Genetic classification of B-cell precursor adult acute lymphoblastic leukemia patients enrolled in LAL19 trial from Pethema : response to treatment and survival

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Background

Recent research on ALL biology has shown that the genetic landscape of B-cell precursor acute lymphoblastic leukemia (BCP ALL) is more complex than expected. The nowadays number of BCP ALL genetic subtypes includes 24 distinct biologic entities [1], with concrete 1ary alterations (gene rearrangements, ploidy changes or even point mutations) and some recurrent 2ary alterations (gene deletions and point mutations) that drive patients' outcome. The prognosis of adult patients treated within MRD-oriented trials with recently discovered BCP ALL entities remains to be consistently determined.

Objective

Establish the genetic subtype (primary alteration) of adult BCP ALL patients enrolled in the PETHEMA LAL19 trial (NCT 04179929) for Ph-negative ALL and to correlate them with MRD and survival.

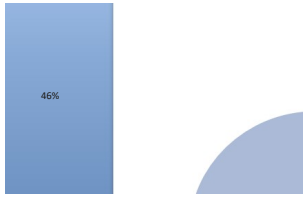
Materials & Methods

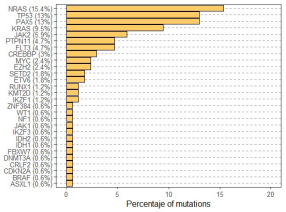
In the PETHEMA LAL19 trial, Ph-negative patients (18-65y) with MRD≥0.01% at day+35 or high-risk genetics receive alloHSCT while MRD<0.01% patients with standard-risk genetics receive maintenance chemotherapy. According to data from previous trials of the group, high-risk genetics is defined by the presence of any KMT2A rearrangement, hypodiploidy <40 chromosomes in partients >35years, biallelic TP53 alteration (deletion+mutation), or concomitant IKZF1+CDKN2A/B deletion.

The genetic analyses are centralized: FISH and NGS DNA panel (Hospital de Salamanca), RNAseq panel (Hospital 12 de Octubre), FISH panel (Hospital La Fe) and SNP array (Josep Carreras Institute/ICO-Hospital Germans Trias i Pujol). MRD determinations reaching $2x10^{-6}$ sensibility are centrally done by next generation flow cytometry in the Cytometry Service, NUCLEUS, University of Salamanca (USAL).

Results

- The genetic subtype was identified in 54% (79/147) of patients. RAS pathway mutations (K/NRAS, FLT3, PTPN11 and NF1) were the most recurrent





- The genetic subtypes showed significant differences in CR achievement and MRD clearance. Ph-like, KMT2Ar and Low-Hypodiploidy (Poor response) were the most resistant BCP ALL subtypes, while High-Hyperdiploidy, TCF3::PBX1 and PAX5 P80R showed Good response to treatment

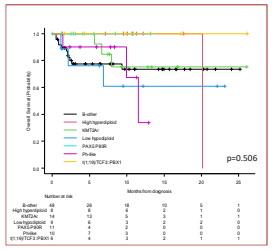
BCP ALL subtype	MRD end Ind-1 (d+35)	
	<0,01%	≥0,01%
B-other (n=53)	53%	47%
Ph-like (n=15)	27%	73%
KMT2Ar (n=15)	53%	47%
Low-hypodiploid (n=9)	33%	67%
PAX5 P80R (n=10)	100%	0%
High-hyperdiploid (n=8)	75%	25%
t(1;19)/TCF3::PBX1 (n=6)	83%	17%

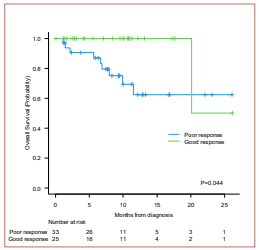
p=0.006

BCP ALL subtype	MRD end Ind-1 (d+35)	
	<0,001%	≥0,001%
B-other (n=53)	40%	60%
Ph-like (n=15)	13%	87%
KMT2Ar (n=15)	33%	67%
Low-hypodiploid (n=9)	33%	67%
PAX5 P80R (n=10)	90%	10%
High-hyperdiploid (n=8)	63%	37%
t(1;19)/TCF3::PBX1 (n=6)	67%	33%

p=0.006

- With a median follow up of 11 months, the differences observed in MRD clearance correlated with patients' survival





Discussion

- The genetic spectrum of BCP ALL is wide, with multiple combinations of 1ary and 2ary alterations, a fact that critically limits to assess an accurate prognosis for each patient

- The presence of 2ary alterations may modulate the prognosis of 1ary alterations

- The low number of patients of this series prevents to know the prognosis of patients with low incidence 1ary alterations such as MEF2Dr, MYCr/BCL2r or ZNF384r

Conclusions

- To know the genetic subtype of each ALL is crucial to better predict relapse risk and to offer the best (personalized) treatment for each patient

- Patients with Ph-like, KMT2Ar or Low-Hypodiploid ALL urgently need alternative therapeutic strategies upfront

References

1. Arber DA, Orazi A, Hasserjian RP, et al. Blood 2022. doi:10.1182/blood.202215850.

Funding & Contact Information

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