkin's lymphoma; SAA, Severe aplastic anemia; MDS, Myelodysplastic Syndrome; CR, Complete Remission.

Engraftment

The median number of CD34+stem cells infused was $6.35 \times 10^6/\text{kg}$ (range, $2.05 \times 10^6/\text{kg}$ - $15.29 \times 10^6/\text{kg}$), and the median number of mononuclear cells infused was $11.82 \times 10^8/\text{kg}$ (range, $3.18 \times 10^8/\text{kg}$ - $18.01 \times 10^8/\text{kg}$). Only one patient failed platelet engraftment because of myelofibrosis. The median time to ANC engraftment was 9.5 days (range, 6-19 days, Figure 2A), and the median time to platelet engraftment was 10 days (range, 5-33 days, Figure 2A).

Graft-versus-Host Disease

All 34 study patients could be evaluated for occurrence of aGVHD. A total of 13 patients developed grade II to IV aGVHD on day 100, resulting in a cumulative incidence of 38.2% (Figure 2B). The median time to the development of grade II to IV aGVHD was 17 days (range, 11-29 days). Four patients developed grade III to IV aGVHD on day 100 resulting in a cumulative incidence of 11.8% (Figure 2B). One of 4 patients with grade III to IV aGVHD had interruption in CsA before day 30, as described above.

During a follow-up period of 12 months, 14 patients developed cGVHD resulting in a cumulative incidence of 41.2%. There were 6 (17.6%) limited chronic GVHD, and 8 (23.5%) extensive chronic GVHD, see Figure 2C. No patient died from cGVHD.

Infectious Complications

Eleven study patients (32.3%) developed probable or proven bacterial infection post-transplantation, and four (4) patients (11.8%) experienced oral fungal infection. None of these patients died during the course of the study. Laboratory evidence of CMV reactivation from peripheral blood PCR was observed in 9 patients (26.5%) and six patients (18.8%) developed Epstein-Barr virus reactivation. All study patients with CMV disease were treated with ganciclovir in combination of intravenous immunoglobulin until CMV DNA detection turned to negative. Two patients died of CMV disease. Anti-CMV therapy was successful in the remaining patients. Moreover, only one study patient developed post-transplant lymphoproliferative disease (PTLD).

Relapse

A total of 5 study patients had relapsed, resulting in a cumulative incidence of 14.7% at 1 years (Figure 2D). One of these 5 patients had high-risk disease. Four relapses occurred in patients who had active disease before transplantation. One relapse occurred before day 100 and 4 relapses occurred between day 100 and 1 year.

Survival and Outcomes

With a median follow-up of 15.5 months (range, 1.5-76 months), the overall survival (OS) at 100 days and 1-year post-transplantation was 79.4% and 58.8%, respectively (Figure 3A). Disease-free survival (DFS) at 100 days and 1-year post-transplantation was 76.5% and 55.9%, respectively (Figure 3B). Eleven patients died during the follow up period of 12 months, and the most frequent causes of death were severe infection (n=4), relapse (n=4), and aGVHD (n=3).

DISCUSSION

Graft-versus-host disease (GVHD) is a common complication after transplantation and remains a major cause of morbidity and mortality, limiting the success of a potentially curative transplant. The most common GVHD prophylaxis has historically been based on a calcineurin inhibitor, Mycophenolate mofetil (MMF) and a short course of methotrexate (MTX). Recent experimental models and biologic insights, however, have greatly improved the understanding of the pathogenesis of GVHD, and newer approaches targeting different components of immune dysregulation are currently being used and further investigated in improving GVHD outcomes. These methods include: alemtuzumab (targeting the CD52 receptor), vorinostat (histone deacetylase inhibitor), bortezomib (inhibition of NF-kappa B, P44/42 mitogen-activated protein kinase pathway), abatacept (Costimulation blockade of CD28:CD80/86 to inhibit T cells), sirolimus (inhibition of mTOR impairs T-cell signaling), baliximab (anti-CD25 antibody), ruxolitinib (JAK inhibitors), Tregs (regulate self-tolerance). Among them, baliximab has been used in HSCT to treat severe steroid-refractory aGVHD with favorable results [20-22]. However, there were only a few prior reports on the use of basiliximab for the prevention of GVHD in haploidentical HSCT. In these reports, the prophylactic regimen of basiliximab without ATG seemed to be safe and effective in preventing GVHD [15,23]. Prophylactic regimens combining basiliximab (20mg/d, day 0 and +4) and ATG(6mg/kg) have been reported by Zhang et al [17] in a haploidentical HSCT study in which the rates of grade II-

IV and grade III-IV aGVHD were 28.6 and 14.3%, respectively, the rates of limited and extensive cGVHD were 19.4 and 13.8%, respectively, with low relapse rate and acceptable transplantation-related mortality. Additionally, a haploidentical bone marrow transplantation study showed that prophylactic regimens

of basiliximab and ATG resulted in a low incidence of GVHD compared to ATG alone (11% vs 33%, P=0.046) [16]. High-dose ATG or basiliximab is relatively costly in the above study, however, the reduced dose of ATG and basiliximab will reduce the patient's financial burden.

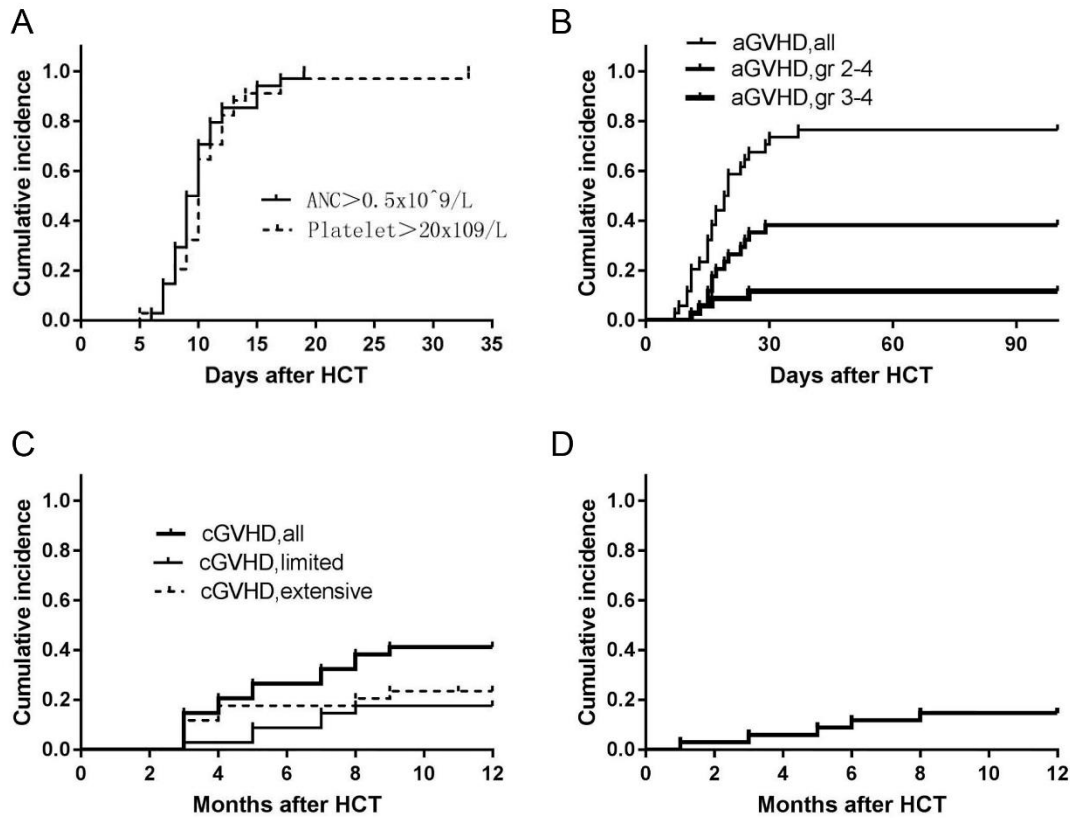


Figure 2. Cumulative incidence of patients. (A. Donor cell engraftment after haplo-HSCT; B. Acute GVHD after haplo-HSCT; C. Chronic GVHD after haplo-HSCT; D. Relapse after haplo-HSCT)

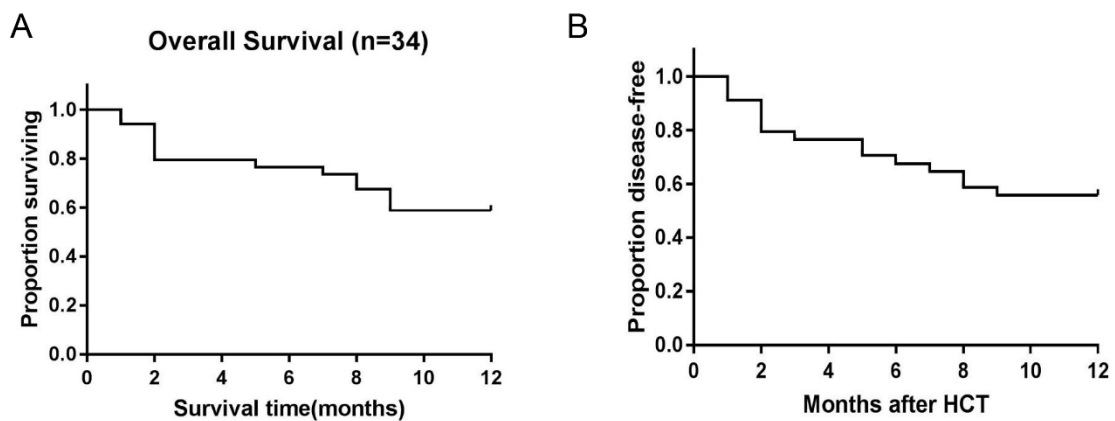


Figure 3. Overall Survival and disease-free survival of 34 patients receiving haplo-HSCT. (A. Overall Survival; B. Disease-free survival)

Since stronger immunosuppressive agents are usually needed in haploidentical HSCT than in matched HSCT, dose-finding studies for ATG have been performed in recipients of haploidentical HSCT. our results appeared to compare favorably to that of Shinichi Kako et al. [24] who administered thymoglobulin at a dose of 5 mg/kg in HLA-mismatched haploidentical transplantation. Using this treatment strategy, Kako et al observed acute and chronic

GVHD in six and five of 12 patients studied, respectively. In another study in which haploidentical HSCT was performed with thymoglobulin at a total dose of 12mg/kg II-IV acute GVHD and III-IV acute GVHD were reported in 20% and 7% of the study participants, respectively [25]. A recent pioneering randomized clinical trial regarding haploidentical hematopoietic stem cell transplantation in 224 hematologic malignant neoplasm patients concluded

that patients receiving 6 mg/kg ATG or 10 mg/kg ATG showed incidence rate of 100-day class II to IV aGVHD were 41.9% and 25.0%, respectively, the cumulative incidence rate of 1.5-year cGVHD were 64.6% and 44.8%, respectively [10]. We conducted this retrospective study to evaluate a novel combination of basiliximab, low dose ATG and conventional immunosuppressive agents for the prevention of GVHD in recipients of haplo-HSCT. The cumulative incidence of grade II to IV and grade III to IV aGVHD was 38.2% and 11.8%, respectively. It is noteworthy that the incidence of GVHD in this retrospective analysis was lower than that of 5-6 mg/kg ATG, and not significantly higher than that of 10-12 mg/kg ATG. Considering that no patient received 1 antigen mismatched graft (HLA 9/10), this is a very encouraging finding. Our findings suggested that the approach used in the study might have induced sufficient immunosuppression in the host to prevent GVHD in haplo-HSCT.

In patients undergoing allogeneic HSCT, the extent of HLA mismatch between donor and recipient has been a barrier to successful donor cell engraftment [26]. Although consistent engraftment was achieved after HSCT from related donors with a single mismatch at the HLA-A, -B, or -DR locus, the rate of graft failure increased after HSCT from related donors with 2 or 3 HLA antigen mismatches [27]. In our study, only one patient failed in platelet engraftment because of myelofibrosis. This is very encouraging considering that no patients received 1 antigen mismatched graft.

Low incidence of CMV (26.5%) and EBV (18.8%) reactivation was noted in our study. In comparison, the incidence of CMV reactivation was as high as 74% in a previous study [28]. Our results are comparable to a recent retrospective study in which patients received 12 mg/kg ATG for haplo-HSCT. The investigators observed CMV reactivation and EBV reactivation in 81% and 61% of the study participants, respectively [25]. Recent studies reported that Epstein-Barr virus related post transplantation lymphoproliferative disorder (PTLD) after allo-HSCT was associated with a mortality rate of as high as 50% to 90% [29,30] and a PTLN rate of 9.7% in the context of ATG based conditioning [31]. Fortunately, the incidence of EBV-reactivation and PTLN in our patients was low, and no PTLN-related death occurred. Since the observed high rate of EBV-reactivation and CMV reactivation were predominantly related to the degree of T-cell depletion or impairment [32], it is known that at high concentrations (0.1–1.0 mg/mL), ATG induces lysis of both resting and activated T cells (via human classic complement pathway activation), whereas at low concentrations, it induces apoptosis of activated cells (by Fas/Fas-ligand interaction) while sparing resting cells [33,34]. GVHD prophylaxis using basiliximab and low-dose ATG may be effective by selective elimination of

highly activated donor-specific alloreactive T cells, while sparing non-activated T cells.

High-risk disease status at the time of HCT was an independent predictor of disease progression/recurrence, TRM, and shorter event-free and overall survival. According to a study in which patients received a total dose of 13.5 mg/kg ATG combined with other immunosuppressive agents, the 1-year OS and incidence rates of relapse were 48.1% and 16%, respectively, 38 of 50 patients were CR at the time of HCT [28]. A recent clinical trial regarding haplo-HSCT that patients receiving 5 mg/kg ATG showed that the 1-year OS, PFS and incidence rates of relapse were 33.3%, 24.3% and 59%, respectively [24]. In addition, it was reported by Lee K.H et al in 83 patients treated with 15 mg/kg ATG [25] that the 1-year event-free and OS rates were 56% and 45%, respectively, for patients with acute leukemia in CR; 9% and 9%, respectively, for patients with relapse/refractory acute leukemia. The incidence rates of relapse were 27% and 32%, respectively, for patients with acute leukemia in CR1 and CR2, 79%, for patients with relapse/refractory acute leukemia. In our study, patients (29/34) with high-risk disease status at the time of HCT, we found that the relapse rate of haplo-HSCT was 14.7% at 1 year; and 1-year overall survival (OS) and disease-free survival (DFS) were achieved in 58.8% and 55.9% of the patients, respectively. The 1-year relapse rate with high-risk disease status at the time of HCT was lower than those reported in the literature, in which 13.5 mg/kg ATG, 5 mg/kg ATG, or 15 mg/kg ATG were used. And 1-year OS and DFS of patients were better than those reported in the literature. These results suggested that this new regimen effectively decreased the disease recurrence post transplantation and improved patient quality of life. This brings hope for patients with high-risk disease.

To summarize, our results suggested that basiliximab combined with low-dose ATG was a safe and effective transplant regimen in the context of haplo-HSCT. In our study, this approach yielded encouraging engraftment results with low incidence of viral reactivation, and did not significantly increase the incidence of acute GVHD, as well as reduced the risk of relapse and improved patient quality of life. Since this was a retrospective study involving a small number of patients from a single institution, prospective clinical trials are warranted to further investigate this approach.

ACKNOWLEDGMENTS

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DECLARATION OF COMPETING INTEREST

The author reports no conflicts of interest in this work.

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