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Allogeneic hematopoietic stem cell transplantation (allo-HSCT) with reduced intensity conditioning regimens in children and adolescents with very high risk acute lymphoblastic leukemia (VHR ALL)

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Abstract

The aim: To compare the efficacy of reduced intensity conditioning (RIC) and myeloablative conditioning (MAC) for allo-HSCT in children and adolescents suffering from VHR ALL.

Patients and methods: 88 ALL patients (pts) with a median age of 12 (range, 1–21) underwent allo-HSCT between 12/2000 and 12/2009. The indication for allo-HSCT in children and adolescents was VHR ALL: late responder on chemotherapy (induction failure), poor-risk cytogenetics (t(9;22), t(4;11)), and MRD(>10⁻²), infants with 11q23 rearrangement, short first remission, primary resistance, or resistant relapse. RIC allo-HSCT was performed in 24 pts (RIC-group): 13 pts were in I or II complete remission (CR), and 11 pts were in resistant relapse. The indication for RIC allo-HSCT was poor performance status, organ dysfunction due to previous therapy or infection complication at the moment of allo-HSCT. MAC was used in 64 pts (MAC-group): 36 pts were in I and II CR at the moment of HSCT, 28 pts were III and IV CR, or in resistant relapse. RIC consisted of Flu 150 mg/m²/d + Mel (140 mg/m²/d)±ATG or Flu 150 mg/m²/d + Bu 8 mg/kg±ATG; MAC consisted of Bu 16 mg/kg (or Treo 36–48 mg/m²) + Cy 120 mg/kg ±ATG. Allo-HSCT from matched related donors was performed in 22 pts (RIC, n=6), and from matched unrelated donors in 62 pts (RIC, n=18).

Results (table 1, 2): In the RIC-group, the granulocyte engraftment ≥0.5×10⁹/l was on D+18 (in ranges D+13–31). For pts in I or II CR at RIC allo-HSCT 9 of 13 are alive. Overall 7-year survival (OS) and disease-free survival (DFS) were 69% and 45%, respectively. Four pts died within 100 days: infection (3), and aGVHD (1). Relapse occurred in 2 pts (15%): both relapsed pts achieved CR after chemotherapy+DLI in 1st pt, and immunosuppression withdrawal in 2nd pt. CR was achieved in 4 of 11 pts after alloHSCT at resistant relapse. But 1-year OS was 0%. Patients died from infection (3), aGVHD (1), and disease progression (7).

MAC-group: granulocyte engraftment ≥0.5×10⁹/l was on D+21 (in ranges D+10–49). Eighteen of 36 pts are in CR after MAC allo-HSCT in I or II CR. Overall 7-year survival (OS) and DFS were 47% and 39%, respectively. 11 pts relapsed after MAC allo-HSCT (30%), but 2 of them achieved CR after chemotherapy+DLI. Nine pts died from relapse: aGVHD, 6; infection, 1; transplant related toxicity, 1; and non-engraftment, 1. Four from 28 pts after MAC allo-HSCT in relapse either III or IV CR are in CR (14–101 months; median 53 months). Other pts

died of relapse (12), infection (8), and aGVHD (4).

Conclusion: RIC allo-HSCT of VHR ALL in CR pts ≤ 21 yo is effective and comparable with MAC allo-HSCT. These results make way for new approaches for pts in VHR ALL in CR, indicate their sensitivity to immunoadoptive therapy and produce the base for clinical trials.

Table 1. Outcomes after allo-HSCT

Condition regime	Status at the moment of allo-HSCT (n)	Relapse n (%)	TRM n (%)	1 year-OS	7-OS	1-EFS	7-EFS
RIC	I or II CR (13)	2(15)	4(30)	69%	69%	68%	45%
	Relapse (11)	7(64)	4(36)	0	0	0	0
MAC	I or II CR (36)	11(31)	9(25)	68%	47%	68%	39%
	Relapse (28)	12(43)	12(43)	20%	14%	20%	1

Table 2. Complication after allo-HSCT

	RIC (%)	MAC (%)
Acute GVHD grade 1–4	55	53
Chronic GVHD	88	54
Infection	88	83
Hepatotoxicity	50	30
Neurotoxicity	25	25
Hemorrhagic	13	33

Keywords: reduced intensity conditioning, acute lymphoblastic leukemia, children and adolescents.

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