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Survival Benefit of Intravenous Busulfan (120 mg/M^2) and Fludarabine Myeloablative Regimen for Treatment of Myeloid Malignancies

Niparuck P[1]*, Pukiat S[1], Puavilai T[1], Ativitavas T[2], Chantrathammachart P[1], Boonyawat K[1], Wacharapomin P[1], Angchaisuksiri P[1], Chuncharunee S[1], Jootar S[1], Atichartakarn V[1] and Ungkanont A[1]

[1]*Division of Hematology, Department of Medicine, Ramathibodi Hospital, Mahidol University, Thailand*
[2]*Division of Oncology, Department of Medicine, Ramathibodi Hospital, Mahidol University, Thailand*

Abstract

Background: Intravenous fludarabine and busulfan 130 mg/m^2 (Flu/Bu) conditioning regimen has induced the long term survival with a low treatment related mortality rate. However, there have been few reports on long term survival of patients undergoing allo-HSCT with intravenous Flu/Bu regimen. Therefore, we conducted a retrospective study of 42 patients diagnosed with myeloid malignancies received allo-HSCT with intravenous fludarabine and busulfan (120 mg/m^2) regimen between 2006 and 2015 at Ramathibodi hospital. The aim of our study was to observe the long term survival and the complication after transplantation.

Findings: Thirty- four, three and five patients were AML, MDS and CML-CP respectively. With a median follow-up of 95 months, 1- year EFS and 8- year EFS were 82 and 70% respectively. Overall survival (OS) rate at 1 and 8 years were equally observed in 88%. Patient younger than age 45 years had significantly longer OS than patients aged 45 years and older (96 vs 70%, p=0.019). Eight- year OS in AML, MDS and CML were 88, 67 and 100% respectively. Acute and chronic graft versus host disease were found in 29 and 46.3% of 41 evaluable patients respectively. Whereas the rates of sinusoidal obstruction syndrome, sepsis, CMV reactivation, cyclosporine and tacrolimus induced thrombotic microangiopathy were 2, 10, 12, 5 and 2% respectively. Non- relapse mortality rate at day +100, 1 and 8 year were only 9.5, 13.8 and 13.8% respectively. There was no neurological toxicity, severe mucositis, secondary malignancy or therapy related MDS syndrome in this study.

Conclusion: Allogeneic hematopoietic stem cell transplantation with intravenous fludarabine and busulfan at the dose of 120 mg/m^2 was well tolerated and demonstrated impressive treatment outcomes in young adult patients diagnosed with myeloid malignancies.

Keywords: Intravenous busulfan conditioning regimen; Fludarabine; Myeloid malignancies; Sinusoidal obstructive syndrome; Graft versus host disease; Treatment related mortality; Overall survival

Introduction

Busulfan based chemotherapy is the most common conditioning regimen for allogeneic hematopoietic stem cell transplantation (allo-HSCT) in myeloid malignancies, oral busulfan combined with intravenous cyclophosphamide (Bu/Cy) is widely used for transplantation, however, it induces the high rate of non relapsed mortality (NRM) in adults with acute myeloid leukemia (AML) undergoing myeloablative HSCT due to unpredictable intestinal absorption and unstable bioavailability of oral busulfan causing lethal hepatic sinusoidal obstruction syndrome (SOS) [1-5]. Nowadays, a number of current studies have demonstrated that treatment with intravenous (i.v.) busulfan conditioning regimen has lower NRM rate than oral busulfan based regimen [6-8]. Three- year- NRM and 3- year- overall survival (OS) following busulfan 130 mg/m^2 plus fludarabine (flu) regimen in AML/ Myelodysplastic syndrome (MDS) patients with the median age of 46 years are 34 and 78% of cases, respectively [9]. In addition, i.v. Flu/Bu 130 mg/m^2 also induced low mortality and high survival rates in older AML/MDS patients (age ≥ 55 years) receiving allo-HSCT, 1 year NRM and 2 year OS were 19 and 46%, respectively [10]. Nevertheless, there have been few published data of intravenous busulfan based regimen for allo- HSCT in Asian patients even the incidence and the severity of aGVHD have been found lower than those in the Western patients after using myeloablative and reduced intensity regimens [11-14]. Therefore, we conducted a retrospective study of 42 patients diagnosed with myeloid malignancies; acute myeloid leukemia (AML), myelodysplastic syndrome (MDS) and chronic myeloid leukemia in chronic phase (CML-CP) who underwent matched related donor (MRD) allo-HSCT, using intravenous fludarabine and busulfan (120 mg/m^2) regimen at Ramathibodi Hospital during January 2006-June 2015. We decreased i.v. busulfan dose to 120 mg/m^2/day since our first patient receiving busulfan 130 mg/m^2/day had developed severe intestinal mucositis. Endoscope and colonoscope were performed and showed flattening villi of intestine but no evidence of graft versus host disease on random biopsies. The aim of this study was to evaluate the long term outcomes of busulfan 120 mg/m^2 in combination with fludarabine for treatment of myeloid malignancies.

Materials and Methods

Thirty- four acute myeloid leukemia (AML), 3 myelodysplastic syndrome (MDS) and 5 chronic phase of chronic myeloid leukemia (CML-CP) patients received fludarabine 40 mg/m^2/day i.v. together with busulfan 120 mg/m^2/day i.v. for 4 consecutive days (D -6 to D -3). All patients received peripheral blood stem cell and all patients except

***Corresponding author:** Pimjai Niparuck, Division of Hematology, Department of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand, Fax: +662-2011785; E-mail: niparuckblue@gmail.com

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one had full matched related donor (10/10). Cyclosporine (3.0 mg/kg/day) was given to all patients from day -1 and was tapered from day 60 or 90. Methotrexate was administrated i.v. at a dose of 15 mg/m^2 on day 1 and 10 mg/m^2 on days 3, 6 and 11. The remaining one patient who had a single allele human leukocyte antigen (HLA)-DQ mismatched donor, anti- thymocyte globulin (thymoglobulin, rabbit antibody) 2.5 mg/kg was also given on days -3 and -2. The days of neutrophil and platelet engraftment were defined as the first of three consecutive days with absolute neutrophil count>500/mm^3 and platelet count>20,000/mm^3 without platelet transfusion, respectively. Bone marrow study and hematopoietic chimerism analysis using XY- FISH or STR- *DNA fingerprinting* were evaluated on days 30, 100, 180 and 360 after stem cell infusion. *The stage and grading of acute and chronic GVHD were classified according to the* consensus conference on acute GVHD (aGVHD) grading 1994 and 2005 NIH consensus project cGVHD severity score, respectively [15,16].

Results

Of the 42 patients, median age was 39 years (17- 56 years), seven patients were older than 45 years. Thirty- four, three and five patients were AML, MDS and CML-CP, respectively. All CML patients underwent allo-HSCT in the early years of the tyrosine kinase inhibitor era (year 2006 - 2008). The patients characteristics and treatment regimens prior to allo-HSCT are shown in Table 1. Median number of infused CD 34 cells was 4.87×10^6/kg (2.7 - 7.02×10^6/kg). Median times to neutrophil and platelet engraftment were 13 days (10 - 25 days) and 14 days (9 - 25 days), respectively. There was no graft failure in our study. Of the 41 evaluated patients, 37 patients (90.2%) achieved full donor chimerism and 29 patients (70%) achieved full donor chimerism before day 100. The remaining four patients didn't achieve full donor chimerism and had relapsed disease after HSCT for 2- 9 months, all patients were acute myeloid leukemia in complete remission (CR1).

Event free and overall survival

With a median follow- up of 95 months, 1- year event free survival (EFS), 3- year EFS, 1-year overall survival (OS) and 3- year OS were 82, 78, 88 and 88%, respectively. Whereas 8- year EFS and 8- year OS were 70 and 88%. At 8 years, patient aged<45 years had significantly longer OS than patients over the age of 45 years (96 vs 70%, p = 0.019) and only 25% of patient older than 50 years survived to the 3-year follow up (Figure 1). There was no statistically difference in OS and EFS between patients aged 15-30 years and 31-45 years. MDS patients had shorter survival (67%) than AML (88%) and CML (100%), however, there was no statistically significant (p = 0.337). Unfavorable cytogenetic risk did not affect the overall survival in AML patients, nevertheless, AML patients with favorable/ intermediate risk tended to have longer EFS than patients with unfavorable cytogenetic risk, 8-year EFS were 82 and 60%, respectively, p = 0.075 (Figure 1). Eight- year EFS for AML, CML and MDS were 70, 80 and 100%, respectively (p = 0.583).

Post transplantation complication

Acute and chronic GVHD were observed in 29 and 46.3% of 41 evaluable patients, respectively. Grade II-IV aGVHD was 8 patients (19.5%), most common site of aGVHD was skin (19.5%) whereas most common site of cGVHD were liver (26.8%), eyes (26.8%) and mouth (26.8%). The remaining one patient could not be evaluated the donor chimerism and evidence of GVHD since he died early after his transplant from bacterial sepsis (day +21). The rate of acute GVHD (aGVHD) was increased significantly in patients aged ≥ 50 years (p = 0.045) while the sex disparity or female donors to male recipients didn't affect the risk of GVHD. There was no complication of intestinal mucositis in this study, only 3 patients (7%) developed grade 1 diarrhea (increase of less than 4 stools/day over baseline) and diarrhea disappeared spontaneously in 5-7 days. The rates of sinusoidal obstruction syndrome (SOS), sepsis, cytomegalovirus (CMV) reactivation, cyclosporine and tacrolimus induced thrombotic microangiopathy (TMA) were 2, 10, 12, 5 and 2% respectively. In addition, two other patients (5%) developed cyclosporine induced acute kidney injury (AKI), patients complication after HSCT are shown in Table 2. The kidney function in both patients were improved after changing immunosuppressant, one patient had taken tacrolimus and another one received cellcept as primary GVHD prophylaxis. There was no complication of peripheral neuropathy, mental status change or seizure in our patients.

Of the 42 patients, NRM rate at day +100 was 9.5% (4 patients), three out of 4 patients developed aGVHD, two of them died from sepsis after heavy immunosuppressive therapy for GVHD and another patient diagnosed with aGVHD grade IV (skin stage 4 and gut stage 3), she died after 4 weeks of GVHD therapy from multifactorial causes; tacrolimus induced TMA, pulmonary edema and AKI from colistin. While the last one died 3 weeks after donor cell infusion due to bacterial sepsis. The NRM rate at 1 and 8 year were 13.8 and 13.8% out of 36 evaluable patients, respectively, 6 remaining patients were excluded since they had morphologic relapse and received treatment with chemotherapy. There was no MDS and secondary malignancy after using this regimen.

Discussion

As we mentioned above, our first patient receiving allo-HSCT with intravenous fludarabine/busulfan 130 mg/m^2/day developed severe intestinal mucositis. Therefore, at the beginning of intravenous Flu/Bu therapy for myeloid malignancies, we reduced the dose of busulfan in our conditioning regimen from 130 mg/m^2/day to 120 mg/m^2/day, which we expected to decrease conditioning regimen related mortality

Characteristic	Number (%)
Female: Male	24 (57): 18(43)
Age (median: 39 years)	42
16- 30 years	12 (28.6)
31- 45 years	21 (50)
46- 60 years	9 (21.4)
Disease	42
AML	34 (81)
MDS	3 (7)
CML- CP	5 (12)
Disease status at time of HSCT (AML)	34
CR1	28 (82)
CR2	3 (9)
No CR	3 (9)
Cytogenetic risk (AML)	34
Favorable	3 (9)
Intermediate	21 (62)
Unfavorable	10 (29)
Gene Mutation	12
FLT3-ITD	1 (8)
NPM1	2 (17)
CEBPA	1 (8)
No mutation	9 (75)
Donor-recipient HLA match	42
10/10 matched	41 (97.6)
Single allele mismatched	1 (2.4)

Table 1: Pre-transplant patient characteristic.

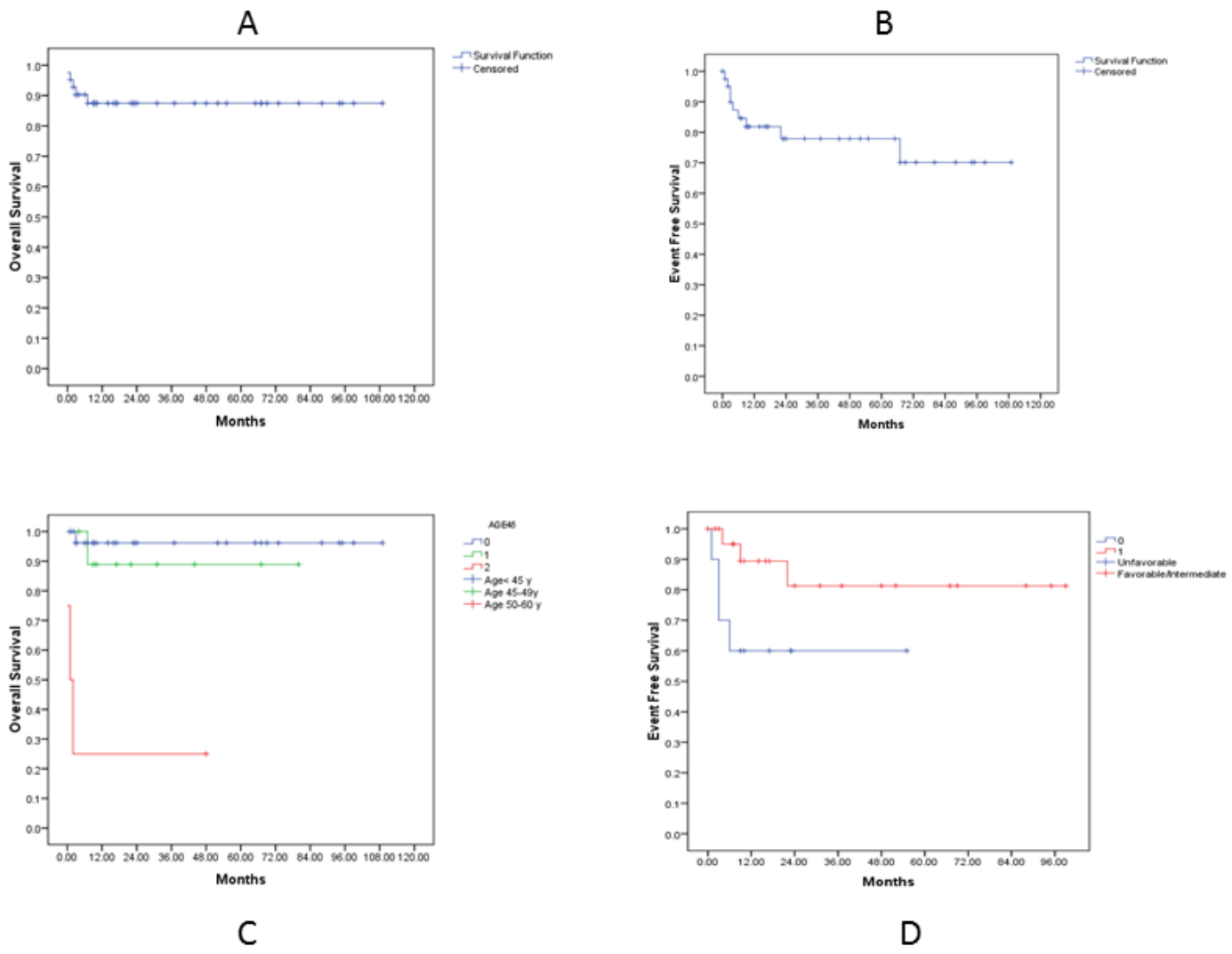

Figure 1: A. Overall survival of transplant patients; B. Event free survival of transplant patients; C. Overall survival according to age group; D. Event free survival according to cytogenetic risk.

or complication. However, after using this regimen in our center we found that Flu/Bu 120 mg/m² provided good transplant outcomes with less transplant complication. Almost 70% of patients achieved rapid engraftment and rapid full donor chimerism with low relapse and mortality rates at 1 and 8 year after HSCT. The incidence of SOS and grade 2-4 aGVHD were 2 and 19.5%, respectively. Although the incidence of cGVHD in our study was still high (46.3%), almost all patients with cGVHD were not severe and were manageable with corticosteroids. There was no gut cGVHD and only 15% of our patients developed lung cGVHD. According to Lima et al. the incidence of SOS, diarrhea, mucositis, peripheral neuropathy, mental status change and seizure in 96 AML/MDS patients receiving once daily intravenous busulfan (130 mg/m²/day) and fludarabine (40 mg/m²/day) conditioning regimen were 2, 30, 95, 7, 1 and 1%, respectively. Whereas the incidence of aGVHD and cGVHD in MSD- HSCT patients were 59 and 53%, respectively, the rate of grade 2-4 aGVHD was 15% and extensive cGVHD was found in 16% [17]. The regimen related and treatment related mortality in Lima study group were 1% and 3%, respectively. Although both fludarabine and busulfan can penetrate central nervous system (CNS) leading to severe neurological toxicity, our patients had no seizure, headache or mental status change.

In addition, intravenous Flu/Bu 120 mg/m² also provided good outcome in our AML patients, 8-year EFS was 70% with 60% in unfavorable risk. Although Alatrash et al. showed that i.v. Flu/Bu 130 mg/m² contributed low mortality and high survival rates in AML/MDS patients aged ≥ 55 years treated with allo-HSCT [10], our results demonstrated high NRM rate in patients older than 45-50 years and the incidence of aGVHD was increased significantly in patients aged ≥ 50 years. In our view, the patients' overall health and host immunity status in older Thai AML/MDS patients may be associated with an increased risk of severe infection after transplantation.

Conclusion

Even in the absence of PK-monitoring, this study illustrated that intravenous fludarabine and busulfan 120 mg/m² regimen is well tolerated and safe for use in adult patients diagnosed with myeloid malignancies, nevertheless, treatment with this regimen in older

Complication	Number (%)
SOS	1 (2.4)
Sepsis	4 (9.5)
CMV reactivation	5 (11.9)
Thrombotic microangiopathy	3 (7.1)
Diarrhea	3 (7.1)
Oral mucositis	2 (4.7)
Peripheral neuropathy/ mental status change/seisure	0
Renal tubular acidosis and acute kidney injury	2 (4.7)
Acute GVHD	12
Grade 1-2	8 (66.7)
Grade 3-4	4 (33.3)
Organ of aGVHD	12
Skin	8 (66.7)
Liver	5 (41.7)
Gut	4 (33.3)
Chronic GVHD	19 (46.3)
Limited stage	10 (52.6)
Extensive stage	9 (47.4)
Severity of cGVHD	19
Mild	10 (52.6)
Moderate	8 (42.1)
Severe	1 (5.3)
Organ of cGVHD	19
Skin	7 (36.8)
Eyes	11 (57.9)

Table 2: Post-transplantation complications.

patient requires close monitoring of the transplant complication. The immune reconstitution after HSCT warrants further study particularly in older patients.

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