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Molecular Pathways and Treatments for Pediatrics B cell Acute Lymphoblastic Leukemia

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Introduction

The presence of excessively large numbers of immature, poorly differentiated white blood cells in the blood is a symptom of leukaemia, which commonly starts with bone marrow abnormalities. Acute Lymphoblastic Leukemia (ALL) is the most common blood malignancy in children. Each year, 4,000 children in the United States are diagnosed with cancer, accounting for 30% of all juvenile cancers. More than 80% of these all cases are caused by clonal expansion of aberrant B cell progenitors (B-ALL). In recent years, it has been discovered that cytosolic signal transduction and molecular abnormalities play a key role in the pathogenesis of B-ALL; abnormalities include gene mutations, aberrant protein interactions, an unrested cell cycle, and enhanced autophagy.

Understanding these aberrations could aid in the development of gene-targeted therapies. In the wake of medical advancements, more risk factors for B-ALL have been uncovered; reducing these risk factors could thereby reduce the disease's incidence. The cure rate for B-ALL has increased dramatically in recent years. Despite this improvement, the relapse rate for B-ALL patients remains at 15%. Multiple drug resistance or aberrant expression of intracellular enzymes could be linked to treatment failure. This review described juvenile B-ALL, including its pathogenesis, risk factors, current treatment, and treatment efficacy and failure monitoring. The development of novel target therapy to reduce the prevalence of B-ALL and the chance of recurrence could be aided by a better knowledge of the underlying processes of B-ALL.

Treatments

Risk-directed therapy is currently the primary treatment for childhood B-ALL. The age of the child at the time of diagnosis is considered. The initial white blood cell count, immune phenotypic and cytogenetic characteristics of the blast population and the quickness of response to early treatment are all taken into account. Chemotherapy is the standard treatment, which lasts 2–3 years. At the end of the induction period, many patients achieve complete remission (CR). A multidrug regimen consisting of three phases (induction, consolidation, and maintenance), during which therapy or prophylaxis directed at the Central Nervous System (CNS) is provided in multiple sessions, is required for such treatment to be successful. Induction's main goal is to achieve an initial CR and re-establish normal hematopoiesis. Weekly vincristine and anthracycline for 3–4 weeks, daily corticosteroids, and asparagine's are all part of induction therapy. The routine use of preventative CNS therapy in the treatment of paediatric ALL represents a significant therapeutic development. Treatment for the Central Nervous System (CNS) usually begins during the induction phase and continues until the end of the treatment regimen. Intrathecal chemotherapy replaces craniospinal irradiation in several CNS preventative treatment regimes.

The consolidation phase of treatment focuses on intensive CNS therapy in conjunction with long-term intensive systemic therapy. This therapy phase begins immediately after the patient has achieved CR. Consolidation chemotherapy aims to stop leukaemia from regrowing, reduce residual tumour burden, and avoid drug resistance in other leukemic cells. Cytarabine, methotrexate, anthracyclines, and alkylating agents are commonly used in combination with other medicines with distinct pharmacological mechanisms than those used in the induction phase. These medications are given on a regimen that maximises drug synergy while minimising drug resistance. Patients often get a less intensive continuation regimen (maintenance chemotherapy) after finishing the consolidation (or intensification) phase of therapy, which includes daily oral 6-mercaptopurine, weekly methotrexate with periodic vincristine, corticosteroid, and intrathecal therapy. The next 2–3 years are spent in the maintenance phase. Extending the maintenance period after that provides few benefits. After treatment, about 15% of patients relapse, and patients who relapse have a 10% overall survival rate. As a result, new ALL therapy techniques with better CR and lower medication toxicity are needed. Through increased expressions of p21 and p27, resveratrol has been shown to induce apoptosis, cell cycle arrest, or inhibit cell proliferation in recent years. Caspases 3 has been unregulated due to decreased expression of anti-apoptotic proteins such as myeloid cell leukaemia 1 and Bcl-2 and increased expression of proapoptotic proteins such as Bax, Bcl-2-like protein 11 and Bad. Everolimus is also an mTOR inhibitor, which increases cell death by inducing autophagy. This medication causes cell malfunction by inducing apoptosis through caspase-independent mechanisms and altering mitochondrial permeability. Everolimus destroys cancerous cells by inducing Para ptosis. Selumetinib, a mitogen activated protein kinase (MEK) inhibitor, could be used to treat ALL. It inhibits ERK-dependent cell growth by acting on MEK1/2.

Treatment Failure

Multiple medication resistance is linked to the occurrence of recurrence in B-ALL patients. The most prevalent cause of MDR is the up regulation of drug efflux pumps on leukemic cells after medication treatment, which lowers the intracellular drug concentration. A number of intracellular signalling pathways, including MAPK, ERK, and JNK, govern the production of ATP-Binding Cassette (ABC) transporters, which actively pump medicines out of cells. ABCB1, ABCC1, and ABCG2 are genes that code for the ABC transporter pump. ABCB1 gene expression has been found to be higher in ALL cell lines, and increased ABCB1 expression has been linked to a worse prognosis and shorter disease-free survival rates. Glutathione (GSH) and its related enzymes, which are part of the cell defence system against chemo drug-induced reactive oxygen species stress, are another MDR mechanism. Glutathione reductive is the primary enzyme in the GSH redox cycle, and it modulates redox homeostasis in leukemic cells to minimise chemo sensitivity.

Monitoring Treatment Efficacy

Any ALL therapy should be evaluated for treatment effectiveness. MicroRNA and soluble interleukin receptor levels, in addition to the standard blood test, are employed to assess treatment efficacy. Deregulated expression of miR-128, miR-146a, miR-155, miR-181a, and miR-195 was discovered in a whole genome microRNA analysis of ALL patients. MiR-146a, miR-155, miR-181a, and miR-195 expression were all down regulated after 6 months of treatment. The soluble interleukin 2 receptor (sIL-2R) has been established as a biomarker for non-lymphoma Hodgkin's disease activity as well as tumour volume. Other lymph proliferative diseases, such as chronic lymphocytic leukaemia and ALL, have increased sIL-2R expression. Before entering the bloodstream, immature blast cells release sIL-2R. As a result, sIL-2R can be used to track the effectiveness of ALL treatment.