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**Composite Index for Risk Prediction in Relapsed Childhood Acute Lymphoblastic Leukaemia (ALL)**

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Somatic genetic abnormalities are key initiators and drivers of disease in acute lymphoblastic leukaemia (ALL). Several chromosomal abnormalities have proven clinical utility as prognostic and predictive biomarkers at initial diagnosis. However, the role of genetic biomarkers in relapsed ALL is less well understood and has rarely been studied comprehensively within a clinical trial.

We evaluated the role of genetics in predicting outcome among children with relapsed B-cell precursor ALL treated on the international trial, ALLR3.

We analysed cytogenetic, copy number alteration (CNA) and sequence mutation data at relapse in representative cohorts of patients. Patients with a very early relapse (<18 months from first diagnosis) and those patients with an isolated marrow relapse who had an early relapse (<6 months from stopping frontline therapy) were treated as clinical high risk (HR) whereas all other patients were treated as clinical standard risk (SR).

Clinical HR patients accounted for 25% of the cohort and had a significantly inferior overall survival (OS) compared to SR patients: 25% (95% CI 15-37) v 65% (57-72), p<0.0001. A total of 427 patients were assigned to pre-defined cytogenetic risk groups which were predictive of survival post-relapse in both univariate and multivariate analysis adjusting for clinical risk: good risk (GR) cytogenetics (*ETV6-RUNX1*, high hyperdiploidy) 5 years OS 68% (60-75); intermediate risk (IR) cytogenetics (*TCF3-PBX1*, *IGH* translocations, B-other ALL) 47% (38-55); and HR cytogenetics (*BCR-ABL1*, *MLL* translocations, near haploidy, low hypodiploidy, iAMP21, *TCF3-HLF*) 26% (14-40), p<0.001. However, the prognostic effect of cytogenetic risk group was strongest within the clinical SR group. A representative cohort of 240 patients with marrow involvement was screened for CNA and

mutations affecting key genes in ALL. Over 75% patients harboured at least one CNA or mutation: *CDKN2A/B* (39%), *IKZF1* (22%), *PAX5* (20%), *TP53* (17%), *ETV6* (16%), *KRAS* (12%), *NRAS* (12%), *NR3C1* (9%), *PAR1* (8%), *PTPN11* (8%), *RB1* (4%), *EBF1* (4%), *BTG1* (4%), *FLT3* (4%), *CBL* (1%). Cox models adjusted for clinical risk revealed that only four genes were associated with outcome. Patients with a *TP53* alteration or a deletion of either *NR3C1 or BTG1* had an inferior progression free survival (PFS) with hazard ratios of 2.07 (95% CI 1.20-3.58), p=0.009 and 2.26 (1.38-3.70), p=0.001, respectively. In addition, cytogenetic GR patients with a *NRAS* mutation had an inferior PFS compared with other GR cytogenetic patients 2.54 (1.24-5.22), p=0.01. The integration of clinical and cytogenetic risk groups with *TP53*, *NR3C1*, *BTG1* and *NRAS* gene status revealed three groups: (1) Favourable - clinical SR patients with GR cytogenetics and without a *TP53, NR3C1, BTG1* or *NRAS* abnormality; (2) Intermediate - clinical SR patients with GR cytogenetics and a *TP53, NR3C1, BTG1 or NRAS* abnormality plus clinical SR patients with IR cytogenetics; and (3) Adverse - all clinical and cytogenetic HR patients. The three groups accounted for 35%, 35% and 30% patients, respectively, and had markedly distinct OS rates: 78% (61-89), 56% (46-65) and 27% (19-35), p<0.001, respectively. Multivariate Cox models including variables for treatment and minimal residual disease did not materially alter the results. Receiver operating characteristic (ROC) curve analysis revealed that the new index had significantly greater predictive power than clinical risk alone for both PFS and OS: area under the curve = 0.73 v 0.67, p=0.02 and 0.75 v 0.69, p=0.03, respectively. In conclusion, we have integrated key genetic information with clinical risk to improve risk prediction in relapsed ALL and propose a three-tier index which could be used to develop risk-directed therapy.