Fludarabine-Busulfan-Cyclophosphamide Conditioning Regimen for Hematopoietic Stem Cell Transplantation in Patients with LRC Class III β-thalassemia Major

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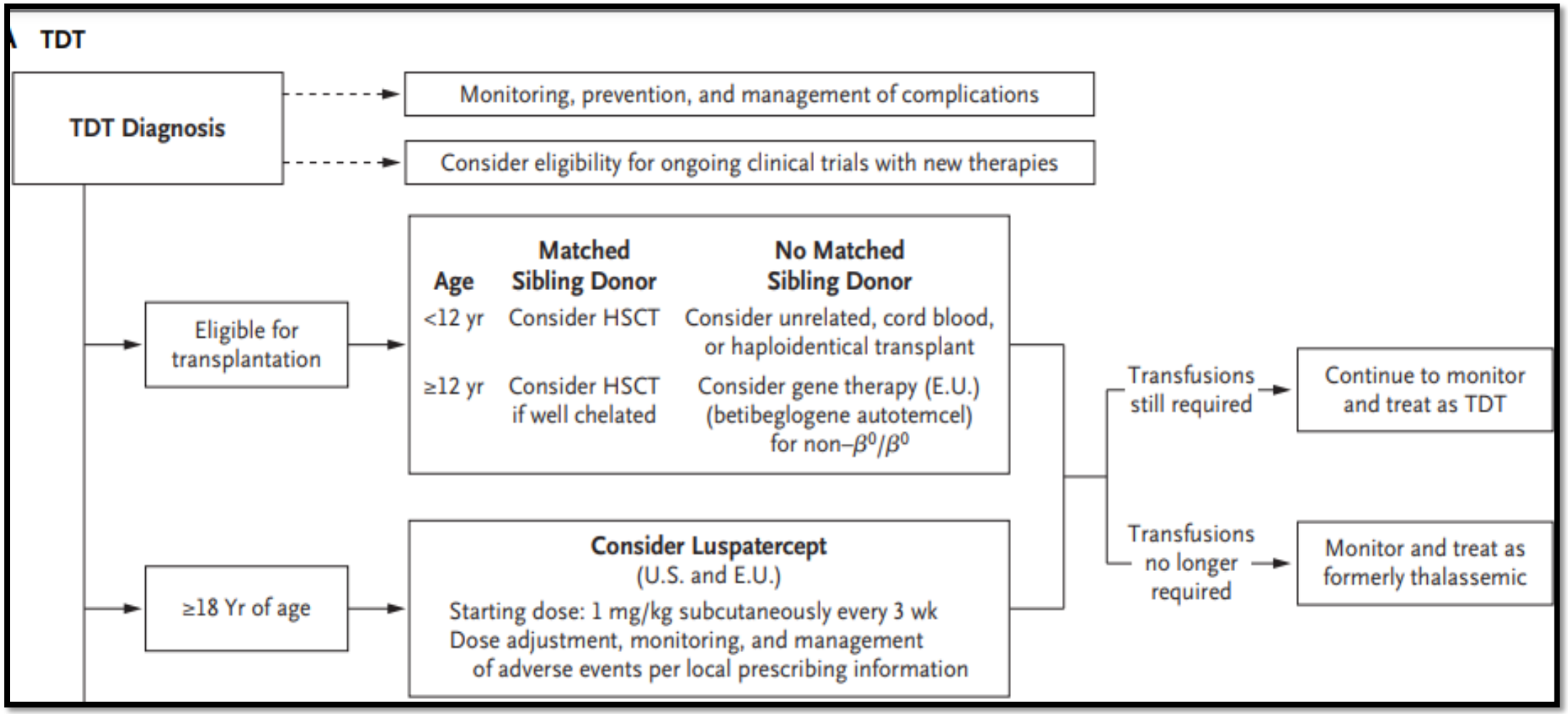
Allogeneic Hematopoietic Stem Cell Transplantation and Major Thalassemia

- The success of transplant procedures in patients with beta-thalassemia major goes hand-in-hand with improvements in disease knowledge, better supportive care, discoveries in immunogenetics, increase in stem cell sources, and enhancement of conditioning regimens.

Available options for the management of β-thalassemia



Taher AT, Musallam KM, Cappellini MD. β-Thalassemias. New England Journal of Medicine. 2021 Feb 25;384(8):727-43

Outcomes of HSCT in β-thalassemia (depending on LRC at the time of transplantation)

- HSCT has been proposed as a possible curative option since the 1980s and can be ethically recommended to patients with an available matched donor.

- Pediatric HSCT has better results than adult HSCT.

- In **adult** patients (age >17 years), organ damage related to **iron overload** is more advanced and transplant-related mortality is therefore higher.

Outcomes of HSCT in β-thalassemia (depending on LRC at the time of transplantation)

- **Class III** patients are considered to be at high-risk and have **inferior outcomes** following HSCT.

- The probability of survival, thalassemia-free survival, rejection and non-rejection mortality for the entire group of these patients were **66%**, **62%**, **4%** and **37%** respectively.

Lucarelli G, Gaziev J. Blood Rev. 2008 Mar;22(2):53-63. Cold Spring Harb Perspect Med 2012;2:a011825

Allogeneic Hematopoietic Stem Cell Transplantation and Major Thalassemia Conditioning Regimen

- Considering the specific features of β-TM (hyperplastic bone marrow and allosensitization due to multiple blood transfusions), a myeloablative conditioning regimen of busulfan followed by cyclophosphamide (Bu/Cy) has been considered the gold standard.

- This regimen was associated with **hepatic and cardiac toxicity** due to the iron overload and the toxic hepatic and cardiac effects of BU and CY, respectively.

Allogeneic Hematopoietic Stem Cell Transplantation and Major Thalassemia Conditioning Regimen

- Long-term blood transfusion can result in an immune response against allo-HLA, and thus patients with TM undergoing HSCT display a relatively **high incidence of graft rejection**.

- Several new approaches have reduced the toxicity of conditioning regimens and decreased the incidence of GvHD, improving patients post transplant health-related quality of life.

Study Design and Participants

* A prospective non-randomized clinical trial

Inclusion criteria:

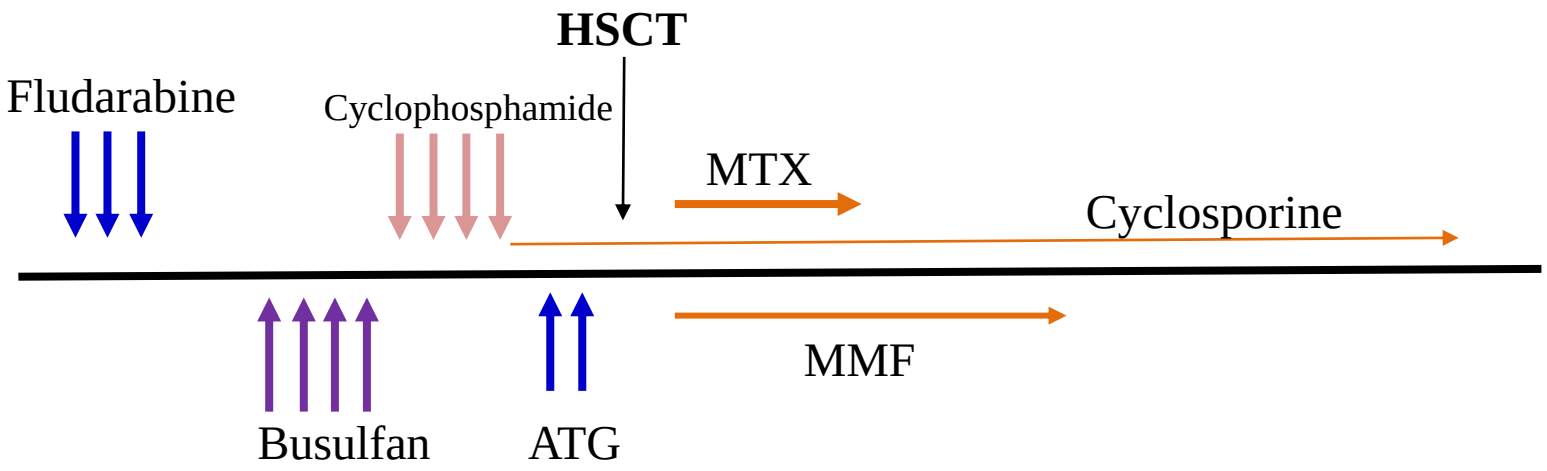
- Patients with β-thalassemia major confirmed by DNA genetic testing
- Age at HSCT >15 years old
  - 15-17 years old with LRC Class III
  - Adult (> 17 years old)
- 10/10 HLA-full matched donor

Exclusion criteria:

- previous HSCT and experienced graft rejection
- Cardiac ejection fraction of < 50%
- pathology of hepatic cirrhosis

Study Design

Fludarabine-Busulfan-Cyclophosphamide Conditioning Regimen



Fludarabine: 40 mg/m2 iv daily from dayes -14 to -12
Busulfan: Weight based dose from days -9 to -6
Cyclophosphamide: 40 mg/kg from days -5 to -2
ATG: 1.25 -2.5 mg/kg daily from days -2 to -1

MMF:15 mg/kg iv BID from dayes +1 to +20
MTX: +1(10mg/m2), +3, +6 (6 mg/ m2)
Cyclosporine: from day -3

Patients and Donors Characteristics

N=23

Patient's age at HSCT (years), Mean ± SD		18.75 ± 2.15
Donor's age (years), Mean ± SD		19.83 ± 11.44
Patient's sex, n (%)	Male	12 (52.2%)
	Female	11 (47. 8%)
Donor's sex, n (%)	Male	13 (56.5%)
	Female	10 (43.5%)
Sex matching status, n (%)	Matched	12 (52.2%)
	Mismatched	11 (47. 8%)
ABO-matching status, n (%)	Matched	13 (56.5%)
	Mismatched	10 (43.5%)
Donor type	Sibling	19 (89.6%)
	Other relative	2 (8.7%)
	Unrelated	2 (8.7%)
CMV Seropositivity, n (%)	Patients	21(91.3%)
	Donors	23(100%)

Graft Characteristics

Graft Characteristics		
MNC (× 10^8/kg) Mean±SD		5.69 ± 2.20
CD3 cell (× 10^6/kg) Mean±SD		196.68 ± 49.64
CD34 cell (× 10^6/kg) Mean±SD		3.33 ± 1.37
Stem cell Source, n (%)	Peripheral blood	22 (95.7%)
	Bone marrow	1 (4.3%)

Engraftment Status

ANC engraftment median (range)	**12.5 (10-17) days**
Platelets engraftment median (range)	**16.5 (10-26) days**

- One primary graft failure
  An 18 y/o male, who received bone marrow stem-cell from sex mismatch, ABO mismatch unrelated donor

- One patient developed mixed chimerism between 70-90% with normal Hb electrophoresis

Acute GvHD

N= 8 (36.36%)		
Grade	2-4	8 (34.7%)
	3-4	7 (30.4%)
Skin acute GvHD n (%)	6 (75%)	
Liver acute GvHD n (%)	2 (25%)	
Gut acute GvHD n (%)	2 (25%)	

Chronic GvHD

N= 8 (34%)		
Grading of Overall Severity	Mild	4 (50%)
	Moderate	4 (50%)
	Severe	0
Skin n (%)	8 (34.7%)	
Liver n (%)	7 (30.4%)	
Lung n (%)	1 (4.3%)	

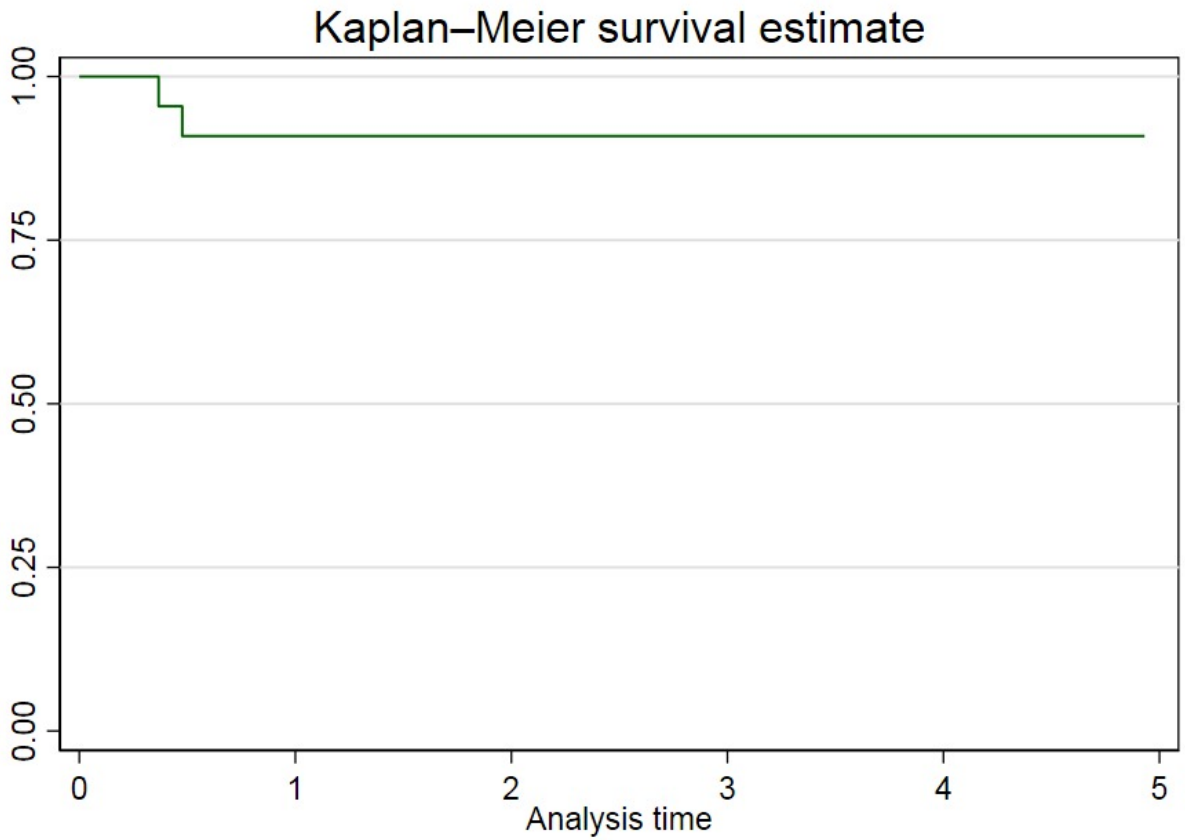
Mortality, N=3 (13%)

Case	1	2	3
Couse of death	Sepsis	Sepsis + GvHD	Primary graft failure
Age(y)	18	19	18
Gender	female	male	male
Time of death	+6 mo	+4 mo	+3 mo
Stem-cell source	PB	PB	BM
Donor type	Sibling	Other relative	Unrelated
GvHD	yes	yes	no
Sex-mismatch	no	no	yes
ABO-mismatch	no	no	yes

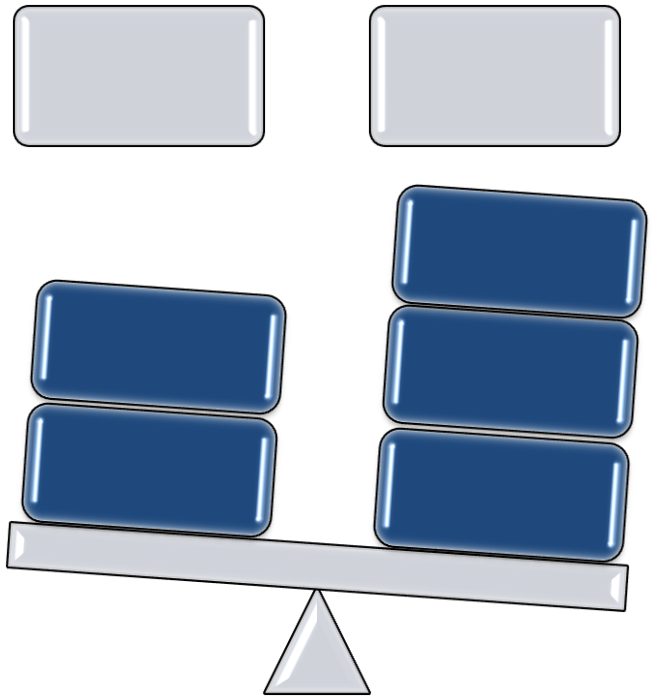
Overall Survival

Overall survival, % (95% CI)	
1-year OS	90.91 (68.30-97.65)
3-year OS	90.91 (68.30-97.65)
5-year OS	90.91 (68.30-97.65)

Median Follow-up time: 3.1 years

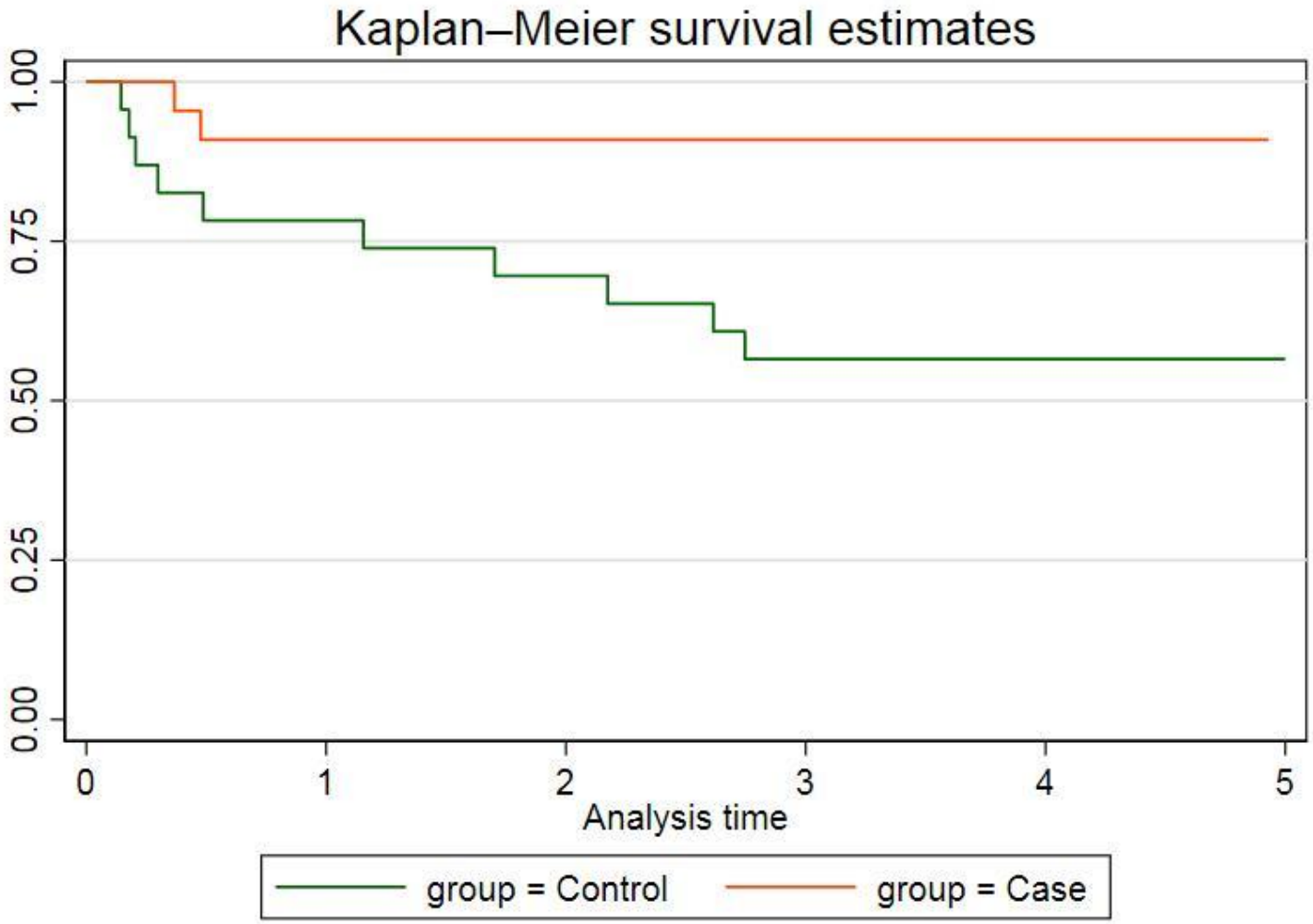


A Comparative Analysis



	BU-FLU (N=23)	BU-FLU-CY (N=23)	P-value
Age (mean)	19.7	18.5	0.23
Gender (F/M)	10/13	12/11	0.44
Pre-HSCT Ferritin	2059	2843	0.29
Liver biopsy (1-2/3-4)	13/7	12/10	0.44

	BU-FLU (N=23)	BU-FLU-CY(N=23)	P-value
ANC engraftment (days) median (range)	17 (10-120)	12.5 (10-17)	**0.04**
Platelet engraftment (days) median (range)	23 (8-120)	16.5 (10-26)	**0.03**
CMV reactivation	10 (43.48%)	12 (54.5%)	0.32
Graft Failure	2 (8.6%)	1 (4.3%)	0.51
Acute GvHD	16 (70.03%)	8 (36.36%)	**0.02**
Chronic GvHD	13/18 (72%)	8/23 (36%)	**0.03**
Mortality	10 (43.4%)	3 (13%)	**0.01**
Median follow-up time	5 years	3.1 years	
1-year OS	78.26 (55.42-90.32)	90.91 (68.30-97.65)	**0.01**
3-year OS	56.52 (34.32-73.76)	90.91 (68.30-97.65)	



Treatment	HR 0.18 (0.041-0.85)	P-value 0.031

Flu-Bu-Cy for conditioning >>> 82% decrease in mortality

Our study

- Median duration of follow-up of 38 months
- OS and TFS were 90.91 (superior to previous standard regimen)
  - ➢Flu-Bu-CY is a **safe & effective** conditioning regimen

- The frequency and timing of engraftment in our study is comparable with other published data.

- Acute GvHD was observed in 8 (36.36%) cases which is substantially lower than reports recently published by other centers and control group.

- The low prevalence of GvHD in our study may be related to the combination of CSA, cellcept, and methotrexate for GvHD prophylaxis.

- In our case group only one graft rejection was observed.

The following factors most likely contributed to our results:

  - The intensity of myeloablative (Bu/Cy) and immune suppression (Flu and ATG)

  - It was anticipated that the HSCT with mobilized peripheral blood might lead to quicker engraftment because of the higher number of HSCs

Limitations

- Relatively small number of patients
- A single-center study

Thank you!