Cytokine Release Syndrome After Peripheral Blood Haploidentical Stem Cell Transplantation With Post-Transplant Cyclophosphamide: Time of Onset Matters

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Background

The use of post-transplant cyclophosphamide (PT-Cy) has favored haploidentical hematopoietic stem cell transplantation (haplo-HSCT) when an HLA-matched donor is not available or when an urgent transplant is needed. Although a high percentage of patients receiving PT-Cy haplo-HSCT develop cytokine release syndrome (CRS) after infusion, it only seems to affect prognosis in the reduced proportion of patients that develop severe CRS[1-3].

Objectives

The aim of our study is to analyze new CRS characteristics and their prognostic implication on both transplant-related mortality (TRM) and overall survival (OS).

Materials & Methods

From the cohort of 637 patients who underwent allo-HSCT at our center between January 2012 and December 2020, 150 patients who received PT-Cy haplo-TPH were selected for this retrospective analysis. Regarding CRS analysis, 16 patients were excluded due to the impossibility to distinguish between infectious and CRS fever.

Results (1)

Median follow-up was 18 months (37 months for alive patients). Most patients (86%) developed CRS. The cohort was divided into two groups: patients who developed early-onset CRS (≤24h after infusion, 50%) and those with late-onset CRS or no CRS (table 1).

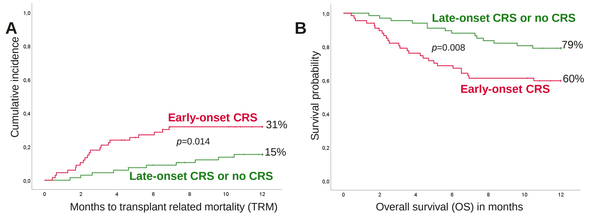
Table 1. Comparison between patients who developed early-onset CRS and the rest of the cohort

Variable		Early-onset CRS (≤24h after infusion)	Late-onset CRS (>24h after infusion) or no CRS	p-value
Patient age at transplantation in years, median (range)		59 (16-73)	53 (17-70)	0.196
Male gender (%)		63	46	0.082
HCT-CI ≥3 (%)		33	27	0.571
DRI high/very high (%)		16	19	0.822
Previous allo-HSCT (%)		6	10	0.531
Active disease at transplantation (%)		48	22	**0.002**
Non-myeloablative conditioning (%)		82	63	**0.003**
Haplo-HSCT platform	Modified Baltimore (%)	85	60	**<0.001**
	Modified Bacigalupo (%)	10	37	**<0.001**
CD34+ dose per 10^8/kg, median (range)		6 (3.4-9.3)	6.5 (4-9.3)	0.167
CD3+ dose per 10^7/kg, median (range)		25.2 (4.6-112.7)	18.2 (5.3-81.8)	**0.005**
Graft cryopreservation (%)		4	24	**0.001**
aGvHD (any grade, %)		67	85	**0.015**
Severe aGvHD (grade ≥3, %)		8	18	0.069
SOS (%)		10	3	0.082

Results (2)

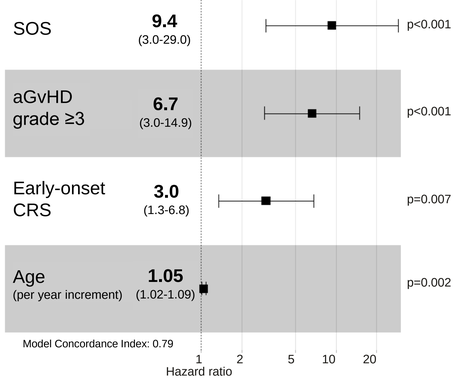
Patients who developed early-onset CRS had a significant increase in first-year TRM and lower first-year overall survival as show in figure 1.

Figure 1. Impact of early-onset CRS development on TRM (A) and OS (B).



Early-onset CRS was also significant in a multivariate analysis of first-year TRM, as shown in figure 2.

Figure 2. Cox proportional hazards model for first-year TRM



Results (3)

Several risk factors were associated with developing early-onset CRS in a multivariate analysis (table 2).

Table 2. Risk and protective factors for developing early-onset CRS

Variable	Hazard ratio	p-value
Modified Baltimore haplo-HSCT platform	7.54	<0.001
Active disease at transplantation	2.94	0.015
Increased infused CD3+ cells (per 10^7/kg increment)	1.05	0.002
Graft cryopreservation	0.14	0.005

Conclusions

- We propose the definition of early-onset CRS as the one that is developed within 24h after haplo-HSCT infusion. Patients who develop early-onset CRS have a higher TRM and lower OS.
- However, this is a single-center retrospective study and further studies will be required in order to confirm these findings.

References

1. Cytokine release syndrome after haploidentical hematopoietic cell transplantation: an international multicenter analysis. *Bone Marrow Transplant*.
2. Grade 3-4 cytokine release syndrome is associated with poor survival in haploidentical peripheral blood stem cell transplantation. *Leuk Lymphoma*.
3. Severe Cytokine Release Syndrome after Haploidentical Peripheral Blood Stem Cell Transplantation. *Biol Blood Marrow Transplant*

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