

Conference Abstracts

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Peripheral Lymphocyte Depletion as a Genotype-Specific Precision Biomarker in PTPN11-Mutated Juvenile Myelomonocytic Leukemia

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Abstract

Background

Juvenile myelomonocytic leukemia (JMML) is a genetically defined pediatric myelodysplastic/myeloproliferative neoplasm, yet substantial outcome heterogeneity persists within canonical RAS/MAPK genotypes. We investigated whether peripheral lymphocyte composition reflects genotype-specific disease biology and can provide a readily available layer of prognostic refinement.

Methods

In this retrospective cohort, 96 children with JMML treated between January 2008 and November 2022 were analyzed. Baseline clinical, hematologic, cytogenetic, molecular, and flow-cytometric data were collected; lymphocyte-subset phenotyping was available for 66 patients and mutation profiling for 89. Overall survival was assessed through April 2025. Patients were stratified by driver genotype, and the cohort median lymphocyte percentage of 36.6% was evaluated using Kaplan–Meier analysis and Cox regression.

Results

Peripheral lymphocyte composition differed significantly across molecular subgroups. Patients

with KRAS-only somatic mutations had a higher peripheral-blood lymphocyte percentage than those with PTPN11-only mutations ($48.1\% \pm 9.0\%$ vs $32.1\% \pm 13.0\%$; $P=0.0226$). Conversely, the NRAS-only subgroup showed a substantially lower CD3+ T-cell fraction than the PTPN11-only, mutation-negative, and compound-mutated subgroups ($32.8\% \pm 14.0\%$ vs $55.8\% \pm 17.0\%$, $70.4\% \pm 17.0\%$, and $59.1\% \pm 10.0\%$; $P=0.0050$, $P=0.0040$, and $P=0.0023$, respectively). Patients harboring PTPN11 mutations had inferior survival compared with those without PTPN11 mutations ($P=0.0037$). A lymphocyte-percentage cutoff of 36.6% did not stratify survival in the overall cohort ($P=0.1051$). However, within PTPN11-mutated JMML, patients with lymphocyte percentages above 36.6% had significantly better survival than those below this threshold ($P=0.0270$), whereas no association was observed in patients without PTPN11 mutations ($P=0.7497$).

Conclusion

JMML exhibits genotype-conditioned immune heterogeneity. Peripheral lymphocyte depletion identifies a clinically distinct high-risk phenotype specifically within PTPN11-mutated disease, transforming an inexpensive routine measurement into a candidate precision-stratification tool.

Prospective multicenter validation could establish molecular classification and treatment selection.
this marker as a practical complement to

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