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Blood 142 (2023) 1449–1450

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

605.MOLECULAR PHARMACOLOGY AND DRUG RESISTANCE: LYMPHOID NEOPLASMS

Mapping Chemo-Resistance Profiles of Pediatric Acute Leukemia through Integration of Ex-Vivo Drug Screens with Molecular Data

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Introduction
While novel approaches for treatment of acute lymphoblastic leukemia (ALL) in children have resulted in significant improvements in survival rates, survivors are faced with potentially life-long challenges as a result of the highly toxic treatment and the outcome for patients who relapse remains poor. The current risk-adapted treatment for ALL in children includes multiple drugs administered sequentially or in combination, with little variation in timing or intensity. Factors that affect varying treatment response between patients and cellular mechanisms that underly response to individual drugs are still under exploration. In this study, we investigate the relationship between ex-vivo drug resistance, transcriptomes, epigenomes and clinical outcome, with the aim of better understanding underlying determinants of treatment response.
Methods
Pediatric patients diagnosed with B-ALL between 1992 and 2008 in the Nordic countries were included in the study (n = 598). For these patients, ex-vivo drug response to ten clinically used drugs was determined using the fluorometric microculture cytotoxicity assay (FMCA). Clinical data, including follow-up information (overall survival and relapse free survival) was available for all patients. Additionally, DNA-methylation (450K array, n = 383) and gene expression profiling (RNA-seq, n = 119) was performed on a subset of diagnostic patient samples. The patients were stratified into low, medium and high resistance groups based on ex-vivo drug response. The low and high resistance groups were compared with regard to differentially methylated CpG sites or expressed genes associated with individual drug response profiles.
Results
Overall survival was significantly lower for patients with higher ex-vivo drug resistance to dexamethasone, doxorubicin and thioguanine compared to patients that displayed sensitivity to these drugs ($p < 0.05$). Similarly, relapse free survival was significantly lower for patients with ex-vivo resistance to cytarabine, dexamethasone, doxorubicin, prednisolone and thioguanine ($p < 0.05$). After adjusting for sex and risk group, according to the Nordic Society of Pediatric Hematology and Oncology (NOPHO) protocol, in a Cox proportional hazards model, higher hazard ratios for relapse were observed in the highly resistant group across all drugs. We identified distinct DNA methylation and gene expression patterns in patients with low and high resistance, indicating the presence of predetermined molecular resistance fates. These resistance patterns included 665 genes that were differentially expressed (absolute log2FC > 1, Benjamini-Hochberg adjusted p value < 0.05) and 1 422 CpG sites with differential methylation status (absolute mean β-value difference > 0.2, Benjamini-Hochberg adjusted p value <

0.05) in resistant compared to sensitive groups, for one or multiple drugs. With the aim of identifying the genes with the largest impact on drug resistance, we selected the most differentially expressed genes and the genes with the largest difference in methylation status between resistant and sensitive samples. Among these, we identified ~20 putative genes of interest for future studies into resistance mechanisms based on potential functional prioritization.

Conclusion

Our findings confirm that drug response profiles are associated with outcome in pediatric ALL, reflecting response in vivo. We show molecular evidence for differentiating low- and high-resistant types based on diagnostic gene expression and DNA methylation profiles, suggesting contribution of certain molecular signatures to drug response. Our data integrating molecular data with drug response profiles may help identifying such changes of importance in drug resistance mechanisms.

Disclosures Schmiegelow: *Novo Nordisk Foundation:* Current holder of *stock options* in a privately-held company, Research Funding; *Illumina, Jazz Pharmaceuticals, Servier, Amgen, Medscape:* Honoraria.

https://doi.org/10.1182/blood-2023-180693