Impact of Using Low Dose versus High Dose Antithymocyte Globulin Based Conditioning Regimen on the Outcome of Peripheral Blood Stem Cell Transplantation in Children with β-Thalassemia

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Introduction

Allo-HSCT has grown in popularity to become the only curative option widely available for thalassemia major patients worldwide. The decision to use ATG must balance the circumstances in which ATG may be beneficial by reducing the incidence of GvHD with the situations in which ATG may be either neutral or harmful by increasing the risk of EBV/PTLD and other infections as well as relapse.

Aim

To study the impact of using low dose versus high dose ATG based conditioning regimen on the outcome of peripheral blood stem cell transplantation in children with β-thalassemia major.

Objectives

To reduce the dose of ATG without significantly increasing the incidence of acute and chronic GvHD and without adversely affecting other outcomes.

Methods

This current study was conducted on 40 patients with β-TM (Pesaro class II, III) were admitted for allogeneic peripheral blood stem cell transplantation from matched related donor including 22 males and 18 females with their age ranged from 2 to 18 years, categorized according to the dose of ATG into two groups; group I included 20 patients who received myeloablative regimen; (Bu/Cy/Low dose ATG-30 mg) and group II with 20 patients who had received (Bu/Cy/High dose ATG-110 mg). Allo-HSCT outcome was assessed with the following parameters: time to engraftment, acute and /or chronic GvHD, incidence and types of infections, regimen related toxicities.

Summary

The majority of cases in both groups aged (2 to 12 years) with majority of patients in both groups were Pesaro II (85% in low dose group and 75% in high dose group). There were no differences in the clinical features between the two groups, including age, sex, Pesaro risk classes, disease status at transplant and diagnosis/transplant lag. No significant difference was found regarding the dose of stem cells infused. No significant difference was observed as regards the time of platelet engraftment in both groups. Patients in low dose group achieved faster neutrophil engraftment. There was a higher risk of mucositis in high dose group. No significant difference in the incidence of acute and chronic GvHD between both groups. One year survival and DFS were similar in both groups.

Results

Table: (1) Comparison between the studied groups as regards regimen-related toxicity:

Regimen-related toxicity		ATG dose				Chi-Square	
		Low dose		High dose			
		N	%	N	%	X^2	P-value
Mucositis	No	6	30.00	0	0.00	9.436	0.024*
	GI	8	40.00	11	55.00		
	GII	2	10.00	4	20.00		
	GIII	4	20.00	5	25.00		
Infections	Culture negative	9	45.00	3	15.00	9.667	0.046*
	Bacterial	7	35.00	14	70.00		
	Viral	3	15.00	0	0.00		
	Fungal	1	5.00	2	10.00		
	Bacterial/Fungal	0	0.00	1	5.00		
Other complications	Renal	2	10.00	1	5.00	8.700	0.368
	Engraftment syndrome	1	5.00	2	10.00		
	HTN	2	10.00	1	5.00		

Figure (1): Comparison between studied groups as regards incidence & type of infecions

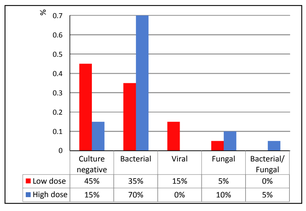


Figure (2): Comparison between the studied groups as regards the time of neutrophil engraftment.

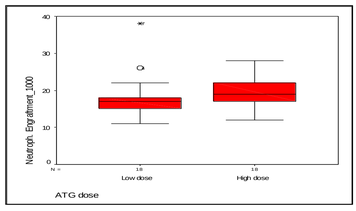


Table (2): Comparison between the studied groups as regards post-transplant complications:

Post-transplant complications	ATG dose				Chi-Square	
	Low dose		High dose			
	N	%	N	%	X^2	P-value
Graft Failure	1	5.00	0	0.00	1.026	0.311
Hemorrhagic Cystitis	5	25.00	3	15.00	0.625	0.429
PRES	4	20.00	2	10.00	0.784	0.376
VOD	0	0.00	1	5.00	1.026	0.311

Figure (3): Comparison between the studied groups as regards the time of platelet engraftment.

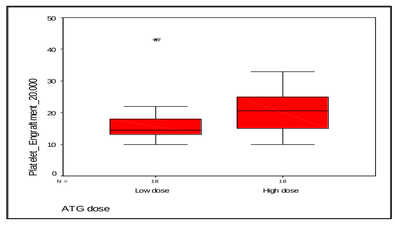


Table (3): Comparison between the studied groups as regards the occurrence and grades of acute and chronic GvHD:

		ATG dose				Chi-Square	
		Low dose		High dose			
		N	%	N	%	X^2	P-value
Acute GvHD		7	35.00	3	15.00	2.133	0.144
Acute GvHD grade	I	4	57.14	2	66.67	1.270	0.736
	II	1	14.29	1	33.33		
	III	1	14.29	0	0.00		
	IV	1	14.29	0	0.00		
Chronic GvHD		3	15.00	1	5.00	1.111	0.292
Chronic GvHD	Extensive	2	75.00	0	0.00	4.000	0. 460
	Limited	1	25.00	1	100.00		

Figure (4): Kaplan-Meier survival curve for one year survival with ATG dose.

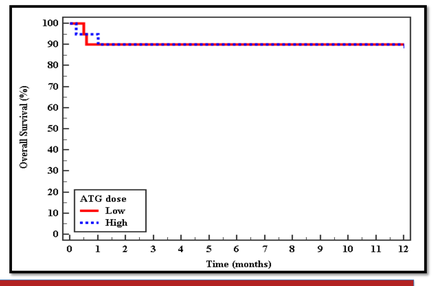
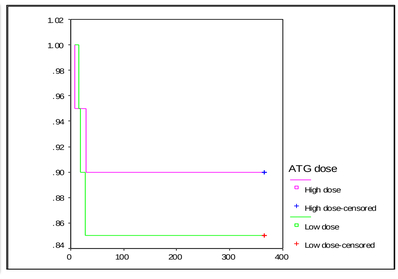


Figure (5): Kaplan-Meier survival curve for DFS with ATG dose



Discussion

Oral mucositis occurred more frequently in the high-dose ATG group (45%) than the low-dose group (30%), likely due to higher infection rates and delayed engraftment (Table 1). Infections remain a major cause of post-transplant morbidity and mortality. In our study, infection rates were significantly higher in the high-dose ATG group (85%) compared to the low-dose group (55%), likely due to stronger immunosuppression and prolonged neutropenia (figure 1). These findings are consistent with *Boga et al., 2018* who showed that while higher ATG doses may reduce chronic GvHD, they increase the risk of severe infectious complications. Hemorrhagic cystitis and PRES occurred at similar rates in both groups. Veno-occlusive disease, though rare, was observed in one patient (5%) in the high-dose ATG group, aligning with previous reports of its low incidence in β-thalassemia major patients (Table 2). *Kim et al. (2013)* identified ATG-based conditioning as a risk factor, while an Egyptian study by *Fahmy et al. (2016)* reported a low VOD incidence of 3.4% in β-thalassemia major patients. No differences were observed as regards the time of platelet engraftment. In the univariate analysis, there was an early neutrophil engraftment in low dose group which was significantly delayed with median value of (14.00 vs. 17.5 days) (figure 2,3). Although the two groups in our study received similar GvHD prophylaxis regimen, the incidence of acute GvHD in our results appeared to be higher but not statistically significant in the low dose group than in the high dose group; 7 patients out of 20 (35%) vs. 3 patients out of 20 (15%) respectively. In addition, the incidence of chronic GvHD was also higher but not statistically significant in the low dose group; 3 patients out of 20 (15%) vs. only one patient out of 20 (5%) (Table 3). A similar incidence of acute GvHD was reported by *Mahmoud et al., 2015*, who reported that acute GvHD grade II–IV occurred in 15% while chronic GvHD occurred in 12% of the high dose group patients. Studies including *Liu et al. (2015)* reported no significant difference in acute or chronic GvHD between low- and high-dose ATG, findings later supported by *Lin et al. (2019)*. Similarly, *Admiraal et al. (2015)* found no added benefit of high-dose ATG in pediatric patients, but noted a higher incidence of EBV/PTLD. *Kennedy et al. (2018)* also observed lower severity of chronic GvHD with higher ATG doses, though this came at the cost of increased infectious complications. One-year survival was 90% in both groups, with comparable DFS (85% in the low-dose vs. 90% in the high-dose group), showing no significant difference between regimens (figure 4,5). Consistent with our findings, several studies *(Kennedy et al., 2018; Issa et al., 2019; Narita et al., 2019; Wang et al., 2014; Azevedo et al., 2015)* reported no significant difference in overall survival or disease-free survival between low- and high-dose ATG groups.

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