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REDEFINING LOW RISK HIGH HYPERDIPLOIDY IN PAEDIATRIC ACUTE LYMPHOBLASTIC LEUKAEMIA

Topic: 01. Acute lymphoblastic leukemia - Biology & Translational Research

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Background:

High hyperdiploidy (HeH) with a modal number of 51 to 67 chromosomes occurs in ~30% of B-cell precursor acute lymphoblastic leukaemia (ALL). Although strongly associated with good outcome, relapses do occur and its prevalence means that HeH accounts for up to 25% of all relapses. No consensus exists regarding risk factors in this subgroup.

Aims:

The objective of this study was to comprehensively evaluate all relevant risk factors to define a very low risk subgroup within HeH which could be used prospectively to define patients eligible for treatment de-escalation.

Methods:

Analysis was performed using the UKALL97/99 (n=456, discovery) and UKALL2003 (n=725, validation) cohorts with median follow-up times of 10.6 and 9.4 years, respectively. Event-free survival (EFS), relapse rate (RR) and overall survival (OS) rates were calculated at 10 years and compared using univariate and multivariate analyses Cox regression models. To determine the optimal number of chromosomes needed to predict outcome, we used area under ROC curve, general linear model and targeted projection pursuit. We measured C-index, Mallows' Cp for each combination for selecting the fittest model. Multivariate analysis, general linear model, network analysis and coefficient of the risk model determined the optimal combination of chromosomes for predicting outcome and Bayesian information criterion with forward stepwise criteria for model selection.

Results:

HeH karyotypes gain between 5 and 19 chromosomes so analysing all possible combinations and permutations of trisomies was impossible. Hence, we calculated the optimum number of chromosomes required to maximise prediction. Using the discovery cohort, we generated all possible combinations of one to six trisomies and found that four chromosomes produced the maximum prediction power. Multivariate Cox modelling defined chromosomes 5, 17, 18 and 20 as the optimal prognostic set. Using these four chromosomes, we developed and validated good risk (GR) and poor risk HeH profiles. The GR profile comprised patients with (a) +17 and +18 together or (b) either +17 or +18 but not +5 or +20. The poor risk (PR) comprised all other HeH cases. The size of the risk groups were similar in the validation and discovery cohorts: GR 80-82%, PR 18-20%. There was no correlation between HeH risk group and age, sex, white cell count or end of induction MRD. Patients with a HeH-PR profile had an increased RR in both cohorts: hazard ratio 2.50 (95% CI 1.51-4.14) & 3.80 (2.14-6.75), both $p<0.001$; which was independent of MRD. Threshold analysis revealed 0.03% to be the optimal MRD threshold and the RR for HeH-GR cases by MRD

Image:

	All HeH cases	HeH-PR	HeH-GR	Triple trisomy (+4,+10,+17)
	n (%)	n (%)	n (%)	n (%)
Number of cases	725	146	579	299
Proportion of HeH cases	100%	20%	80%	41%
NCI risk group				
Standard	550 (76)	107 (73)	443 (77)	229 (77)
High	175 (24)	39 (27)	136 (23)	70 (23)
End of induction MRD				
<0.03%	462 (73)	85 (70)	377 (74)	187 (73)
≥0.03%	170 (27)	37 (30)	133 (26)	68 (27)
Relapse				
No	670 (93)	122 (85)	548 (96)	284 (97)
Yes	47 (7)	22 (15)	25 (4)	10 (3)
Outcome at 10 years (95% CI)				
Relapse risk	7% (5-9)	16% (10-23)	5% (3-7)	4% (2-7)
Event Free survival	90% (87-92)	81% (73-86)	92% (90-94)	92% (88-94)
Overall survival	94% (92-95)	86% (79-91)	96% (94-97)	96% (93-97)
Prediction Accuracy				
C-index	-	0.64		0.60
Area under the curve	-	0.64		0.61

Summary/Conclusion:

The UKALL-HeH profile defines two distinct HeH risk groups. Patients with a UKALL-HeH GR profile have an excellent outcome and represent low risk subgroup of HeH which could be considered for treatment de-escalation.

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