Original Article

Pharmacotherapy of Acute Lymphoblastic Leukemia in Pediatric Patients: A Review of Efficacy and Adverse Effects

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ABSTRACT

Acute Lymphoblastic Leukemia (ALL) is a hematological malignancy highly prevalent in children. B-cell ALL is characterized by uncontrolled proliferation of B lymphoblasts, which impairs normal hematological function and causes clinical symptoms such as persistent fever, bone pain, swollen lymph nodes, petechiae, pallor, and bruising. The therapy for pediatric ALL encompasses four main approaches: surgical intervention, immunotherapy, radiotherapy, and chemotherapy. Despite numerous medical advances over the years, only a few drugs have been approved for pediatric ALL. This review focuses on the mechanisms of action, efficacy, and adverse effects of pharmacotherapeutic agents that have been used to manage pediatric ALL over the years, such as vincristine, asparaginase, anthracyclines, 6-mercaptopurine, methotrexate, cyclophosphamide, cytarabine, and glucocorticoids. The review also highlights significant aspects of the prevalence of ALL in pediatric populations, the influence of genetics on ALL occurrence, and the fundamentals of treatment regimens. Survival rates in pediatric ALL are significantly higher compared to other malignancies; however, the treatment has a wide range of adverse effects that affect the patient's quality of life during and post-treatment. Treatment options such as immunotherapy, stem cell transplantation, targeted therapy, gene modification, and novel drugs are constantly evolving and offer the potential for better management, especially in high-risk groups. Although the rate of remission and full recovery after treatment is quite high in pediatric ALL, the search for more effective and less toxic therapies remains a top priority, especially in cases of disease relapse.

Key words: Acute Lymphoblastic Leukemia, Hematological malignancy, Pediatric ALL

Acute Lymphoblastic Leukemia (ALL) is a lymphoid cell malignancy with a high survival rate, primarily caused by genetic mutations. ALL is highly prevalent in children aged between 1-4 years, with a slight male predominance [1]. The process of disease development starts when the B and T lymphoblasts begin uncontrolled proliferation and are glued at this stage in the differentiating pathway, unable to form B and T cells. This causes a multifaceted imbalance in the body's normal hematological processes, with large amounts of premature lymphoblasts released into the blood.

Symptoms of ALL are diverse and vague; they typically include persistent fever, bone pain, swollen lymph nodes, petechiae, pallor, bruising, and dyspnea caused by mediastinum enlargement. Many patients have a history of recurring infections, fatigue, and skin rashes. To confirm the diagnosis, a repeated biopsy of bone marrow is necessary in certain patients [1, 2].

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There are currently four independent cancer treatment approaches: surgical removal, immunotherapy, radiotherapy, and chemotherapy. According to the US Food and Drug Administration, only 11 drugs were approved for pediatric malignancies between 1980 and 2017, due to the specific factors to be considered for a therapy to treat pediatric cancers [3].

This review aims to provide a comprehensive overview of ALL in children, with a focus on the major pharmacotherapeutic approaches such as vincristine, asparaginase, anthracycline, 6-mercaptopurine, methotrexate, and cyclophosphamide, as well as their MOAs, particularly in the context of the high-risk subgroup, i.e., pediatric patients.

Prevalence of ALL in Children

Childhood malignancies are rare, and within this slim chance, ALL is the most common type of malignancy in pediatric patients. Leukemias account for more than 25% of all cancers diagnosed in children under the age of 19, and this percentage is continually rising. ALL express a bimodal peak, with a high

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chance of occurring in children aged 1-4 years and 10 years and above. In terms of ethnic variability, cases are more common in children of American Indian, Native Alaskan, and Hispanic descent, with white children affected twice as much as black children [2, 4].

Recurrence of the condition, which affects 15-20% of children and results in early-age mortality, is less common in adults. When predicting the course of an illness, factors such as the patient's age and white blood cell (WBC) count are crucial. Treatments for ALL in children and youngsters have resulted in a five-year disease-free period, with an estimated 85–90% cure rate [5].

Genetics: A Major Predisposing Factor of ALL

There are multiple predisposing factors of ALL, including exposure to radiation, viral infections, race, and sex of an individual or toxic encounter with a potent drug, wherein genetic variation is a major factor, particularly in pediatric cases. Most leukemia subtypes arise from a cascade of genetic changes caused by an interplay of these alternations. Until recently, the genetic foundation of ALL was poorly understood. The modifications in cytogenetic assays and techniques, including single nucleotide polymorphism microarray analysis and next-generation sequencing, have enabled detailed characterization of ALL's genomic complexity [6].

Crucial genetic alterations for ALL include chromosomal rearrangements that result in the expression of chimeric fusion proteins, aneuploidy, deletions, gains of DNA, and DNA sequence mutations. Early chromosomal translocations and intrachromosomal rearrangements could be the first signs of leukemia. A few of them can be found in neonatal blood samples several years before leukemia symptoms appear. One-fourth of childhood ALL are caused by high hyperploidy. Many mutations distort the principal cellular mechanisms, including the transcriptional stage of lymphoid development and differentiation, cell cycle regulation, growth factor receptor, JAK-STAT signaling, nucleoside metabolism, and epigenetic modification. Although the specific role of the extra chromosome 21 in leukemia is not known, patients with Down syndrome are about 20 times more likely to develop the disease [7, 8].

A few inherited diseases are linked with a higher risk of developing leukemia, including Fanconi anemia, Bloom syndrome, ataxia telangiectasia, Down syndrome, Shwachman syndrome, and neurofibromatosis. Furthermore, siblings of children with leukemia are more likely to develop hematological malignancies, lending credence to the theory that genetics plays a role in ALL. Increased risk of pediatric ALL has also been linked to genetic polymorphisms that impair the patient’s ability to biotransform and transport xenobiotics effectively [9].

Pharmacotherapy of ALL: Induction, Intensification, and Maintenance Therapy

A multidrug regimen is used in drug therapy for ALL to abstain from the development of resistance. Drug combinations and treatment duration are adjusted according to the severity of the disease and the likelihood of recurrence. The main goal of drug therapy for ALL is to induce remission and restore the normal blood cell count in the body (Table 1). Furthermore, as the treatment progresses, the emphasis shifts to eradicating residual disease, preventing CNS involvement, and minimizing treatment-related toxicities. After complete remission is achieved, monitoring for relapse or secondary malignancies and long-term disease control is a significant concern. The treatment is divided into three phases, namely induction, intensification, and maintenance.

Induction therapy

Induction therapy for ALL aims to achieve complete remission by reducing the leukemic cell burden to undetectable levels in the blood and bone marrow, eventually restoring normal hemopoiesis. It typically lasts for 4-6 weeks, and the patient is compulsorily hospitalized in the initial phases of therapy. Originally, complete remission was defined as less than 5% detectable blasts under the microscope at the end of induction. Patients with induction failure may be considered for an allogeneic bone marrow transplant. During this phase, drugs like vincristine, corticosteroids, and asparaginase are used, with most regimens adding anthracycline (either doxorubicin or daunorubicin). The effectiveness of induction is a reliable indicator of overall treatment outcomes [10].

Intensification/Consolidation therapy

The consolidation regimen varies depending on the individual condition but usually uses similar drugs as induction and may include intrathecal chemotherapy and cranial radiation for CNS prophylaxis [11]. Consolidation therapy aims to eradicate the submicroscopic residual disease that remains after complete remission. Patients with higher-risk diseases are given more intensive consolidation regimens that last longer, but they are usually completed in 6 to 9 months, mostly as outpatients. It also focuses on decreasing drug resistance and therefore inculcating agents that were not used during the initial remission period, like mercaptopurine, thioguanine, methotrexate, cyclophosphamide, etoposide, and cytarabine. Submicroscopic levels of minimal residual disease can be calculated using polymerase-chain-reaction amplification of gene rearrangements specific to an individual patient [7, 10].

Maintenance therapy

Following high-intensity chemotherapy, a low-intensity maintenance regimen is required to maintain the antileukemic

effect against remaining malignant lymphoblasts and to prevent relapse. Maintenance therapy consists of daily 6-MP, weekly methotrexate, and vincristine, and a 5-day prednisone pulse every 3 months. Maintenance is administered for 2–3 years after induction, beyond which no benefit has been demonstrated. Active forms of oral methotrexate (MTX) and 6-mercaptopurine (6-MP) are principal agents for this phase, and they are known to cause severe myelosuppression, necessitating regular blood count tests throughout the treatment [11].

Table 1: Brief description of various phases, treatment goals, duration, and agents employed in the commonly used regimen for ALL.

Phase	Treatment Goals	Typical Duration	Key Components
Induction	Achieve complete remission	4-6 weeks	Combination of vincristine, prednisone, asparaginase, and anthracyclines
Consolidation	Eliminate residual disease	6-9 months	Intensive chemotherapy, including high-dose methotrexate and cytarabine
Maintenance	Maintain remission and prevent relapse	2-3 years	Long-term therapy with methotrexate, 6-mercaptopurine, and corticosteroids
CNS Prophylaxis	Prevent CNS involvement	Throughout treatment	Intrathecal administration of methotrexate or cytarabine
Re-Induction (if needed)	Re-establish remission in case of relapse	Variable	Similar to induction phase therapy, it may include additional agents

Drugs used in chemotherapy for childhood acute lymphoblastic leukaemia.

VINCRISTINE

Vincristine, an alkaloid extracted from vinca, is used in combination with other chemotherapeutic drugs to treat pediatric ALL and other cancers such as malignant lymphoma, malignant melanoma, breast cancer, and neuroblastoma. It is an essential drug in the ALL protocol, primarily used during the chemotherapy induction phase. Vincristine acts rapidly, demonstrating satisfactory results for inducing remission, but is not very effective for maintenance therapy, for which it is administered at long intervals [12]. Its mechanism of action involves disruption of the formation of microtubules in the mitotic spindle, which causes mitotic cells to arrest. Microtubules are essential cytoskeleton components that play important roles in cell division, intracellular transport, and the maintenance of cellular morphology. By attaching itself to tubulin subunits within the microtubule lattice, vincristine suppresses microtubule polymerization. Microtubule elongation is inhibited by this interaction, which disrupts the formation and functionality of the mitotic spindle. This process promotes cell cycle arrest at the metaphase stage, which eventually leads to apoptosis [13].

Vincristine's mode of action particularly targets rapidly dividing cells (malignant cells in this case), thereby mitigating a few adverse effects (associated with normal cells). Vincristine possesses dose-dependent neurotoxicity, which is the main reason for its limited use. Vinca alkaloids such as vinblastine, vinorelbine, and vinflunine have varying toxicity profiles; the most neurotoxic one is vincristine. Vincristine causes peripheral neuropathy in 30% to 40% of patients. Vincristine-induced peripheral neuropathy could be a motor, sensory, autonomic, or cranial type of neuropathy manifesting with different signs. Other adverse effects include alopecia, ataxia, nerve palsies, seizures, and autonomic dysfunction [14].

Table 2: Mode of action, duration, and adverse effects of primary drugs used in pediatric ALL

Drug	Mechanism of Action	Duration	Common Adverse Effects
Vincristine	Inhibits microtubule formation, disrupting mitosis	6–8 weeks (induction, maintenance)	Neuropathy, alopecia, seizures
Asparaginase	Depletes asparagine, essential for leukemic cell growth	4–6 weeks (induction)	Allergic reactions, pancreatitis, hepatotoxicity
Anthracyclines	Intercalates into DNA, inhibiting topoisomerase II	6–8 weeks (Induction)	Cardiotoxicity, photosensitivity, peptic ulcer
6-Mercaptopurine	Inhibits purine metabolism, affecting DNA synthesis and apoptosis	Continuous (consolidation, maintenance)	Jaundice, myelosuppression, regenerative hyperplasia
Methotrexate	Inhibits dihydrofolate reductase, blocking DNA synthesis	Variable (maintenance)	Mucositis, megaloblastic anaemia, myelosuppression

Cyclophosphamide	Alkylates DNA, causing cross-links and strand breaks	6–8 weeks (induction, consolidation)	Haemorrhagic cystitis, amenorrhoea, gonadal toxicity
Cytarabine	Inhibits DNA polymerase, leading to DNA chain termination	7–10 days (consolidation)	Myelosuppression, hepatic enzyme elevation, cerebral toxicity
Glucocorticoids	Anti-inflammatory and induces apoptosis in leukemic cells	4–6 weeks (induction)	Osteoporosis, hyperglycemia, neuropsychiatric effects

ASPARAGINASE

L-asparaginase, an enzyme, was included in the childhood lymphoblastic leukemia regimen because leukemic cells lack the asparagine synthase enzyme, indicating a difference in physiological properties between normal and leukemic cells. Asparagine is a non-essential amino acid that normal cells produce from aspartic acid or can be obtained through diet. Enzyme L-asparagine synthetase, encoded by the ASNS gene, catalyzes the transfer of an amino group to aspartic acid form asparagine and aids the synthesis of L-asparagine. Lymphoblastic leukemic cells lack asparagine synthetase, so they cannot synthesize asparagine. Instead, they depend on medium or exogenous asparagine to promote protein synthesis and cell growth [15].

Asparaginase works by hydrolysing asparagine and glutamine in the serum, depleting the extracellular source of these amino acids that all cells require for survival. Inadequate levels of cellular asparagine stop cellular development and reduce DNA, RNA, and protein synthesis, triggering apoptotic cell death mechanisms. Currently, three types of asparaginase are available for treating ALL, which are obtained from the bacteria *E. coli* and *E. chrysanthemi*. Native E. coli asparaginase, pegylated (PEG) asparaginase, and asparaginase E. chrysanthemi all have distinct immunogenic profiles, making the latter suitable for treating patients who experience hypersensitivity to *E. coli*-derived formulations [16].

Asparaginase, as a non-human protein, has the potential to cause an immune response in patients, resulting in the formation of asparaginase antibodies and significantly decreasing asparaginase efficacy. All asparaginase formulations have different glutamine pharmacokinetics; they preferentially exhibit selectivity for asparagine and hydrolyze glutamine to a lesser extent. PEG asparaginase has the longest half-life (5.7 days), whereas asparaginase E. chrysanthemi has the shortest half-life (15.6 hours). Therapeutic drug monitoring, including regular measurement of asparagine concentrations and asparaginase antibody detection, is an essential part of asparaginase therapy for ALL owing to factors like interpatient variability concerning asparaginase activity, the development of hypersensitivity, and differences in the pharmacokinetic properties among the different asparaginase preparations [16, 17].

There are several problems associated with the clinical application of bacterial asparaginase, the most serious is depletion of protein synthesis within the body, which can result in pancreatitis, hyperglycemia, hepatotoxicity, elevated triglyceride levels, and coagulation abnormalities (associated with deficiency of serpin). Allergic reactions caused by anti-asparaginase antibodies in the bloodstream, which manifest as clinical hypersensitivity symptoms such as anaphylaxis, pain, edema, urticaria, erythema, rash, and pruritis [15, 18].

ANTHRACYCLINE

Anthracyclines are cytotoxic drugs extracted from *Streptomyces spp.* (synthesized by multi-enzymatic pathways in BCGs) and used to treat various malignancies. The most potent and widely used anthracyclines are daunorubicin (the first discovered) and doxorubicin. Despite their significant cytotoxic effect as single agents, anthracyclines are used with chemotherapy or novel formulations to improve therapeutic efficacy while minimizing toxicity. All anthracyclines show similar mechanisms of action through multiple pathways [19].

When these drugs reach the cell's nucleus, they intercalate between DNA base pairs, causing uncoiling of the DNA helical structure, thus inhibiting macromolecular biosynthesis. This inhibits the activity of DNA topoisomerase II and relaxes supercoils in DNA. It prevents the DNA double helix from resealing, effectively stopping replication. Another mode of action exhibited by these drugs, particularly doxorubicin, is the generation of free radicals that cause DNA and cell membrane damage by targeting rapidly growing cells [20, 21]. Additionally, in the presence of cytochrome P450, redox reactions generate excess reactive oxygen species that cannot be detoxified, resulting in oxidative stress and lipid peroxidation ultimately leading to cell apoptosis. The use and dosage of anthracyclines should be limited because they are toxic to both malignant cells and other quickly dividing body cells, like those in the bone marrow. Adverse effects of these drugs range from reversible chemo-related acute effects such as nausea, vomiting, diarrhea, gastrointestinal disturbances, stomatitis, rashes, alopecia, and bone marrow suppression to long-term severe life-threatening effects such as cardiotoxicity, gonadotoxicity, and therapy-related malignancies [22].

Cardiotoxicity is the principal side effect of anthracycline chemotherapy. If not thoroughly customized for a particular

patient for dose and frequency, it may manifest as a chronic complication that leads to congestive cardiomyopathy, cardiac contractile dysfunction, ventricular dysfunction, arrhythmias, and heart failure. The acute form is characterised by abnormal electrocardiographic changes such as reduced left-ventricular ejection fraction, ST- and T-wave alterations, and rhythm disturbances. Due to its cardiotoxic profile, doxorubicin and other anthracycline administration is monitored routinely by assessing baseline left ventricular ejection fraction. Some delayed side effects observed are anorexia, photosensitivity, nail discoloration, skin hyperpigmentation, amenorrhoea, peptic ulcer, seizures, and oligospermia. Low-dose therapy, co-administration with cardioprotective agents, and nanoencapsulation technology have all been used to improve the therapeutic window of conventional anthracyclines [19, 21, 22].

6-MERCAPTOPURINE (6-MP)

Mercaptopurine is an antimetabolite that is used in the maintenance therapy of ALL. It belongs to the purine analogs class of medications and is frequently used in combination with methotrexate for a synergistic effect. Methotrexate enhances the bioavailability of 6-MP by inhibiting xanthine oxidase. 6-MP is an analog of the purine bases adenine and hypoxanthine, which interfere with nucleic acid biosynthesis by inhibiting the conversion of inosine monophosphate to adenine and guanine nucleotides. As a prodrug, 6-MP undergoes intracellular enzymatic metabolism in the purine biosynthesis pathway, resulting in the formation of 6-thioguanine nucleotides and thioinosine monophosphate, which eventually incorporate into RNA and DNA double strands competing with natural guanine. This substitution of the endogenous purines with synthetic ones creates a mismatch pattern within the system, and because the aberrant base is in the template strand, the DNA, RNA, and protein synthesis is stopped, resulting in decreased cell proliferation, cytotoxicity, and apoptosis [5, 23, 24].

Mercaptopurine therapy exhibits adverse effects that are either dose-dependent or dose-independent. Non-dose-dependent allergic symptoms include nausea, flu-like symptoms, fever, rash, and arthralgias; administering 6-MP at night may help alleviate these symptoms. Dose-dependent adverse reactions may include elevated transaminase levels, pancreatitis, jaundice, myelosuppression, nodular regenerative hyperplasia, leukopenia, and hepatosplenic lymphoma. Genetic deficiency of thiopurine methyl transferase increases the risk of 6-MP-induced myelosuppression, gut damage, and mucositis, whereas its overexpression makes acute leukemia cells resistant to mercaptopurine. Various forms of hepatotoxicity are observed during the therapy, as indicated by elevated liver enzymes, jaundice, and liver biopsy depicting mixed hepatocellular-cholestatic injury, variable inflammation, and bile duct injury [15, 24].

METHOTREXATE

Methotrexate (MTX), a folic acid analog, is highly effective antineoplastic drugs that, along with 6-MP, serves as the foundation for maintenance therapy in treating ALL. High-dose MTX can induce and maintain long-term remission. It is an antimetabolite known to exhibit cell cycle-specific action in the S phase. Once taken up by the human-reduced folate carriers, it metabolizes to a more active polyglutamate form in the presence of the enzyme foly polyglutamate synthase. This methotrexate-polyglutamate form inhibits dihydrofolate reductase, an enzyme that converts dihydrofolic acid to tetrahydrofolic acid (tetrahydrofolate). Tetrahydrofolate is an important biomolecule because it aids in the synthesis of the nucleotides in both DNA and RNA by acting as a principal co-enzyme in purine synthesis by aiding one carbon transfer reaction; it also catalyses amino acid interconversion, so inhibiting dihydrofolate reductase hinders DNA synthesis. This inhibition is often called pseudo-irreversible because MTX has nearly 50,000 times greater affinity for the enzyme than the normal substrate, resulting in a significant cytotoxic effect on the cell. Furthermore, methotrexate-polyglutamate inhibits thymidylate synthase, decreasing RNA and protein synthesis [15, 25].

Low-dose methotrexate may cause megaloblastic anaemia along with other GIT-related subsidiary side effects such as nausea, vomiting, mucosal ulcers, and loss of appetite. Major adverse effects are elicited in the bone marrow and liver. To keep a check on liver damage, ultrasound scanning and liver biopsy may be performed. Other side effects of high doses include mucositis, neurotoxicity, pancytopenia, nephrotoxicity, and dermal toxicity. Folinic acid and thymidine are effective in counteracting methotrexate toxicity, allowing for higher dose administration. To monitor and control these events, intravenous hydration, dose modification, leucovorin rescue, and determination of serum creatinine and MTX levels are measured [23, 26, 27].

CYCLOPHOSPHAMIDE

Cyclophosphamide is a nitrogen mustard used to treat various leukemias, including ALL. It is used in the intensification and re-induction regime alongside other drugs and is known to have radiomimetic effects and cytotoxicity. Cyclophosphamide has a non-specific cell cycle effect, causing damage to both actively dividing and resting cells. Cyclophosphamide is a prodrug that does not damage local cells. However, after hepatic metabolism in the presence of enzyme cytochrome P-450, it is converted to hydroxycyclophosphamide, which is then metabolised to aldophosphamide. The formation of aldophosphamide and its cleavage results in active metabolites, namely acrolein and phosphoramide mustard. Acrolein does not show any anti-tumor activity. When interacting with biomolecules,

phosphoramide reacts with species such as carboxyl, sulfhydryl, and phosphate. The alkylation reaction causes abnormal base pairing, scission of strands, and cross-linking in DNA strands, particularly at the guanine residue's nitrogen-7 position. These processes ultimately produce an antimitotic effect by inhibiting DNA, RNA, protein synthesis, and cell death [28].

Common adverse effects reported with the use of cyclophosphamide include hemorrhagic cystitis, myelosuppression, alopecia, amenorrhoea, nausea, and vomiting. Most of these are precipitated by the inactive metabolite acrolein, which causes vascular fragility and the release of pro-inflammatory mediators such as tumour necrosis factor. To prevent these, the patient should increase fluid intake to force diuresis and eliminate it faster. The main adverse effects of cyclophosphamide are seen in the urinary bladder and as gonadal toxicity. The severity of symptoms is determined by the dosage and timing of administration, which are customised for each patient. Adequate hydration, bladder irrigation, and concurrent administration of mesna, which is a prophylactic cytoprotective drug, are used to counter the negative effects of high-dose cyclophosphamide [15, 29].

OTHER DRUGS

a. Cytarabine

Cytarabine, an antineoplastic antimetabolite agent, is commonly used for myeloid leukaemias. However, it has also proved to be effective for the consolidation and re-induction phases of chemotherapy for ALL. It is a pyrimidine antagonist also known as cytosine arabinoside or Ara-C. Once phosphorylated in the body, it converts to triphosphate form and exerts its action by blocking the synthesis of cytidilic acid and competing with cytidine to incorporate into the DNA strand specifically in the S phase of the cell cycle. DNA polymerase is inhibited, and DNA repair is affected overall, resulting in the cessation of replication and a cytotoxic action [30]. The most adverse side effect of cytarabine is myelosuppression, which manifests with compiled effects like leukopenia, thrombocytopenia, anaemia, and mucositis. Cerebral toxicity including symptoms such as seizures and dementia, is also not uncommon and may occur following intrathecal administration. Less severe side effects include diarrhea, stomatitis, dermatitis, and hepatic enzyme elevation [15, 31].

b. Glucocorticoids

Glucocorticoids like dexamethasone and prednisolone are used in the chemotherapy of ALL during all three phases, but principally during remission induction. These drugs exhibit lymphoblastic cytotoxicity and effective CNS penetration. Dexamethasone is generally preferred over prednisolone due to its longer half-life, anti-inflammatory properties, increased cytotoxicity, and better CNS penetration. These agents exhibit their action by entering the cell's cytoplasm, binding to the glucocorticoid receptor, and triggering a series of reactions that result in specific gene expression, which eventually inhibits cytokine production, induces cell cycle arrest, and apoptosis [32, 33]. The main long-term adverse effects of using these steroids include osteoporosis, muscle wasting, metabolic alterations, and neuropsychiatric effects that are of serious concern [34].

Future Directions for ALL Treatment

The survival rate for pediatric ALL is a staggering 90% in first-world countries, but approximately 10% of relapse cases are a cause of concern. In addition to conventional drugs, promising treatments such as immunotherapy, targeted therapy, and stem cell transplantation have emerged in recent years. For patients who do not respond well to the induction remission approach, stem cell transplantation from a feasible donor is considered a better option. In relapsed ALL cases, combination chemotherapy with or without immunotherapy (blinatumomab) and/or targeted therapy (inotuzumab, imatinib, or dasatinib) may be done. Blinatumab (a bispecific T-cell engager) binds to a protein called CD3 on healthy T-cells and CD19 on malignant B-cells, linking them together; T-cells exert their cytotoxic potential and destroy the malignant cells.

Chimeric Antigen Receptor (CAR) T-cell therapy is a type of immunotherapy in which the patient's T-cells are genetically altered to redirect them toward a particular receptor in malignant cells to destroy them [35]. Targeted therapy is of significance in specific cases like that of Philadelphia Chromosome Positive (Ph+) B ALL, where a combination of imatinib/dasatinib/nilotinib (tyrosine kinase inhibitor) with chemotherapy is found to be way more effective than chemotherapy alone. Imatinib inhibits active sites of tyrosine kinases, thereby inactivating the signaling pathways that promote leukemogenesis. High-intensity X-ray beams that potentially destroy malignant cells or cease their growth may also be given to patients as a part of radiation therapy. Radiation therapy is not preferred for very young children as it destroys healthy cells too [36].

CONCLUSION

Pharmacotherapeutic agents discovered decades ago continue to play a vital role in treating ALL in paediatric patients. Despite the risk of life-threatening side effects and relapse, these agents will continue to dominate ALL pharmacotherapy. Further modification of the current regimen, combined with modern alternative therapy options will lower the possibility of treatment failure while improving survivors' quality of life. Ongoing research on targeted therapies, gene alteration, and

novel drug approaches will not just strengthen the current survival probability but also broaden the future therapeutical approaches for hematological malignancies.

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