Reduced Intensity versus Full Myeloablative Conditioning in Allogeneic Stem Cell Transplantation for Acute Myeloid Leukemia

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Abstract

Introduction: Allogeneic hematopoietic stem cell transplantation (HSCT) has been reported to be a successful curative treatment in AML patients. Myeloablative conditioning (MAC) is used more frequent as a preparing regimen. This study attempts to compare the outcome of patients who has received MAC and reduced- intensity conditioning (RIC).

Methods: Totally, 618 patients with AML underwent HSCT at our center between 1991 and 2011. Of these, 564 received MAC (Busulfan plus Cyclophosphamide) and 54 patients received RIC consisting of Fludarabine and Busulfan. Patients with suitable performance were assigned in the MAC study group while patients who did not meet these criteria were assigned to the RIC group.

Results: The median age at transplantation was 27 years for MAC and 30 years for RIC group (P value= 0.12). The median follow-up of survivors was 1.75 years for MAC and 4.5 years for RIC. The 3-year OS for MAC and RIC groups was 74.2% and 80.7% (P value= 0.75), respectively. The 3-year DFS was 67.2% for MAC and 69.7% for RIC, (P value= 0.73). The 3-year incidence of relapse for MAC and RIC groups was 16.80% and 26.40%, respectively (P value= 0.05).

Conclusion: the results of the study showed borderline significance (P value=0.05) for incidence of relapse between MAC and RIC groups. However, to make accurate results longer follow up is required. No significant difference in OS and DFS was found between two groups. Further long- term follow- up of more cases is necessary to confirm this difference statistically. Our results indicated that the introduction of RIC allogeneic HSCT for AML patients, especially in elderly, was safe and feasible.

Key words: Allogeneic Hematopoietic Stem Cell Transplantation**,** Acute Myeloid Leukemia, Myeloablative Conditioning**,** Reduced Intensity Conditioning

Introduction

Acute myeloid leukemia (AML) is characterized by an increase in the number of myeloid cells in the marrow and an arrest in their maturation.(1) AML is the most frequent acute leukemia affecting adults; in fact incidence increases with age.(2) AML is now the commonest indication for allogeneic hematopoietic stem cell transplantation in adults.(3) Allogeneic hematopoietic stem cell transplantation (HSCT) has been reported to be a successful curative treatment for patients with AML.(4, 5) Previously, myeloablative conditioning (MAC) has been the standard regimen for patients undergoing HCT for AML.(6) However, MAC is associated with significant risk of transplant-related mortality (TRM).(7) Consequently, Reduced-intensity conditioning (RIC) regimens have been developed to facilitate HSCT in older patients and those with significant medical comorbidities.(8, 9) RIC HSCT has been shown to be a practical and effective alternative for AML patients who are not suitable for MAC. RIC depends chiefly on graft-versus leukemia (GVL) effect of the immunocompetent cells in the graft, rather than the high-dose chemotherapy for the antitumor effect.(10, 11) Some data suggest that outcomes with RIC are

dependent on underlying disease type, disease stage at transplantation, comorbidity and the degree of reduced conditioning intensity.(12-14) A recent prospective comparison of MAC versus RIC HSCT in AML patients showed equivalent rates of TRM, relapse, and overall survival between the two groups.(12) There are inadequate data comparing the outcomes after MAC and RIC.(15-18) Thus, in this study we compare the outcome of AML patients who underwent HSCT with MAC versus RIC at our center.

Patients and Methods

Between 1991 and 2011, 618 patients with AML underwent allogeneic HSCT at the Hematology-Oncology and Stem Cell Transplantation Research Center affiliated to Tehran University of Medical Sciences. In this study, we did bone marrow aspiration and biopsy to recognize the type and the FAB classification of AML. For patients with AML diagnosis which referred to our center for transplantation, the diagnostic specimens were reviewed by hematologists at our center again and at least one month before transplantation they underwent another bone marrow aspiration/ biopsy. Patients were assigned AML subtypes based on current 2008 WHO criteria.(19) For MAC regimen transplantation, patients have to be in appropriate age, show adequate organ function such as cardiac ejection fraction, capacity of the lungs and must have a normal Karnofsky performance. The patients who do not meet these criteria should undergo transplant with RIC regimen. The decision to pursue MAC rather than RIC was based on the criteria listed above. RIC regimen was started from Jan 2001 at our center. All donor-recipient pairs had HLA typing class I and II results that were based on serology and PCR tests.

Conditioning regimens and graft- versus- host disease (GvHD) prophylaxis: Patients who underwent RIC (n= 54) were conditioned with a combination of fludarabine (30 mg/m^2 for 5 days) and BU (Busulfan 4 mg/kg oral for 4 days); 13 of them also received anti- thymocyte globulin (ATG). Other patients received MAC (n= 564) regimen consisted of BU (Busulfan 4 mg/kg for 4 days) and En (Endoxan 60 mg/kg for 2 days); among them, 18 received ATG too.

The same regimen of GvHD prophylaxis consisted of cyclosporine (1.5 mg/kg IV) and Methotrexate (10 mg/m^2) was administered.

We used standard criteria for grading acute and chronic GvHD.(20)

Supportive care: All patients were admitted to isolated rooms with high-efficiency air filters and treated with special nutritional program. They received fluconazole for fungal prophylaxis, acyclovir for cytomegalovirus and herpes simplex virus prophylaxis, trimethoprim/sulfamethoxazole for pneumocystis jiroveci pneumonia prophylaxis. They were transfused irradiated packed cell or single- donor platelet as needed. Complete blood count, creatinin and other biochemistry profiles as well as serum cyclosporine level were checked to avoid toxicity and other transplant related complications.

Engraftment: Neutrophil engraftment was defined as the first of three following days with an absolute neutrophil count of $\geq 0.5\times10^9$/µl. Platelet recovery was defined as the time after transplantation needed to achieve a blood platelet count exceeding 20,000/µl without transfusion support for 7 consecutive days. Donor cell engraftment was determined by STR chimersim analysis methods.(21) Relapse was diagnosed by morphological evidence of disease in the peripheral blood, marrow and extramedullary sites.

Endpoints: In this study, endpoints were disease-free survival (DFS), overall survival (OS), transplant-related-mortality (TRM), morphologic leukemia relapse (hematologic and/or extramedullary), acute and chronic GvHD. OS was measured as the time interval between the date of transplantation and the date of death due to any cause; surviving patients were censored at the date of last contact. DFS was defined as time to clinical or hematologic relapse or death from any causes other than relapse; patients who remained alive in complete remission were censored at time of last contact. TRM was measured as death during continuous complete remission after transplantation. Relapse was defined as clinical evidence and hematologic leukemia recurrence. For analyses of aGvHD, patients alive at day 100 without having experienced aGvHD considered censored. Chronic GvHD is defined only for patients surviving at least 100 days after transplantation; patients without cGvHD were censored at last contact.

Statistical analysis: Groups were compared using Mann-Whitney U test for continuous variables and chi-square test for categorical variables. Overall and disease-free survival curves were calculated by the Kaplan-Meier method;(22) and groups were

Table- 1. Patient characteristics.

	MAC	RIC
No. of patients	564	54
Median age (range) in years	27 (1-63)	30 (2-57)
Sex		
Male	292 (51.8%)	34 (63.0%)
female	272 (48.2%)	20 (37.0%)
Conditioning regimen		
Busulfan/Endoxan	543 (96.2%)	
Busulfan/Fludarabine		39 (72.2%)
ATG/Busulfan/Endoxan	18 (3.2%)	
ATG/Busulfan/Fludarabine		13 (24.1%)
Busulfan/Endoxan /CAMPATH	1 (0.2%)	
Busulfan/Endoxan/VP16	2 (0.4%)	
Fludarabin/Endoxan		2 (3.7%)
AMLWHO subtype		
AML NOS	13 (2.3%)	1 (1.8%)
AML :M0	8 (1.4%)	
AML :M1	44 (7.8%)	2 (3.7%)
AML :M2	217 (38.5%)	25 (46.3%)
AML :M3	29 (5.1%)	3 (5.6%)
AML :M4	161 (28.5%)	17 (31.5%)
AML :M5	62 (11.0%)	3 (5.6%)
AML :M6	15 (2.7%)	2 (3.7%)
AML :M7	2 (0.7%)	
Other	11 (2.0%)	1 (1.8%)
Disease status before transplantation		
CR1	419 (74.3%)	45 (83.3%)
≥CR2	117 (20.7%)	7 (13.0%)
PIF	18 (3.2%)	2 (3.7%)
Relapse	10 (1.8%)	
Type of donor		
HLA-identical sibling	529 (93.8%)	54 (100%)
HLA-match-other relative	14 (2.5%)	
HLA-match-unrelated	1 (0.2%)	
one locus HLA- mismatched	20 (3.5%)	
Source of SCT		
Bone marrow	32 (5.7%)	3 (5.6%)
Peripheral blood	527 (93.4%)	51 (94.4%)
BM+PM	3 (0.5%)	
Cord Blood	2 (0.4%)	
GVHD prophylaxis		
CSA/MTX	545 (96.6%)	12 (22.2%)
CSA	17 (3.0%)	42 (77.8%)
MTX/Tacrolimus	1 (0.2%)	
CSA/MTX/MMF	1 (0.2%)	
Median follow-up of survivors (range) in years	1.75 (0.1-16.5)	4.5 (0.5-10.5)

compared using the Log-Rank test statistic.(23) Cumulative incidence function (CIF) was used to estimate the relapse, TRM, acute and chronic GvHD as endpoints in a competing risk setting.(24, 25)

Death without relapse was the competing event for relapse; and relapse was performed as the competing event for TRM.

Death before day 100 considered as a competing event for acute GvHD. Death after day 100 was considered as a competing event for chronic GvHD. Groups were compared by the Grays' method in the competing risk settings.(26) The level of significance was set to 0.05. The packages cmprsk(27) and survival(28) in the R software(29) were used to conduct the statistical analyses.

Results

The demographic, clinical, and biologic characteristics of 618 patients who received HSCT for AML are summarized in Table- 1. 564 patients were in MAC group and 54 patients were in RIC group. Of all patients, 292 (51.8%) and 34 (63.0%) were male in MAC and RIC group, respectively. The median age at transplantation was 27 years for MAC and 30 years for RIC and their difference was not statistically significant between these two study groups (p=0.12). In MAC group 419 of 564 patients

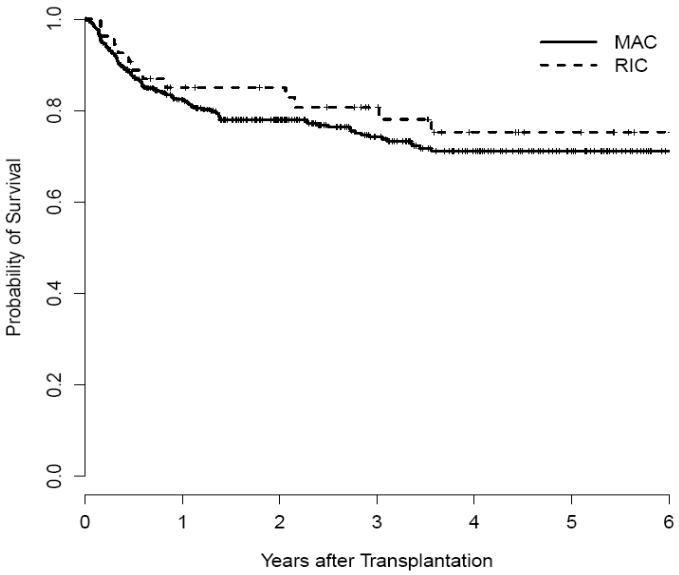

Figure- 1. Overall Survival of Allogeneic HSCT in Acute Myeloid Leukemia (RIC vs. MAC).

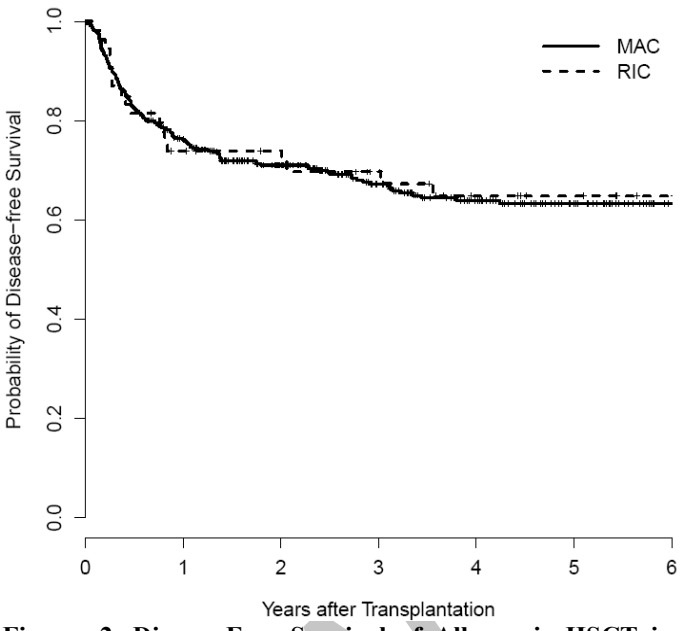

Figure- 2. Disease-Free Survival of Allogeneic HSCT in Acute Myeloid Leukemia (RIC Vs. MAC).

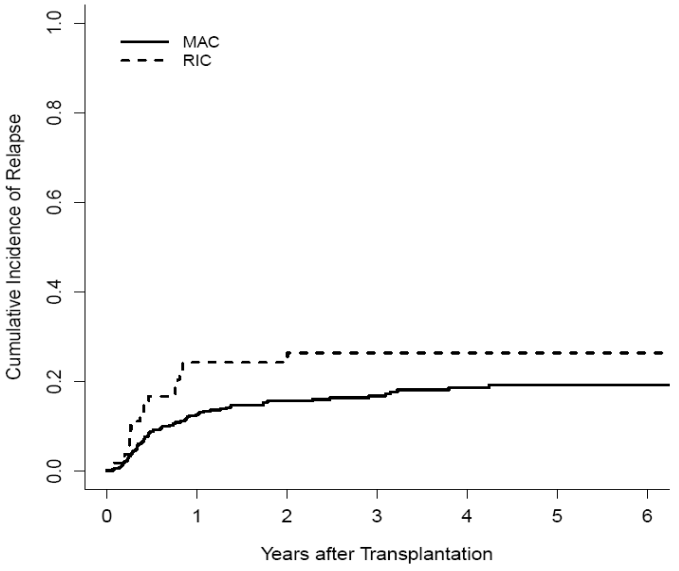

Figure- 3. Probability of Relapse in MAC vs. RIC.

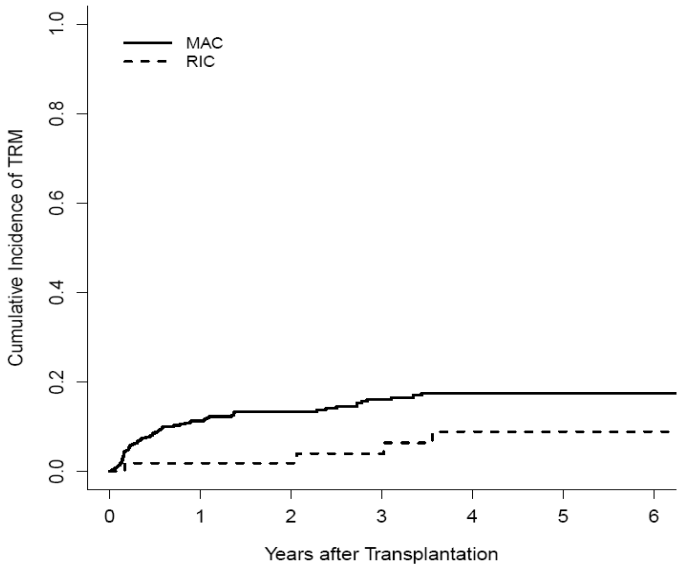

Figure- 4. Transplant-Related Mortality in MAC vs. RIC.

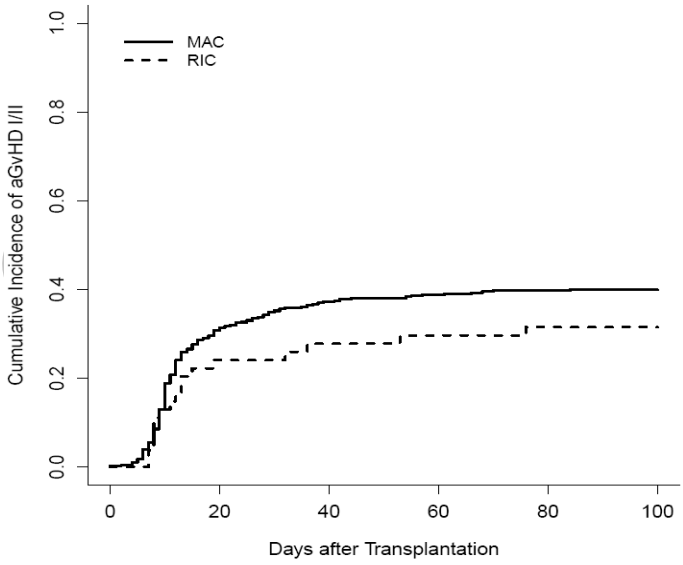

Figure- 5. Probability of Grade I/II aGVHD in MAC versus RIC.

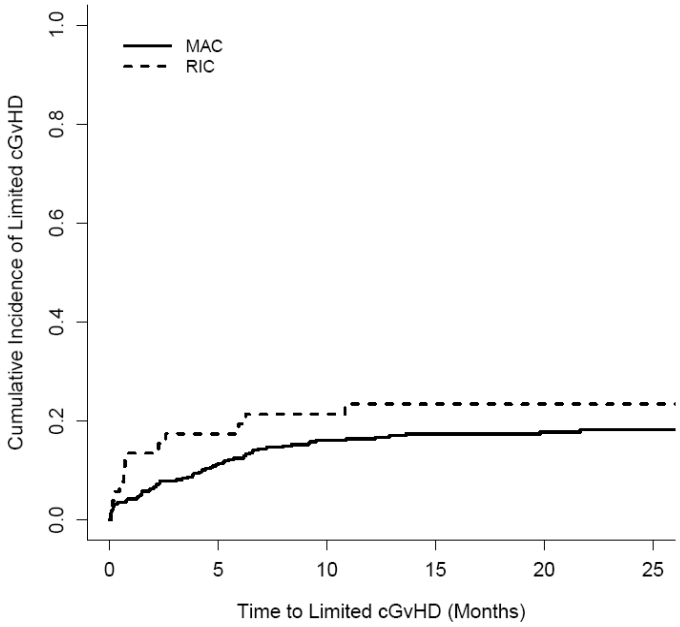

Figure- 6. Probability of limited cGVHD in MAC versus RIC.

(74.3%) and in RIC, 45 of 54 patients (83.3%) were in CR1 and the remaining patients were in CR2+ or relapse phase at HSCT transplantation. 3-year OS in the MAC and RIC groups was 74.2% (95% CI: 69.9%, 78.7%) and 80.7% (95% CI: 70.5%, 92.3%), respectively (p= 0.75, Figure- 1). The probability of DFS at 3 years after MAC was 67.2% (95% CI: 62.7%, 71.9%) and after RIC was 69.7% (95% CI: 58.3%, 83.3%, p= 0.73, Figure- 2).

The median follow-up of survivors for MAC was 1.75 years (1 month to 16.5 years) and for RIC was 4.5 (0.5 to 10.5) years. At present, 447 (79.3%) patients in MAC group and 40 (74.1%) patients in RIC group are alive. The most common causes of death were relapse (MAC: 38, RIC: 8), GvHD (MAC: 34, RIC: 3) and infection (MAC: 21, RIC: 3). The median duration needed to achieve an Absolute Neutrophil Count (ANC) $\geq 0.5\times10^9/\mu l$ were 12 days (range: 6-55) and 10 days (range: 6-16) for MAC and RIC groups, respectively (P= 0.001). The median duration required to achieve a platelet count of $\geq 20\times10^9/\mu l$ was 16 days in two groups (P= 0.735). The incidence of relapse at 3 years was 16.80% (95% CI: 13.4%, 20.5%) for MAC and 26.40% (95% CI: 15.3%, 38.8%), for RIC (P = 0.05, Figure- 3). The TRM at 3 years was 16.10% (95% CI: 12.7%, 19.8%) in the MAC versus 4% (95% CI: 0.7%, 12.2%) in the RIC (P= 0.12, Figure- 4). Acute GvHD occurred in 58.0% and 33.3% of MAC and RIC groups, respectively. The cumulative incidence of grade I/II aGvHD by day 32 after MAC was 35.9% (95% CI: 31.9%, 39.9%) and after RIC was 25.9% (95% CI: 15.1%, 38.1%, P= 0.225), (Figure- 5). Furthermore, the cumulative incidence of grade III/IV aGvHD after MAC was 14.1% (95% CI: 11.4%, 17.1%) and after RIC was 1.9% (95% CI: 0.2%, 8.7%, p=0.005). Chronic GvHD occurred in 23.9% of MAC and 50.0% of RIC groups, respectively. Limited chronic GvHD was occurred in15.3% and 23.1% of MAC and RIC groups, respectively. The 1- year cumulative incidence of cGVHD was 26.2% in the MAC group (95% CI: 22.0%, 30.6%) versus 46.6% in the RIC group (95% CI: 32.4%, 59.6%, P= 0.001). The 1-year cumulative incidence of limited cGvHD was 16.4% (95% CI: 13.0%, 20.2%) in the MAC group and 23.4% (95% CI: 12.8%, 35.8%) in the RIC group (p=0.29, Fig.6).

Discussion

In our study we reviewed the differences of myeloablative and reduced intensity regimens in AML patients who received allogeneic hematopoietic stem cell transplantation. The main objective of our study was to investigate the effect of MAC or RIC regimen on relapse, TRM, OS, DFS and GvHD in AML patients.

Reduced intensity conditioning (RIC) regimen is increasingly being used in Acute Lymphoblastic Leukemia patients who undergoing allogeneic hematopoietic stem cell transplantation.(30, 31) Gupta et al,(32) reported that there was no significant difference in the incidence of relapse among patients undergoing MAC compared to RIC. The results of this study were similar to findings reported by Oran et al,(7) and center for international blood and marrow transplant research (CIBMTR).(16) In our study, there was a 10.0% higher risk of relapse within the RIC group with borderline p-value (p= 0.05). However, to confirm whether there is a significant difference, more cases with long-term follow-up are required. In a study conducted by Gupta et al,(32) the cumulative incidence of grade II-IV aGvHD on day 180 wasn't significantly different in MAC and RIC groups. Also, there were no differences in the cumulative incidence of grade III-IV aGvHD. The 1-year cumulative incidence of chronic GvHD was similar between two study groups. Our survey showed no significant difference in grade I/II aGvHD and mild cGvHD between two study groups. Shi-Xia et al,(33) meta-analysis showed that there was no significant difference in overall survival between MAC and RIC regimens, but there was lower DFS at longer follow-up in RIC. In our analysis, there was no significant difference in 3-year overall survival and 3-year event-free survival between two groups. In this retrospective observational study, we showed that survival outcomes between the two approaches were similar in patients with AML. Our results are compatible with findings reported in several previous studies.(14, 17, 18, 34- 40)

Conclusion

The results of the study indicated that RIC regimen following by Allogeneic HSCT is a feasible approach for AML patients. Meanwhile, in order to prove advantages or disadvantages of these two approaches more prospective randomized clinical trials along with intention- to treat analysis are strongly recommended.

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