



How I Treat Adult Acute Lymphoblastic Leukemia in India

Prasanth Ganesan¹ Smita Kayal¹

¹Department of Medical Oncology, Regional Cancer Center, Jawaharlal Institute of Postgraduate Medical Education & Research (JIPMER), Puducherry, India

Ind J Med Paediatr Oncol 2021;42:584–594.

Address for correspondence Prasanth Ganesan, MD, DM, Medical Oncology, 3rd Floor, Superspecialty Block (SSB), Jawaharlal Institute of Postgraduate Medical Education & Research (JIPMER), Dhanvantari Nagar, Puducherry 605006, India (e-mail: p.ganesan@jipmer.edu.in).

Introduction

Survival in pediatric acute lymphoblastic leukemia (ALL) has improved from less than 10% (in the 1960s) to over 90% in developed countries.¹ These improvements were driven by optimized, risk-stratified chemotherapy and enhanced supportive care. The incorporation of tyrosine kinase inhibitors (TKIs) in Philadelphia chromosome-positive (Ph+ve) ALL has improved survival in this subset.² However, older age makes significant impacts on survival in ALL. Though the survival among adolescents and younger adults (AYA, 19–40 years) has improved (5-year survival: 50–70%), gains in older adults (41–60 years) with ALL have been more modest (5-year survival: 30–40%).^{3,4} Even in the best centers in the world, till recently, survival among “elderly” ALL (>60–65 years) was poor, and only 10 to 15% were being “cured” with conventional chemotherapy.^{3,5}

Adverse disease biology partly explains the drop in survival with age.⁶ Older patients have higher proportions of Ph-positivity, and “Ph-like” changes, with a lesser proportion with “good risk” cytogenetics like the t(12;21) translocation. Better outcomes are demonstrated in AYA ALL with intensive (“pediatric-type”) chemotherapy protocols.^{7,8} However, these regimens have increased toxicity and treatment-related mortality (TRM), especially in older individuals and “real-world” patients.^{9–12} India has the highest population of adolescent and young adults globally, and most centers see a significant proportion of patients in this age group.^{13,14} Indian centers report a high incidence of

infectious complications (including multidrug resistant bacterial infections) during delivery of intense therapies for acute leukemias.^{15,16} Even if minimal residual disease (MRD) assessment is done, there is limited access to stem cell transplantation.¹⁴ Thus, multiple factors contribute to poorer outcomes in adult ALL, and the challenges are country and center specific.

In this review, we use a series of representative case scenarios to discuss the management process in adult ALL. The discussions focus on presenting the standard of care while simultaneously highlighting issues specific to India. The broad principles of the decision-making process are outlined without too much detailing of the features of individual protocols.

Case 1: Young Adult with Standard-Risk Acute Lymphoblastic Leukemia

A 32-year-old female, housewife, mother of two children from a poor socioeconomic background presented with weakness and recurrent fever for 2 months. Her presentation blood counts were: hemoglobin 50 g/L (5 g/dL), white blood cells (WBCs): $23.4 \times 10^9/L$ (23,400/mm³), and platelets: $34 \times 10^9/L$ (34,000/mm³). Peripheral smear showed 65% blasts. Bone marrow was completely replaced by blasts confirmed as precursor B-cell (pre-B) lymphoblastic leukemia by flow cytometry. Conventional cytogenetics showed normal karyotype, and reverse transcription polymerase chain reaction (RT-PCR) for

DOI <https://doi.org/10.1055/s-0041-1731979>.
ISSN 0971-5851.

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BCR-ABL was negative. She started induction therapy with modified BFM-95 protocol.

Adult versus Pediatric protocols

Multiple trials have shown superior results using “pediatric” type protocols in AYA patients with ALL (–Table 1).^{17–19} Patients up to the age of 50 years have been included in these studies, and the current consensus is to use pediatric protocols whenever feasible for treating young adults. At our center, we use BFM-95, a standard and frequently-used “pediatric” regimen. Inadequate prednisolone response and adverse biology (BCR/ABL or MLL rearrangements) are considered high-risk, while, T-cell ALL (T-ALL), older ages (>6 years), and initial WBC > 10 × 10⁹/L constitute medium risk. We used a modified version of this protocol where most patients received the standard risk treatment with modifications done only for those who are MRD+ve.²⁰ Previous studies from India (–Table 2) have reported 40 to 60% survival among AYA ALL treated with this protocol.^{12,14} Though higher TRM was noted in older Indian studies, a large multicenter study from India has shown that pediatric protocols can safely be delivered in AYA patients without excess mortality.^{11,14} Concerns about toxicities remain and, even in developed countries, a quarter of AYA patients are treated with “adult” protocols.²¹

Case-1 Continued

At the end of induction, the bone marrow (day 35) was in remission, and MRD was negative (<0.01%). She continued standard therapy (phase Ib followed by high-dose methotrexate, reintensification [IIa and IIb], prophylactic cranial radiation [dose: 12 Gy], and maintenance). During maintenance, she frequently delayed her follow-up visits leading to treatment interruptions. She and her husband were counseled multiple times by a social worker to maintain adherence. Ultimately, she completed 2 years of maintenance therapy and remained in CR 6 months after completing treatment.

Role of Cranial Radiation

Prophylactic cranial radiation is usually used in adult ALL, while newer pediatric protocols omit this in low-risk disease. Concerns about long-term radiation effects (neurological and neuroendocrine) may be lower in an older individual compared with a very young child.²² At our center, we choose to continue to offer cranial RT for adult ALL to reduce the risk of CNS relapses.

Role of Rituximab

Conventional chemotherapy based on “pediatric” protocols yields survival of 50 to 60% in AYA ALL.⁴ Addition of rituximab has improved event-free survival (EFS) by 10–15% without a statistically significant improvement in overall survival [OS] in CD20+ adult ALL treated in the GRAALL-2005/R study (which used the GRAALL 2003/2005 backbone of chemotherapy, an intense “pediatric-type” regimen).²³

This is another consideration in CD20+ve patients (about one-third of pre-B ALL), reducing relapse by 10 to 15%. At our center, we usually do not add rituximab for all patients due to cost considerations.

Role of Counseling and Maintaining Treatment Adherence

Nonadherence and abandonment occur in 11 to 15% of Indian ALL patients.^{11,14,24,25} Young adults have to tackle multiple social and economic issues. These patients have a high risk of demotivation and nonadherence which may manifest during the long treatment course. Treatment delays reduce the relapse-free survival from 69% to 43%.¹² The benefits of an “intensive” regimen will not be realized unless the patients strictly adhere to the treatment timelines. It is vital to have a team of supportive personnel (social workers, psychooncologists, etc.) who can work closely with these patients and proactively identify non-adherent behavior and intervene appropriately to realize maximum benefit. Oncologists/hematologists involved in the care of leukemias should make attempts to get adequate support (social workers/psychooncologists/support from nongovernment organizations [NGOs]) to prevent treatment nonadherence and abandonment. Experience from pediatric ALL shows that it is possible to achieve this, even in a governmental setup.^{26–28}

Case 2: Adult Acute Lymphoblastic Leukemia with High-Risk Disease

A 49-year-old male presented with a 1-week history of breathing difficulty and facial puffiness. He had neck nodes, mediastinal widening, and superior vena cava (SVC) syndrome. Hemogram showed hemoglobin: 100 × 10⁹/L (10 g/dL), WBC count: 112 × 10⁹/L (112,000/mm³), and platelet counts: 98 × 10⁹/L (98,000/mm³). Peripheral smear showed 90% blasts, and bone marrow with phenotyping confirmed a diagnosis of T-cell lymphoblastic leukemia (positive: CD3, CD7, CD5, terminal deoxynucleotide transferase (TdT); negative: CD19, CD10). There were no neurological symptoms, hypoxia, and cerebrospinal fluid was negative for malignant cells. After establishing hydration and measures to control tumor lysis, he started BFM-95 induction.

T-Cell versus B-Cell Acute Lymphoblastic Leukemia

T-ALL comprises approximately 15 to 25% of total cases of adult ALL.^{29,30} T-ALL is more likely to have higher white cell count, mediastinal enlargement, and CNS involvement.^{31–33} Historically, outcomes in T-ALL outcomes were inferior, but with contemporary risk-adapted protocols, survival has improved to 85%–90% in pediatric T-ALL. Adult trials of German multicenter study group for adult ALL (GMALL), group for research on adult ALL (GRAALL), UKALL, and hyper-CVAD have shown CR rates of 75 to 90% and 5-year OS of 35 to 50% for T-ALL.^{34,35} However, in AYA patients, intense protocols with dexamethasone, higher intensity of L-asparaginase and high-dose methotrexate (5 g/m) yields survival of 60 to

Table 1 Comparison of adult and pediatric protocols

Component of therapy	Pediatric	Adult	Our preference in adult ALL therapy	Remarks
Steroids	Higher cumulative doses Dexamethasone > prednisolone	Lesser doses overall	Prednisolone Though dexamethasone may reduce relapses, there is a higher risk of infectious complications	High risk of hyperglycemia and infections in adults
L-asparaginase	Higher cumulative doses	Lesser doses	We usually cap the dose of L-asparaginase at 10,000 when using the BFM protocol. For older individuals above 50–60 we minimize the use of L-asparaginase or omit this during induction	Risk of complications is very high in individuals over 50
Peg-asparaginase	Most modern protocols have switched to peg	Most modern protocols have switched to peg	With peg-asparaginase availability from Indian companies, the cost has reduced; but it is still higher than conventional L-asparaginase. We do not use it regularly because of the cost issues	Though the efficacy is similar to conventional asparaginase, the compliance may be improved with the peg preparation
Vincristine	Higher doses Some pediatric protocols do not cap at 2 mg	Capped at 2 mg per dose Lower cumulative doses	Capped at 2 mg. When used as prophylaxis drugs like voriconazole can worsen toxicity; hence withhold 24 hours before vincristine	High risk of neuropathy in adults
Methotrexate	Higher doses like 5 g/m ² easily delivered Recent data with Capizzi's type regimens	Creatinine clearance issues in individuals >50 years; hence ≥5 g is difficult to administer. No data with Capizzi's type methotrexate	We use a 3 g/m ² dose for pre-B ALL and 5 g/m ² for T-ALL when using BFM protocol	Risk of nephrotoxicity, especially in older individuals. Need for drug-level monitoring
AlloSCT in first remission	Usually not considered except for persistent MRD+ or MLL rearrangements Many protocols prefer intensification	Usually considered for MRD positive, Ph+ve, MLL rearrangements, and other protocol defined high-risk features	CR1 alloSCT is offered for high-risk as defined by Ph+ve, MLL+, and persistent (postconsolidation) MRD+ve patients	Multiple factors need to be considered as shown in Table 3.
Anthracyclines	Tailored use Less preferred due to long-term risks	Usually, a component of therapy at standard doses	Usually omitted or lesser number of doses in elderly ALL	–
Cranial radiation prophylaxis	Omitted in most modern protocols	Usual component	Dose of 12 Gy for prophylaxis and 18 Gy for CNS+ disease	Concerns about long-term cognitive and endocrine effects in children. Fewer concerns in adults

Abbreviations: ALL, acute lymphoblastic leukemia; AlloSCT, allogeneic stem cell transplantation; CNS, central nervous system; MRD, minimal residual disease; Peg, pegylated; Ph+ve, Philadelphia chromosome-positive; pre-B ALL, precursor B-cell; T-ALL, T-cell ALL. MLL, mixed lineage leukemia; BFM, Berlin-Frankfurt-Munster;

70%.³⁶ Indian studies have shown 5-year EFS and OS of 50 ± 7.4 and 61 ± 7.6% for pediatric T-ALL treated on MCP-841 protocol and 5-year EFS of 38 ± 6.2% for adult T-ALL treated with modified GMALL protocol.^{25,37} At our center, we use BFM-95 for adult T-ALL up to 50 years of age and a modified GMALL for older/or, less-fit patients.

Case-2 Continued

After completing BFM-95 induction IA, the bone marrow was in morphological CR, but MRD by flow cytometry was

positive (0.24%). He received three courses of the high-risk regimen of BFM-95. Subsequently, his marrow became MRD-negative and he is currently on maintenance.

Role of Minimal Residual Disease Assessment in Acute Lymphoblastic Leukemia

A tailored approach based on the MRD status must be considered in all patients currently treated for ALL.³⁸ The best technique (multi-parameter flow cytometry vs. PCR-based assessment) and time point (end of induction vs. end of consolidation), for assessment of MRD is still

Table 2 Selected studies of adult ALL from India

Type	Ph type	Center	City	n	Median age in years(range)	Treatment	EFS% (y)	OS%
Ph-negative ALL	1997–2003	PGIMER ²⁵	Chandigarh	118	>12	Modified BFM	29 (3)	NR
	1995–2009	CMC ⁷⁹	Vellore	113	15–60	Modified GMALL ^a	51 (5)	51(5)
	2000–2013	CI(14)	Chennai	232	21 (18–30)	BFM and GMALL	36 (5)	39(5)
	2012–2018	HCC ⁸⁰	Multiple	572	21 (15–29)	Multiple ^b	56 (2)	73(2)
	2013–2016	TMH ⁸¹	Mumbai	349	15–25	BFM	59 (3)	61(3)
PH-positive ALL	2011–2016	RGCI ⁸²	New Delhi	63	35 (14–76)	COG/UKALL ^c	31 (4)	46(4)
	2009–2012	TMH ⁸³	Mumbai	65	28 (15–53)	MCP/BFM/other ^e	30 (2)	29(2)
	2012–2017	HCC ⁸⁰	Multiple	158	21(15–29)	Multiple ^{b,d}	47 (2)	67(2)

Abbreviations: ALL, acute lymphoblastic leukemia; BFM, Berlin-Frankfur-Munster; CI (WIA), cancer institute (WIA), Adyar; CMC, Christian Medical College; COG, Children's Oncology Group; EFS, event-free survival; GMALL, German multicenter study group for adult ALL; HCC, Hematology Cancer Consortium; MCP, Multicenter protocol-841; OS, overall survival; Ph+ve, Philadelphia chromosome-positive; PGIMER, Post Graduate Institute of Medical Education & Research; RGCI, Rajiv Gandhi Cancer Institute, Dwarka; TMH, Tata Memorial Hospital; UKALL, United Kingdom Multicenter ALL protocol.

^aOnly T-cell ALL were analyzed in this study.

^bPediatric (87%), adult (13%); BFM (74%), COG (8.5%), MCP-841 (3.7%), GMALL (10.4%), hyper-CVAD (2.3%), and others (1%).

^cImatinib till 2021, then dasatinib; alloSCT in 16 patients; and EFS was superior with alloSCT (36 vs. 27%).

^dImatinib, 83% and dasatinib, 17%.

unresolved.^{39,40} T-ALL patients take longer to clear MRD than B-ALL, and MRD may be assessed 2–3 months postinduction. At our center, we assess MRD postinduction and if positive, we move to the high-risk (HR 1, 2, 3) arm of the same protocol. MRD–ve patients continue with standard-dose consolidation therapy. Patients who become MRD–ve after further chemotherapy are considered for allogeneic stem cell transplantation (alloSCT) in CR1. Patients with persistent MRD post consolidation do poorly even with additional chemotherapy or an alloSCT (10–20% long term survival). The decision-making in these patients has to be individualized ►Table 3 and the overall approach presented in ►Fig. 1).

AlloSCT in CR1 in adult Acute Lymphoblastic Leukemia

Though alloSCT reduces relapses (by 10–15%), the benefit has to be weighed against the risk of non-relapse mortality (NRM) and other long-term problems. The MRC UKALL12/ECOG 2993 trial was the largest (“genetic randomization”) trial comparing conventional therapy (adult-type ALL protocol) with allogeneic transplant in CR1. Patients with matched donors received CR1 alloSCT while those without donors continued chemotherapy. Though alloSCT reduced relapses, this benefit was negated by increased NRM, especially in those older than 45 years.⁴¹ Thus, the decision to allotransplant must consider the disease risk (baseline, and MRD), patient's fitness (age, comorbidities, performance status), type of protocol being used (pediatric-inspired vs. adult), donor-type for the procedure (matched vs. haploidentical vs. cord blood), experience of the center, and also the possibility of later access to novel therapies (chimeric antigen receptor T cells, blinatumomab, inotuzumab, etc.) ►Table 3).⁴²

Among these, MRD-positivity is the most critical disease factor determining the decision of alloSCT in CR1 in adults with ALL. For patients treated with intense chemotherapy protocols and achieve MRD–ve status, the use of alloSCT in CR1 may not be required despite the presence of other high-risk factors.⁴³

When the decision has been made to proceed with an alloSCT, conditioning using myeloablative regimens using total body irradiation (TBI) are preferred in patients with ALL.^{44,45} At our center, for Ph–ve ALL, we reserve alloSCT in CR1 (myeloablative conditioning with fludarabine–busulfan) for young (<50 years) and fit patients with one or more conventional high-risk features (high-risk cytogenetics, early thymic precursor [ETP] ALL) only when a matched sibling donor is available. In the absence of a matched sibling donor, these patients are usually treated in the high-risk arm of the BFM-95 protocol. However, if they have persistent MRD after consolidation therapy, the long-term chance of survival is 12%.⁴⁶ In these patients, we offer alloSCT in CR1. Decisions on haploidentical transplants in these patients are taken after very detailed discussions.

Treatment of Early Thymic Precursor Acute Lymphoblastic Leukemia

The ETP ALL accounts for 15 to 35% of T-ALL and is characterized by a unique immunophenotype (cCD3⁺, sCD3[–], CD1a[–], CD2⁺, CD7⁺, CD8[–], CD5 dim, and positivity for stem cell and myeloid markers, including HLA-DR, CD13, CD33, CD34, or CD117).^{47,48} Outcomes are inferior (lower remission rates post-induction and higher MRD positivity), but may be improved by contemporary response-adapted treatment regimens (alloSCT in CR1 reserved for persistent MRD

Table 3 How we choose a patient for CR1 alloSCT in adult ALL

Factor	Strongly consider alloSCT in CR1 ^a (Green)	Discuss the option of alloSCT in CR1 ^b (Yellow)	AlloSCT in CR1 not to be considered (Red)
Baseline risk factors	Ph+ve disease MLL rearrangements Complex karyotype	ETP ALL MPAL	No baseline risk factors
MRD status	Positive postconsolidation	Positive postinduction but negative postconsolidation	MRD negative
Age group (y)	<40–45	45–60	>60–65
Donor	Fully matched sibling or MUD	Haploidentical donors	No donor available
Center TRM with alloSCT	5–10%	10–20%	>20%
Patient factors	<ul style="list-style-type: none"> Committed patient and family Finances available Able to stay in local place for 6–12 months 	Any one of these factors missing	All these factors are missing

Abbreviations: AlloSCT, allogeneic stem cell transplantation; ALL, acute lymphoblastic leukemia; ETP, early thymic precursor; MPAL, mixed phenotypic acute leukemia; MRD, minimal residual disease; MUD: matched unrelated donor; MLL, mixed lineage leukemia; TRM, treatment-related mortality.

Note: In the “red” group, we usually do not offer alloSCT in CR1.

^aIn the “green” group, we offer allotransplant in first complete remission (CR1) and strongly encourage patients to consider this option, especially when all factors are favorable.

^bIn the “yellow” group, when any of the factors are not favorable, we have detailed discussions with the patient and family about the pros and cons and make an informed decision.

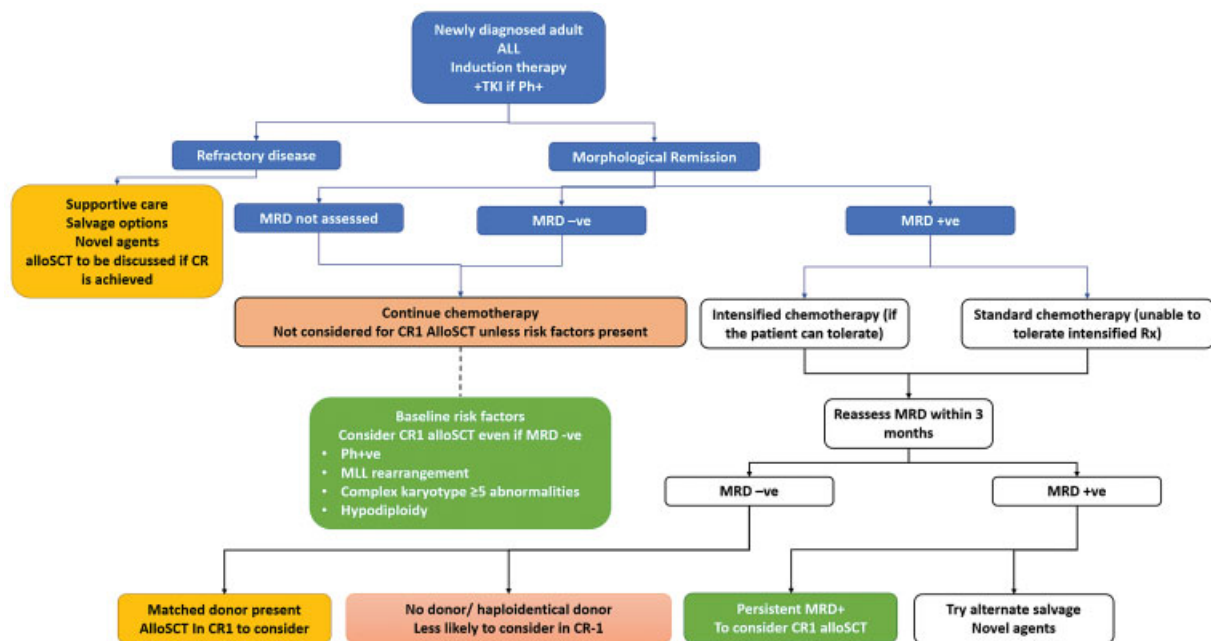


Fig. 1 Approach to adult acute lymphoblastic leukemia (ALL). Decision-making process for adult ALL in India. The green boxes represent strong indications for allogeneic stem cell transplantation (alloSCT) in first complete remission (CR1), where it would be offered to all those with a sibling donor. The yellow boxes represent situations where there is benefit from alloSCT in terms of reduction of relapses. However, the procedural risk may be high (e.g., only a haploidentical donor is available or when the patient is older or has multiple comorbidities). In these situations, the decision must be individualized after clear discussions with the patient and family. Decision-making must consider the center’s experience in alternative-donor transplants. The blue box represents persistent MRD; these patients are at high risk of relapse. Their outcomes are poor with continued chemotherapy, but data also suggests that patients who are MRD+ve at the time of transplant have worse outcomes than those who undergo transplants with MRD-ve marrow. Hence, these situations also require detailed discussions. The red boxes are situations where alloSCT in CR1 is not considered (no donor, MRD-ve, and no high-risk features). MRD, minimal residual disease; Ph+ve, Philadelphia chromosome-positive; TKI, tyrosine kinase inhibitor; MLL, mixed lineage leukemia;

positivity).^{35,49} The use of L-asparaginase may be important; hence “pediatric” type protocols may be preferred for ETP ALL over protocols such as hyper-CVAD.⁵⁰ At this point, there is limited published data on ETP ALL from India. We currently treat adult ETP ALL with BFM-95 protocol on and reserve alloSCT for persistent MRD post consolidation.

Case 3: Elderly Patient with Acute Lymphoblastic Leukemia

A 73-year-old retired school teacher had been feeling unwell for 2 months. *He had been diagnosed with anemia, and had received two packed red blood cells.* A repeat blood count showed hemoglobin: $65 \times 10^9/L$ (6.5 g/dL), WBC count: $2.3 \times 10^9/L$ ($2,300/mm^3$), and platelet count: $45 \times 10^9/L$ ($45,000/mm^3$). Bone marrow was replaced with lymphoblasts (CD19+, CD20+, CD3–ve, and pre-B ALL). BCR-ABL was negative. He had well-controlled hypertension, poorly controlled blood glucose, and took cardiac medications after bypass surgery for triple-vessel coronary artery disease 3 years ago. On examination, he was cheerful, accepting of his diagnosis, and had a performance status of 1. Treatment options and outcomes were discussed in detail with the patient and the family.

Treatment of Elderly Acute Lymphoblastic Leukemia: Curative or Palliative Intent?

Outcomes of ALL patients over the age of 60 years is poor with conventional chemotherapy. The SEER database showed a 3-year survival of 24% in 60 to 64-year-old patients. The SEER database showed a 3-year survival of 24% in 60–64-year-old patients, which dropped to 12% at 70–74 years and 8% in those between 75–79 years of age.⁵ The patient and family need to understand these bleak outcomes. CR after induction is achieved in less than half the patients, and a quarter may suffer early mortality.⁵¹ Though small studies have shown improvement in outcomes with more “intensive” regimens,⁵² these have not been consistently replicated.

We have a detailed discussion with older patients about the reality of the situation. The patient presented here had evident comorbidities which would limit delivery of intense chemotherapies. However, the family was insistent on trying whatever would be possible.

Case-3 Continued

The family wanted to consider some form of “curative” therapy despite understanding the risks. He started modified GMALL induction (steroids, $3 \times$ weekly doses of vincristine and one dose of daunorubicin). He had multiple complications (hyperglycemia, vincristine-induced ileus, and gram-negative sepsis), and required intensive care. Blood counts improved by week 5, and marrow on D35 was in remission. MRD assessment was not performed. The general condition had worsened considerably by this time, and the patient was deemed unfit for further intensive chemotherapy. He started an oral “maintenance” treatment with daily 6-mercaptopurine and weekly methotrexate.

Unfortunately, the disease relapsed after 5 months. The patient opted for home-based supportive care without further anticancer therapy.

The outcomes of relapsed ALL is dismal even with allogeneic transplantation. Some improvement in survival may be achieved with the newer agents like inotuzumab and blinatumomab. However, considering the costs involved in sourcing these newer agents, salvage therapies are not usually practical in these patients.

Improving Outcomes in Elderly Acute Lymphoblastic Leukemia with Targeted Treatments: The Future Looks Bright

The current approaches with conventional therapies are unlikely to make a huge difference in the outcomes of elderly ALL. Newer strategies with a combination of targeted agents and less-intense chemotherapy has shown benefit. Rituximab with GMALL protocol produced a modest 5-year OS of 23% in patients with ALL > 55 years of age.⁵³ Recent studies have shown improved outcomes in elderly ALL (short-term survival >50%) with the use of inotuzumab and blinatumomab.^{54,55} Ironically, the outcomes of Ph+ve ALL in the elderly may have improved due to the use of TKIs. Low-intensity chemotherapy with dasatinib produced a 5-year OS of 36% in a European study where the median age was 69 years.⁵⁶

Case 4: Adult with Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia

A 43-year-old male presented with a 4-week history of fatigue and intermittent fever; hemoglobin: $77 \times 10^9/L$ (7.7 g/dL), WBC: $85 \times 10^9/L$ ($85,000/mm^3$), and platelets: $48 \times 10^9/L$ ($48,000/mm^3$) with 88% blasts in peripheral smear. Bone marrow examination and flow cytometry confirmed the diagnosis of pre-B-ALL. Conventional karyotyping showed 46, XY with t(9;22) and peripheral blood was positive for BCR-ABL p190 transcripts. He was started on BFM-95 induction with dasatinib added on day 6 after the BCR-ABL report was available.

Ph+ve ALL accounts for approximately 25 to 30% of adult ALL and up to 50% of cases in older adults and the elderly.⁵⁷ The addition of TKIs to chemotherapy improves CR rates (90–100%) and the survival (38–54%) in adult Ph+ve ALL.^{58–62}

Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia which Tyrosine Kinase Inhibitors to Choose and How to Add the Tyrosine Kinase Inhibitors?

Dasatinib versus imatinib: there is no trial directly comparing dasatinib and imatinib for adult Ph+ve ALL. Cross-trial comparisons suggest that both produce similar CR after induction (>95%). However, dasatinib treated patients are more likely to achieve complete molecular responses at 3 months (complete molecular response at 65% with dasatinib vs. 30 to 45% with imatinib) and better central nervous system penetration.^{58,61,62} In children

with Ph+ve ALL, EFS (71 vs. 49%) and OS (88 vs. 69%) were superior with dasatinib when compared to imatinib.⁶³ Mutations may develop during TKI therapy and 75% of those with dasatinib resistance harbor the T315I mutation.⁵⁶ Ponatinib produces a high complete molecular remission rate (77%) and survival (3-year DFS of 79%) in newly diagnosed Ph+ALL, but is currently not marketed in India.⁶⁴ There is only one study with nilotinib in Ph+ve ALL, and it showed good activity.⁶⁵ Based on these results, and the recent availability of generics, we prefer to use dasatinib (start at 100 mg OD and increase to 140 mg OD if tolerated) in Ph+ALL. We may start at a lower dasatinib dose (70 mg) in patients with an active infection. TKI-resistant mutations, including T315I mutations, can occur during therapy and have been described even at baseline in Ph+ve ALL.⁵⁶ We don't perform mutation studies at baseline in Ph+ALL and do this testing only if the patients develop resistance.

Case-4 Continued

During induction, the patient had grade-4 neutropenia complicated by neutropenic sepsis and grade-2 mucositis which delayed the completion. Postinduction the bone marrow was in CR, and the patient was counseled for an alloSCT but there was no matched donor available. Post-first-phase consolidation, patient had a major molecular response (MMR). However, in the absence of a fully matched donor, he continued dasatinib with chemotherapy. Monitoring of his disease status is being done by quantitative BCR-ABL assessment by PCR once in 3 months.

Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia: Intensity of Chemotherapy

Several studies from Europe (GIMEMA, EWALL, PETHEMA, and GRALL) have shown that less intensive chemotherapy (steroids ± vincristine) combined with TKI (-imatinib/dasatinib) results in high CR rates (95–100%) and low induction mortality (<3%) in Ph+ve ALL.^{56,62,66–68} GRAAPH-2005 showed lesser mortality and comparable molecular responses with reduced intensity induction and imatinib (5-year OS [48.3 vs. 43%]).⁶² However, post-remission consolidation chemotherapy has to be continued, and allogeneic transplant must be considered in CR1, whenever feasible. We use reduced-intensity induction (steroid, vincristine, and dasatinib) in adult Ph+ve ALL, followed by the continuation of conventional consolidation and maintenance chemotherapy (with TKI in all phases) for those not planned for CR1 alloSCT. Since the optimal duration of TKI is not known, we choose to give it for at least 5 years.

What is the status of alloSCT in CR1 in Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia?

Pediatric studies have reported equivalent outcomes with chemotherapy plus TKI or alloSCT, but for adults, alloSCT

remains the standard.^{69,70} In the TKI era, an OS of 35 to 55% at 2 to 5 years has been achieved without alloSCT, but the OS increases to 60 to 70% when patients are allotransplanted in CR1.^{60,70} The best outcomes with alloSCT, are seen in a young fit patient with molecular remission following TKI-based induction and with a matched sibling donor or a fully matched unrelated donor. In older adults and in those with comorbidities, the risk of NRM negates the benefit of transplant. Even after alloSCT, continued TKI reduces relapses and must be started as soon as stable engraftment is achieved.⁷¹ Unresolved issues are: (1) Whether early CMR (at 3 months) can omit the alloSCT and do well with chemotherapy+TKI alone?, (2) whether the use of more potent third-generation TKI (ponatinib) will obviate the benefit of alloSCT?, and (3) can alloSCT overcome the negative prognostic impact of factors like high-risk genetics (*IKZF2* mutations, *T315I* mutation, and *CKND2A/2B* deletions) and persistent MRD?

Our practice offers CR1 alloSCT for all young and fit adult patients with Ph+ve ALL who have matched sibling donors who have achieved at least a major molecular response with induction therapy. We continue TKI maintenance therapy posttransplant for at least 5 years.

Case 5: Patient with Relapsed Acute Lymphoblastic Leukemia

A 30-year-old male was diagnosed with pre-B ALL 4 years ago and was treated at another center with GMALL protocol. He had achieved complete response by day 30 and marrow and completed intensive chemotherapy and maintenance 6 months back. He had recently noted petechial spots and had pancytopenia due to relapsed B-ALL. He had come to us for further management.

How to choose patients for salvage therapy in relapsed ALL?

The outcomes of relapsed is poor, with long-term survival of 7% reported from the large UKALL12/ ECOG 2993 study.⁷² However, among patients who were able to achieve CR2 with salvage, and allografted from an HLA-matched sibling, the outcome improved to approximately 23% in the same study. Other factors that determine better outcomes with salvage therapies are younger age and longer remission duration. Isolated nervous system or testicular relapses, or MRD–ve disease at the end of salvage chemotherapy will also predict better outcomes.^{73,74}

At our center, considering that there is limited availability of stem-cell transplant facilities and a long waitlist, we offer salvage for select patients (long treatment-free interval, and ability undergo alloSCT). Since intensive chemotherapy alone without consolidation allogeneic transplant is unlikely to cure relapsed ALL, we offer only palliative therapy for patients who are not planned for allogeneic transplantation. An important factor enabling the decision-making is the achievement of an MRD–ve CR2 status after salvage chemotherapy.

Case-5 Continued

We counseled the patient regarding treatment options. He achieved MRD–ve remission (CR2) after salvage with the FLAG (fludarabine, cytarabine, and granulocyte colony stimulating factor) regimen and received an allogeneic transplant from his fully matched sibling. He is currently in remission 6 months post alloSCT.

Optimum Salvage Regimens

Randomized trials have not compared the salvage regimens used in relapsed ALL. Wide variations have been reported in the responses with these regimens which have been extensively reviewed elsewhere.⁷⁵ About 40 to 50% of adults with relapsed ALL achieve CR2 after salvage. FLAG ± idarubicin is a popular option, especially in patients who have had early relapses. It is reasonable to use regimens containing steroids and/or L-asparaginase with high dose cytarabine like the UKALL and BFM relapse protocols in patients with late relapse. Hyper-CVAD is another option that produces >40% CR in relapsed ALL.⁷⁶

Newer drugs have significantly improved CR rates, MRD–ve rates, and survival in relapsed patients. Drugs like inotuzumab and blinatumomab have shown efficacy in large randomized trials and should be incorporated if a given patient can access these agents.^{54,77} Chimeric antigen receptor T cell therapy (CAR-T) is another radical strategy that has dramatically improved outcomes in relapsed ALL.⁷⁸

Key Take-Home Points

- For a newly diagnosed fit, young adult (<50 years), we prefer to use a “pediatric” regimen (→ Fig. 1).
- MRD assessment must be done at the end of induction, and intensification of therapy, and allogeneic transplant in CR1 must be considered for those who are MRD+ve (>0.01%)
- For Ph+ve ALL, induction therapy can consist of only vincristine, steroids, and TKI (dasatinib is preferred over imatinib). Consider alloSCT in CR1 whenever there is a fully matched donor available.
- Consider rituximab in CD20+ adult ALL.
- For the elderly ALL, outcomes are poor, and a clear discussion is essential before starting intensive chemotherapy regimens.
- Outcomes are poor in relapsed ALL and salvage therapy must be planned for selected patients when resources are limited. The following features predict better survival in relapsed disease: late relapse, good general condition, and achievement of MRD–ve status after salvage therapy. When these factors are not present, palliative treatment should be discussed
- Since optimum therapy of ALL requires very long-term commitment, appropriate strategies must be in place for social and psychological support to ensure adherence to treatment.

Funding

No external sources of funding

Conflicts of Interest

None of the authors have any relevant conflicts of interests to declare.

References

- 1 Pui C-H, Evans W EA 50-year journey to cure childhood acute lymphoblastic leukemia. *Semin Hematol* 2013;50(03):185–196
- 2 Schultz K R, Bowman W P, Aledo A, et al. Improved early event-free survival with imatinib in Philadelphia chromosome-positive acute lymphoblastic leukemia: a children's oncology group study. *J Clin Oncol* 2009;27(31):5175–5181
- 3 Lennmyr E, Karlsson K, Ahlberg L, et al. Swedish Adult Acute Lymphoblastic Leukaemia Group (SVALL). Survival in adult acute lymphoblastic leukaemia (ALL): A report from the Swedish ALL Registry. *Eur J Haematol* 2019;103(02):88–98
- 4 Stock W, Luger S M, Advani A S, et al. A pediatric regimen for older adolescents and young adults with acute lymphoblastic leukemia: results of CALGB 10403. *Blood* 2019;133(14):1548–1559
- 5 Geyer M B, Hsu M, Devlin S M, Tallman M S, Douer D, Park J H Overall survival among older US adults with ALL remains low despite modest improvement since 1980: SEER analysis. *Blood* 2017;129(13):1878–1881
- 6 DeAngelo D J, Jabbour E, Advani A. Recent advances in managing acute lymphoblastic leukemia. *Am Soc Clin Oncol Educ Book* 2020;40(40):330–342
- 7 Toft N, Birgens H, Abrahamsson J, et al. Results of NOPHO ALL2008 treatment for patients aged 1–45 years with acute lymphoblastic leukemia. *Leukemia* 2018;32(03):606–615
- 8 DeAngelo D J, Stevenson K E, Dahlberg S E, et al. Long-term outcome of a pediatric-inspired regimen used for adults aged 18–50 years with newly diagnosed acute lymphoblastic leukemia. *Leukemia* 2015;29(03):526–534
- 9 Huguet F, Leguay T, Raffoux E, et al. Pediatric-inspired therapy in adults with Philadelphia chromosome-negative acute lymphoblastic leukemia: the GRAALL-2003 study. *J Clin Oncol* 2009;27(06):911–918
- 10 Patel B, Kirkwood A A, Dey A, et al. Pegylated-asparaginase during induction therapy for adult acute lymphoblastic leukaemia: toxicity data from the UKALL14 trial. *Leukemia* 2017;31(01):58–64
- 11 Jain P, Korula A, Deshpande P, et al. Adult acute lymphoblastic leukemia: limitations of intensification of therapy in a developing country. *J Glob Oncol* 2018;4:1–12
- 12 Ganesan P, Sagar T G, Kannan K, et al. Acute lymphoblastic leukemia in young adults treated with intensive “pediatric” type protocol. *Indian J Hematol Blood Transfus* 2018;34(03):422–429
- 13 United Nations, Department of Economic and Social Affairs. The World Population Prospects: 2015 Revision. Available at: <https://www.un.org/en/development/desa/publications/world-population-prospects-2015-revision.html#:~:text=The%20current%20world%20population%20of,2015%20Revision%E2%80%9D%2C%20launched%20today>. Accessed June 18, 2021
- 14 Ganesan P, Jain H, Bagal B, et al. Outcomes in adolescent and young adult (AYA) acute lymphoblastic leukemia (ALL): a report from the Indian acute leukemia research database (INWARD) of the hematology cancer consortium (HCC). *Blood* 2019;134(01):1306
- 15 Philip C, George B, Ganapule A, et al. Acute myeloid leukaemia: challenges and real world data from India. *Br J Haematol* 2015;170(01):110–117
- 16 Biswal S, Godnaik C. Incidence and management of infections in patients with acute leukemia following chemotherapy in general wards. *Ecancermedalscience* 2013;7:310
- 17 Curran E, Stock W. How I treat acute lymphoblastic leukemia in older adolescents and young adults. *Blood* 2015;125(24):3702–3710

- 18 Rytting M E, Jabbour E J, O'Brien S M, Kantarjian H. Acute lymphoblastic leukemia in adolescents and young adults. *Cancer* 2017;123(13):2398–2403
- 19 Boissel N, Baruchel A. Acute lymphoblastic leukemia in adolescent and young adults: treat as adults or as children? *Blood* 2018;132(04):351–361
- 20 Möricke A, Reiter A, Zimmermann M, et al. German-Austrian-Swiss ALL-BFM Study Group. Risk-adjusted therapy of acute lymphoblastic leukemia can decrease treatment burden and improve survival: treatment results of 2169 unselected pediatric and adolescent patients enrolled in the trial ALL-BFM 95. *Blood* 2008;111(09):4477–4489
- 21 Muffly L, Alvarez E, Lichtensztajn D, Abrahão R, Gomez S L, Keegan T. Patterns of care and outcomes in adolescent and young adult acute lymphoblastic leukemia: a population-based study. *Blood Adv* 2018;02(08):895–903
- 22 Pui C H, Pei D, Sandlund J T, et al. Long-term results of St Jude Total Therapy Studies 11, 12, 13A, 13B, and 14 for childhood acute lymphoblastic leukemia. *Leukemia* 2010;24(02):371–382
- 23 Maury S, Chevret S, Thomas X, et al. Rituximab in B-lineage adult acute lymphoblastic leukemia. *N Engl J Med* 2016;375(11):1044–1053
- 24 Bhatia S, Landier W, Shangguan M, et al. Nonadherence to oral mercaptopurine and risk of relapse in Hispanic and non-Hispanic white children with acute lymphoblastic leukemia: a report from the children's oncology group. *J Clin Oncol* 2012;30(17):2094–2101
- 25 Malhotra P, Varma S, Varma N, et al. Outcome of adult acute lymphoblastic leukemia with BFM protocol in a resource-constrained setting. *Leuk Lymphoma* 2007;48(06):1173–1178
- 26 Jatia S, Prasad M, Paradkar A, et al. Holistic support coupled with prospective tracking reduces abandonment in childhood cancers: a report from India. *Pediatr Blood Cancer* 2019;66(06):e27716
- 27 Roy N Moulik, Kulkarni K P, Kumar A. Tracking children with acute lymphoblastic leukemia who abandoned therapy: experience, challenges, parental perspectives, and impact of treatment subsidies and intensified counseling. *Pediatr Hematol Oncol* 2016;33(05):327–337
- 28 Alam A, Kumar A. Impact of financial support and focussed group counselling on treatment abandonment in children with acute lymphoblastic leukaemia. Experience over 22 years from North India. *Psychooncology* 2019;28(02):372–378
- 29 Dores G M, Devesa S S, Curtis R E, Linet M S, Morton L M. Acute leukemia incidence and patient survival among children and adults in the United States, 2001–2007. *Blood* 2012;119(01):34–43
- 30 Marks D I, Paietta E M, Moorman A V, et al. T-cell acute lymphoblastic leukemia in adults: clinical features, immunophenotype, cytogenetics, and outcome from the large randomized prospective trial (UKALL XII/ECOG 2993). *Blood* 2009;114(25):5136–5145
- 31 Patrick K, Vora A. Update on biology and treatment of T-cell acute lymphoblastic leukaemia. *Curr Opin Pediatr* 2015;27(01):44–49
- 32 Patrick K, Wade R, Goulden N, et al. Improved outcome for children and young people with T-acute lymphoblastic leukaemia: results of the UKALL 2003 trial. *Blood* 2014;124(21):3702
- 33 Möricke A, Zimmermann M, Valsecchi M G, et al. Dexamethasone vs prednisone in induction treatment of pediatric ALL: results of the randomized trial AIEOP-BFM ALL 2000. *Blood* 2016;127(17):2101–2112
- 34 Litzow M R, Ferrando A A. How I treat T-cell acute lymphoblastic leukemia in adults. *Blood* 2015;126(07):833–841
- 35 Hoelzer D, Thiel E, Arnold R, et al. Successful subtype oriented treatment strategies in adult T-ALL; results of 744 patients treated in three consecutive GMALL studies. *Blood* 2009;114:324
- 36 Raetz E A, Teachey D T. T-cell acute lymphoblastic leukemia. *Hematology (Am Soc Hematol Educ Program)* 2016;2016(01):580–588
- 37 Arya L S, Padmanjali K S, Sazawal S, et al. Childhood T-lineage acute lymphoblastic leukemia: management and outcome at a tertiary care center in North India. *Indian Pediatr* 2011;48(10):785–790
- 38 Della Starza I, Chiaretti S, De Propriis M S, et al. Minimal residual disease in acute lymphoblastic leukemia: technical and clinical advances. *Front Oncol* 2019;09(726):726
- 39 Ribera J M, Oriol A, Morgades M, et al. Treatment of high-risk Philadelphia chromosome-negative acute lymphoblastic leukemia in adolescents and adults according to early cytologic response and minimal residual disease after consolidation assessed by flow cytometry: final results of the PETHEMA ALL-AR-03 trial. *J Clin Oncol* 2014;32(15):1595–1604
- 40 Dhédin N, Huynh A, Maury S, et al. GRAALL group. Role of allogeneic stem cell transplantation in adult patients with Ph-negative acute lymphoblastic leukemia. *Blood* 2015;125(16):2486–2496
- 41 Goldstone A H, Richards S M, Lazarus H M, et al. In adults with standard-risk acute lymphoblastic leukemia, the greatest benefit is achieved from a matched sibling allogeneic transplantation in first complete remission, and an autologous transplantation is less effective than conventional consolidation/maintenance chemotherapy in all patients: final results of the International ALL trial (MRC UKALL XII/ECOG E2993). *Blood* 2008;111(04):1827–1833
- 42 El F akih R, Ahmed S, Alfraih F, Hanbali A. Hematopoietic cell transplantation for acute lymphoblastic leukemia in adult patients. *Hematol Oncol Stem Cell Ther* 2017;10(04):252–258
- 43 Giebel S, Marks D I, Boissel N, et al. Hematopoietic stem cell transplantation for adults with Philadelphia chromosome-negative acute lymphoblastic leukemia in first remission: a position statement of the European Working Group for Adult Acute Lymphoblastic Leukemia (EWALL) and the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation (EBMT). *Bone Marrow Transplant* 2019;54(06):798–809
- 44 Abdelaty M M, Gawaly A, Fathy G M, Kabbash I, Taha A. Irradiation free conditioning regimen is associated with high relapse rate in Egyptian patients with acute lymphoblastic leukemia following allogeneic hematopoietic stem cell transplantation. *J Egypt Natl Canc Inst* 2020;32(01):28
- 45 Park H, Byun J M, Koh Y, et al. Comparison of different conditioning regimens in allogeneic hematopoietic stem-cell transplantation shows superiority of total body irradiation-based regimen for younger patients with acute leukemia: a nationwide study. *Clin Lymphoma Myeloma Leuk* 2019;19(11):e605–e615
- 46 Gökbuğet N, Kneba M, Raff T, et al. German Multicenter Study Group for Adult Acute Lymphoblastic Leukemia. Adult patients with acute lymphoblastic leukemia and molecular failure display a poor prognosis and are candidates for stem cell transplantation and targeted therapies. *Blood* 2012;120(09):1868–1876
- 47 Jain N, Lamb A V, O'Brien S, et al. Early T-cell precursor acute lymphoblastic leukemia/lymphoma (ETP-ALL/LBL) in adolescents and adults: a high-risk subtype. *Blood* 2016;127(15):1863–1869
- 48 Haydu J E, Ferrando A A. Early T-cell precursor acute lymphoblastic leukaemia. *Curr Opin Hematol* 2013;20(04):369–373
- 49 Wood B L, Winter S S, Dunsmore K P, et al. T-lymphoblastic leukemia (T-ALL) shows excellent outcome, lack of significance of the early thymic precursor (ETP) immunophenotype, and validation of the prognostic value of end-induction minimal residual disease (MRD) in Children's Oncology Group (COG) study AALL0434. *Blood* 2014;124(21):1
- 50 Shah B D, Borate U, Kota V K, et al. Multi-institution review of adult early T-cell precursor acute lymphoblastic leukemia/lymphoma (ETP-ALL). *Blood* 2015;126(23):3715
- 51 Gökbuğet N. How I treat older patients with ALL. *Blood* 2013;122(08):1366–1375

- 52 Ribera J M, García O, Gil C, et al. PETHEMA Group. Comparison of intensive, pediatric-inspired therapy with non-intensive therapy in older adults aged 55-65 years with Philadelphia chromosome-negative acute lymphoblastic leukemia. *Leuk Res* 2018;68:79-84
- 53 Goekbuget N, Beck J, Brueggemann M, et al. Moderate intensive chemotherapy including CNS-prophylaxis with liposomal cytarabine is feasible and effective in older patients with Ph-negative acute lymphoblastic leukemia (ALL): results of a prospective trial from the German multicenter study group for adult ALL (GMALL. *Blood* 2012;120(21):1493
- 54 Kantarjian H, Ravandi F, Short N J, et al. Inotuzumab ozogamicin in combination with low-intensity chemotherapy for older patients with Philadelphia chromosome-negative acute lymphoblastic leukaemia: a single-arm, phase 2 study. *Lancet Oncol* 2018;19(02):240-248
- 55 Advani A S, Moseley A, O'Dwyer K M, et al. Results of SWOG 1318: a phase 2 trial of blinatumomab followed by pomp (prednisone, vincristine, methotrexate, 6-mercaptopurine) maintenance in elderly patients with newly diagnosed Philadelphia chromosome negative B-cell acute lymphoblastic leukemia. *Blood* 2018;132(01):33
- 56 Rousselot P, Coudé M M, Gokbuget N, et al. European Working Group on Adult ALL (EWALL) group. Dasatinib and low-intensity chemotherapy in elderly patients with Philadelphia chromosome-positive ALL. *Blood* 2016;128(06):774-782
- 57 Secker-Walker L M, Craig J M, Hawkins J M, Hoffbrand A V Philadelphia positive acute lymphoblastic leukemia in adults: age distribution, BCR breakpoint and prognostic significance. *Leukemia* 1991;5(03):196-199
- 58 Daver N, Thomas D, Ravandi F, et al. Final report of a phase II study of imatinib mesylate with hyper-CVAD for the front-line treatment of adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. *Haematologica* 2015;100(05):653-661
- 59 Lim S N, Joo Y D, Lee K H, et al. Long-term follow-up of imatinib plus combination chemotherapy in patients with newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia. *Am J Hematol* 2015;90(11):1013-1020
- 60 Bassan R, Rossi G, Pogliani E M, et al. Chemotherapy-phased imatinib pulses improve long-term outcome of adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia: Northern Italy leukemia group protocol 09/00. *J Clin Oncol* 2010;28(22):3644-3652
- 61 Ravandi F, O'Brien S M, Cortes J E, et al. Long-term follow-up of a phase 2 study of chemotherapy plus dasatinib for the initial treatment of patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. *Cancer* 2015;121(23):4158-4164
- 62 Chalandon Y, Thomas X, Hayette S, et al. Group for Research on Adult Acute Lymphoblastic Leukemia (GRAALL). Randomized study of reduced-intensity chemotherapy combined with imatinib in adults with Ph-positive acute lymphoblastic leukemia. *Blood* 2015;125(24):3711-3719
- 63 Shen S, Chen X, Cai J, et al. Effect of dasatinib vs imatinib in the treatment of pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia: a randomized clinical trial. *JAMA Oncol* 2020;6(03):358-366
- 64 Jabbour E, Kantarjian H, Ravandi F, et al. Combination of hyper-CVAD with ponatinib as first-line therapy for patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia: a single-centre, phase 2 study. *Lancet Oncol* 2015;16(15):1547-1555
- 65 Kim D Y, Joo Y D, Lim S N, et al. Adult Acute Lymphoblastic Leukemia Working Party of the Korean Society of Hematology. Nilotinib combined with multiagent chemotherapy for newly diagnosed Philadelphia-positive acute lymphoblastic leukemia. *Blood* 2015;126(06):746-756
- 66 Ribera J M, García O, Montesinos P, et al. Treatment of young patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia using increased dose of imatinib and deintensified chemotherapy before allogeneic stem cell transplantation. *Br J Haematol* 2012;159(01):78-81
- 67 Vignetti M, Fazi P, Cimino G, et al. Imatinib plus steroids induces complete remissions and prolonged survival in elderly Philadelphia chromosome-positive patients with acute lymphoblastic leukemia without additional chemotherapy: results of the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) LAL0201-B protocol. *Blood* 2007;109(09):3676-3678
- 68 Rea D, Legros L, Raffoux E, et al. Intergroupe Français des Leucémies Myéloïdes Chronique; Group for Research in Adult Acute Lymphoblastic Leukemia. High-dose imatinib mesylate combined with vincristine and dexamethasone (DIV regimen) as induction therapy in patients with resistant Philadelphia-positive acute lymphoblastic leukemia and lymphoid blast crisis of chronic myeloid leukemia. *Leukemia* 2006;20(03):400-403
- 69 Schultz K R, Carroll A, Heerema N A, et al. Children's Oncology Group. Long-term follow-up of imatinib in pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia: children's oncology group study AALL0031. *Leukemia* 2014;28(07):1467-1471
- 70 Fielding A K, Rowe J M, Buck G, et al. UKALLXII/ECOG2993: addition of imatinib to a standard treatment regimen enhances long-term outcomes in Philadelphia positive acute lymphoblastic leukemia. *Blood* 2014;123(06):843-850
- 71 Giebel S, Czyz A, Ottmann O, et al. Use of tyrosine kinase inhibitors to prevent relapse after allogeneic hematopoietic stem cell transplantation for patients with Philadelphia chromosome-positive acute lymphoblastic leukemia: a position statement of the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation. *Cancer* 2016;122(19):2941-2951
- 72 Fielding A K, Richards S M, Chopra R, et al. Medical Research Council of the United Kingdom Adult ALL Working Party Eastern Cooperative Oncology Group. Outcome of 609 adults after relapse of acute lymphoblastic leukemia (ALL); an MRC UKALL12/ECOG 2993 study. *Blood* 2007;109(03):944-950
- 73 Locatelli F, Schrappe M, Bernardo M E, Rutella S. How I treat relapsed childhood acute lymphoblastic leukemia. *Blood* 2012;120(14):2807-2816
- 74 Gökbuget N, Stanze D, Beck J, et al. German Multicenter Study Group for Adult Acute Lymphoblastic Leukemia. Outcome of relapsed adult lymphoblastic leukemia depends on response to salvage chemotherapy, prognostic factors, and performance of stem cell transplantation. *Blood* 2012;120(10):2032-2041
- 75 Frey N V, Luger S M How I treat adults with relapsed or refractory Philadelphia chromosome-negative acute lymphoblastic leukemia. *Blood* 2015;126(05):589-596
- 76 Faderl S, Thomas D A, O'Brien S, et al. Augmented hyper-CVAD based on dose-intensified vincristine, dexamethasone, and asparaginase in adult acute lymphoblastic leukemia salvage therapy. *Clin Lymphoma Myeloma Leuk* 2011;11(01):54-59
- 77 Kantarjian H, Stein A, Gökbuget N, et al. Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. *N Engl J Med* 2017;376(09):836-847
- 78 Park J H, Rivière I, Gonen M, et al. Long-term follow-up of CD19 CAR therapy in acute lymphoblastic leukemia. *N Engl J Med* 2018;378(05):449-459
- 79 Abraham A, George B, Ahmed R, et al. Outcome of treatment with a low cost protocol in adults with T cell acute lymphoblastic leukemia in a tertiary care center in India. *Leuk Lymphoma* 2014;55(04):947-949
- 80 Ganesan P, Jain H, Bagal B, et al. Outcomes in adolescent and young adult acute lymphoblastic leukaemia: a report from the Indian Acute Leukaemia Research Database (INWARD) of the Hematology Cancer Consortium (HCC. *Br J Haematol* 2021;193(01):e1-e4

- 81 Rajendra A, Jain H, Bonda V NA, et al. Outcomes and prognostic factors in adolescents and young adults with ALL treated with a modified BFM-90 protocol. *Blood Adv* 2021;5(05):1178–1193
- 82 Agrawal N, Verma P, Yadav N, et al. Outcome of Philadelphia positive acute lymphoblastic leukemia with or without allogeneic stem cell transplantation in a retrospective study. *Indian J Hematol Blood Transfus* 2019;35(02):240–247
- 83 Dangi U, Senagar M, Menon H. Treatment outcomes in Ph+ALL- a single center experience. *Indian J Hematol Blood Transfus* 2013; 29(04):274–400