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Research paper

# Idarubicin-intensified BUCY2 conditioning regimen improved survival in high-risk acute myeloid, but not lymphocytic leukemia patients undergoing allogeneic hematopoietic stem cell transplantation: A retrospective comparative study

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ABSTRACT

The intensity of conditioning regimen is highly correlated with outcomes of allogeneic hematopoietic stem cell transplantation (allo-HSCT). We have previously reported that idarubicin (IDA) intensified BUCY2 regimen could reduce relapse and improve survival for high-risk hematological malignancies undergoing allo-HSCT. However, there is no published study comparing the efficacy of IDA-BUCY2 regimen for high-risk acute myeloid leukemia (AML) versus acute lymphocytic leukemia (ALL). We further retrospectively compared therapeutic outcomes of intensified conditioning regimen on 140 high-risk AML and ALL patients in the data analyses. IDA 15 mg/m$^2$/d was administered by continuous infusion from day −11 to −9, followed by intravenous injection of busulfan (BU) (3.2 mg/kg/d) from day −6 to −4, and intravenous injection of cyclophosphamide (CY) (1.8 g/m$^2$/d) from day −3 to −2 in IDA-BUCY2 regimen. For high-risk AML, cumulative probabilities of 3-year relapse rates in IDA-BUCY2 and traditional BUCY2 regimens were 16.9%, 43.3% ($P$ = 0.016). Cumulative probabilities of 3-year overall survival (OS) and disease-free survival (DFS) were 69.2% vs 44.0% ($P$ = 0.024), and 66.9% vs 38.2% ($P$ = 0.01). However, two regimens showed no significant differences for high-risk ALL. Multivariate analysis also indicated that IDA intensified BUCY2 conditioning was the favorable variable to reduce relapse and elevate survival for high-risk AML patients. In conclusion, IDA-BUCY2 regimen reduces relapse and improves survival for high-risk AML undergoing allo-HSCT, but not presenting uniform therapeutic effects for high-risk ALL.

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## 1. Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is considered as a potentially curative approach for patients with clinical or cytogenetic high-risk hematological malignancies [1–3]. Otherwise, disease-free survival (DFS) of these patients is only in the range of 10–40% even after allo-HSCT [4–7]. Relapse of underlying disease is still the obstacle for the success of this strategy.

Increasing conditioning intensity is an important option to improve survival of high-risk acute leukemia because conditioning dose-intensity is highly correlated with relapse rate (RR) after allo-HSCT [8,9]. High-dose busulfan (BU) combined with cyclophosphamide (CY) is a worldwide used classical myeloablative regimen for allo-HSCT [10,11]. Recently, different studies have been explored to intensify BUCY2 regimen with new promising anti-leukemic agents. Etoposide (VP-16) has been introduced to

*Abbreviations:* allo-HSCT, allogeneic hematopoietic stem cell transplantation; IDA, idarubicin; AML, acute myeloid leukemia; ALL, acute lymphocytic leukemia; OS, overall survival; DFS, disease-free survival; RR, relapse rate; BU, busulfan; CY, cyclophosphamide; VP-16, etoposide; CR, complete remission; Ara-C, cytarabine; MLL, mixed lineage leukemia; PBSCs, peripheral blood stem cells; rhG-CSF, recombinant human granulocyte colony-stimulating factor; ANC, absolute neutrophil count; GVHD, graft versus host disease; CsA, cyclosporine A; MTX, methotrexate; MMF, mycophenolate mofetil; TRM, transplant-related mortality; RRM, relapse-related mortality; CML, chronic myeloid leukemia; EBMT, European Group for Blood and Marrow Transplantation; TBI, total body irradiation; HR, hazard ratio; CI, confidence interval; CMV, cytomegalovirus; HVOD, hepatic veno-occlusive disease; NR, no remission; FISH, fluorescein in situ hybridization.

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combine with BUCY2, but benefit of this intensified regimen is controversial. Zander AR et al. [12] reported that estimated 5-year DFS reached up to 80.5% and no relapse was observed when acute myeloid leukemia (AML) patients in first complete remission (CR1) were prepared with BU/CY/VP-16 regimen before allo-HSCT. Furthermore, VP-16 in combination with BUCY2 was also found to be a highly active regimen for patients with high-risk or advanced myeloid malignancies which achieved low RR and long-term survival [13]. Nevertheless, in other studies the outcome of acute leukemia undergoing allo-HSCT was not improved by the addition of VP-16 to BUCY2 regimen [14]. High-dose cytarabine (Ara-C) combined with BUCY2 regimen has also been demonstrated promising in high-risk/refractory/recurrent acute leukemia, but the number of patients is limited [8,15].

Idarubicin (IDA) is another potential anti-leukemic agent adding to classical conditioning regimen. As a new anthracycline, IDA has been reported to be associated with lower incidence of resistant leukemia, higher CR rate and better long-term survival than traditional anthracyclines. Moreover, IDA has lower cardiotoxicity and higher penetration rate to central nerve system comparing with daunorubicin [16]. Previously, it was demonstrated that combination of IDA with standard regimen improved the outcome of AML treated with autologous HSCT (auto-HSCT) in CR1 [17,18]. When comparing the outcomes of IDA- and VP-16-intensified conditioning regimens for allo-HSCT in 48 high-risk acute leukemia patients, the results revealed that IDA-intensified regimen achieved better survival [19]. In our previous retrospective study on the outcome of 94 patients with high-risk hematological malignancies undergoing allo-HSCT, we found that IDA-intensified BUCY2 (IDA-BUCY2) regimen reduced RR and improved survival comparing with BUCY2 regimen as well [20]. However, up until now, a large population study comparing the outcomes and efficacies of IDA intensified regimen in patients with high-risk AML versus acute lymphocytic leukemia (ALL) has not been performed.

Therefore, in the present research, we aimed to further conduct this comparative study regarding the therapeutic effects of IDA intensified BUCY2 regimen for high-risk AML and ALL. Our results showed that IDA-BUCY2 regimen reduced relapse and improved survival in high-risk AML undergoing allo-HSCT. However, it did not show the same benefits in high-risk ALL.

## 2. Materials and methods

### 2.1. Patient eligibility

This is a single-center, retrospective comparative analysis of 140 consecutive patients with high-risk acute leukemia who underwent their first allo-HSCT between May 2007 and August 2014 at our center. Fifty-seven patients were included from our previous research with extended follow-up [20]. The median age was 29 years (range: 12–57 years). There were 73 high-risk AML and 67 high-risk ALL patients. The definitions of high-risk AML were as follows: no response to induction chemotherapy, relapse within 6 months after induction or consolidation therapy, relapse with 6 months after induction therapy that could not be relieved using the original induction therapy, ≥2 relapses or relapse after auto-HSCT, unfavorable cytogenetics [21,22], or a history of preceding neoplasia and/or chemotherapy [23], in no remission (NR) [24]; The definitions of high-risk ALL consisted of age >35 years, elevated WBC count ($30 \times 10^9$/L for B cell lineage or $100 \times 10^9$/L for T cell lineage), beyond CR1 [25], or high-risk cytogenetic abnormalities, determined according to the National Comprehensive Cancer Network 2013 guidelines, such as hypodiploidy, complex karyotype (≥5 chromosomal abnormalities), t(9;22) or BCR-ABL, t(v;11q23) or mixed lineage leukemia (MLL) rearrangements. This study was reviewed and approved by the ethics committee at Union Hospital, Tongji Medical College, Huazhong University of Science and Technology. Informed consent was obtained in accordance with the Declaration of Helsinki.

### 2.2. Donor-recipient HLA typing

All donor-recipient pairs were based on HLA serologic typing which was performed for class I antigens and HLA molecular typing for the DRB1 and DQB1 loci. HLA-A, -B, -C, -DRB1 and -DQB1 were confirmed using high-resolution molecular method for all patients and unrelated donors.

### 2.3. Conditioning regimens

The IDA-BUCY2 regimen was as follows: IDA administered by continuously intravenous injection (15 mg/m$^2$/d, from day −11 to −9), followed by intravenous injection of BU (3.2 mg/kg/d in divided doses, from day −6 to −4) and intravenous injection of CY (1.8 g/m$^2$/d, from day −3 to −2). The modified BUCY2 regimen was as follows: oral hydroxycarbamide (80 mg/kg, on day −9), intravenous injection of Ara-C (2 g/m$^2$ on day −8), followed by intravenous injection of BU (3.2 mg/kg/d in divided, from day −7 to −5), CY (1.8 g/m$^2$/d from day −4 to −3) and oral Me-CCNU (250 mg/m$^2$ on day −2). Patients were hospitalized in single room utilizing high efficiency air filtration systems. Supportive care was administered as described previously [20].

### 2.4. Collection of hematopoietic cells

Donor peripheral blood stem cells (PBSCs) were collected following standard mobilization protocols. Recombinant human granulocyte colony stimulating factor (rhG-CSF) of 8–10 μg/kg was administered subcutaneously once daily to mobilize peripheral blood. PBSCs were harvested on day 4 and 5 after rhG-CSF administration and were infused without manipulation on the same day of collection.

### 2.5. Hematopoietic reconstitution and chimerism analysis

Neutrophil engraftment was defined as absolute neutrophil cell (ANC) of $0.5 \times 10^9$/L or more for 3 consecutive days and the platelet engraftment defined as achieving platelet count ≥$20 \times 10^9$/L without transfusion for at least 7 days. Chimerism and molecular monitoring was typically evaluated in recipient bone marrow cells usually on days +30, +90, +180 and +360 after transplantation. Chimerism was determined in recipient peripheral blood cells by fluorescein in situ hybridization (FISH). If the donor and recipient were of the same sex, then the chimerism was evaluated using a PCR-based assay that detects short tandem repeats in DNA. Full donor chimerism was defined by the detection of 95% or more donor cells in whole-blood samples.

### 2.6. Graft versus host disease (GVHD) prophylaxis

Patients received basic GVHD prophylaxis consisted of cyclosporine A (CsA) together with short-term methotrexate (MTX). CsA of 2.5 mg/kg d, was administered by continuously intravenous infusion from day −1 until bowel function returned to normal, then the patients was switched to oral formulation. The serum concentration of CsA was adjusted to maintain between 150 and 250 ng/ml until day +50. If no acute GVHD (aGVHD) occurred, CsA was tapered by 5% weekly and discontinued on day +180. MTX was administered intravenously at dose of 15 mg/m$^2$ on day +1 and 10 mg/m$^2$ on days +3, +6 and +11. Mycophenolate mofetil (MMF, 7.5 mg/kg, orally twice daily) and anti-CD25 monoclonal antibody

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