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Review Article

A Review on Drugs Used in the Management of Pediatric Leukemia

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Abstract

Leukemia is a cancer of the blood and bone marrow. This is the most common type of cancer in children and accounts for more than a quarter of all pediatric cancers. This causes white blood cell abnormalities and weakens the body. This immune system deficiency reduces the body's ability to fight infections or simple airborne diseases, leading to widespread overtreatment of common pathogens and cancer treatments. There are two main types, the most common being acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). A small percentage may have chronic myeloid leukemia (CML) and Juvenile myelomonocytic leukemia (JMML). This review provides an overview of the incidence, presenting symptoms, and treatments. Pediatric leukemia treatment involves a combination of chemotherapeutic agents, targeted therapies, and supportive care measures tailored to the specific subtype and risk factors Each type of leukemia has defining characteristics that affect prognosis and treatment. Basic knowledge about these diseases is necessary for better management. Early recognition of symptoms is central to the management of oncologic emergencies.

Keywords: Leukemia; Acute Lymphoblastic Leukemia (ALL); Acute Myeloid Leukemia (AML); Chronic Myeloid Leukemia (CML); Juvenile Myelomonocytic Leukemia (JMML); Treatment; Chemotherapeutic Agents; Targeted Therapies, Supportive Care

Introduction

Leukemia is the most common cancer in children. This is a malignant tumor caused by the proliferation of hematopoietic cells leading to disruption of normal marrow function and bone marrow failure. The clinical manifestations of leukemia are due to uncontrolled proliferation of the malignant clone and bone marrow failure [1].

Pediatric leukemia is one of the deadliest cancers, with one of the highest mortality rates worldwide [2]. Pediatric leukemia, once considered a single disease, was first discovered around the 4th century. Leukemia is often described either as "acute", which develops quickly, or "chronic", which develops slowly [3]. At the end of the 19th century, leukemia was classified into four types: acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), chronic myeloid leukemia (CML), and Juvenile myelomonocytic leukemia (JMML). It is now known that the diagnosis of leukemia includes multiple types of hematopoietic neoplasms that are both complex and unique. Each subtype can be distinguished by morphological differences, cytogenetic abnormalities, immunophenotype and, clinical features [1]. These distinctive features influence both prognosis and optimal treatment options [4]. (Table 1). About 40% of all childhood cancers are cases of acute leukemia. CML is rare in children and can be treated as it is in adults. On the other hand, chronic leukemia is more common in adults than in children. They typically progress at a slower rate than acute leukemias and pose greater treatment challenges [1].

Pediatric leukemia treatment involves a combination of chemotherapeutic agents, targeted therapies, and supportive care measures tailored to the specific subtype and risk factors. The treatment of childhood ALL, with the exception of mature B-cell ALL, commonly has several components: induction, consolidation, interim maintenance, delayed intensification, and maintenance. The goal of induction is to achieve remission, previously defined as less than 5% blasts in the bone marrow, recovery of blood counts and no evidence of leukemia at other sites. Induction therapy generally consists of 3 or 4 drugs, which includes a glucocorticoid, vincristine, asparaginase, and possibly an anthracycline. This type of therapy induces complete remission based on morphology in more than 98% of patients [3]. (Table 2).

Indeed, all untreated patients will eventually progress to a fatal burst phase (BP), which is sometimes preceded by an acceleration phase (AP). The development of Tyrosine Kinase Inhibitors (TKIs) over the past 20 years has represented an outstanding revolution in the management and outcomes of CML and is a paradigm for targeted therapy of cancer [3]. The TKI (tyrosine kinase inhibitor) used in CML is shown in table 3.

Leukemia subtypes	Clinical presentation	Cell involved	Statistics
Acute Lymphocytic Leukemia (ALL)	Frequent infections, bruising and bleeding, Extreme fatigue, frequent headaches, swelling, Lack of appetite, stomach issues, and weight loss, bone or joint pain:	Immature B or T cell and macrophages	Common in children
Acute Myeloid Leukemia (AML)	Fever, fatigue, weight loss, night sweats, loss of appetite, headaches, abdominal discomfort, shortness of breath, frequent infections, Easy bruising or bleeding	Immature myeloid WBCs	Both adults and children
Chronic Myeloid Leukemia (CML)	Fatigue and weakness, shortness of breath during everyday activities, fever, night sweats, unexplained weight loss, abdominal discomfort or feeling of fullness (due to an enlarged spleen), bone pain, easy bruising or bleeding	Myeloid stem cells	Rare in children
Juvenile Myelomonocytic Leukemia (JMML)	Pallor, Fatigue, Weakness, Fever, Dry Cough, Enlarged Liver and/or Spleen, Enlarged Lymph Nodes, Anemia, Thrombocytopenia, Recurrent Infections, Decreased Appetite, Maculopapular Rash, Bone and Joint Pain	Myeloid stem cells	Rare in children

Table1: Types of Pediatric Leukemia [1,2,6,13,14,16,36].

Management of pediatric leukemia [1,2]

Phases of therapy

The treatment of childhood ALL, with the exception of mature B-cell ALL, commonly has several components: induction, consolidation, interim maintenance, delayed intensification, and maintenance.

Consolidation therapy

Consolidation therapy is administered soon after remission is achieved to further reduce the leukemic cell burden before the emergence of drug resistance and relapse in sanctuary sites (e.g., testes, central nervous system [CNS]). During this phase, patients receive different drugs such as cyclophosphamide, cytarabine, and/or 6-mercaptopurine (6-MP). Consolidation therapy has been shown to improve the long-term survival of patients with standard-risk disease. For patients with late relapse, the risks associated with hematopoietic stem cell transplantation (HSCT) often outweigh the potential benefits, making intensified chemotherapy alone the recommended approach for achieving long-term remission (with over 50% of patients achieving this outcome). Standard drugs are used in higher doses, along with additional agents such as etoposide [4].

Interim maintenance involves administering non-myelosuppressive chemotherapy, such as vincristine and intravenous methotrexate (MTX), to maintain remission and allow bone marrow recovery. This phase typically lasts for 4-8 weeks.

Delayed intensification repeats the first 2 months of induction and consolidation therapy for high-risk and very-high-risk ALL patients, incorporating some new agents (e.g., substituting dexamethasone for prednisone, doxorubicin for daunorubicin, and 6-thioguanine for 6-MP) while repeating others. The goal is to eliminate

residual drug-resistant cells. Pioneered by the BFM group, this phase has been found beneficial for patients across all risk groups, including standard-risk and low-risk ALL [5].

Maintenance, or continuation therapy, is the final and longest phase of treatment. It includes intrathecal MTX administered at least every 3 months, vincristine and steroid pulses every 1-3 months, daily 6-MP, and weekly MTX. The doses of the last two agents are adjusted based on peripheral neutrophil counts to optimize therapy. While vincristine and steroid pulses may improve outcomes, they can be associated with side effects such as avascular necrosis of the bone and vincristine neuropathy. The benefit and frequency of these pulses remain subjects of debate, which ongoing trials may help resolve.

Management of relapse

Relapse occurs in 20% of children with ALL when blasts reappear after complete remission (CR) is achieved. The vast majority of relapses involve the bone marrow, but other sites can include the CNS or testes. Isolated CNS relapse (< 5% of total relapses) or isolated testicular relapse (1-2% of total relapses) is rare with current ALL therapy. However, if these relapses occur more than 18 months from diagnosis, they often have a good outcome with local and aggressive systemic chemotherapy [4]. Patients at high risk for further relapse and poor survival include those with B-lineage ALL experiencing early bone marrow relapse (which may be combined with other sites, such as the CNS) and all patients with T-lineage ALL. Early relapse is defined as bone marrow relapse occurring within 36 months of initial diagnosis or within 6 months of completing primary therapy; outcomes for these patients are poor, with only 35-40% achieving long-term remission. Late relapse occurs outside this timeframe, and outcomes are better, with over half of these patients achieving long-term remission. Unfortunately, the vast majority of patients with T-lineage ALL experience early relapse. In relapsed ALL patients, a multidrug-resistant clone often emerges, making leukemia cells more resistant to chemotherapy. Nevertheless, patients often respond to the same agents initially used for induction; the challenge is maintaining remission. The standard treatment for ALL with first relapse includes reinduction chemotherapy to achieve a second remission (CR2), followed by post-reinduction consolidation therapy for those who achieve CR2 [5].

Second relapse or refractory disease

Despite successful reinduction and consolidation, many patients with ALL eventually experience a second relapse. For second and subsequent relapses, no standard treatment regimen has been established, leaving oncologists to choose from various combinations of drugs. Long-term survival after a second relapse remains poor, typically ranging from 10-20%, leading some families to opt for palliative care. In August 2017, the FDA approved the first CAR T-cell therapy. Tisagenlecleucel is a CD19-directed genetically modified autologous T-cell immunotherapy indicated for patients aged 25 years or younger with B-cell precursor ALL that is refractory or in second or later relapse [6].

Reinduction

Most standard regimens for relapsed ALL use a four-drug induction backbone, consisting of a glucocorticoid, vincristine, an anthracycline (such as daunorubicin or doxorubicin), and asparaginase. This approach was shown as early as the 1980s to achieve a second remission in more than 90% of relapsed ALL patients in a Pediatric Oncology Group Study (POG 8303). The COG AALL01P2 trial used this four-drug regimen, supplemented with additional intensive chemotherapy blocks, including cyclophosphamide/etoposide and/or high-dose cytarabine. In this trial, 68% of the 63 patients in early relapse achieved CR2, and 96% of the 54 patients in late relapse achieved CR2. The UK ALL R3 regimen studied 212 patients with relapsed ALL, comparing the anthracycline drugs mitoxantrone and idarubicin in a four-drug induction regimen. This study found a long-term progression-free survival rate of 64% at 3 years in the 103 patients treated with mitoxantrone [7].

Cranial irradiation

Although cranial irradiation (CXRT) effectively prevents overt CNS relapse, concerns about subsequent neurotoxicity and brain tumors have led to efforts to replace it with intensive intrathecal and systemic chemotherapy. The UKALL XI trial (1990-97) compared high-dose intravenous methotrexate (HDMTX) (6–8 g/m^2) combined with intrathecal methotrexate (ITMTX) against ITMTX alone. It showed decreased isolated and combined CNS relapse rates for patients with standard-risk ALL with the former. For high-risk ALL patients, HDMTX with ITMTX was compared to CXRT with ITMTX. While CNS relapses were significantly fewer with CXRT and ITMTX, the 10-year event-free survival (EFS) was not significantly

different (55.2% vs. 52.1%). The DLCSG ALL-7 and ALL-8 trials (1988-1997) omitted CXRT except for 2% of patients with overt CNS-3 disease and still demonstrated an overall CNS relapse rate of only 5.5% [8]. Pui., *et al*. confirmed these findings in the Total XV study (2000-2007), where prophylactic CXRT was omitted for all patient groups, including CNS-3, resulting in an overall CNS relapse rate of 3.9%. Currently, the necessity of prophylactic CXRT for patients with very-high-risk ALL remains unclear. The current COG VHR ALL and Ph+ ALL trials do not routinely administer prophylactic CXRT, although patients with CNS-3 continue to receive CXRT [9].

Hematopoietic stem cell transplantation (HSCT)

HSCT has been utilized in very high-risk (VHR) patients during their first remission (CR1) and in patients with ALL relapse who are at high risk for further relapse, such as those with early bone marrow (BM) relapse. Although most patients with relapse achieve a second remission (CR2), two-thirds of those with early relapse eventually experience a second relapse, making HSCT a recommended option for this group. However, improved outcomes for certain categories of VHR ALL patients, such as those with Philadelphia chromosome-positive (Ph+) ALL receiving chemotherapy with imatinib, have led to ongoing debates about the role of HSCT in VHR ALL.

In acute myeloid leukemia (AML), HSCT is generally recommended for patients with high-risk features such as complex karyotype, monosomal karyotype, or certain genetic aberrations like FUS-ERG fusion. HSCT is typically reserved for high-risk patients in first complete remission (CR1), while standard-risk patients are usually treated with chemotherapy alone. In acute lymphoblastic leukemia (ALL), HSCT is indicated for patients with high-risk features like poor response to induction therapy, presence of minimal residual disease (MRD), or certain genetic abnormalities. HSCT is usually reserved for high-risk patients in CR1, while lower-risk patients are treated with chemotherapy. For relapsed ALL, HSCT is generally recommended, especially for patients with early relapse or T-cell ALL. Alternatives to HSCT, such as immunotherapy and chimeric antigen receptor (CAR) T-cell therapy, have emerged and may serve as a bridge to HSCT or even be curative in some cases, potentially reducing the need for HSCT in certain situations [10].

In a collaborative study between the Children's Oncology Group (COG) and the Center for International Blood and Marrow Transplant Research (CIBMTR), Eapen., *et al*. examined 374 children with ALL in CR2 after a marrow relapse. The children received either a matched sibling donor hematopoietic stem cell transplant or continued chemotherapy. The study confirmed better leukemia-free survival for patients with early relapse who received total body irradiation (TBI)-based conditioning regimens. The presence of minimal residual disease (MRD) before HSCT is a negative predictor of outcome; however, it remains unclear whether aggressive attempts to reduce MRD before HSCT improve long-term survival. Similarly, the ALL-REZ BFM 90 trial showed that MSD HSCT benefited patients with higher-risk relapse (10-year event-free survival [EFS] of 40% vs. 20% for chemotherapy alone) but did not improve 10-year EFS for lower-risk patients (10-year EFS of 52% vs. 49% for chemotherapy alone). With advances in HSCT techniques and supportive care, alternative donors, such as matched unrelated donors, can also be used with equivalent survival outcomes if an MSD is not available [11].

Molecular-targeted therapy

Molecularly targeted therapy has become an important treatment approach for pediatric leukemia, particularly in acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL). In AML, targeted therapies directed at specific genetic lesions like IDH1/2 and FLT3 mutations are now standard treatment options, often used in combination with chemotherapy. Examples include the IDH2 inhibitor enasidenib and the FLT3 inhibitor gilteritinib. In Philadelphia chromosome-positive (Ph+) ALL, the BCR-ABL tyrosine kinase inhibitor imatinib is approved for children and is standard front-line therapy, used in combination with chemotherapy. Imatinib has shown excellent efficacy, with a 4-year progression-free survival rate of 70% in one trial involving 50 children receiving the longest duration of imatinib. For Ph-like ALL, tyrosine kinase inhibitors and JAK2 inhibitors are being evaluated in clinical trials. In T-cell ALL, the addition of the targeted agent nelarabine to chemotherapy improved 4-year disease-free survival in one trial. However, challenges remain, including drug resistance, which can emerge after a period of response to targeted therapies. Strategies to overcome resistance, such as using combinations of targeted agents or combining targeted therapy with chemotherapy or immunotherapy, are being actively investigated [12].

Cellular therapy

The use of cellular therapy in pediatric leukemia involves various approaches, including hematopoietic stem cell transplantation (HSCT), donor leukocyte infusion (DLI), natural killer (NK) cell in-

fusion, and chimeric antigen receptor (CAR) T-cell therapy. HSCT is the most commonly used cellular therapy, offering a graft-versus-leukemia (GVL) effect. It is often used for high-risk or relapsed cases of acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL). DLI involves the infusion of T cells from the donor after HSCT. This approach can provide a GVL benefit for relapsed chronic myeloid leukemia and EBV-induced lymphoproliferative disease, and occasionally for induced durable remissions in relapsed ALL. NK cell infusions have been used in the setting of haploidentical transplantations and killer cell Ig-like receptor (KIR) ligand mismatches. This approach has shown benefit in a minority of AML patients, but its value in ALL is uncertain [2]. CAR T-cell therapy involves collecting the patient's own T cells, genetically engineering them to express a CAR that targets a specific molecule on cancer cells, and then reinfusing them after lymphodepletion with conditioning chemotherapy. Studies targeting CD19 have reported high rates of complete and long-lasting remissions in patients with refractory ALL. However, toxicities such as cytokine release syndrome (CRS), B-cell aplasia, and cerebral edema can be fatal.

The FDA approved tisagenlecleucel, for the treatment of patients up to 25 years of age with B-cell precursor ALL that is refractory or in second or later relapse. This approval includes a risk evaluation and mitigation strategy, which requires special certification for hospitals and clinics administering the treatment and additional training for physicians and staff [13].

Radiotherapy

Radiotherapy is used to prevent relapse of leukemia in the central nervous system (CNS) and testes. In acute lymphoblastic leukemia (ALL), cranial radiation therapy (CRT) was historically given to high-risk patients, but the proportion receiving CRT has decreased significantly over time. Studies have shown that with modern intensive chemotherapy regimens, CRT can often be safely omitted, even in high-risk patients, without compromising outcomes. This is because chemotherapy is now more effective at controlling CNS disease. Radiation therapy can have significant long-term side effects in children, including cognitive impairment, endocrine disorders, and increased risk of secondary cancers. Therefore, the trend has been to minimize radiation exposure whenever possible. For patients who do require radiation, the dose and field size have been reduced over time to limit toxicity. Radiation is now primarily reserved for cases where chemotherapy alone is insufficient, such as CNS relapse or testicular involvement [14].

Triple intrathecal (IT) therapy

It includes methotrexate, cytarabine, and hydrocortisone, to improve central nervous system (CNS) control in pediatric leukemia compared to standard IT methotrexate alone. Studies have shown that triple IT therapy can reduce the rate of isolated CNS relapses compared to IT methotrexate alone. However, it does not necessarily translate to improved overall event-free survival (EFS) or overall survival (OS). In the Children's Oncology Group (COG) AALL1131 study, triple IT therapy was compared to IT methotrexate in children with high-risk B-cell acute lymphoblastic leukemia (HR B-ALL). The study found no significant difference in 5-year disease-free survival or overall survival between the two groups. While triple IT therapy may have benefits in reducing CNS relapses, the overall impact on long-term outcomes appears limited. Additionally, there are concerns about potential increased toxicities with the more intensive triple IT regimen [15].

BFM (Berlin-Frankfurt-Münster) regimen

The BFM group has developed and refined intensive chemotherapy protocols for the treatment of childhood acute lymphoblastic leukemia (ALL) over several decades. The BFM regimens, such as the ALL IC-BFM 2002 and 2009 protocols, stratify pediatric ALL patients into standard, intermediate, and high-risk groups based on clinical and genetic factors. This allows for risk-adapted therapy. The BFM protocols typically include induction, consolidation, reinduction, and maintenance phases of treatment. High-risk patients may receive stem cell transplantation after the third high-risk course. The BFM group has also investigated the role of central nervous system (CNS)-directed therapy, such as cranial radiation and intrathecal chemotherapy, in preventing CNS relapses in pediatric ALL. Overall, the BFM group has been a leader in developing and refining intensive, risk-adapted chemotherapy protocols that have dramatically improved survival for children with ALL over the past few decades [13].

Nelarabine

Nelarabine is a purine nucleoside analog that is metabolized to arabinosylguanine nucleotide triphosphate (araGTP); araGTP incorporates into DNA and inhibits DNA synthesis, resulting in apoptosis. Nelarabine has been studied in the past two decades and was approved in 2005 as third-line treatment of T cell leukemia/lymphoma[11]. The maximum tolerated dose (MTD) was determined to be 60 mg/kg/day in children and 40 mg/kg/day in adults. Nelara-

bine is converted to ara-G byadenosine deaminase and transported into cells by a nucleoside transporter. Ara-G is subsequently phosphorylated to ara-G triphosphate (ara-GTP), thereby initiating the therapeutic effect by inhibiting DNA synthesis. Clinical responses to nelarabine have been demonstrated in various T-cell malignancies and appear to correlate with a relatively high intracellular concentration of ara-GTP compared to nonresponders. Therefore, this unique drug feature of nelarabine accounts for clinical utilization in treating adult and paediatric patients with relapsed or refractory T-cell acute lymphoblastic leukemia or T-cell lymphoblastic lymphoma. Neuropathy is the most predominant adverse effect associated with nelarabine and the incidence correlates with the dose administered [16].

Anthracyclines

Anthracyclines, a class of chemotherapy medicines used to treat pediatric leukemia. The main anthracyclines include daunorubicin, doxorubicin, and mitoxantrone. Common side effects include nausea and vomiting, discoloured urine, bone marrow suppression, mouth sores and ulcers, changes in heart function, red flush or ache along vein, changes in nails, and inflammatory skin reaction. Interactions with other medicines can occur, and extravasation can cause tissue damage. The risk of cardiomyopathy is a significant concern, particularly with long-term exposure. Daunorubicin was found to be less cardiotoxic than doxorubicin, while epirubicin is approximately isoequivalent. Mitoxantrone is estimated to be more cardiotoxic than doxorubicin, but the current dose equivalency ratio may underestimate its true cardiotoxicity [17].

Cytarabine (Ara-C)

Cytarabine (Ara-C) is a key chemotherapy drug used in pediatric leukemia treatment, particularly acute myeloid leukemia (AML), and acute lymphoblastic leukemia (ALL). Ara-C, which is a nucleoside analog that inhibits DNA synthesis and repair, leading to cell death. Ara-C can be given as a continuous infusion or in short daily doses. High-dose Ara-C (HD-Ara-C) has been introduced for the treatment of AML, with doses up to 3,000 mg/m^2 administered as a 1-hour infusion every 12 hours for 6 days[50]. Ara-C can be given intravenously, subcutaneously, or intrathecally (into the spinal fluid). The common side effects are nausea, vomiting, diarrhea, myelosuppression, and neurological toxicity. Severe neurological toxicity, including personality changes, movement disorders, and speech difficulties, can occur with high-dose Ara-C. The role of Ara-C in acute promyelocytic leukemia (APL), is controversial. A study showed that Ara-C could be omitted when using all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) in pediatric patients[51]. A polygenic Ara-C response score has been developed to identify pediatric patients with AML who are more likely to respond to Ara-C-based therapy [18].

Vincristine

It is a widely used chemotherapeutic agent in pediatric leukemia, particularly in the treatment of acute lymphoblastic leukemia (ALL). It is known for its neurotoxic side effects, which can be significant. It can cause neurotoxic side effects, including diminished patellar and Achilles tendon reflexes, muscular weakness, hoarseness, jaw pain, constipation, and petosis. These effects are generally mild to moderate in nature. Pharmacokinetics of vincristine are highly variable in children, with slower clearance compared to when used in combination with steroids. This is likely due to the absence of steroids during monotherapy. A study of 25 children with advanced cancer found objective tumor response in 17 patients, with complete remission in nine cases. Common toxicities included alopecia, leukopenia, vomiting, and constipation. Vincristine-induced peripheral neuropathy is a significant concern in pediatric ALL patients. Vincristine remains a key component in the treatment of pediatric ALL, particularly in combination with other chemotherapeutic agents. Its antimitotic and apoptotic effects contribute to its antileukemic activity, although the variability in exposure and sensitivity of leukemic cells can impact its efficacy [19].

Methotrexate

High-Dose Methotrexate (HD-MTX is a potent chemotherapeutic agent used to treat pediatric ALL. It is known for causing delayed elimination and drug-related adverse events, making close monitoring essential. Clinical trials have demonstrated the effectiveness of high-dose methotrexate in improving survival rates for high-risk ALL patients. For example, a study found that high-dose methotrexate was superior to escalating methotrexate in reducing relapse rates. MTX can cause multiple side effects, including nephrotoxicity, mucositis, hepatotoxicity, neurotoxicity, and myelosuppression. Intravenous hydration, leucovorin rescue, and proper monitoring of serum creatinine and MTX levels are crucial to minimize these side effects. MTX is often administered in the clinic, hospital, or at home, depending on the type of cancer, child's age, and method of administration. The schedule and dose depend on the specific treatment plan [20].

Mercaptopurine (6-MP)

Mercaptopurine is a crucial component of maintenance therapy for pediatric acute lymphoblastic leukemia (ALL). Durable remissions in children with ALL require a 2-year maintenance therapy phase that includes daily oral 6-MP. 6-MP exerts its antileukemic effect through conversion to thioguanine nucleotide metabolites that are incorporated into DNA, causing damage. Factors like age, body surface area, and genetic polymorphisms affecting enzymes like thiopurine methyltransferase (TPMT) and inosine triphosphate pyrophosphatase (ITPA) can impact 6-MP metabolism and toxicity. 6-MP is often used in combination with methotrexate during maintenance therapy [21].

Cyclophosphamide

Cyclophosphamide is a crucial component of chemotherapy regimens for pediatric ALL, particularly in combination with other agents like 6-mercaptopurine and methotrexate. Common side effects of cyclophosphamide include leukopenia, which is often reversible by interrupting therapy. Other reported side reactions include hemorrhagic cystitis, alopecia, hepatitis, anorexia, diarrhea, nausea, vomiting, and dizziness. Cyclophosphamide can cause severe myelosuppression, hypersensitivity, urinary outflow obstruction, and potentially fatal interstitial pulmonary fibrosis if given over prolonged periods. The study of pharmacokinetics and pharmacogenetics in children under 2 years of age found no significant differences in clearance during the first two years of life but highlighted differences in dosing protocols across tumour types [22].

Etoposide

It is a chemotherapy medication used to treat pediatric leukemia, particularly acute lymphoblastic leukemia (ALL), and acute myeloid leukemia (AML). Etoposide inhibits topoisomerase II, an enzyme involved in DNA replication and repair, leading to cell death. Etoposide can be given orally or intravenously. The standard dose is 100 mg/m^2 body surface area per 24 hours. Oral etoposide in low dose has been evaluated in relapsed ALL, with a regimen of 50-100 mg/m^2 per day for 21 days. Prolonged schedule etoposide has been studied in refractory or relapsed malignancy, with a regimen of 50-100 mg/m^2 per day for 21 days. Common side effects include nausea, vomiting, diarrhea, and myelosuppression. Severe side effects include neutropenia, thrombocytopenia, and gastrointestinal toxicity. Etoposide is used in combination with other chemotherapy drugs to treat pediatric ALL and AML. In a study of combining temsirolimus with cyclophosphamide and etoposide showed promising results in relapsed/refractory ALL [23].

Clofarabine

It is a second-generation purine nucleoside analogue used to treat pediatric patients with relapsed or refractory acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). Clofarabine inhibits DNA synthesis and repair, leading to cell death and also inhibits ribonucleotide reductase, which is essential for DNA synthesis. Clofarabine disrupts mitochondrial membrane integrity, leading to the release of cytochrome c and other proapoptotic factors, causing programmed cell death. A phase II trial in pediatric patients with relapsed or refractory ALL showed a complete response rate of 18% and a median overall survival of around 3 months. Phase I studies in pediatric patients with multiple relapsed or refractory leukemia showed that clofarabine was active in different leukemia subtypes. The common side effects are nausea, vomiting, diarrhea, myelosuppression, and neurological toxicity. However, its use is associated with significant toxicity, particularly tumor lysis syndrome [24].

Tocilizumab

It is approved for the treatment of adults and pediatric patients 2 years of age and older with chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS). CRS is a potentially severe and life-threatening side effect of CAR T-cell therapy for certain cancers, including pediatric B-cell acute lymphoblastic leukemia (B-ALL). A prospective study evaluated the effectiveness of risk-adapted preemptive tocilizumab administration in preventing severe CRS after CTL019 CAR T-cell therapy in pediatric B-ALL patients. Tocilizumab is used to block the interleukin-6 (IL-6) pathway, which plays a key role in the development of CRS. By administering tocilizumab preemptively, the study aimed to prevent the progression to severe CRS in high-risk pediatric B-ALL patients receiving CAR T-cell therapy. Common side effects of tocilizumab include upper respiratory tract infections, nasopharyngitis, headache, hypertension, increased liver enzymes, and injection site reactions. However, there is also a risk of serious infections, which requires close monitoring [25].

L-asparaginase

L-asparaginase is an essential component of chemotherapy regimens for pediatric acute lymphoblastic leukemia (ALL), playing an

important role in improving long-term survival. L-asparaginase reduces asparagine concentrations in both the plasma and cerebrospinal fluid, depriving tumor cells of this essential nutrient for protein synthesis. Most of the normal cells can synthesize asparagine and are less sensitive to L-asparaginase, while lymphoblasts require large amounts of asparagine and asparagine synthetase in a low level, making them very sensitive to L-asparaginase. L-asparaginase is an integral part of multi-agent chemotherapy regimen for pediatric ALL patient. Positive outcomes and improved long-term survival in pediatric ALL are largely due to the use of L-asparaginase. L-asparaginase is a cornerstone of therapy for pediatric ALL, with a unique mechanism of action and toxicity. Careful monitoring and management of L-asparaginase-associated toxicities are important to ensure optimal treatment outcomes [26].

Pegaspargase

It is a pegylated form of native Escherichia coli derived L-asparaginase, used in the treatment of pediatric acute lymphoblastic leukemia (ALL). Pegaspargase is an integral component of pediatric upfront and relapsed ALL protocols due to its longer half-life and improved immunogenicity profile compared to native asparaginase preparations. It is used to deplete serum asparagine, which is essential for protein synthesis in lymphoblasts, thereby limiting their survival. The most common adverse events associated with pegaspargase include hypersensitivity reactions, asparaginase-associated pancreatitis, thrombosis, liver dysfunction, osteonecrosis, and dyslipidemia. Dose or treatment-limiting toxicity is observed in 25-30% of patients, with hypersensitivity reactions being a significant concern. Desensitization protocols have been developed to manage hypersensitivity reactions to pegaspargase, allowing patients to continue treatment with alternative asparaginase formulations. Pegaspargase is indicated as a component of multi-agent chemotherapy regimens for patients with ALL, and it can be administered intramuscularly (IM) or intravenously (IV) [27].

Calaspargase pegol-mknl (CALASP)

It is a pegylated asparaginase formulation used in the treatment of pediatric acute lymphoblastic leukemia (ALL). CALASP was approved by the FDA on December 20, 2018, as a component of a multi-agent chemotherapeutic regimen for the treatment of ALL in pediatric and young adult patients aged 1 month to 21 years. CALASP is an asparagine-specific enzyme that depletes serum asparagine, essential for protein synthesis in lymphoblasts, thereby limiting their survival. CALASP is administered intravenously every 3 weeks at a dose of 2,500 IU/m*2. A phase III trial (DFCI 11-001) in pediatric patients with newly diagnosed ALL compared CALASP with pegaspargase (PEGASP), shows that CALASP had similar nadir serum asparaginase activity, toxicity, and survival outcomes. Common adverse reactions associated with CALASP include elevated transaminase levels, bilirubin increases, pancreatitis, and abnormal clotting [28].

Tretinoin (ATRA)

Tretinoin (ATRA), also known as all-trans-retinoic acid (ATRA) or Vesanoid, is a medication used to treat acute promyelocytic leukemia (APL) in children. Tretinoin works by targeting and eliminating the PML/RARα abnormality, which is a hallmark of APL. It causes a marked decrease in the concentration of leukemic blast cells in the marrow, leading to a remission. Side effects include headache, fever, feeling weak and unusually tired, bleeding in stomach or colon, increased white blood count, but decreased numbers of infection-fighting cells, increased risk of bleeding or blood clots, changes in vision, dry skin and itching, rash, nausea and vomiting, mouth sores, increased sweating, hair loss, skin more sensitive to the sun, stomach pain, diarrhea or constipation, decreased liver function, high lipid or cholesterol levels in the blood, weight changes, loss of appetite, feeling dizzy, agitated or anxious, tingling, numbness, or pain in the hands or feet, shaking that cannot be controlled, feeling depressed, trouble sleeping, earache or feeling of fullness in ears, hearing loss, changes in skin color, wheezing, problems breathing, or short of breath, blood pressure changes, flushing, chest pain, abnormal heart beats, or heart problems, seizures [29].

Arsenic trioxide

Arsenic trioxide (ATO) is a medication used to treat pediatric acute promyelocytic leukemia (APL). Single-agent arsenic trioxide is effective in treating pediatric APL, with a 2-year overall survival rate of 99% in the standard-risk group and 95% in the high-risk group. Combination with all-trans retinoic acid (ATRA) is effective and safe in pediatric patients with APL, with a 2-year event-free survival rate of 97% in the standard-risk group and 90% in the high-risk group [30]. Common side effects include nausea, vomiting, diarrhea and fatigue. The rare side effects are cardiac toxicity, including arrhythmias and heart failure, due to the high doses of anthracyclines used in combination with ATO. Regular monitoring of blood counts, liver function, and cardiac function is necessary to manage side effects. Long-term follow-up is still needed to assess the durability of the response and potential late effects of treatment [31].

Prednisone

Prednisone is a glucocorticoid that is an essential component of chemotherapy regimens for treating pediatric acute lymphoblastic leukemia (ALL). Prednisone causes apoptosis in malignant lymphoid cells and has significant anti-leukemic activity. It inhibits DNA synthesis and repair, leading to cell death. Prednisone forms the backbone of pediatric ALL treatment, along with other glucocorticoids like dexamethasone. The day 8 prednisone response is an important prognostic indicator and is used in risk group stratification. Prednisone is often used during induction therapy, while dexamethasone may be used during consolidation or delayed intensification [32].

Dexamethasone

Dexamethasone is a cornerstone of treatment for pediatric acute lymphoblastic leukemia (ALL), offering higher antileukemic potency compared to prednisone. It has been shown to reduce relapses and improve survival rates in children with ALL. Studies have compared dexamethasone and prednisone in induction therapy, with dexamethasone demonstrating superior outcomes in preventing central nervous system (CNS) relapse and increasing event-free survival[9]. The randomized trial compared the effects of dexamethasone and prednisone during induction, aiming to determine if dexamethasone provides better event-free survival and overall survival in childhood ALL. Dexamethasone has a higher potency and longer biological half-life compared to prednisone and has better central nervous system (CNS) penetration, which is particularly appealing for T-cell ALL with higher rates of CNS disease. Overall, dexamethasone has shown significant benefits in the treatment of pediatric leukemia, particularly in reducing relapse rates and improving outcomes [32].

Blinatumomab

Blinatumomab is a bispecific T-cell engaging (BiTE) antibody that connects the targeting regions of two antibodies against CD19 and CD3. CD19 is expressed by B-ALL progenitor cells and CD3 is the constant part of the T-cell receptor (TCR) complex that mediates T-cell receptor signaling thus leading to a very tight linkage between malignant B cells and T cells, a cytolytic synapse formed in the close contact zone. Overall, side effects are less common with blinatumomab than conventional chemotherapy. Additionally, even specific toxicities associated with blinatumomab, such as CRS and neurotoxicity, rarely necessitate the interruption of therapy. This observation makes blinatumomab an ideal drug for selected use in vulnerable patients [33].

Inotuzumab ozogamicin

Inotuzumab ozogamicin is an ADC consisting of a cytotoxic agent, calicheamicin, linked to an anti-CD22 antibody. When inotuzumumab ozogamicin binds to CD22 and is internalized, calicheamicin induces DNA breaks. CD22 is widely expressed on B-ALL blasts and is rapidly internalized upon antibody binding, making it an excellent target for immune-targeted chemotherapy in B-ALL. InO, like other novel immune-targeted therapies, offers an attractive way to achieve remission in a patients with relapsed/refractory disease to activate HSCT46. Inotuzumab ozogamicin (InO) is a calicheamicin-conjugated CD22 antibody approved for the treatment of relapsed or refractory (R/R) B-cell precursor acute lymphoblastic leukemia in adults. Common side effects include nausea, vomiting, diarrhea, and fatigue. The rare side effects are sinusoidal obstructive syndrome (SOS) occurred in 7 patients in the phase II trial, particularly when InO treatment was followed by hematopoietic stem cell transplantation (HSCT). Regular monitoring of blood counts, liver function, and cardiac function is necessary to manage side effects [34].

Gemtuzumab ozogamicin

Gemtuzumab ozogamicin (GO) has shown promising results in pediatric leukemia trwatment, particularly acute myeloid leukemia (AML). A study evaluated Gemtuzumab ozogamicin (GO) in children with AML to improve survival rates. The study assessed the effectiveness of GO in children with de novo AML. GO was administered at doses of 2.5-10 mg/m2 in cycles as a single agent or in combination with cytarabine. The study reported common grade 3/4 adverse events, including infections, febrile neutropenia, infusion-related immunological reactions, and gastrointestinal symptoms. The probability of 4-year overall survival was significantly higher in patients who received hematopoietic stem cell transplantation after GO treatment. Gemtuzumab ozogamicin has shown effectiveness in pediatric leukemia, particularly in AML. Studies have highlighted its role in improving survival rates and its potential in treating relapsed or refractory AML in children. The Polish Pediatric Leukemia and Lymphoma Study Group's experience provides valuable insights into the clinical characteristics and outcomes of GO treatment in pediatric AML patients [35].

CAR T-cell therapy

It is a promising new treatment for pediatric leukemia, particularly acute lymphoblastic leukemia (ALL) and non-Hodgkin lym-

phoma (NHL). CAR T-cell therapy uses the body`s T cells to target and eliminate cancer cells. T cells are reprogrammed to recognize and bind to specific proteins on the surface of cancer cells, such as CD19 on B cells. This binding triggers the T cells to release cytotoxins that kill the cancer cells. CAR T-cell therapy is approved for the treatment of relapsed or refractory B-cell precursor acute lymphoblastic leukemia (BCP-ALL) in children. It is also being studied for the treatment of other pediatric malignancies, including non-Hodgkin lymphoma (NHL). Common side effects of CAR T-cell therapy include cytokine release syndrome (CRS), which can cause fever, chills, headache, nausea, and vomiting. Other side effects include neurological toxicities, such as seizures and encephalopathy, and hematological toxicities, such as anemia, thrombocytopenia, and neutropenia. CAR T cells are infused into the patient after lymphodepleting chemotherapy to minimize the chance of suppressor mechanisms affecting CAR T-cell function. The infusion is followed by a cytokine storm, which can cause severe side effects. The persistence of CAR T cells is associated with remission beyond 6 months [36,37].

Tisagenlecleucel

Tisagenlecleucel, also known as Kymriah, is a chimeric antigen receptor (CAR) T-cell therapy approved for the treatment of pediatric patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse. The most common side effects of tisagenlecleucel include cytokine release syndrome (CRS), B-cell aplasia, and cerebral edema. CRS is a potentially life-threatening side effect that requires immediate attention and management. B-cell aplasia is a long-term side effect that can lead to increased susceptibility to infections. The FDA approved tisagenlecleucel with a risk evaluation and mitigation strategy (REMS) to ensure safe administration and management of the therapy. The REMS includes requirements for hospitals and clinics administering the treatment, as well as additional training for physicians and staff [37].

Sulfamethoxazole-trimethoprim (SMX-TMP)

It is a widely used antibiotic combination for the prevention of bacterial infections in pediatric patients with acute lymphoblastic leukemia (ALL). Children with ALL are treated with intensive chemotherapy, which leads to profound immunosuppression, making them susceptible to bacterial infections. Therefore, SMX-TMP is used as prophylaxis against infections caused by both bacteria and Pneumocystis carinii. A randomized, double-blind, placebo-controlled study found that SMX-TMP significantly reduced the frequency of confirmed bacteremia and febrile episodes in granulocytopenic children undergoing induction chemotherapy for ALL. SMX-TMP can cause neutropenia, which may increase the risk of bacterial infections. Oral thrush was more common in the SMX-TMP group, but invasive fungal infections did not occur [38].

Pentamidine

It as a prophylactic agent against Pneumocystis pneumonia (PCP) in pediatric leukemia patients who are unable to tolerate trimethoprim-sulfamethoxazole (TMP-SMZ) due to allergy or myelosuppression. A study found that intravenous pentamidine was effective as second-line prophylaxis against PCP in pediatric oncology patients, with a breakthrough infection rate of 1.3%. Aerosolized pentamidine was also effective in preventing PCP in children with leukemia who were unable to tolerate TMP-SMZ, with no cases of PCP occurring over an average treatment period of 8.11 months. Intravenous pentamidine is an effective second-line prophylaxis against PCP in pediatric oncology patients, with a breakthrough rate similar to that observed with inhaled pentamidine[71] and Aerosolized pentamidine is also a viable option for pediatric leukemia patients who cannot tolerate TMP-SMZ, as it can be administered safely and effectively, even in very young children [28].

Fluconazole

It is commonly used as antifungal prophylaxis in pediatric leukemia patients due to its effectiveness against invasive fungal infections. Fluconazole is recommended as the primary antifungal prophylaxis. A retrospective study evaluating the use of fluconazole during pediatric ALL induction therapy found no significant impact on the rate of fungal infections and no correlation with increased incidence of vincristine side effects such as hyponatremia and peripheral neuropathy. Another study analyzing the safety of fluconazole in pediatrics found that it was generally well tolerated and effective in preventing invasive fungal infections. Invasive fungal infections are a significant concern in pediatric leukemia patients, particularly those with ALL. Fluconazole prophylaxis can help reduce the risk of these infections [39].

Role of TKI in the treatment of CML

Imatinib

Imatinib mesylate is the first TKI approved by the US Food and Drug Administration (FDA) for the management of CML. Imatinib is a highly effective TKI for approximately 60% of CML patients. How-

Drugs	Class	Indication	Side effects
Chemotherapy			
Daunorubicin, doxorubicin, mitoxantrone	Anthracycline antibiotic	Induction, consolidation, intensification	Nausea, vomiting, alopecia, myelosuppression, cardiotoxicity
Cytarabine (Ara-C)	Antimetabolite, antineoplastic agent	Induction, consolidation, intensification	Nausea, vomiting, diarrhea, myelosuppression
Etoposide	Topoisomerase ii inhibitor	Induction, consolidation	Nausea, vomiting, myelosuppression
Vincristine	Vinca alkaloids	Remission induction	Neurotoxicity, constipation, nausea, vomiting, numbness, tingling, jaw pain, hair loss, discomfort on the skin
Methotrexate	Antimetabolite	Consolidation	Mucositis, liver toxicity, myelosuppression, and skin toxicity
Mercaptopurine (6-MP)	Purine antagonist	Consolidation	Myelosuppression, liver toxicity, nausea, vomiting, decreased appetite, diarrhea, fatigue, weakness, skin rash and mouth sores
Cyclophosphamide	Alkylating agent	Consolidation	Mouth sores, changes in skin color, low blood counts, hair loss, nausea, vomiting, abdominal pain, diarrhea, bladder problems, heart problems
Clofarabine	Purine nucleoside analog	Relapsed/refractory all	Nausea, vomiting, febrile neutropenia, pyrexia, diarrhea, skin rash, pruritus, headache, bacteremia, tachycardia, abdominal pain
Nelarabine	Purine nucleoside analog	T-cell all and t-cell lymphoblastic lymphoma	Neurological toxicities, hematological toxicities, gastrointestinal toxicities, infections, cardiovascular toxicities, renal and hepatic toxicities
Enzymes			
L-asparaginase	Enzyme	Remission induction	Nausea, vomiting, pancreatitis, coagulation abnormalities
pegaspargase	Antineoplastics	Remission induction	Nausea, vomiting, loss of appetite, stomach cramps, diarrhea, headache, fever, skin rash, coughing, flushing of the face, swelling, pain, redness, and warmth at the injection site
Calaspargase	Antineoplastics	Remission induction	Pancreatitis, hyperglycemia, elevated liver enzymes, bleeding, allergic reactions
Targeted therapies			
Imatinib, dasatinib, nilotinib, bosutinib	Tyrosine kinase inhibitors (tkis)	Ph+ all and cml	Nausea, diarrhea, muscle pain, fatigue, skin rashes, edema, myelosuppression
Tretinoin (ATRA)	Retinoid	Acute promyelocytic leukemia	Headache, fever, bone pain, skin changes
Arsenic trioxide	Inorganic compound	Acute promyelocytic leukemia	Nausea, vomiting, fatigue, qt prolongation
Corticosteroids			
Prednisone	Glucocorticoid	Induction, maintenance, relapse	Hyperglycemia, fluid retention, mood changes, increased appetite, insomnia
Dexamethasone	Glucocorticoid	Induction, maintenance, relapse	Hyperglycemia, fluid retention, mood changes, increased appetite, insomnia
Monoclonal antibody			
Blinatumomab	T-cell engager (bite) antibody	Relapsed/refractory b-cell precursor all	Nausea, vomiting, diarrhea, or abdominal pain
Inotuzumab ozogamicin	Cd22-directed antibody	Relapsed/refractory b-cell precursor all	Thrombocytopenia, anemia, vomiting, hemorrhage, neutropenia, nausea, leukopenia, febrile neutropenia, abdominal pain, headache

Gemtuzumab ozogamicin	Cd33 directed antibody drug conjugate	Induction, relapsed/ refractory aml	Infusion reactions, hepatotoxicity, myelosuppression
Tocilizumab	Interleukin-6 receptor inhibitor	Cytokine release syndrome	Infection, headache, common cold, irritation at the injection site, high blood pressure, low blood counts, elevated liver enzymes, stomach pain, chills, shortness of breath, coughing, dizziness, low blood pressure, chest pain, swelling
Car t-cell therapy			
Tisagenlecleucel	Cd19-targeted car t cells	Relapsed/refractory b-cell precursor all	Cytokine release syndrome, neurological toxicities, hematological toxicities, infections, hypogammaglobulinaemia, and cytopenias, hepatotoxicity, infusion reactions, and pancreatitis
Antimicrobials			
Sulfamethoxazole-trimethoprim	Sulfonamide antibiotic	Prophylaxis in pneumocystis jiroveci pneumonia	Rash, nausea, vomiting, myelosuppression
Pentamidine	Antibiotic	Prophylaxis in pneumocystis jiroveci pneumonia	Nausea, vomiting, myelosuppression
Antifungals			
Fluconazole	Triazole antifungal	Prophylaxis in high-risk patients	Nausea, vomiting, abdominal pain, headache

Table 2: Drugs used in the management of pediatric leukemia [5,7].

ever, it is less effective than second-generation TKIs, a problem that can lead to suboptimal kinase inhibition leading to resistance and loss of response [41]. Nearly all patients experience some impairment in quality of life, such as fluid retention (periorbital and peripheral), muscle cramps, or gastrointestinal disturbances (nausea, vomiting, and diarrhea) [42].

Nilotinib

Nilotinib is a more potent analog of imatinib and was approved by the US FDA in 2007 for the treatment of patients with CP or AP CML who are resistant to or intolerant to imatinib. Nilotinib is a 2nd generation TKI with greater potency and BCR ABL1 selectivity, and is effective against the majority of BCR ABL1 mutants which confer resistance to imatinib. In two current trials (a registration phase 2 study and an expanded access phase 3b study), nilotinib 400 mg twice daily was administered to patients with refractory BP-CML (82%) or intolerance (18%) to imatinib. CHR rates were 7–24 and 14–41% in myeloid and lymphoid BP-CML, respectively. An emerging concern related to the use of nilotinib is the occurrence of vascular events including peripheral arterial occlusive disease (PAOD), coronary artery disease (CAD), cerebrovascular disease (CVA), hyperglycemia, and hypercholesterolemia [43].

Dasatinib

Dasatinib is a potent, second-generation, small-molecule, multitarget kinase inhibitor of BCR-ABL. The structure of dasatinib is based on a chemical scaffold different from that of imatinib, and has a 325-fold greater potency, with the ability to bind both the inactive and active conformations of the ABL kinase domain. Dasatinib is metabolized by the cytochrome P450 (CYP) 3A4 isozyme to active and inactive metabolites. Therefore, coadministration of dasatinib with CYP3A4 inducers may decrease dasatinib concentrations, while 3A4 inhibitors, such as antiretrovirals, azole antifungals, and macrolides, may increase dasatinib toxicity. Recent data suggest that orally administered dasatinib crosses the blood-brain barrier. Dasatinib concentrations found in the cerebrospinal fluid of patients ranged from 1.4 to 20. 1 nM and were consistent with the observed antitumor activity in the central nervous system. In safety analyses, fluid retention, superficial edema, myalgia, vomiting, and rash were less common with dasatinib than with imatinib, while pleural effusion and grade 3/4 thrombocytopenia were more frequent with dasatinib [44].

Bosutinib

Bosutinib is a second-generation TKI approved by FDA in 2012 for the treatment of chronic-, accelerated-, and blast-phase CML in patients who are intolerant or resistant to prior therapy. Bosutinib exhibits activity against Src kinases, which are involved with malignant cell transformation, tumor progression, and metastasis. The interaction between signal transduction pathways and Src kinases is thought to have a role in promoting progression to accelerated- and blast-phase CML [45]. Bosutinib is more potent than imatinib and is active against most imatinib-resistant mutations, making it a potential alternative treatment. The recommended bosutinib dose for patients with CML is 500 mg orally, once daily with food. Bosutinib is mainly metabolized by cytochrome P450 (CYP) 3A417 and is primarily excreted in the feces. The gastrointestinal and hepatic events were more common with bosutinib [42].

Ponatinib

Ponatinib, a highly potent third-generation TKI, was granted accelerated approval from the US FDA in December 2012 for the treatment of patients with CML who were resistant to, or intolerant to prior TKI therapy. Ponatinib is effective against a vast spectrum of kinase domain mutations, including the T315I gatekeeper mutation [42]. ponatinib is highly active and a response-directed dose schedule leads to higher tolerability/safety and superior survival outcomes even in multi-TKI exposed or T315I-mutated CML. Common adverse events reported were thrombocytopenia, rash, dry skin, and abdominal pain. Serious arterial thrombotic events were observed in 9% of patients [46].

Tyrosine Kinase Inhibitor (TKI)	Dose	Side effects
Imatinib	100-200 mg/day	Rash, fluid retention, edema, weight gain, musculoskeletal aches, diarrhea, skin depigmentation
Nilotinib	200 mg/ day-200 mg BID	Rash, headaches, increased bilirubin, impaired glycemic control, dyslipidemia
Dasatinib	20-50 mg/day	Pleural effusion, cytopenia
Bosutinib	100-200 mg/ day	Gastrointestinal toxicity (diarrhea/colitis), renal dysfunction, liver dysfunction
Ponatinib	15 mg/day	Rash, hypertension

Table 3: Tyrosine kinase inhibitors [23,24].

Conclusion

Along with significant advances in targeted therapy and immunotherapy, chemotherapy remains the primary treatment option for pediatric cancer patients in most low- and middle-income countries. Recognizing the absolute value of chemotherapy drugs is crucial as they have shown to be highly effective in achieving long-term survival in childhood cancer. The diagnosis and treatment of leukemia are complex, and the unique disease subtypes add to this complexity. The presentation of symptoms, treatment, and prognosis vary depending on the subtype. An understanding of the differences between the subtypes is essential. To provide better treatments, support patients in crisis, and identify early warning signs of complications of pediatric leukemia as they are well familiar with this complicated disease.

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