Prognostic Value of Flow Cytometric Minimal Residual Disease Monitoring in Children with Acute Lymphoblastic Leukemia Treated by ALL-MB-2008 Protocol

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AIM

To evaluate the prognostic value of flow cytometric (FC) minimal residual disease (MRD) measurement in children with acute lymphoblastic leukemia (ALL) treated by well-established in Russia and Belarus ALL-MB-2008 protocol.

METHODS

191 consecutive unselected children with ALL aged from 1 to 16 years treated with ALL-MB-2008 protocol were enrolled in the study. In 166 cases (86.9%) B-cell precursor ALL (BCP-ALL) was diagnosed, while 25 children (13.1%) had T-lineage phenotype (T-ALL). BM samples were obtained at the time of initial diagnostics as well as at days 15 (n=188) and 36 (n=191) of remission induction as well as after first consolidation (day 85) or first HR block (n=187). MRD was assessed by 6-10-color FC and recalculated as the percentage among all nucleated BM cells. Samples with MRD level above 0.01% were considered as positive.

RESULTS

Patients' distribution according the MRD-level is shown of fig. 1. FC data at day 15 allowed distinguishing three patients groups with significantly different outcome. Low-risk group (LR) contained 67 patients (35.64%) with MRD lower than 0.1%. 91 cases (48.40%) with MRD-level between 0.1% and 10% were stratified to intermediate-risk group (ImR), while 30 patients (15.96%) with very high MRD (more than 10%) belonged to high-risk group (HR) with poor outcome (fig. 2a). At the end of remission induction (day 36) 36 children (18.85%) with MRD higher than 0.1% had significantly worse outcome compared to remaining ones (fig. 2b). Day 85 data was very discriminative as well (fig. 2c). Day 15 and day 36 FC-MRD data remained significant in different patients group analyzed separately (BCP-ALL, T-ALL, *ETV6-RUNX1(+)-ALL)* . From a clinical standpoint it is relevant to evaluate both LR and HR criteria. LR patients could be clearly defined by low MRD level at day 15 (less than 0.1%) while HR-group could be identified either by high MRD at day 15 (more than 10%) or by moderate and high residual blasts' count at the end of remission induction (more than 0.1%). Multivariate analysis showed that both of these parameters analyzed separately are the poor outcome predictors independent from traditional HR factors as well as from HR-group definition in ALL-MB-2008 protocol. Nevertheless when day 15 and day 36 HR definitions were put in the same multivariate model, only end-induction data sustained its independent prognostic significance (tab. 1). Different ways of MRD-based stratification using both day15 and day 36 data is shown on fig. 3.

CONCLUSION

Thus FC MRD measurement during remission induction of ALL-MB-2008 protocol has independent prognostic value. Day 15 MRD data is better for LR-patients definition while end-induction MRD is the strongest HR factor.

	Patients	Events	Univariate analysis			Multivariate analysis		
			Hazard ratio	95% CI	p	Hazard ratio	95% CI	p
Age								
< 10 years	150	16	1		0.020	1		0.096
≥ 10 years	38	9	2.635	1.163-5,967		2.081	0.878-4.931	
CNS involvement								
No	154	16	1		0.013	1		0.115
Yes	34	9	2.828	1.249-6,401		2.096	0.835-5.259	
Day 8 blasts in 1 µl of PB								
< 1000	175	20	1		0.005	1		0.484
≥ 1000	13	5	4.080	1.529-10,890		0.608	0.151-2.451	
Initial WBC count in PB in BCP-ALL cases (×10⁹/L)								
< 100	150	20	1		0.001	1		0.053
≥ 100	38	5	8.331	3.098-22,403		7.175	0.974-52.832	
Phenotype								
BCP-ALL	163	15	1		0.001	1		0.005
T-ALL	25	10	5.428	2.434-12,106		3.944	1.512-10.291	
Day 15 FC MRD								
<10%	158	12	1		0.001	1		0.349
≥10%	30	13	6.916	3.152-15,177		1.761	0.538-5.764	
Day 36 FC MRD								
<0,1%	153	9	1		0.001	1		0.007
≥0,1%	35	16	9.872	4.354-22,384		4.456	1.498-13.251	
ALL-MB-2008 risk group								
SR+ImR	174	18	1		0.001	1		0.866
HR	14	7	6.226	2.592-14,958		0.870	0.173-4.370	

Table 1. Univariate and multivariate analysis of different high risk criteria impact to the probability of unfavorable outcome

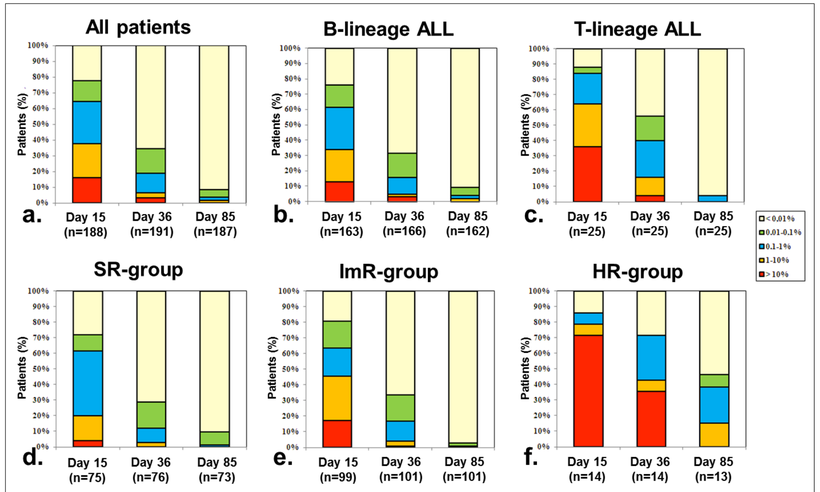

Figure 1. Patients distribution according the MRD level in a whole group **(a)**, BCP-ALL **(b)**, T-ALL **(c)** and in risk groups defined by ALL-MB-2008 stratification system **(d-f)**

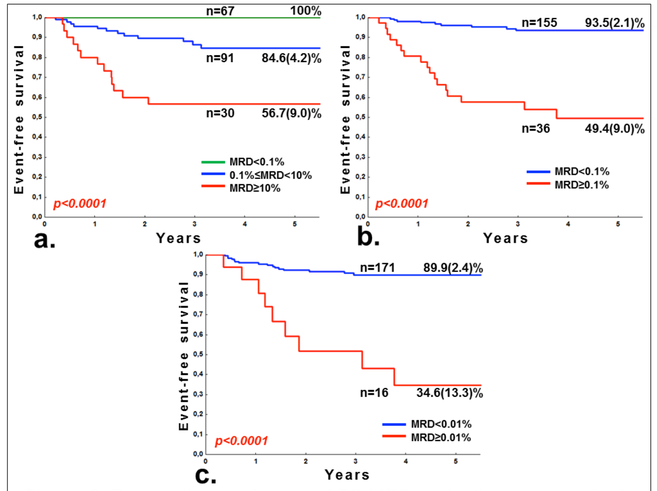

Figure 2. Prognostic significance of FC MRD evaluation on day 15 **(a)**, day 36 **(b)** and day 85 **(c)** of ALL-MB-2008 protocol

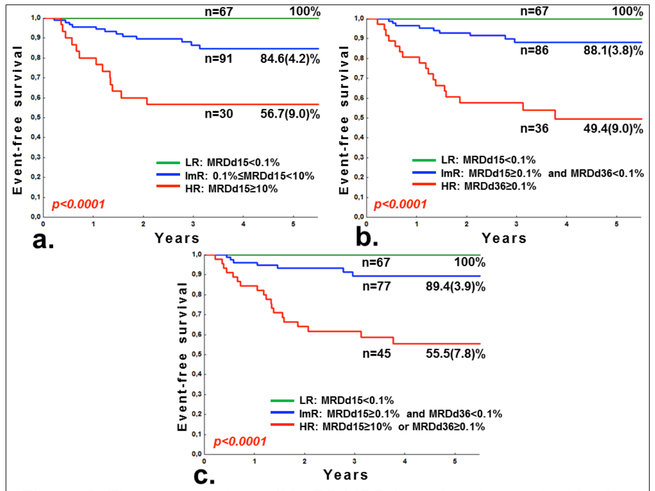

Figure 3. Three ways of possible FC MRD-based patients' stratification using day 15 data **(a)**, or combination of day 15 and day 36 data **(b-c)**

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