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POSTER ABSTRACTS

614.ACUTE LYMPHOBLASTIC LEUKEMIAS: THERAPIES, EXCLUDING TRANSPLANTATION AND CELLULAR IMMUNOTHERAPIES

Vinpocetine Mediates Therapeutic Activity Alone and in Combination with Chemotherapy in T-Cell Acute Lymphoblastic Leukemia

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Introduction: T-cell acute lymphoblastic leukemia (T-ALL) is a highly aggressive cancer affecting immature T-cells and constitutes about 15% of pediatric acute lymphoblastic leukemia (ALL) cases. Despite advances in treatment, 20% of patients have or develop treatment-resistant disease, and their survival rates are only 15-25% even with additional intensive chemotherapy and hematopoietic stem cell transplant. Furthermore, the current intensive treatment regimens have long-term side effects in most patients. Therefore, there is a pressing need for new, more targeted, and less toxic treatment options for children with T-ALL. Genomic analysis of leukemia samples has enabled identification of chromosomal aberrations and gene mutations associated with T-ALL leukemia development and progression. Single cell analysis of genes expressed in pediatric T-ALL bone marrow samples at diagnosis identified blast-associated signature genes that correlated with poorer event-free survival, suggesting their involvement in leukemia progression and highlighting the potential for further investigation of the signature as an avenue to develop novel T-ALL therapies. A non-conventional genome-oriented approach was applied to the data utilizing the Library of Integrated Network-Based Cellular Signatures (LINCS) resource to identify drugs that are predicted to reverse the T-ALL blast signature. Vinpocetine, a vinca alkaloid derivative, was identified as a potential therapeutic candidate.
Methods: Leukemia cell cultures were treated with incremental concentrations of vinpocetine, alone or in combination with a standard chemotherapeutic agent (vincristine or doxorubicin) for 72 hours and relative cell densities were determined by luminescent viability assay. Interactions between drugs were evaluated by mathematical modeling using the fractional product method. Orthotopic T-ALL patient-derived xenografts (PDXs) were established in immune-compromised NSG mice by intravenous injection and peripheral blood samples were collected at intervals for detection of leukemic blasts (human CD45+) by flow cytometry. Mice with low disease burden (<5% peripheral blasts) were randomized to groups and treated every third day with 10 or 20 mg/kg vinpocetine or an equivalent volume of vehicle administered intraperitoneally. Mice were weighed and their health status was evaluated at intervals to monitor for toxicity.
Results: Treatment with vinpocetine resulted in a dose-dependent reduction in cell density in T-ALL cell line (Jurkat, HPB, and PEER) cultures relative to vehicle treatment, with IC50 values between 62.6 -64.4 uM, supporting the therapeutic potential of vinpocetine in T-ALL. Vinpocetine also interacted synergistically with vincristine or doxorubicin to provide enhanced therapeutic efficacy against Jurkat cells, indicated by a greater reduction in cell number compared to either single agent. This promising finding underscores the potential of vinpocetine as a supplemental therapy to improve responses or allow for dose reduction of existing chemotherapeutic agents for T-ALL therapy. In a preliminary dose-finding study, treatment with 20 mg/kg vinpocetine was well-tolerated with no overt evidence of toxicity and there was a slight trend toward decreased disease burden.
Conclusion: Our study explores the therapeutic potential of vinpocetine for treatment of T-ALL. The observed inhibitory effects on leukemia cell expansion and enhanced efficacy with standard chemotherapies identify vinpocetine as a promising novel treatment approach for T-ALL. Dose escalation studies are needed to evaluate therapeutic effects of vinpocetine in mouse models.

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