Acute lymphoblastic leukemia in children: A short review

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Abstract

Acute lymphoblastic leukemia is as the most common childhood cancer. The definite etiology of childhood ALL is unknown. The pathogenesis of ALL is described as the disruption of lymphocyte proliferation and differentiation. The most common signs and symptoms of ALL are fever, hepatosplenomegaly, lymphadenopathy, pallor, and bleeding. Diagnosis is based on conducting complete blood cell, peripheral blood smear, bone marrow aspirate, immunophenotype, and cytogenetics tests. A number of demographic, clinical, and paraclinical characteristics of patients have been determined as prognostic factors. To select the appropriate treatment protocol, patients are risk stratified. In induction therapy, vincristine, corticosteroid, and asparaginase are given for the low- and standard risk groups and a four-drug induction therapy including vincristine, corticosteroid, asparaginase, and anthracycline are given for high- and very high-risk group for B cell ALL. The induction phase follow with post-induction courses including consolidation, interim maintenance, delayed intensification, and maintenance phases. ALL in pediatrics has a good prognosis and high cure rate.

1. Introduction

Acute leukemias constitute 97% of all childhood leukemias and are subdivided into acute lymphoblastic leukemia (ALL) 75%, acute myeloblastic leukemia (AML), also known as acute non-lymphocytic leukemia 20%, acute undifferentiated leukemia 0.5%, and acute mixed-lineage leukemia 1.5% (1). ALL is considered as the most common childhood cancer. It is the malignancy of lymphoid progenitors in bone marrow, peripheral blood, and extra medullar (2). In this narrative review, we consider briefly different aspects of ALL in children including epidemiology, etiology, pathophysiology, clinical presentation, diagnosis, prognostic factors, risk stratification, treatment, and clinical outcome.

2. Epidemiology

ALL peaks between ages 2-5 years. Then,

the rate fell to 20 cases/million for 8- to 10-year-olds (3). It is accounted for 25-30% of all childhood cancers (1). The annual incidence rate of this type of cancer is 3-4 cases per 100,000 children within the United States (US) (1). In the US, about 5,960 new cases of ALL diagnosed and 1,470 deaths in 2018. A descriptive study on cancer registry database of Fars province in Iran from 2001 to 2008 demonstrated that leukemias constitute about half (47.8%) of all cancers in children (4).

ALL occurs more frequently in whites than in African Americans. This difference is approximately more than threefold between 2- to 3-year-old age group (3). Its incidence is highest in children aged 1-4 years, then drops sharply through childhood (5-14 years), adolescence, and young adulthood (15-39 years).

3. Etiology

The definite etiology of childhood ALL is unknown. Following factors have been reported to be involved: 1) Infection with certain viral

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pathogens such as EBV (5); 2) Genetic predisposition such as Down syndrome (trisomy 21) (6); 3) Chemicals including in utero exposure to ionizing radiation (e.g., X rays), atomic survivors in Japan during World War II; 4) Environmental factors such as exposure to electromagnetic fields, pesticides, maternal use of alcohol, and cigarette smoking; and 5) Drugs such as etoposide and doxorubicin (1, 3).

4. Pathophysiology

The pathogenesis of ALL apparently involves loss of either signaling pathway leading to disruption of lymphocyte proliferation and differentiation. The mutated cells settle in the bone marrow and populate. The entire marrow space may be occupied by immature lymphocytes called lymphoblasts (3).

5. Clinical Presentation

Clinical signs and symptoms offer clues to the area affected. Obviously, the uncontrolled growth of the immature cells results in depletion of normal cells in the bone marrow (normochromic normocytic anemia, thrombocytopenia and neutropenia). The patient's chief complaint or symptoms presented at the time of diagnosis are as follows: Unexplained fever (61%), bleeding (48%), bone pain, limp, and refusal to bear weight (23%).
On physical examination, many patients have lymphadenopathy (50%), splenomegaly (63%), and hepatosplenomegaly (68%). Other clinical findings are ocular pain, blurred vision, abdominal pain, frequent infection, stridor, orthopnea, fatigue, pallor, headache, oliguria, anuria, bone tenderness, petechia & purpura, headache, vomiting, seizure, lethargy (1, 3)

6. Diagnosis

A thorough clinical history taking and physical examination combined with the interpretation of diagnostic tests are necessary to establish the diagnosis of childhood ALL. Beside these measures, paraclinical and laboratory tests are necessary to determine the diagnosis of ALL.

6.1. Laboratory data
6.1.1. Complete Blood Count

Increased or decreased WBC count: < 10,000/μL in 50% of cases, >50,000/μL in about 20% of cases
Hemoglobin < 10 g/dL in 80% of cases
Thrombocytopenia (platelet < 100,000/μL) in 75% of cases

6.1.2. Peripheral blood smear

Smear usually shows characteristic leukemic lymphoblasts.

6.1.3. Chemistry panel

Tumor lysis syndrome: Elevated uric acid, potassium, and phosphorous along with secondary hypocalcemia
Elevated serum creatinine secondary to uric acid or calcium phosphate crystal disposition in the renal tubules
Slightly abnormality of liver function tests due to leukemic infiltrate
Elevated lactate dehydrogenase

6.2. Imaging Chest X-ray

About 5-10% of cases have a mediastinal mass that may cause difficult breathing.

6.3. Bone marrow aspirate and biopsy

Presence of > 25% leukemic lymphoblasts is diagnostic.

6.4. Immunophenotyping & Morphology

Morphologic confirmation of lymphoblasts in bone marrow with immunophenotyping. May have combinations of:
Precursor B: CD 10+, 19+, 20+, 22+, TdT+
Precursor T: CD 2+, 3+, 5+, 7+, TdT+
Lymphoblasts may have some minimal myeloid marker including: CD 13+, 33+, 34+

6.5. Cytogenetics

Cytogenetic studies are both diagnostic and prognostic. They include ploidy, DNA index, and chromosome translocations or rearrangements (7).

6.6. Lumbar puncture

CSF examination for lymphoblasts: >5 blasts/hpf is positive (1, 3).

7. Prognostic factors

Prognostic factors that are included in the risk classification of pediatric ALL are as follows:

7.1. Age

Children younger than 1 year and those with 10 years or older have a worse prognosis. Children between 1-10-year-old tend to have better cure rates. The worst prognosis is for infants under 1 year (1).

7.2. White blood cell count

Children who have very high WBC count (more than 50,000 cells/mm3), are at high risk and need more intensive therapy (1). The total WBC count at the time of diagnosis is the most powerful clinical predictor of outcome in childhood ALL (3).

7.3. Immunophenotype

The best favorable prognostic immunophenotype is the B-lymphoblastic ALL. T-lymphoblastic ALL has a worse prognosis. It may be because of its relation with older age and with higher WBC at the time of diagnosis. Current protocols also consider intensified therapy for mature B-cell ALL. This is due to fact that mature B-cell ALL was related to early relapses and CNS involvement and finally poor prognosis (1).

7.4. Cytogenetics

The cytogenetic variables related to good prognosis are the combinations of trisomies of chromosomes 4, 10, and 17, and the translocations involving ETV6-RUNX. The variables related to poor prognosis are the translocations involving the MLL rearrangement on 11q23 (not MLL deletion), the Philadelphia chromosome t (9;22) (q34; q11). However, the presence of tyrosine kinase inhibitors in intensification therapy for Philadelphia chromosome improves treatment outcome (1).

7.5. DNA index

The most common cytogenetic abnormalities found in ALL are disorders by ploidy. DNA index more than 1.16 (chromosome number 50) is related with good outcome. The reason for this phenomenon may be related to reduced apoptosis threshold and increased sensitivity to chemotherapeutic agents. The prognosis of patients with DNA index less than 0.81 (less than 44 chromosomes and/or hypoploidy) is poor (1).

High hyperdiploidy (51-67 chromosomes, HeH) is a genetic subtype of B-cell precursor ALL (BCP-ALL) with a characterization of at least five non-random chromosomal gains, most commonly X, 4, 6, 8, 10, 14, 17, 18, and 21. It occurs with a frequency of 25-30% in BCP-ALL; however, it is very rare in T-cell ALL. This subtype is associated with favorable prognosis (overall survival of 90%) and favorable prognostic factors (ages between 1-10 years with a low WBC count). Prognostic factors such as age, WBC count, specific trisomies, and early response to treatment can affect the prognostic feature of this subtype (8). One study showed that individuals with 58-66 chromosomes had better outcome than those with 51-56 chromosomes.

7.6. CNS disease

CNS involvement at time of diagnosis has a poor prognostic factor even the intensification of therapy with CNS irradiation and additional intrathecal therapy for the treatment of these patients. Also, CNS2 status (fewer than 5 WBCs/μL in CSF) is related to a poorer outcome (1).

7.7. Early response to induction therapy

Complete remission at the end of induction therapy is related to favorable prognosis. Patients who are not in the remission after this phase have a very poor prognosis (1).

Sensitive laboratory methods such as polymerase chain reaction of antigen receptor genes or flow cytometry can now identify patients that harbor minimal residual disease (MRD). Patients with more than 0.01% leukemic cells at the end of induction phase are likely to have a worse prognosis and their treatment should be intensified (1).

Patients who have a clear peripheral blood MRD by day 8 and have no detectable bone marrow MRD at day 29, has excellent prognosis (1). Age, gender, WBC count, and NCI risk have not any effect on death and relapse rate in patients with

Table 1. The treatment protocol for Standard/Average-Risk Acute Lymphoblastic Leukemia.

Induction (4 weeks)	**Oral dexamethasone for 28 days (6 mg/m2/day in three divided doses)**
	IV vincristine (1.5 mg/m2 on days 0, 7, 14 and 21),
	IV Pegylated L-asparaginase (2500 units/m2, on day 4),
	Age-adjusted intrathecal cytarabine (age 1 to less than 2 years 30 mg; age 2 to less than 3 years 50 mg; age 3 years and older 70 mg) on Day 1
	Age-adjusted intrathecal methotrexate (age 1 to less than 2 years, 8 mg; age 2 to less than 3 years, 10 mg; older than 3_8.99 years, 12 mg; older than 9 years, 15 mg on day 8 and 29)
Consolidation (4 weeks)	Oral 6-mercaptopurine (75 mg/m2/d on days 1_28 of consolidation)
	IV vincristine (1.5 mg/m2 on day 1)
	Age-adjusted (see above) intrathecal metho-trexate on days 1, 8, and 15 for patients without CNS disease at diagnosis
Interim maintenance 1 (8 weeks)	IV vincristine. 1.5 mg/m2 (max dose 2 mg) on days 1, 11, 21, 31 and 41
	IV methotrexate starting dose of 100 mg/m2/dose on day 1 thereafter escalate by 50 mg/m2/dose on days 11, 21, 31, and 41 (discontinue escalation and resume at 80% of last dose if there is a delay because of myelosuppression or mucositis)
	Age-adjusted intrathecal methotrexate (see Induction) on day 31
Delayed intensification (8 weeks)	Oral dexamethasone (10 mg/m2/d on days 1_7 and 15_21 days)
	IV vincristine (1.5 mg/m2 on days 1, 8, and 15) IV
	pegylated L-asparaginase (2500 u/m2 on day 4)
	Doxorubicin (25 mg/m2, IV push, on days 1, 8, and 15),
	IV cyclophosphamide (1000 mg/m2 over 30 min on day 29)
	Oral 6-thioguanine (60 mg/m2/day on days 29_(12),
	IV cytarabine (75 mg/m2/day, on days 29_32 and 36_39)
	Age-adjusted intrathecal methotrexate (see Induction) on day 1 and 29
Interim Maintenance 2 (8 weeks)	IV vincristine. 1.5 mg/m2 (max dose 2 mg) on days 1, 11, 21, 31 and 41
	IV methotrexate starting dose is two-thirds of the maximum tolerated dose attained in interim maintenance 1 on day 1 thereafter escalate by 50 mg/m2/dose on days 11, 21, 31, and 41 (discon-tinue escalation and resume at 80% of last dose if there is a delay because of myelosuppression or mucositis).
	Age-adjusted intrathecal methotrexate (see Induction) on day 1 and 31
Maintenance (12-week cycles and is repeated until 2 years for girls and 3 years for boys from the start of interim maintenance 1)	Oral dexamethasone 3 mg/m2/dose BID on Days 1-5, 29-33, and 57-61
	IV Vincristine 1.5 mg/m2 on day 1, 29, and 57
	Oral mercaptopurine 75 mg/m2/dose on days 1_84
	Oral methotrexate 20 mg/m2/dose weekly (omit on the days when receive IT methotrexate)
	IT Methotrexate (age adjusted) on day 1

T cell ALL receiving HD MTX (9).

7.8. Absolute lymphocyte count

The normal lymphocyte range in children is between 3,000 and 9,500 lymphocytes in 1 microliter of peripheral blood. Lymphocytopenia, previously named lymphopenia, is defined by less than 3,000 lymphocytes per microliter of peripheral blood in children (10).

The causative cancers for lymphocytopenia are especially hematologic or lymphatic malignancies like lymphoma, Kaposi sarcoma, and also

Table 2. The treatment protocol for High-Risk/Very-High-Risk B-Cell Acute Lymphoblastic Leukemia.

Phase	Treatment	Dose
Induction		60 mg/m2/day PO for 28 days (dexamethasone 10 mg/m2/day is used for children ,10 years of age for 14 days)
		1.5 mg/m2/week IV, days 1, 8, 15, 22
		25 mg/m2/week IV, days 1, 8, 15, 22
		2500 units/m2/day IV, day 4
		Age-adjusted IT, day 0
Consolidation (9 weeks)	Cyclophosphamide	1000 mg/m2/day IV, days 1 and 29
	Cytarabine	75 mg/m2/day IV, days 1_4, 8_11, 29_32, 36_39
	Mercaptopurine	60 mg/m2/day PO, days 1_14 and 29_42
	Vincristine	1.5 mg/m2/day IV, days 15, 22, 43, 50
	PEG-asparaginase	2500 units/m2 IV days 15, 43
	Methotrexate	Age-adjusted IT, days 1, 8, 15, 22
Interim maintenance 1 (63 days)	Vincristine	1.5 mg/m2 per day IV days 1, 15, 29 and 43
	High-dose methotrexate	5000 mg/m2 IV over 24 h on days 1, 15, 29, and 43
	Leucovorin	15 mg/m2/dose starting at hour 42 after the start of high-dose methotrexate infusion
	Methotrexate	Age-adjusted IT days 1 and 29
	6-Mercaptopurine	5 mg/m2/dose by mouth from days 1_56
Delayed Intensification (8 weeks)		
Reinduction (4 weeks)	Dexamethasone	10 mg/m2/day PO, days 1_7, 15_21
	Vincristine	1.5 mg/m2/day IV, days 1, 8, 15
	Doxorubicin	25 mg/m2/day IV, days 1, 8, and 15
	PEG-asparaginase	2500 units/m2/day IM, day 4,
	Methotrexate	Age-adjusted IT day 1
Reconsolidation (4 weeks)		
	Cyclophosphamide	1000 mg/m2/day IV day 29
	Thioguanine	60 mg/m2/day PO days 29_42
	Cytarabine	75 mg/m2/day SC or IV days 29_32 and 36_39
	Methotrexate	Age-adjusted IT days 29 and 36
	Vincristine	1.5 mg/m2 IV days 43 and 50
	PEG-asparaginase	2500 units/m2 IM day 43
Interim maintenance II (56 days), given for very-high-risk patients only	Vincristine	1.5 mg/m2 per day IV days 1, 11, 21, 31, and 41
	Capizzi style Methotrexate	Starting dose is 100 mg/m2, then escalate by 50 mg/m2/dose on days 1, 11, 21, 31, and 41
	PEG-asparaginase	2500 IU/m2/dose on days 2 and 22
	Methotrexate	Age-adjusted IT days 1 and 31

Maintenance (12 weeks)		
	Vincristine	1.5 mg/m2/day IV days 1, 29, and 57
	Prednisone	40 mg/m2/day PO days 1_5, 29_33, and 57_61
	Mercaptopurine	75 mg/m2/day PO days 1_84
	Methotrexate	20 mg/m2/day PO days 8, 15, 22, 29 (hold cycles 1_2 when
		receiving IT methotrexate), 36, 43, 50, 57, 64, 71, and 78
		Age-adjusted IT day 1also day 29 of cycles 1 and 2 for patients who did not receive CNS radiation

leukemia (12). As well, chemotherapy or radiation therapy may lead to lymphocytopenia (11).

An absolute lymphocyte count (ALC) less than 600 lymphocytes per microliter or a differential count of fewer than 8% lymphocytes in the peripheral blood, has been recently introduced as a significant parameter and included in a proposed seven-factor prognostic scoring system of ALL. There is an inverse correlation with disease PFS in these cases (12).

Recent studies show that higher ALC at the end of induction phase associates with favorable features and initial treatment response. Higher ALC is more prevalent among patients with B-lineage ALL, favorable presenting features and in those who achieved MRD negativity on day 43 of treatment (13). Higher ALC at the time of diagnosis is related to better OS and PFS, and also higher complete remission rates (14). It is now a powerful new prognostic factor for different types of cancers (15), but it does not appear to be an independent predictor of outcome (13, 16).

7.9. Day -14 bone marrow response

Early response to treatment in bone marrow morphology can predict outcome and augmentation of therapy for the patients with slow early response. Children with a reduction of bone marrow lymphoblasts within 14 days of initiating antineoplastic therapy (rapid early responders) have a more favorable prognosis. This makes a major impact on clinical outcome in these patients (17).

Studies have showed that day -15 bone marrow can better predict outcome than prednisolone response and day -33 bone marrow (18). In addition, a day-14 M3 (lymphoblasts in bone marrow equal to or more than 25%) results in worse outcome compared to those with a rapid early response. Based on this, the treatment outcome of patients with an M3 marrow at day 14 (M3/M3) by augmentation therapy was significantly better than those with M2 at day 14 (lymphoblasts in the bone marrow from 5 to 24%) received standard therapy (17).

In the current Children's Oncology Group (COG) trials, patients with NCI high- or standard-risk ALL and an M2 or M3 marrow at day 14 are classified as slow early responders (17). Better clinical outcome has been reported in patients who experience a remission (major reduction of blasts in bone marrow) within 1 to 2 weeks of chemotherapy than those without remission (19).

8. Risk stratification groups

The COG uses a classification system based on risk and response. In this classification system, first the patients are categorized into standard- or high- risk groups based on the NCI risk. After induction therapy, again, risk is classified according to the rapidity and completeness of response to therapy, the presence or absence of cytogenetic abnormalities, and CNS involvement. So, the patients are assigned into risk groups that determined the intensity of post induction therapy according to prognostic characteristics;

Low-risk group was defined as NCI standard risk group (favorable age; between 1-9.99-years, low WBC count; <50,000 /µL), favorable cytogenetic changes including hyperdiploidy, including extra copies of 4, 10, and often 17, ETV6-RUNX1 rearrangement (formerly known as TEL-AML1), and rapid response to treatment (Day 8 peripheral blood MRD <0.01%, Day 29 bone marrow MRD <0.01%).

Standard-risk group have NCI standard

Table 3. Treatment protocol for Low-Risk B-Lineage Acute Lymphoblastic Leukemia

Induction (4 weeks) same as standard/average-risk ALL

Consolidation (19 weeks)

Methotrexate IV 1 g/m2 as 24-h infusion on days 8, 29, 50, 71, 92, and 113 with delayed leucovorin rescue (10 mg/m2) orally or IV every 6 h for five doses beginning 42 h after start of methotrexate infusion

6-Mercaptopurine 50 mg/m2 orally daily on weeks 1_133

Intrathecal methotrexate (age-adjusted as above) on days 8, 29, 50, 71, 92, and 113

Vincristine 1.5 mg/m2 IV on days 15, 22, 78, and 85

Dexamethasone 3 mg/m2/dose BID on days 15_21 and 78_84

Maintenance (16-week cycle)

Maintenance lasts for total of 2.5 years timed from the date of diagnosis. It includes vincristine and dexamethasone pulses every 16 weeks and PO methotrexate weekly. Age-adjusted intrathecal methotrexate is given every 12 weeks.

risk and rapid response to treatment without favorable cytogenetic changes.

High-risk group was defined with the following features: high NCI risk group (unfavorable age; > 10-years, high WBC count; > 50,000 / µL), MRD >0.01% at day 28 to 36 of therapy, and unfavorable cytogenetic changes including extreme hypodiploidy (44 or fewer chromosomes), t (9;22) (Philadelphia chromosome) BCR/ABL1, rearrangement, t(4;11) KMT2A (MLL) rearrangement.

Very high-risk group are the high-risk patients at the start of therapy who then have a poor response to initial therapy. These higher risk patients are those with age more than 13-year-old and/or failure to achieve complete remission at the end of induction therapy (>5 percent lymphoblasts in day 28 bone marrow or the presence of MRD), and unfavorable cytogenetic changes.

9. Treatment protocol

As previously mentioned, the patients assigned into standard- or high- risk groups based on NCI risk classification. Following induction therapy, the patients were re-classified into low-, standard-, high-, and very high-risk categories to determine the treatment intensity according to COG treatment protocol (1).

In summary, the COG protocols use a three-drug induction therapy (vincristine, a corti-costeroid, and asparaginase) for the low- and standard risk group and a four-drug induction therapy (vincristine, a corticosteroid, asparaginase, and an anthracycline) for high- and very high-risk group for B cell ALL. This recent induction regimen is also considered for all patients with the T cell immunophenotype. All patients are received dose-adjusted IT MTX during this phase.

After achieving complete remission, the post-induction courses are given to patients. These include consolidation, interim maintenance, delayed intensification, and maintenance phases. The pattern of treatment phases has been summarized in Figure 1. Details of each phase including agents type, dose, route of administration, and duration of treatment for standard/average-risk, high-risk/very-high-risk B-cell, low-risk B-lineage, and T-Cell ALL in children are also listed in tables 1 to 4. The total duration of therapy in female and male children are about 2.5 and 3.5 years, respectively.

10. Clinical outcome

The desired outcome for the treatment of childhood ALL is to achieve a rapid and complete remission after induction therapy (<5% blasts in BM14, MRD 8 &29 <0.01%).

With presently available therapy, 96% to 99% of the children achieve to the therapeutic goal and are classified as rapid early responders. If the treatment goal is not achieved, then patients are

Table 4. Treatment protocol for T-Cell Acute Lymphoblastic Leukemia.

Induction (4 weeks)	IV vincristine 1.5 mg/m2 weekly on days 1, 8, 15, and 22
	Oral prednisone 30 mg/m2/dose BID for 28 days
	IV PEG-asparaginase 2500 IU/m2 on day 4
	IV daunorubicin 25 mg/m2 weekly on days 1, 8, 15, and 22
	IT cytarabine (age adjusted) at the time of diag-nostic lumbar puncture or day 1
	IT methotrexate (age adjusted) on days 8 and 29
Consolidation (8 weeks)	IV vincristine 1.5 mg/m2 on days 15, 22, 43, and 50
	IV or SubQ cytarabine 75 mg/m2 days 1_4, 8_11, 29_32, and 36_39
	IV PEG-asparaginase 2500 IU/m2 on days 15 and 43
	IV cyclophosphamide 1000 mg/m2 on days 1 and 29
	Oral 6-mercaptopurine 60 mg/m2/dose on days 1_14 and 29_42
	IT methotrexate (age adjusted) on days 1, 8, 15, and 22
Interim maintenance (Capizzi methotrexate) (8 weeks)	IV vincristine 1.5 mg/m2 on day 1, 11, 21, 31, and 41
	IV methotrexate starting at 100 mg/m2/dose on day 1 then escalate by 50 mg/m2/dose on days 11, 21, 31, and 41
	IV PEG-asparaginase 2500 IU/m2 on days 2 and 22
	IT methotrexate (age adjusted) on days 1 and 31
Delayed intensification (8 weeks)	IV vincristine 1.5 mg/m2 on days 1, 8, 15, 43, and 50
	IV or SubQ cytarabine 75 mg/m2 on days 29_32 and 36_39
	IV PEG-asparaginase 2500 IU/m2 on days 4 and 43
	Oral dexamethasone 5 mg/m2/dose BID on days 1_7 and 15_21
	IV doxorubicin 25 mg/m2 on days 1, 8, and 15
	IV cyclophosphamide 1000 mg/m2 on day 29
	Oral thioguanine 60 mg/m2/dose on days 29_42
	IT methotrexate (age adjusted) on days 1, 29, and 36
Maintenance (12-week cycles that is repeated until 2 years for girls and 3 years for boys from the start of interim maintenance)	IV vincristine 1.5 mg/m2 on days 1, 29, and 57
	Oral prednisone 20 mg/m2/dose BID on days 1_5, 29_33, and 57_61
	Oral mercaptopurine 75 mg/m2/dose on days 1_84
	Oral methotrexate 20 mg/m2/dose weekly (dose needs to be skipped on the days of IT methotrex-ate)
	IV doxorubicin 25 mg/m2 on days 1, 8, and 15
	IV cyclophosphamide 1000 mg/m2 on day 29
	Oral thioguanine 60 mg/m2/dose on days 29_42
	IT methotrexate (age adjusted) on days 1, 29, and 36

classified as slow early responders and goes for intensified treatment.

After remission induction, the purpose is to maintain the complete remission through the other phases of treatment. Children who are free of disease for longer than 5 years are considered as "cured".

The success rate in treating childhood ALL is now more than 80% as. More than 95% the children with low risk disease will survive their leukemia. The OS rates for the standard risk patients is between 90% to 95%. The OS rates for high (rapid/ slow early responders with T-cell leukemia, B cell leukemia) and very high risk leukemia are about 90% and 80%, respectively (1, 3, 24). The OS rate of childhood leukemia in Shiraz,

Patient assessment
Patient characteristics (NCI risk)
- Age
- WBC count
Leukemic cell characteristics
- Karyotype

Stratified according to risk groups
1. Standard risk group
(Age 1- 9.99 y/o, WBC <50,000/µl)

2. High risk group
(Age <1, >10 y/o, WBC >50,000/µl)

Remission induction
Prednisolone or dexamethasone
PEG-asparaginase
Intrathecal chemotherapy (MTX)
Anthracycline (daunourubicin)– if high risk

Reclassification of risk
Rapidity & completeness of response to therapy
- Rapid early responder: (<5% blasts in BM14, MRD 8, 29 <0.01%)
- Slow early responder: M2 (5-25% blasts) or M3 (>25% blasts) on day-15
Cytogenetic abnormalities (favorable/unfavorable)
CNS involvement

Consolidation/interim maintenance
Improving outcome
Eradicating clinically undetectable disease
Non- cross resistant drug different from induction regimen/ more dose-intensive use of the same drugs
- *Low/average- risk*
VCR, 6-MP, IT MTX
- *Higher risk/ slow early responder*
more intensive chemotherapy with cyclophosphamide, LD cytarabine, MTX, VCR, and asparaginase

Reinduction (Delayed intensification/interim maintenance)

(for further decrease leukemic burden)

Delayed intensification

STD risk: improves EFS
High risk with dose intensification: Improves EFS and decreased late relapses

Drugs in induction and consolidation phases
Or agents lack cross-resistance with those already received CTX, MTX, and limited amounts of DOX.
Interim maintenance

Dexamethasone, VCR, Weekly MTX, 6-MP, IT MTX

Maintenance
(for slowly dividing cells, the immune system to eradicate leukemia cells, promoting apoptosis)
- Lengths varies by protocol
- Daily oral 6MP and weekly oral MTX for 12 weeks
- Monthly pulses of VCR and glucocorticoid steroids
- Periodic intrathecal chemotherapy
Ph+ ALL: oral TKIs (imatinib or dasatinib).
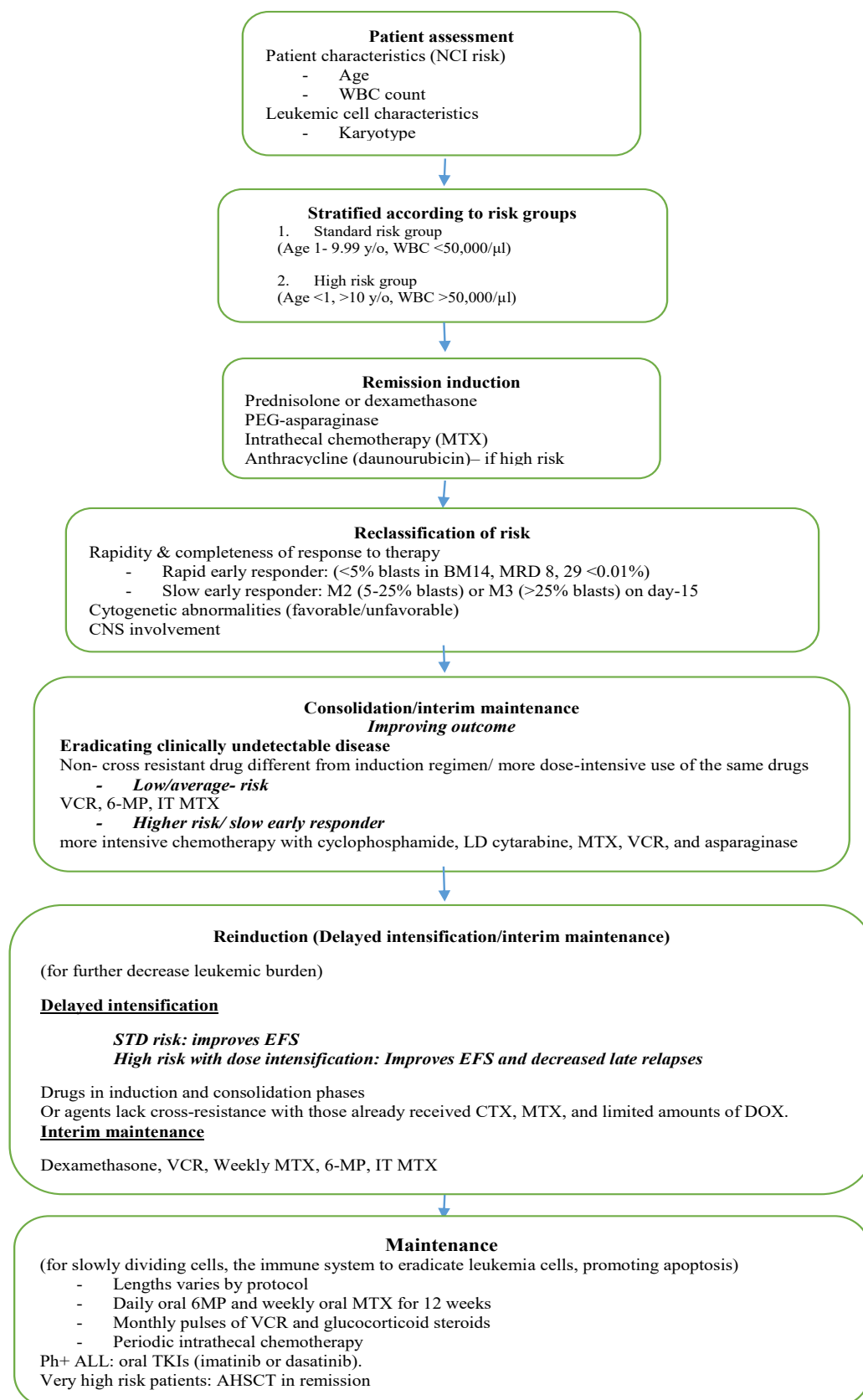Very high risk patients: AHSCT in remission

Figure 1. The overview of treatment of children with acute lymphoblastic leukemia

Table 5. Suggested targeted therapy drugs for the treatment of children ALL.

		Drug classification	Drugs
Molecularly targeted agents			
Tyrosine kinase inhibitors	Ph-positive ALL	BCR-ABL1 TKIs	Imatinib
		BCR-ABL1 inhibitor	Dasatinib
		More potent than imatinib, Better EFS, OS, and CNS control disease	
		BCR-ABL1 inhibitors, harboring the gatekeeper ABL1 T315I mutation	Pontinib
		Excellent 2-year EFS in adults.	
		Caution in pediatric due to side effects such as thrombosis and pancreatitis	
	Ph-like ALL - CRLF2 rearrangement	under investigation in clinical and preclinical phases	
		Due to mutations in signaling pathways – JAK-STAT, PI3K, mTOR, and BCL2	
	Ph-like ALL - CRLF2 rearrangement and concomitant JAK mutation	JAK inhibitors	Ruxollitinib (Murine pre-B cell lines and patients- derived xenograft model)
	Ph-like ALL - ABL-class gene fusions (ABL1, ABL2, CSF1R, LYN, PDGFRA, or PDGFRB), Ph-like ALL – rare kinase alteration	ABL inhibitors can be combined with chemotherapy	
	NTRK3	Crizotinib	
	PTK2B	FAK inhibitors	
	TYK2	TYK2 inhibitors	
	KMT2A-rearranged ALL	DOT1L, bromodomain, menin, and histone deacetylate inhibitors	
	Treatment failure ALL	inhibitor of the anti-apoptotic regulator BCL-2	Venetoclax
	Relapsed ALL	Proteasome and mTOR inhibitors	
	Relapsed and/or Refractory T-ALL	Purine nucleoside analog	Nelarabine

southern Iran, in years 2004 to 2008 has been reported to be 56.6±0.1% (25).

Generally, ALL in pediatrics has a good prognosis and high cure rate. Outcome has improved considerably over the past four decades, with an increase of 5-year overall survival from 31% in 1975 to nearly 70% in 2009.

Most children with ALL who experience relapse during therapy or within the first year of completing therapy. After the second year of therapy and for every year thereafter, relapses become much less common.

11. Targeted therapy drugs

Development of targeted therapies for the cancer treatment can also bring myriad benefits

Continued Table 5.

Immunotherapy			
		Results in higher response rate and improved outcome in patients with relapsed/refractory B-ALL	
Monoclonal anti-bodies to surface antigens	Anti-CD20	lower rates of relapse and improved EFS and OS with rutuximab	rituximab, ofatumumab
	Anti-CD22	Higher complete remission, PFS, and OS in adults with inotuzumab	inotuzumab ozogamicin
		Approved as a single agent for adult patients	others:
		Longer 2-year overall survival in pediatrics with inotuzumab	epratuzumab,
		Not approved for children younger than 18 years, yet	moxetumomab pasudotox, and combotox
	Anti-CD19	MRD-positive (≥ 0.1%)	Blinatumomab
		In patients with refractory Ph-negative ALL, relapse after at least two previous therapies, or in relapse after having an allogeneic haemopoietic cell transplantation.	Other: den-intuzumab mafodotin
		Better OS, CR with whole hematologic recovery, EFS, and quality of life	
Chimeric antigen receptor (CAR) T cells	Anti-CD19 CAR T cells	Children or adolescents and young adults of 25 years or younger with refractory or relapsed disease after two lines of alternative treatment or after haematopoietic cell transplantation	Tisagenlecleu-cel

for children with ALL by increasing the response rate and improving clinical response. These agents include tyrosine kinase inhibitors, monoclonal antibodies, and chimeric antigen receptor T cell (26-29) (Table 5).

12. Conclusion

ALL is as the most common childhood cancer. The definite etiology of childhood ALL is unknown. To select the appropriate treatment protocol, patients are stratified into standard- or high-risk groups based on NCI risk classification. In induction therapy, vincristine, corticosteroid, and asparaginase are given for the low- and standard risk groups and a four-drug induction therapy including vincristine, corticosteroid, asparaginase, and anthracycline are given for high- and very high-risk group for B cell ALL. The induction phase follow with post-induction courses including consolidation, interim maintenance, delayed intensification, and maintenance phases. The total duration of therapy is about 2.5 years in girls and 3.5 years in boys. The success rate in treating childhood ALL is now more than 80%.

Conflict of Interest

None declared.

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