

The prognostic significance of minimal residual disease monitoring by WT1 gene expression in peripheral blood before and after allogeneic transplantation in AML patients

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Background & Aims

The high risk AML patients may benefit from the allogeneic stem cell transplantation (allo-SCT) as a consolidation of complete remission (CR). In the absence of an universal marker for minimal residual disease (MRD), little information is still about the importance of MRD prior to allo-SCT. The aim was to confirm our previous experience with prognostic relevance of WT1- MRD status before allo-SCT in AML patients in CR. Another aspect was to assess the significance of WT1- MRD monitoring in these patients after allo-SCT.

Methods

The expression of WT1 gene was measured by real-time polymerase chain reaction in peripheral blood according the European Leukemia Net recommendations. Between 2005-2019, we have analyzed 147 consecutive AML pts with high WT1 expression at diagnosis, transplanted in CR1 or CR2. Median age was 46 years (range; 21-66), men 76, good risk 21, intermediate risk 91, high risk 35. A total of 116 pts were transplanted in CR1 and 31 pts in CR2. In 128 pts PBPC were used, in 19 pts bone marrow. The donors were identical siblings in 30 pts, 9 haploidentical, matched unrelated donors in 73 pts and mismatched UDs in 35 pts. Conditioning was myeloablative in 117 pts, RIC in 30 pts. At the time of allo-SCT 107 pts were WT1-negative (WT1 < 50 copies) and 40 pts were WT1-positive.

Table 1. Clinical and transplant characteristics

	WT1 negative (107)	WT1 positive (40)	p
Age - years, median (range)	46 (21-66)	48 (31-63)	ns
Sex male / female	58 / 49	18 / 22	ns
Cytogenetic risk (ELN)			ns
favorable	18	3	
intermediate	65	26	
unfavorable	24	11	
CR1 / CR2	84/23	32/8	ns
HSCT-CI - 0, 1, 2, 3, 4, 5, 6	50, 31, 16, 7, 2, 1, 0	19, 6, 4, 4, 2, 4, 1	0,03
PBPC/BM	93 / 14	35 / 5	ns
Donor			0,03
IS	21	9	
haplo	4	5	
MUD	60	13	
MMUD	22	13	
Conditioning			ns
MA	85	32	
RIC	22	8	
aGVHD grade			ns
1-2	33	18	
3-4	12	7	
0	60	15	
cGVHD			ns
mild	15	3	
moderate	11	6	
severe	12	4	
0	69	27	
NA	2	0	

Table 2. Multivariate analysis (Cox regression model)

Factor	Overall survival			Event-free survival		
	HR	95% CI	p	HR	95% CI	p
Pre-transplant WT1 positive vs negative	2,25	1,23 - 4,12	0,009	2,57	1,5 - 4,41	0,0006
ELN risk intermediate		ns		2,58	1,0 - 6,65	0,05
poor		ns		2,92	1,08 - 8,19	0,042
Age		ns			ns	
HSCT-CI score		ns			ns	
Conditioning RIC vs MA		ns			ns	
Donor type		ns			ns	
aGVHD gr III-IV	4,51	1,99 - 10,22	0,0003	2,62	1,24 - 5,54	0,001
cGVHD		ns			ns	

Figure 1. Overall survival and event-free survival according pre-transplant WT1- MRD status

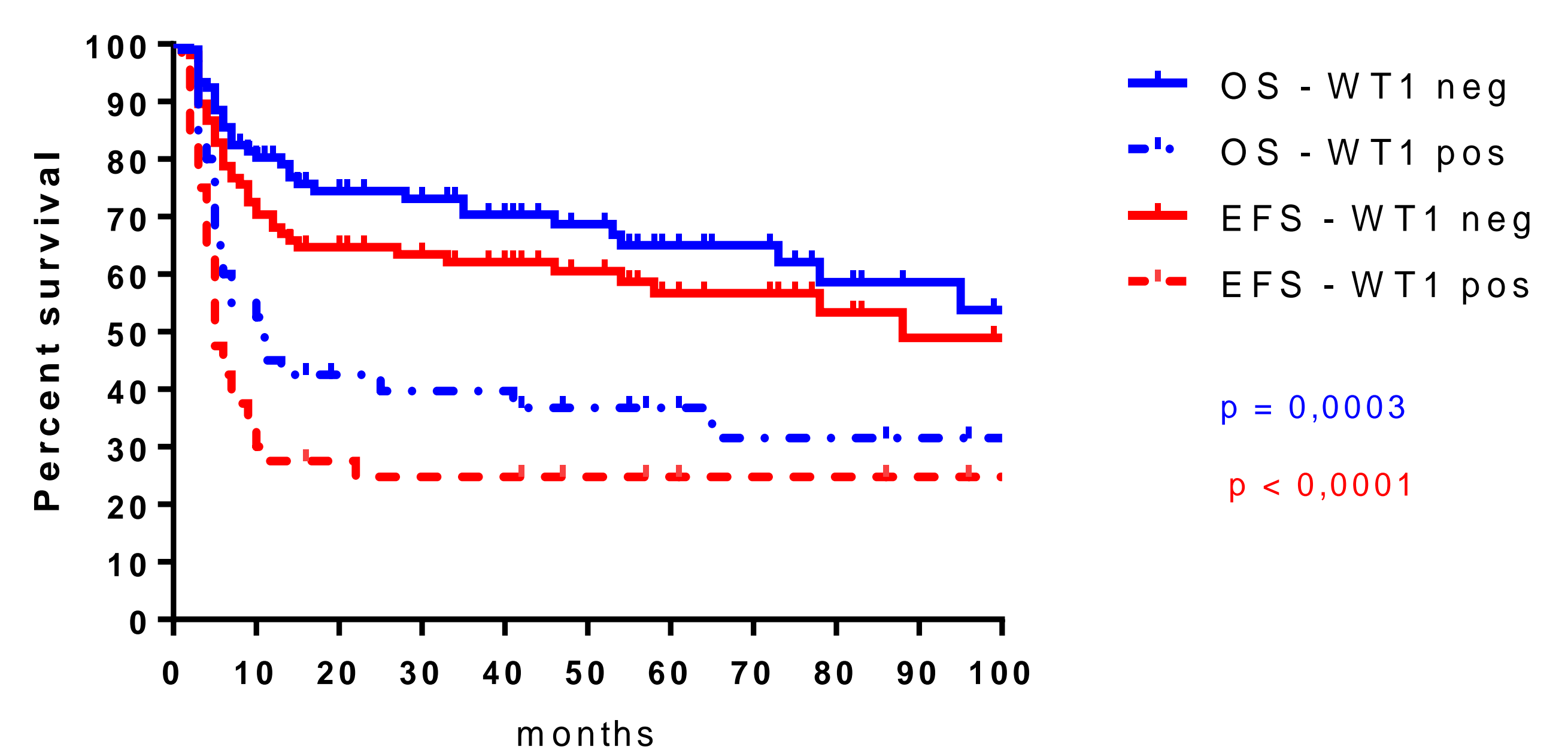


Table 3. Follow-up according molecular / haematological relapse

status	Immune intervention	chemotherapy	DLI	aGVHD cGVHD	Deaths /cause	3-years OS
Molecular relapse only (n=12)	7 (58%)	4x low dose AraC/AzaC	3 (25%)	6 (50%) 5 (42%)	6 x NRM	56%
Molecular + haematological relapse (n=38)		10x low dose 23x standard	28 (74%)	19 (50%) 15 (39%)	22 x relapse 6 x NRM	40%
Never relapsed (n=93)			2 (2%)	44 (48%) 29 (33%)	24 x NRM	75%

RESULTS AND CONCLUSION

Median follow-up was 21 months. Estimated 5-years OS and EFS (Fig.1) was significantly better in WT1 neg cohort (65% and 57% vs 37% and 25% resp, p= 0,0003 and <0,0001), as well as 5-years RI was significantly lower in WT1 neg group (25% vs 60%, p<0,0001). 5-years NRM was not significantly different (24% and 27%). Multivariate analysis revealed WT1-MRD positivity and aGVHD grade 3-4 as a significantly negative prognostic factors for OS. Higher ELN risk groups, aGVHD grade 3-4 and WT1 positivity were negative predictors for EFS (Table 2).

Overall 50 pts developed WT1-MRD positivity in post-transplant period, in forty cases the therapeutical intervention was performed. Haematological relapse occurred in 42 pts, in all relapsed patients where WT1-MRD was monitored (38 pts) we detected the positivity, in median of 28 days (0-485) before haematological relapse. 3-years OS in pts with molecular relapse only (12 pts) was 56% vs 74% in non-relapsed group (p=ns). (Table 3).

The results of the analysis confirmed our previous experience that WT1 status before allo-SCT is a strong prognostic factor for both OS and relapse risk.

WT1-positive patients should be considered for more intensive pre-transplantation therapy or earlier immunomodulatory intervention after allo-SCT (pre-emptive DLI).

Our experience suggests that this marker is also useful for monitoring MRD after allo-SCT. Well-defined clinical studies will be needed to assess the importance of therapeutic intervention based on WT1-MRD positivity.