Unfavorable influence of minimal residual disease on the outcome of allogeneic hematopoietic cell transplantation in acute lymphoblastic leukemia in the first remission

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Context

Persistent of minimal residual disease (MRD) is the most important adverse prognostic factor for patients with acute lymphoblastic leukemia (ALL), irrespective of classical risk factors identified at onset. Detection of MRD in the post-induction phase of treatment in ALL is the only generally accepted risk factor that is considered a direct indication for inclusion in the treatment of allogeneic hematopoietic stem cell transplantation (allo-HSCT). A number of studies in recent years have shown that MRD determined before transplantation may increase the risk of disease relapse in ALL patients.

Objective

To assess the impact of pre-transplant MRD status determined by MFC on the long-term results of allo-HSCT in ALL patients.

Patients & Methods

The study involved 98 patients with ALL in the 1st CR (n=58) and 2nd or 3rd CR (n=40) who underwent allo-HSCT in our center from November 2015 to July 2021 (Table 1). The median follow-up was 11.7 (1-65.5) months. To determine MRD, 12-color MFC was performed on bone marrow samples obtained before allo-HSCT. The probabilities of OS, DFS and the probability of relapse (PR) were estimated using the Kaplan–Meier method. Cox proportional hazards model was used to assess the influence of various independent factors (donor type, conditioning regimen, graft source, GVHD prophylaxis, pre-transplant MRD status, age) on PR.

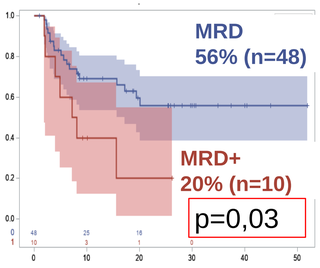
Table 1. Patient's characteristics.

Parameters	ALL (n=98)	
	MRD+(n=24)	MRD-(n=74)
Median observation, months	11,7 (1-65,5)	
Median time from 1st CR to allo-HSCT, months	8 (4-18)	3,4 (2,3-11)
Sex (male/female)	11/13	38/36
Age (median, interval)	33 (17-61)	30 (19-63)
Disease status • 1st CR • 2nd CR and 3rd CR	10 (42%) 14 (58%)	48 (65%) 26 (35%)
ALL variant • T-cell • B-cell	7 (29%) 17 (71%)	15 (20%) 59 (80%)
Donor type • MRD • MUD • MMUD • HAPLO	 5 (21%) 4 (17%) 4 (17%) 11 (45%)	 14 (19%) 19 (26%) 14 (19%) 27 (36%)
Conditioning regimen • MAC • RIC	 7 (29%) 17 (71%)	 30 (41%) 44 (59%)

Results

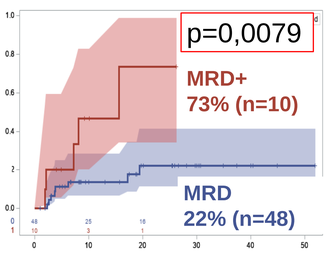
10 patients in 1st CR and 14 patients in 2nd or 3rd CR were identified as MRD+ before allo-HSCT. OS of MRD+ patients in 1st CR did not significantly differ from MRD- patients, although it was worse (28% vs. 78%, p=0.09). Significant differences were found in the DFS of MRD+ and MRD- patients: 20% vs. 56% (p = 0.0317), PR was also significantly higher in MRD+ (73% vs. 22%, p=0.0079). OS, DFS and PR in MRD+ and MRD- patients in 2nd or 3rd remission were comparable.

3-year disease free survival



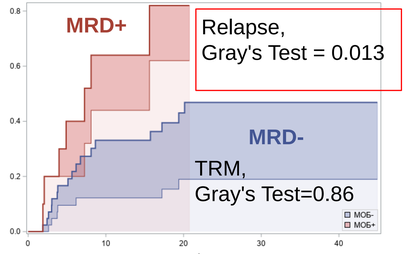
time after allo-HSCT, mon

Probability of relapse



time after allo-HSCT, mon

Cumulative frequency of competing events depending on MRD status



time after allo-HSCT, mon

The risk of relapse directly depends on the pre-transplant MRD status (Grey's test p = 0.013), but there is no significant relationship between the risk of transplant related mortality (Grey's test p = 0.86)

In our study, the presence of MRD before allo-HSCT (HR=3.858) was independent factor influencing the probability of relapse (Table 2).

Table 2. Impact of various factors on the probability of relapse (multivariate analysis)

	HR	95% CL for HR	p
MRD before allo-HSCT	3,858	1,717–8,668	0,0011
Disease status (1st CR/2nd and 3rd CR)	0,634	0,289–1,390	0,2553
Age (>40y/<40y)	0,559	0,167–1,868	0,3446
MAC/RIC	0,908	0,412–2,001	0,8106
Donor type	1,008	0,212–2,347	0,9895
GVHD prophylaxis	0,787	0,319–1,943	0,5834

Conclusions

MRD determined by MFC is an independent predictor of the risk of relapse after allo-HSCT in ALL patients. Detection of MRD in patients with ALL in 1st CR before allo-HSCT is necessary to stratify the risk and identify patients who need post-transplant therapy.

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