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Evaluate the Efficacy of Myeloablative Conditioning Regimens for Allogeneic Hematopoietic Stem Cell Transplantation in Acute Myelogenous Leukemia at BTH, Vietnam

Thu Hanh Nguyen, Huu Than Huynh, Hung Quang Tran, Quang The Nguyen, Phu Duc Vinh Huynh, Nam Duy Hoang, Tuan Xuan Ma, Duong Thi Thuy Do, Dung Chi Phu, Man Van Huynh

Stem Cell Transplantation Department, Blood Transfusion Hematology Hospital, Ho Chi Minh City, Vietnam

Corresponding Author: Man Van Huynh, Stem Cell Transplantation Department, Blood Transfusion Hematology Hospital, Ho Chi Minh City, Vietnam
E-mail: huynhvanman@yahoo.com
The first author (Thu Hanh Nguyen) and the second author (Huu Than Huynh) contributed equally works to this study

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ABSTRACT

Background: Busulfan plus cyclophosphamide (Bu/Cy) is considered one of the classical myeloablative conditioning regimens. However, its toxicity can significantly increase mortality rates. To reduce both acute and long-term complications after hematopoietic stem cell transplantation (HSCT), newer conditioning regimens are being investigated. The purposes of this study were to assess the efficacy and safety of busulfan plus cyclophosphamide (Bu/Cy) and busulfan plus fludarabine (Bu/Flu) conditioning regimen for allogeneic HSCT (allo-HSCT) in acute myelogenous leukemia (AML).

Materials and Methods: We conducted a single-center, retrospective analysis of AML, both adults and children, who underwent either Bu/Cy or Bu/Flu conditioning regimen for allo-HSCT and received peripheral blood stem cell transplants from HLA-matched donors.

Results: From 2005 – 2019, 49 AML patients receiving Bu/Cy and 21 receiving Bu/Flu were identified, meeting inclusion criteria. The two groups showed no significant differences in age, gender, disease status pre-transplant, the median time to neutrophil and platelet engraftment. Bu/Flu patients had a shorter duration of neutropenia (median 7 days vs 10 days, p = 0.001) and shorter duration of thrombocytopenia (median 10 days vs 15 days, p = 0.016) than Bu/Cy. No difference was observed in disease-free survival (DFS) and overall survival (OS) between the two groups. Both univariate and multivariate analyses showed that age, disease status pre-transplant, and chronic graft-versus-host disease (GvHD) are related to worse DFS and OS.

Conclusion*:* With similar efficacy to Bu/Cy but faster neutrophil and platelet recovery time, Bu/Flu is suitable as a pre-HSCT conditioning regimen for patients with AML.

Keywords: Allo-HSCT; Conditioning regimen; AML; Vietnam

INTRODUCTION

AML is a disorder of hematopoietic neoplasms that involves myeloid precursors, reducing their ability to differentiate into mature blood cells and instead generating malignant cells. Currently, patients who undergo consolidation chemotherapy after remission induction therapy can achieve a median complete remission (CR) duration of 12 to 18 months, with a 5-year disease-free survival rate of less than 30%. Almost all patients will relapse without post-remission therapy; hence, strategies to prevent relapse in AML are pivotal to optimizing survival outcomes [1].

Recently, bone marrow transplant, also known as HSCT, has stood out as the most effective strategy thanks to its anti-leukemic activity due to the graft versus leukemia effect[2]. AML is the principal indication for allogeneic allo-HSCT. However, its toxicity can significantly increase mortality rates, especially with previous myeloablative regimens. To reduce both acute and long-term complications after HSCT, newer conditioning regimens are being investigated.

HSCT was first introduced in Vietnam at our institution in 1995, with AML being the most frequent indication. The Bu/Cy myeloablative conditioning regimen remains in use for the allo-HSCT procedure. Starting in 2016, Bu/Flu was introduced as a second preparative regimen. Our aim is to evaluate the efficacy and safety of these two regimens, Bu/Cy and Bu/Flu, in patients with AML.

MATERIALS AND METHODS

Design and setting

In this retrospective study, we analyzed patients with AML, both adults and children, who underwent either a Bu/Cy or Bu/Flu conditioning regimen for allo-HSCT at Ho Chi Minh City Blood Transfusion and Hematology Hospital, Vietnam, from June 2005 to December 2019. This study was approved by the Ethics Committees of the University of Medicine and Pharmacy at Ho Chi Minh City (number 152/HĐĐĐ-ĐHYD).

Conditioning regimens

In patients given the Bu/Cy regimen, busulfan was administered orally at a dose of 4 mg/kg or through IV at 3.2 mg/kg on days -7, -6, -5, and -4, and IV cyclophosphamide at 60 mg/kg on days -3 and -2. In patients given the Bu/Flu regimen, IV busulfan was administered at a dose of 130 mg/m^2 on days -6, -5, -4, and -3, and IV fludarabine at 40 mg/m^2 on days -6, -5, -4, and -3.

GvHD was prevented with cyclosporin A, IV at a dose of 3 mg/kg for 20 days followed by oral administration, targeting trough concentrations of 200-400 ng/ml. Methotrexate was also given at a dose of 15 mg/m^2 on day 1 and 10 mg/m^2 on days 3, 6, and 11.

Infection prophylaxis and supportive care

All patients received an infection prophylaxis regimen with ciprofloxacin, fluconazole/itraconazole, acyclovir, and trimethoprim/sulfamethoxazole. All patients also received 5 µg/kg daily of granulocyte-colony-stimulating factor (G-CSF) from neutropenia (an absolute neutrophil count <0.5 × 10^9/L) for 2 days. Irradiated red blood cell and platelet transfusions were given if the patient's hemoglobin was ≤ 80 g/L or the platelet count was ≤ 20 × 10^9/L.

Post-HSCT follow-up

Cytomegalovirus (CMV) DNA is quantified by polymerase chain reaction (PCR) once every week until day 100. A bone marrow aspiration and biopsy were performed on day 30. Chimerism testing via PCR-based short tandem repeats (STR-PCR) or fluorescent in situ hybridization (FISH) to identify sex chromosomes was performed on day 30, 60, 90, 180, and 365 if the donor and recipient were of different genders.

Source of donor

All patients received peripheral blood stem cells transplants from HLA-matched donors.

Clinical outcomes

The primary endpoints include OS and DFS. OS was calculated from the day of transplant to death from any cause, loss to follow-up, or last follow-up. DFS was counted from the day of transplant to relapse, death from any cause, or last follow-up, whichever came first.

Secondary endpoints include the day of neutrophil engraftment, time to neutrophil engraftment, the day of platelet engraftment, time to platelet engraftment, and post-transplant adverse events such as oral ulcerations, infection, acute and chronic GvHD, venoocclusive disease (VOD), and treatment-related mortality (TRM). Engraftment was defined as the first of three consecutive days post-transplant with an absolute neutrophil count (ANC) > 0.5 × 10^9/L. The time to neutrophil engraftment was counted from when ANC ≤ 0.5 × 10^9/L until the neutrophil recovery time. Platelet engraftment was the first of seven consecutive days post-transplant

with a platelet count ≥ 20 × 10^9/L without transfusion support. The time to platelet engraftment was counted from when platelet ≤ 20 × 10^9/L until the platelet recovery time. For complete chimerism, > 95% cells were of donor origin, while this figure was ≤ 95% for mixed chimerism [3].

Statistical analysis

OS and DFS were estimated with the Kaplan-Meier model. Univariate analyses were performed using log-rank test. Cumulative incidences of relapse rate (RR) were estimated with competing risk analysis using Gray method. Death and graft failure were treated as competing events of RR. Statistical significance was set at $p < 0.05$. Statistical analysis was performed using SPSS version 13 (SPSS Inc., Chicago, IL, USA).

RESULTS

Patient characteristics

Table 1 describes patient characteristics of the 70 patients included in the study (median age, 35.5 years (range 2-51), 37 female (52.9%)). In terms of conditioning regimen, 49 patients were treated with Bu/Cy and 21 with Bu/Flu. The median follow-up time was 18.17 months (range 0.49-174.42 months), with Bu/Cy patients being followed for 30.85 months (1.02-174.42) and Bu/Flu patients for 10.12 months (0.49-35.45). Between these two groups, there were no statistically significant differences in age, gender, disease status pre-transplant, the hematopoietic cell transplantation-comorbidity-index (HCT-CI) score, gender difference, ABO compatibility between donor-recipient, or CD34+ doses. All patients and donors were CMV immunoglobulin G (IgG)-positive and M (IgM)-negative. At the end of the study, 43 patients remained alive and 27 died.

Engraftment

Engraftment of neutrophil following HSCT was achieved in all patients. The median duration of neutropenia was 10 days (range 5-19) for Bu/Cy patients and 7 days (range 4-14) for Bu/Flu patients ($p = 0.001$). The median time to neutrophil engraftment was 11 days (range 9-22) for Bu/Cy patients and 12 days (range 10-19) for Bu/Flu patients ($p = 0.12$). In terms of platelet recovery, all patients achieved engraftment except for five patients (10.2%) in the Bu/Cy group ($p = 0.31$). The median duration of thrombocytopenia was 15 days (range 8-41) for Bu/Cy patients and 10 days (range 8-34) for Bu/Flu patients ($p = 0.016$). The median time to platelet engraftment was 18 days (range 12-63) for Bu/Cy patients and 16.5 days (range 14-39) for Bu/Flu patients ($p = 0.24$). Detection of chimerism was performed in 49 patients on day 30 (29 patients in the Bu/Cy group and 20 in the Blu/Flu group), all of whom showed complete chimerism. Unavailable testing methods at our institution at the time led to a lack of chimerism status in the remaining 21 patients.

Post-transplant adverse events

Table 2 summarizes the adverse events within the first 100 days after the transplant. There were no differences in the incidence of adverse events between the Bu/Cy and Bu/Flu groups. Of note, no patients treated with Bu/Flu experienced VOD or graft rejection, while corresponding figures for the Bu/Cy group were 14% and 2%, respectively.

Relapse and survival

A total of 19 patients (27.1%) relapsed at the end of the study (Bu/Cy 17 patients, 34.7%; Bu/Flu 2 patients, 9.5%). At 2 years post-transplant, there was no difference between the two groups in RR (Figure 1A; Bu/Cy RR 37.4%, 95% CI 22.9%-51.9%; Bu/Flu RR 11.9%, 95% CI 0-27.4%; $p = 0.17$), DFS (Figure 1B; Bu/Cy 58.3%, 95% CI 44.4%-72.2%; Bu/Flu 63.9%, 95% CI 35.9%-91.9%; $p = 0.41$), and OS (Figure 1C; Bu/Cy 58%, 95% CI 43.9%-72.1%; Bu/Flu 68.4%, 95% CI 42.7%- 94.1%; $p = 0.59$). Both univariate and multivariate analyses showed that age, disease status pre-transplant, and chronic GvHD are related to worse DFS and OS (Tables 3, 4).

Table 1. Patient characteristics

Characteristic	All (n = 70)	Bu/Cy (n = 49)	Bu/Flu (n = 21)	p
Age (median, range)	35.5 (2 – 51)	35 (2 – 51)	37 (5 – 51)	0.54
Gender (n, %)				
Male	33 (47.1)	24 (49)	9 (57.1)	0.64
Female	37 (52.9)	25 (51)	12 (42.9)	
Disease status pre-transplant (n, %)				
CR1	58 (82.9)	40 (81.6)	18 (85.7)	1
Relapse or Secondary	12 (17.1)	9 (18.4)	3 (14.3)	
HCT-CI score (n, %)				
0	65 (92.9%)	46 (93.9%)	19 (90.5)	0.63
≥ 1	5 (7.1%)	3 (6.1%)	2 (9.5)	
Donor-recipient gender difference (n, %)				
Yes	26 (37.1)	16 (32.7)	10 (47.6)	0.24
No	44 (62.9)	33 (67.3)	11 (52.4)	
ABO compatibility between donor and recipient (n, %)				
Matched	47 (67.1)	35 (71.4)	12 (57.1)	0.54
Minor mismatched	9 (12.9)	6 (12.3)	3 (14.3)	
Major mismatched	12 (17.1)	7 (14.3)	5 (23.8)	
Major and minor mismatched	2 (2.9)	1 (2)	1 (4.8)	
CD34 doses (x 10^6/kg)	7.2	7.32	7.2	0.72
MNC doses (x 10^8/kg)	7.29	7.88	6.25	0.41

CR1, first complete remission; HCT-CI, hematopoietic cell transplantation-specific comorbidity index; MNC, mononuclear cell

Table 2. Adverse events in the first 100 days post-transplant

Adverse event	Bu/Cy (%) (n = 49)	Bu/Flu (%) (n = 21)	p
Fever	91.8	95.2	1
Oral ulceration	93.9	85.7	0.36
CMV reactivation	80	66.7	0.34
VOD	14	0	0.09
GvHD			
Acute	28.6	23.8	0.78
Acute, grade III-IV	6.1	9.5	0.63
Chronic	49	42.9	0.8
Graft rejection	2	0	1
TRM	8.2[a]	9.5[b]	1

TRM, treatment-related mortality; VOD, venoocclusive disease
a Causes of death were VOD (2 patients), grade IV GvHD (1 patient) and intracranial hemorrhage (1 patient)
b Causes of death were grade IV GvHD (1 patient) and severe pneumonia (1 patient)

Table 3. Summary of univariate analysis

Variable	p	
	DFS	OS
Age, ≥35 vs < 35 years	0.009	0.007
Gender, femal vs male	NS	NS
Genders of donor and recipient, same vs different	NS	NS
HCT-CI score, 0 vs □ 1 point(s)	NS	NS
ABO compatibility between donor and recipient, matched vs mismatched	NS	NS
Pre-transplant diagnosis, AML CR1 vs relapse/secondary AML	0.002	0.004
Conditioning regimen, Bu4/Cy vs Bu4/Flu	NS	NS
Acute GvHD, No vs Yes	NS	NS
Chronic GvHD, No vs Yes	0.021	0.02

Table 4. Summary of multivariate analysis

Variable	DFS			OS		
	HR	95% CI	p	HR	95% CI	p
Age, ≥ 35 vs < 35 years	2.75	1.15-6.54	0.023	2.79	1.16-6.66	0.021
Pre-transplant diagnosis, AML CR1 vs relapse/secondary AML	3.39	1.43-8.03	0.006	2.81	1.19-6.66	0.019
Chronic GvHD, No vs Yes	0.39	0.17-0.88	0.023	0.41	1.19-0.93	0.032

DISCUSSION

Patients with AML are currently only curable through allogeneic HSCT [4-8]. It has been shown to reduce relapse incidence and increase both relapse-free survival and overall survival[6]. A determining factor for a successful outcome following HSCT is the choice of conditioning regimen. Since its introduction in 1987, Bu/Cy has been one of the most commonly used myeloablative regimens without total body irradiation (TBI) worldwide. With superior outcomes to TBI-based regimens, Bu/Cy is the traditional conditioning regimen for most young patients with AML. Elderly or medically infirm patients, however, more frequently experience treatment-related toxicity with Bu/Cy, leading to the combination of Bu and fludarabine, or Bu/Flu, to offset Cy's side effects[9- 11]. Compared to Cy, Flu is as likely to be immunosuppressive, while its distinct alkyl group does not deplete the liver of glutathione, which can be reserved for busulfan metabolism[12]. Flu is even more appealing as it retains Bu-induced myeloablation and cytotoxicity through promoting alkylator-induced DNA damage.

Neutropenia and thrombocytopenia are almost always universally seen in patients undergoing high-dose chemotherapy and HSCT. Longer periods of neutropenia lead to life-threatening infections, while those of thrombocytopenia result in higher rates of infusion, hemorrhagic events, and hemorrhage-related deaths. Neutrophil and platelet recovery times were not statistically different between patients receiving Bu/Cy and Bu/Flu in our study, similar to reports by Raida[13], Fedele[14] and Liu [15]. In contrast, Patel et al. described a faster length of both neutrophil and platelet recovery in the Bu/Flu cohort compared to Bu/Cy [16], while only shorter platelet engraftment was seen in the Bu/Flu group, as reported by Rambaldi et al[17]. Additionally, patients receiving Bu/Flu had a shorter duration of ANC ≤ 0.5×10^9/L and platelet ≤ 20×10^9/L than the Bu/Cy group ($p < 0.05$), consistent with the results of Liu et al[15].

Our study also showed no difference in OS or DFS between the two groups (Figure 1B and Figure 1C). While the Bu/Cy cohort had a higher RR-2-year than the Bu/Flu cohort (Figure 1A), this result was no longer statistically significant following the log-rank test, presumably due to unequal sample sizes and varying the length of follow-up between the groups (a larger sample size and longer follow-up in the Bu/Cy group). This outcome is in accordance with the fact that Bu/Flu has been shown to be non-inferior to Bu/Cy as a preparative regimen in HSCT from multiple trials[11,16,17,13-15,18]. Nevertheless, studies that demonstrated better patient outcomes with Bu/Cy in comparison with Bu/Flu, namely Lee et al. in adults[19] and Harris et al. in children[20], included more heterogeneous populations of patients, such as those with lymphoblastic leukemia and non-malignant diseases. Indeed, upon further investigation, subgroup analysis of patients with myeloid leukemia in both studies showed similar outcomes between the Bu/Cy and Bu/Flu arms [20,19]. In practice, Bu/Cy or Bu/Flu alone are insufficient as conditioning regimens for lymphoblastic leukemia, while TBI-based regimens remain the standard of care for these individuals.

Appropriate choice of preparative regimens in HSCT is especially critical for elderly patients. Deteriorating functions of vital organs (pulmonary, hepatic, cardiac, renal), poor risk cytogenetics, and myelodysplasia-related changes significantly increase transplant-related morbidity and mortality[21]. These can be minimized by a reduced-intensity (RIC) regimen, although at the cost of a higher relapse rate [22,23]. The Bu/Flu regimen is particularly appealing in this population, as it has similar immunosuppressive but better safety profiles compared to Bu/Cy. A retrospective study by Magenau et al. on 148 patients with AML undergoing HSCT conditioned with either reduced or myeloablative doses of Bu (Flu/Bu2, n = 63; Flu/Bu4, n = 85) showed more favorable OS in Flu/Bu4 recipients, with equivalent mortality rates of [24]. These data, together with our results, indicate that Bu4/Flu is feasible and effective as a myeloablative regimen, especially for high-risk patients. Finally, delivery of Bu can be an important issue. At our institution, Bu is administered once daily, compared to four times a day as seen in traditional Bu/Cy regimens or Bu/Flu regimens adopted by several studies[19,17,13,25]. Recently, once-daily Bu is more favored due to its similar pharmacokinetic parameters but higher Bu peak concentration when given four times daily, leading to better drug distribution in distal regions with fewer vascular supply (e.g., central nervous system, cerebrospinal fluid, testicles, etc.)[26]. Furthermore, once-daily intravenous administration is convenient and can decrease post-transplant adverse events, such as VOD [27].

Compared to fixed-dose delivery, once-daily and pharmacokinetically guided dosing of Bu is a novel approach that can potentially improve patient outcomes undergoing HSCT[28.]

CONCLUSION

In conclusion, with similar efficacy to Bu/Cy but faster neutrophil and platelet recovery time, Bu/Flu is suitable as a pre-HSCT conditioning regimen of choice for patients with AML.

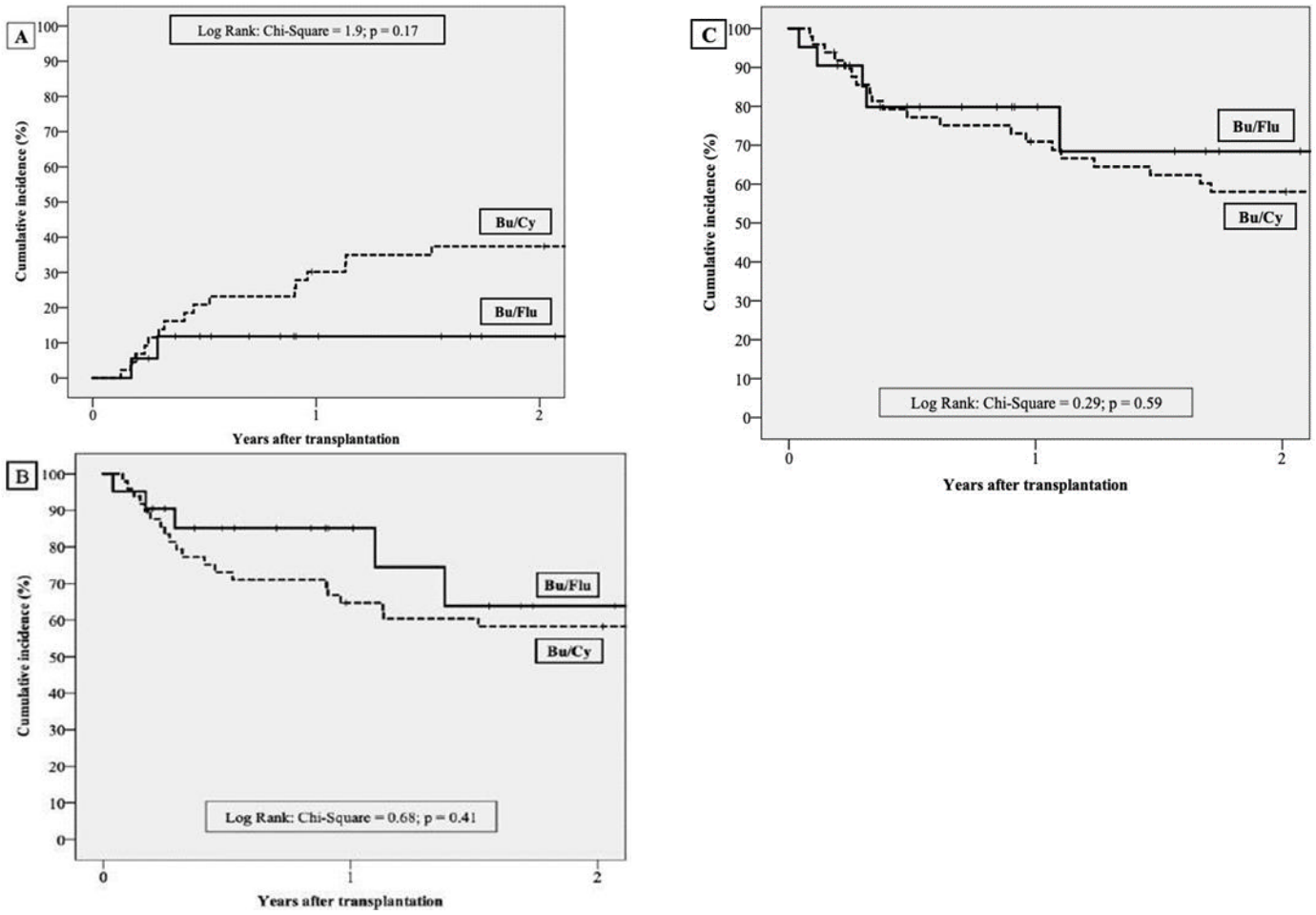

Figure 1. (A) Relapse rate; (B) Disease-free survival; and (C) Overall survival

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