



# How I Treat Adult Acute Lymphoblastic Leukemia in India

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## Introduction

Survival in pediatric acute lymphoblastic leukemia (ALL) has improved from less than 10% (in the 1960s) to over 90% in developed countries.<sup>1</sup> 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.<sup>2</sup> 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%).<sup>3,4</sup> 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.<sup>3,5</sup>

Adverse disease biology partly explains the drop in survival with age.<sup>6</sup> 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.<sup>7,8</sup> However, these regimens have increased toxicity and treatment-related mortality (TRM), especially in older individuals and “real-world” patients.<sup>9–12</sup> India has the highest population of adolescent and young adults globally, and most centers see a significant proportion of patients in this age group.<sup>13,14</sup> Indian centers report a high incidence of

infectious complications (including multidrug resistant bacterial infections) during delivery of intense therapies for acute leukemias.<sup>15,16</sup> Even if minimal residual disease (MRD) assessment is done, there is limited access to stem cell transplantation.<sup>14</sup> 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/mm<sup>3</sup>), and platelets:  $34 \times 10^9/L$  (34,000/mm<sup>3</sup>). 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

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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).<sup>17–19</sup> 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 × 10<sup>9</sup>/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.<sup>20</sup> Previous studies from India (–Table 2) have reported 40 to 60% survival among AYA ALL treated with this protocol.<sup>12,14</sup> 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.<sup>11,14</sup> Concerns about toxicities remain and, even in developed countries, a quarter of AYA patients are treated with “adult” protocols.<sup>21</sup>

### 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.<sup>22</sup> 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.<sup>4</sup> 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).<sup>23</sup>

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.<sup>11,14,24,25</sup> 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%.<sup>12</sup> 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.<sup>26–28</sup>

### 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 × 10<sup>9</sup>/L (10 g/dL), WBC count: 112 × 10<sup>9</sup>/L (112,000/mm<sup>3</sup>), and platelet counts: 98 × 10<sup>9</sup>/L (98,000/mm<sup>3</sup>). 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.<sup>29,30</sup> T-ALL is more likely to have higher white cell count, mediastinal enlargement, and CNS involvement.<sup>31–33</sup> 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.<sup>34,35</sup> 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<br>Dexamethasone > prednisolone  | Lesser doses overall  | Prednisolone<br>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<br>Some pediatric protocols do not cap at 2 mg  | Capped at 2 mg per dose<br>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 <sup>2</sup> easily delivered<br>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 <sup>2</sup> dose for pre-B ALL and 5 g/m <sup>2</sup> 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<br>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<br>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%.<sup>36</sup> 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.<sup>25,37</sup> 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.<sup>38</sup> 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 <sup>25</sup> | Chandigarh | 118 | >12                        | Modified BFM                | 29 (3)   | NR    |
|                 | 1995–2009 | CMC <sup>79</sup>    | Vellore    | 113 | 15–60                      | Modified GMALL <sup>a</sup> | 51 (5)   | 51(5) |
|                 | 2000–2013 | CI(14)               | Chennai    | 232 | 21 (18–30)                 | BFM and GMALL               | 36 (5)   | 39(5) |
|                 | 2012–2018 | HCC <sup>80</sup>    | Multiple   | 572 | 21 (15–29)                 | Multiple <sup>b</sup>       | 56 (2)   | 73(2) |
|                 | 2013–2016 | TMH <sup>81</sup>    | Mumbai     | 349 | 15–25                      | BFM                         | 59 (3)   | 61(3) |
| PH-positive ALL | 2011–2016 | RGCI <sup>82</sup>   | New Delhi  | 63  | 35 (14–76)                 | COG/UKALL <sup>c</sup>      | 31 (4)   | 46(4) |
|                 | 2009–2012 | TMH <sup>83</sup>    | Mumbai     | 65  | 28 (15–53)                 | MCP/BFM/other <sup>e</sup>  | 30 (2)   | 29(2) |
|                 | 2012–2017 | HCC <sup>80</sup>    | Multiple   | 158 | 21(15–29)                  | Multiple <sup>b,d</sup>     | 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.

<sup>a</sup>Only T-cell ALL were analyzed in this study.

<sup>b</sup>Pediatric (87%), adult (13%); BFM (74%), COG (8.5%), MCP-841 (3.7%), GMALL (10.4%), hyper-CVAD (2.3%), and others (1%).

<sup>c</sup>Imatinib till 2021, then dasatinib; alloSCT in 16 patients; and EFS was superior with alloSCT (36 vs. 27%).

<sup>d</sup>Imatinib, 83% and dasatinib, 17%.

unresolved.<sup>39,40</sup> 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.<sup>41</sup> 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).<sup>42</sup>

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.<sup>43</sup>

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.<sup>44,45</sup> 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%.<sup>46</sup> 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<sup>+</sup>, sCD3<sup>–</sup>, CD1a<sup>–</sup>, CD2<sup>+</sup>, CD7<sup>+</sup>, CD8<sup>–</sup>, CD5 dim, and positivity for stem cell and myeloid markers, including HLA-DR, CD13, CD33, CD34, or CD117).<sup>47,48</sup> 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

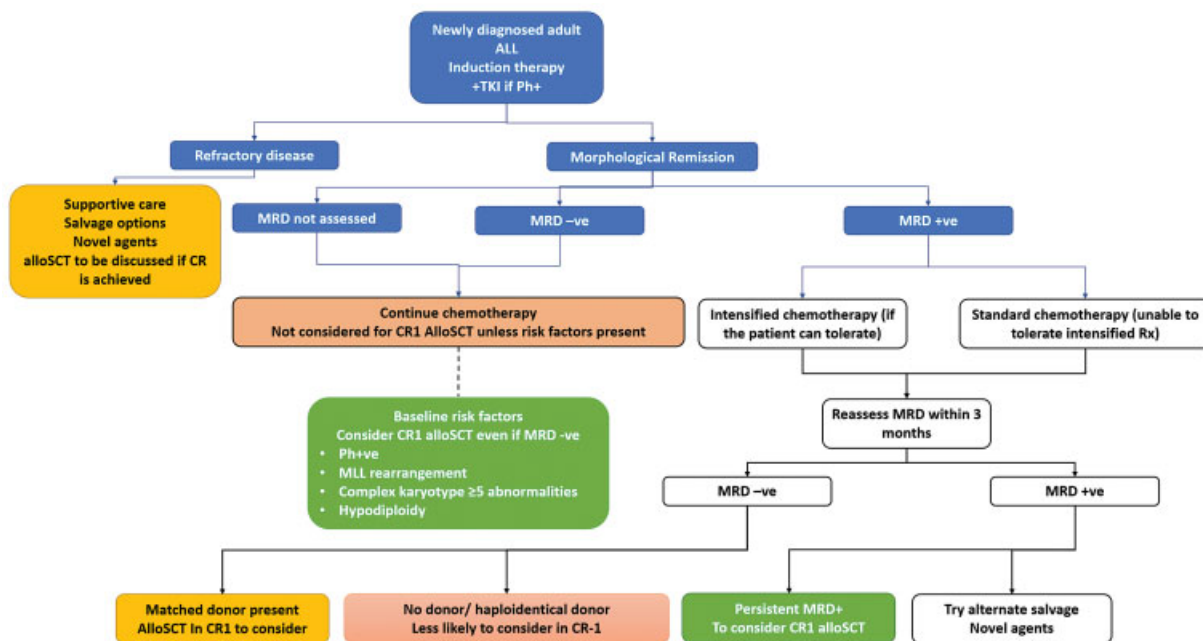
| Factor                  | Strongly consider alloSCT in CR1 <sup>a</sup> (Green)   | Discuss the option of alloSCT in CR1 <sup>b</sup> (Yellow) | AlloSCT in CR1 not to be considered (Red) |
|-------------------------|---|--|---|
| Baseline risk factors   | Ph+ve disease<br>MLL rearrangements<br>Complex karyotype  | ETP ALL<br>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"> <li>Committed patient and family</li> <li>Finances available</li> <li>Able to stay in local place for 6–12 months</li> </ul> | 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.

<sup>a</sup>In 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.

<sup>b</sup>In 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).<sup>35,49</sup> The use of L-asparaginase may be important; hence “pediatric” type protocols may be preferred for ETP ALL over protocols such as hyper-CVAD.<sup>50</sup> 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.<sup>5</sup> 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.<sup>51</sup> Though small studies have shown improvement in outcomes with more “intensive” regimens,<sup>52</sup> 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.<sup>53</sup> Recent studies have shown improved outcomes in elderly ALL (short-term survival >50%) with the use of inotuzumab and blinatumomab.<sup>54,55</sup> 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.<sup>56</sup>

### 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.<sup>57</sup> The addition of TKIs to chemotherapy improves CR rates (90–100%) and the survival (38–54%) in adult Ph+ve ALL.<sup>58–62</sup>

#### 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.<sup>58,61,62</sup> In children

with Ph+ve ALL, EFS (71 vs. 49%) and OS (88 vs. 69%) were superior with dasatinib when compared to imatinib.<sup>63</sup> Mutations may develop during TKI therapy and 75% of those with dasatinib resistance harbor the T315I mutation.<sup>56</sup> 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.<sup>64</sup> There is only one study with nilotinib in Ph+ve ALL, and it showed good activity.<sup>65</sup> 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.<sup>56</sup> 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.<sup>56,62,66–68</sup> GRAAPH-2005 showed lesser mortality and comparable molecular responses with reduced intensity induction and imatinib (5-year OS [48.3 vs. 43%]).<sup>62</sup> 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.<sup>69,70</sup> 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.<sup>60,70</sup> 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.<sup>71</sup> 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.<sup>72</sup> 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.<sup>73,74</sup>

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 allogenic 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.<sup>75</sup> 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.<sup>76</sup>

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.<sup>54,77</sup> Chimeric antigen receptor T cell therapy (CAR-T) is another radical strategy that has dramatically improved outcomes in relapsed ALL.<sup>78</sup>

### 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 allogenic 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.

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

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