How I treat acute lymphoblastic leukemia in older adolescents and young adults

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At the intersection between children and older adults, the care of adolescent and young adult (AYA) patients with acute lymphoblastic leukemia (ALL) poses unique challenges and issues beyond those faced by other age groups. Although the survival of AYA patients is inferior to younger children, growing evidence suggests that AYAs may have improved outcomes, with disease-free survival rates of 60% to 70%, when treated with pediatric-based approaches. A holistic approach, incorporating a multidisciplinary team, is a key component of successful treatment of these AYA patients. With the appropriate support and management of toxicities during and following treatment, these regimens are well tolerated in the AYA population. Even with the significant progress that has been made during the last decade, patients with persistence of minimal residual disease (MRD) during intensive therapy still have a poor prognosis. With new insights into disease pathogenesis in AYA ALL and the availability of disease-specific kinase inhibitors and novel targeted antibodies, future studies will focus on individualized therapy to eradicate MRD and result in further improvements in survival. This case-based review will discuss the biology, pharmacology, and psychosocial aspects of AYA patients with ALL, highlighting our current approach to the management of these unique patients. (Blood. 2015;125(24):3702-3710)

Introduction

Acute lymphoblastic leukemia (ALL), a relatively rare malignancy, is one of the few cancers that impacts the entire lifespan, from neonates to the very elderly. Although survival now approaches 90% for most children with ALL, older adolescents and young adults (AYAs) historically have a much poorer prognosis, with an event-free survival (EFS) of only 30% to 45%. Factors accounting for differences in outcome include heterogeneity in disease biology, host factors (both physiologic and psychosocial), and importantly, the therapeutic approach and experience of the health care teams. Some authors also suggest that AYAs may have had poorer outcomes, in part, because of low rates of clinical trial enrollment. Between 1997 and 2003, fewer than 2% of older adolescents were enrolled in clinical trials, compared with 60% of pediatric patients, potentially due to fewer referrals to institutions where clinical trials are offered, limited numbers of clinical trials available for the AYA population, and psychosocial barriers.

During the last decade, recognition of the unique characteristics of AYAs with ALL, as well as a new focus on clinical research designed specifically for this population, has led to exciting improvements in treatment outcomes, with EFS now approaching 70% for AYA ALL. The National Cancer Institute has defined the AYA cancer population broadly as being between the ages of 15 to 39 years old. Although tremendous heterogeneity in this population clearly exists, and the age cutoff of 40 years is somewhat arbitrarily defined, emerging clinical, psychosocial, and biologic features of the disease suggest this may be a distinct population. This case-based review will focus on the AYA population most commonly treated by adult hematologists-oncologists, ie, patients aged 18 to 39 years old.

Patient 1

A 28-year-old man presents with night sweats, fatigue, palpitations, and abdominal pain. He is found to have a white blood cell count of 23 × 10⁹/L and bulky organomegaly. Bone marrow (BM) biopsy is consistent with precursor B-cell ALL (CD19+, CD20+, CD10+, CD22+, CD79α+, CD34+, and TdT+). Fluorescence in situ hybridization (FISH) is negative for MLL rearrangement, BCR/ABL1, ETV6/ RUNX1, and trisomies 4, 10, and 17. Cytogenetics shows a normal male karyotype.

What is our approach? If available, we would encourage enrollment onto a clinical trial focused on AYAs with ALL that builds upon an intensive pediatric approach to treatment.

Rationale

Treatment approaches for AYAs with ALL vary considerably, with the choice of regimen predicated on the familiarity and expertise of the treating physician, the availability of a clinical trial, and most importantly, the “door” that the patient enters, namely whether entry is into a pediatric or an adult treatment center. In the United Kingdom, AYA inpatient treatment units already exist and this may facilitate a more uniform treatment approach. However, in the United States, patients younger than 18 years of age are traditionally treated in pediatric departments, whereas AYAs older than 18 years of age are treated by adult hematologists/oncologists and therefore receive “adult” ALL regimens. These “adult” regimens typically consist of intensive use of myelosuppressive agents including daunorubicin, cytarabine, and cyclophosphamide, as well as allogeneic stem cell transplantation (SCT) in first remission. In contrast, pediatric regimens focus on the Berlin-Frankfurt-Munster (BFM) backbone of ALL therapy: glucocorticoids, vincristine, asparaginase, early and frequent central nervous system (CNS) prophylaxis, and prolonged maintenance therapy. Retrospective studies from large North American and European groups suggest that AYAs have superior outcomes when treated with “pediatric” regimens, and may approach those of younger children, with 5-year EFS of over 70%.
Below, we recommend that AYA patients be treated on a pediatric-based regimen.

Encouraging survival outcomes for AYAs with ALL treated with “pediatric-inspired” regimens have recently been reported from a number of prospective cooperative group clinical trials performed in Europe and the United States. These trials showed an improvement in both EFS and overall survival (OS) compared with historical controls, with >60% EFS and OS in the majority of studies. Both retrospective and prospective studies have included both B- and T-cell ALL, with quite similar EFS and OS. Importantly, although some groups have noted slightly poorer tolerability, and certain toxicities (such as hepatotoxicity) may be more common in an older population, overall these regimens have demonstrated feasibility in the AYA population. Several of these trials and regimens are outlined in Table 1 and also reviewed in a recent meta-analysis.

The largest prospective study to evaluate the feasibility of a pediatric regimen in AYA ALL patients is the US intergroup study, C10403. Between November 2007 and December 2012, 318 AYAs between 16 and 39 years of age were treated based on the standard arm of the Children’s Oncology Group (COG) regimen (ALL0232). This study demonstrated that toxicities were manageable, with low treatment-related mortality (3%), and that treatment with this pediatric regimen is feasible when administered by an adult hematologist/oncologist to an AYA population up to 40 years of age. On this regimen, the 2-year EFS and OS were 66% and 78%, respectively. Based on these very encouraging early results, the US cooperative groups are now designing a successor study using the C10403 platform that will attempt to incorporate novel targeted agents to further improve treatment outcomes.

Although the majority of recent studies demonstrate a survival benefit using intensive pediatric regimens for AYA, another recently published comparison study of an “adult” regimen (hyper-CVAD) vs a pediatric regimen (BFM-like) found equivalent EFS (~70%). Because this trial was conducted at an institution with a large, experienced leukemia program, the results may not be widely generalizable but suggest that high-volume referral centers may offer benefits beyond chemotherapeutics. In fact, recent data show that outcomes for AYAs with ALL are significantly improved if treatment is administered at a university or National Cancer Institute-sponsored cancer center with expertise in the complex regimens used to treat ALL.

Treating AYA patients with pediatric-based regimens has resulted in impressive increases in EFS from 39% to up to 70%. However, further progress is still needed. Several novel agents that have shown impressive activity for relapsed/refractory disease are being evaluated in the frontline setting and will be included in the next generation of prospective clinical trials for AYAs with ALL. For instance, inotuzumab ozogamicin, a CD22 monoclonal antibody bound to calicheamicin, appears to be safe and active in relapsed/refractory ALL, with response rates of 58% to 82% in recent clinical trials. Blinatumomab, a bispecific T-cell engaging antibody that directs cytotoxic T cells to CD19-expressing target cells, had a 43% response rate in Ph-negative relapsed/refractory precursor B-cell ALL, and recently received US Food and Drug Administration (FDA) approval in relapsed disease. Incorporating these agents into frontline chemotherapy will hopefully help to eradicate minimal residual disease (MRD) and result in further improved survival for AYA patients. Blinatumomab is being added to frontline therapy in an ongoing trial for adults with ALL aged 30 to 70 years (NCT02003222) and a National Cancer Institute-approved study in the AYA population (aged 18 to 39 years) will test the addition of inotuzumab ozogamicin to the C10403 backbone.

Patient 1 (continued)

This patient is started on induction chemotherapy according to the C10403 protocol.

What prevention and monitoring should be performed in this patient during induction therapy?

We recommend administering induction therapy as an inpatient until neutrophil recovery. Early treatment toxicities, including febrile neutropenia, hyperglycemia, and hepatic toxicity occur commonly during induction (typically days 10 to 20) and can be more safely managed with close inpatient observation. We also treat with allopurinol for the first 10 days of induction therapy to prevent hyperuricemia. Following induction therapy, the remainder of treatment can be safely administered as an outpatient.

For antimicrobial prophylaxis, we recommend antiviral (acyclovir) and pneumocystis jiroveci pneumonia prophylaxis (typically trimethoprim-sulfamethoxazole) throughout treatment (including maintenance therapy), keeping in mind that no sulfad drug or non-steroidal anti-inflammatory medications should be given on the days that the patient receives methotrexate. Fungal prophylaxis should include mold coverage during induction therapy. However, broader spectrum azole antifungals cannot be used with vincristine because of the risk of exacerbating vincristine-induced peripheral neuropathy. Therefore, we typically use an echinocandin such as micafungin for prophylaxis during induction and switch to fluconazole for outpatient management during consolidation therapy.

Asparaginase-related toxicities are a challenge when intensive pediatric-inspired regimens are used in the AYA population. The only asparaginase preparation available in North America for frontline ALL therapy is a long-acting pegylated form of asparaginase, or PEG-asp. Little is known about the pharmacokinetics of PEG-asp in AYAs or older adults with ALL. A dose of 2500 IU/m² PEG-asp, which was used in both the COG ALL0232 and the C10403 trials, appears to result in greater hepatic toxicity in the AYA population, particularly during induction chemotherapy; thus, we and others have routinely begun to cap the dose at one vial, or 3750 IU. New methods for safer and more accurate dosing of PEG-asp are available, including a recently FDA-approved assay for measurement of asparaginase activity levels. Pediatric studies have demonstrated that achievement of asparaginase levels of greater than 100U/L for 14 days following a dose of PEG-asp is associated with improved treatment outcomes. Our group and others have begun to prospectively test the use of lower initial doses of PEG-asp with subsequent dose adjustment, if necessary, to achieve adequate (but not excessive) asparaginase levels. Although we are hopeful that level-based dose adjustment may facilitate the safe use of PEG-asp in AYAs, prospective clinical trials are required to validate this hypothesis. Importantly, asparaginase activity levels allow for detection of “silent” inactivation, which may occur without clinical symptoms in up to one-tenth of patients, as a result of antibody neutralization of asparaginase. Switching asparaginase preparations when silent inactivation occurred resulted in improved EFS in a pediatric population.

Asparaginase-related hypersensitivity reactions occur in as many as 20% of children and adults. Therefore, we routinely premedicate our patients with diphenhydramine, hydrocortisone, and acetaminophen prior to each dose of PEG-asp. In C10403, we found that...
<table>
<thead>
<tr>
<th>Patient population</th>
<th>ALL-96 (PETHEMA)</th>
<th>DFCI Adult ALL 01-175</th>
<th>C10403</th>
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</thead>
<tbody>
<tr>
<td><strong>Number of patients</strong></td>
<td>81</td>
<td>92</td>
<td>318</td>
</tr>
<tr>
<td><strong>Median age at diagnosis (range)</strong></td>
<td>20 years (15-30)</td>
<td>28 years (18-50)</td>
<td>24 years (17-39)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>Male: 62%</td>
<td>Male: 61%</td>
<td>Male: 61%</td>
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<tr>
<td><strong>Immunophenotype</strong></td>
<td>Precursor B- and T-cell ALL</td>
<td>Precursor B cell (80%) and precursor T cell (20%)</td>
<td>Precursor B cell (76%) and precursor T cell (24%)</td>
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<tr>
<th>Regimen</th>
<th>ALL-96 (PETHEMA)</th>
<th>DFCI Adult ALL 01-175</th>
<th>C10403</th>
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<tbody>
<tr>
<td><strong>Induction</strong></td>
<td>Vincristine: 2 mg IV (d 1, 8, 15, 22) Daunorubicin: 30 mg/m² IV (d 1, 8, 15, 22) Prednisone: 60 mg/m² (d 1-27), 30 mg/m² (d 28-35) PO/IV Asparaginase: 10000 U/m² IV, (d 10-12, 17-19, 24-26) Cyclophosphamide: 1000 mg/m² (d 36)</td>
<td>Vincristine: 2 mg IV (d 1, 8, 15, 22) Daunorubicin: 30 mg/m² IV (d 1, 2) Prednisone: 40 mg/m² PO (d 1-28) Methotrexate: 4 g/m² IV (d 3, 8 to 24 after daunorubicin) E coli L-asparaginase 25000 IU/m² IV (d 5)</td>
<td>Vincristine: 1.5 mg/m² - maximum 2 mg IV (d 1, 8, 15, 22) Daunorubicin: 25 mg/m² IV (d 1, 8, 15, 22) Prednisone: 60 mg/m² PO/IV (d 1-28) PEG-asparaginase: 2500 IU/m² IM/IV (d 4) Updated remission induction (2 wk) administered if failure to achieve morphologic remission on d 29 bone marrow biopsy</td>
</tr>
<tr>
<td><strong>Consolidation-1/intensification</strong></td>
<td>Methotrexate: 30 mg/m² IV (d 1, 2, 8, 11, 21, 31, 41)</td>
<td>Methotrexate: 30 mg/m² IV/IM weekly</td>
<td>Methotrexate: 100 mg/m² IV starting, with dose escalation (d 1, 11, 21, 31, 41)</td>
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<tr>
<td><strong>Consolidation-2/interim maintenance</strong></td>
<td>Dexamethasone: 18 mg/m² PO (d 1-5)</td>
<td>Mercaptopurine: 50 mg/m² PO (d 1-14)</td>
<td>PEG-as: 2500 IU/m² IMIV (d 15, 43)</td>
</tr>
<tr>
<td><strong>Maintenance/continuation</strong></td>
<td>Mercaptopurine: 50 mg/m² PO (d 1-14), 5 mg/m² (d 15-21) PO/IV</td>
<td>Mercaptopurine: 30 mg/m² IV (d 1, 2, 8, 9) Cyclophosphamide: 600 mg/m² (d 1, 15) Asparaginase: 10000 U/m² IV, (d 1-3, 15-17)</td>
<td>Mercaptopurine: 10 mg/m² PO (d 1, 11, 21, 31, 41) Methotrexate: 20 mg/m² PO weekly (d 8-78) – held on d 29 during 1st 4 courses (when IT methotrexate given)</td>
</tr>
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</table>

**CCR**, continuous complete remission; **d**, day; **E coli**, Escherichia coli; **IM**, intramuscular; **IT**, intrathecal; **PO**, by mouth; **SC**, subcutaneous; **wk**, weeks; **y**, years.
### Table 1. (continued)

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Treatment Plan</th>
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<tbody>
<tr>
<td><strong>ALL-96 (PETHEMA)</strong> 29</td>
<td>DFCI Adult ALL 01-1753</td>
</tr>
<tr>
<td><strong>C10403</strong></td>
<td></td>
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<tr>
<td><strong>Induction</strong></td>
<td>Methotrexate: 50 mg IT (d 0)</td>
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<tr>
<td></td>
<td>Cytarabine: 15 mg IT (d 0)</td>
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<tr>
<td></td>
<td>hydrocortisone: 50 mg IT (d 0)</td>
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<tr>
<td><strong>Induction</strong></td>
<td>Methotrexate: 70 mg/m2 IT (d 1)</td>
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<tr>
<td></td>
<td>Cytarabine: 15 mg IT (d 1)</td>
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<tr>
<td></td>
<td>hydrocortisone: 50 mg IT (d 1)</td>
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<td></td>
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<tr>
<td><strong>Induction</strong></td>
<td>Methotrexate: 50 mg/m2 IT (d 15 and 29)</td>
</tr>
<tr>
<td></td>
<td>Cytarabine: 15 mg IT (d 15 and 29)</td>
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<tr>
<td></td>
<td>hydrocortisone: 50 mg IT (d 15 and 29)</td>
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<tr>
<td><strong>Consolidation</strong></td>
<td>Methotrexate: 15 mg IT (d 1, 8, 15, 22)</td>
</tr>
<tr>
<td></td>
<td>Cytarabine: 40 mg / methotrexate 12 mg/ hydrocortisone 50 mg IT (d 1, 8, 15, 22)</td>
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<tr>
<td><strong>Induction/Consolidation (d 1, 29)</strong></td>
<td>Methotrexate: 15 mg IT (d 1), also given d 29 for first 4 courses</td>
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<tr>
<td></td>
<td>Cytarabine: 30 mg IT</td>
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<tr>
<td><strong>CNS therapy</strong></td>
<td>Methotrexate: 15 mg IT (d 1), also given d 29 for first 4 courses</td>
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<tr>
<td><strong>Maintenance/reinduction (d 1)</strong></td>
<td>Methotrexate: 15 mg IT (d 1)</td>
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<tr>
<td><strong>CNS prophylaxis</strong></td>
<td>Methotrexate: 15 mg IT (d 1), also given d 29 for first 4 courses</td>
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<tr>
<td><strong>Delayed intensification</strong></td>
<td>Methotrexate: 15 mg IT (d 1, 31)</td>
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<tr>
<td><strong>Maintenance</strong></td>
<td>Methotrexate: 15 mg IT (d 1), also given d 29 for first 4 courses</td>
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<tr>
<td><strong>Cranial radiation (18-24 Gy)</strong></td>
<td>Methotrexate: 15 mg IT (d 1), also given d 29 for first 4 courses</td>
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<tr>
<td><strong>EFS 61% (6-y) 58% (4-y) 66% (2-y) OS 69% (6-y) 67% (4-y) 78% (2-y)</strong>*</td>
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#### Other serious toxicities of asparaginase include anemia, pancreatitis, thrombosis, and bleeding. For a more detailed discussion regarding the prevention and treatment of asparaginase toxicities in adults, a comprehensive set of recommendations was recently published by an expert panel.46

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**Patient 1 (continued)**

This patient completes induction therapy per C10403 protocol without significant complications. BM biopsy shows complete remission (CR) with no detectable MRD by flow cytometry.

**When should allogeneic transplant in first CR (CR1) be considered? What role does MRD monitoring play in decisions for treatment?**

A large prospective randomized international collaborative study (MRC UKALL XII/E2993) demonstrated a significant increase in OS for allogeneic transplant in CR1 when compared with a standard adult ALL regimen (63% vs 52%). In contrast, a very recent International Bone Marrow Transplant Registry study of adults 18 to 50 years old found a significant benefit (hazard ratio 3.1; P < .0001) in both disease-free survival (DFS) and OS for patients receiving an intensive pediatric regimen compared with allogeneic transplant in CR1, due to transplant-related mortality. Thus, given the risks and complications of transplant, with 20% to 30% nonrelapse transplant mortality in these studies and the high survival (above 70%) and low mortality (3%) rates now being achieved in AYAs with pediatric inspired regimens, we do not routinely recommend allogeneic SCT in CR1. We do, however, routinely perform HLA typing on all patients at diagnosis, but have traditionally reserved transplant for those with high-risk (HR) presenting features, which we consider to be MLL rearrangement and hypodiploidy. More controversial is the negative prognostic significance of early T-cell ALL. The role of allogeneic transplant in CR1 for a new HR subset, BCR-ABL1–like ALL, remains to be defined and will be discussed briefly in case 2 below.

MRD, measured by flow cytometry or quantitative polymerase chain reaction (qPCR), has emerged as one of the most important prognostic factors in both pediatric and adult ALL and can further inform the decision to transplant in CR1. Pediatric and adult studies demonstrate that detection of MRD at specified time-points (usually following induction or early consolidation therapy) is associated with high relapse rates and poor survival. For instance, in a study from the German Multicenter Group for Adult ALL, detection of MRD following early consolidation therapy was associated with a continued 5-year CR of only 12%. Conversely, the absence of MRD following induction or consolidation therapy using an intensive pediatric regimen has been associated with...
Patient 1 (continued)

Based on the discussion above, we recommend continuing therapy as per protocol (see Table 1). Following intensive postremission consolidation, he continues to maintenance therapy.

During maintenance therapy, we recommend dose escalation of 6-mercaptopurine (6-MP) and methotrexate to maintain adequate myelosuppression, as this has been demonstrated to affect EFS for adolescents with ALL. Of note, recent data from the COG suggest that continuous exposure (rather than frequent starting and stopping) is an important determinant of DFS. However, practitioners should also be aware that genetic polymorphisms in thiopurine methyltransferase (TPMT) can result in severe hematologic toxicity following treatment with thiopurines, such as 6-MP. Because a high proportion of patients have decreased TPMT activity (~10% with intermediate and 0.3% with low or no activity), we now test for genetic polymorphisms in TPMT if patients have prolonged myelosuppression during consolidation therapy or following initiation of maintenance therapy. Other genetic polymorphisms may also contribute to toxicity with 6-MP, such as the recently described NUDT15 variant. It is also important that CNS prophylaxis be continued during maintenance therapy to decrease the risk of CNS relapse. Another crucial aspect of long-term maintenance therapy is the close monitoring of drug adherence to the medications that are entirely administered in an outpatient setting (see further discussion below).

Successful treatment of ALL is, unfortunately, associated with the potential for long-term complications that adversely impact the patient’s quality of life. For instance, the intensive use of glucocorticoids in ALL regimens has been associated with significant rates of osteonecrosis, especially in adolescent females; therefore, any joint pain in these patients should be seriously investigated. Neuropathy related to vincristine use is also a common complication from treatment. Neurocognitive dysfunction can occur, although this is less common in modern regimens, which avoid or reduce the dosing of CNS irradiation. Other complications include endocrine and metabolic abnormalities, cardiac toxicity, and secondary malignancies. We recommend fertility counseling in all young adults treated for ALL. Comprehensive long-term follow-up guidelines are available through the COG at www.survivorshipguidelines.org and in the National Comprehensive Cancer Network Guidelines for Adolescent and Young Adult Oncology.

New data regarding the genetic predisposition to specific treatment toxicities may allow us to further refine our treatment approach to reduce the incidence of these toxicities. For instance, genome-wide analysis has revealed a novel single nucleotide polymorphism in the gene encoding CEP72 that is associated with increased risk of vincristine-induced neuropathy. CEP72 regulates the localization of centrosomal proteins and proper bipolar spindle formation, and knockdown in human ALL cells is associated with augmented vincristine effects. Similarly, the risk of glucocorticoid-induced osteonecrosis in children with ALL is associated with single nucleotide polymorphisms in ACP1, which regulates osteoblast differentiation. Although further study is needed, one could envision testing for these polymorphisms prior to treatment and adjusting doses based on individual results.

Patient 2

A 28-year-old man is diagnosed with precursor B-cell ALL. PCR and FISH for BCR-ABL1 are negative, and cytogenetics reveals a normal male karyotype. He completes induction therapy on C10403, but day 29 BM biopsy following induction shows significant residual disease (5.5%) by flow cytometry. Chromosomal microarray analysis detects the formation of an EBF1-PDGFRA fusion gene.

The recently described BCR-ABL1–like (or Ph-like) signature is associated with an adverse outcome in both children and young adults with ALL. It is characterized by a high frequency of alterations of IKZF1, a gene that encodes the lymphoid transcription factor IKAROS, and carries a gene expression profile similar to that seen in BCR-ABL1+ ALL, but lacks the BCR-ABL1 fusion protein expressed from the t(9;22)(q34.1;q11.2). BCR-ABL1–like ALL is also characterized by overexpression of a number of pathogenetically relevant kinases, some of which may be targeted therapeutically. The incidence of the BCR-ABL1–like signature increases with age and is frequent in AYAs (up to 27% in patients aged 20 to 30 years old). These patients are more likely to have MRD at the end of induction, which, as mentioned above, is an important predictor of DFS. These new insights provide further evidence for differences in the biologic basis of ALL as we age, and provide an exciting new rationale for future research to incorporate appropriate kinase inhibitors that may enhance disease response.

At this time, there is not a standardized clinically available assay to identify this genomic signature; however, many groups are working on screening assays to facilitate identification of these cases. A relatively simple assay based on a low-density microarray of several of the highly expressed genes that comprise this signature has already been successfully used to identify patients with the BCR-ABL1–like signature, validated in large pediatric cohorts, and is pending FDA approval. A variety of other tests, including a panel of FISH probes and/or comparative genomic hybridization are also used to specifically identify recurring fusion genes that result in activated and targetable kinases, including ABL1, ABL2, PDGFRA, JAK1, JAK2, and CRLF2. Already feasible, these assays are likely to come into common, standardized use within the next year or two to facilitate diagnosis of these cases.

In this particular case, when we noted the gross residual disease at day 28 of induction, we suspected a BCR-ABL1–like signature and performed a comparative genomic hybridization array of the diagnostic sample that identified an EBF1-PDGFRA fusion. During consolidation therapy, as reported by others, we added dasatinib at a dose of 100 mg daily to the standard agents used in consolidation therapy. The treatment was well tolerated, and 1 month later the disease was in morphologic remission. By the end of consolidation therapy, MRD by flow was undetectable. This patient had an HLA-matched donor and
proceeded to allogeneic transplant in CR1. Approximately 180 days posttransplant, he is doing well, has achieved full donor chimerism, and MRD remains undetectable.

It is important to note that the therapeutic approach described above is not yet a standard of care for patients with the \textit{BCR-ABL1}\textendash like signature. We have a great deal to learn about the feasibility, timing, and impact of incorporating targeted kinase inhibitors (eg, imatinib, dasatinib, ruxolitinib, and others), as well as the role of allogeneic hematopoietic cell transplant for these patients. MRD monitoring in the \textit{BCR-ABL1}\textendash like cases will also help to refine prognosis and guide treatment choices. Indeed, recently published data demonstrate that MRD measurements can distinguish a subset of relatively good risk vs very poor risk children with \textit{BCR-ABL1}\textendash like ALL.\textsuperscript{25} Nevertheless, this case illustrates the exciting new therapeutic possibilities that will be studied in future intergroup (and possibly, international) trials that have the very real potential for improving DFS for these HR patients.

\textbf{Patient 3}

\textbf{A 30-year-old woman presents with fatigue, easy bruising, shortness of breath, and pancytopenia. A BM biopsy is consistent with precursor B-cell ALL. Cytogenetics demonstrates t(9;22)(q34;q11) with a p190 BCR-ABL1 transcript. How should this patient be treated?}

The presence of t(9;22)(q34;q11), the Philadelphia chromosome (Ph\textsuperscript{+}), resulting in the \textit{BCR-ABL1} fusion gene, increases with age, and occurs in up to 25\% to 30\% of older adults, although it is less common in younger adults.\textsuperscript{8} Although Ph\textsuperscript{+} ALL has historically been associated with poor survival, the addition of tyrosine kinase inhibitors (TKIs) has dramatically improved outcomes for patients of all ages.\textsuperscript{80,81}

Our current approach for these patients is the addition of a TKI to induction therapy with early CNS-directed therapy. The TKI should be given continuously during induction and all postremission treatment courses. Although imatinib, dasatinib, and nilotinib have all been used effectively and have improved DFS in Ph\textsuperscript{+} ALL, we typically use dasatinib because of the potential for increased CNS penetration.\textsuperscript{82} Several different induction regimens added to the TKI have been tested successfully in AYAs, ranging from intensive induction (a BFM-like regimen or hyper-CVAD plus imatinib or dasatinib)\textsuperscript{80,81,83} to minimal therapy. Data from the Italian Cooperative Group demonstrated that CR rates \textgreater 90\% can be achieved with dasatinib and glucocorticoid therapy alone with no early mortality.\textsuperscript{84,85} Given the high CR rates and minimal toxicity of the low-intensity regimens, we currently favor enrollment of patients on a clinical trial utilizing this approach to induction therapy (NCT01256398).\textsuperscript{42} Importantly, we also typically evaluate patients who fail to respond during induction with dasatinib-based therapy for the presence of an abl kinase mutation, because resistant mutations occur more commonly in Ph\textsuperscript{+} ALL.\textsuperscript{86}

Induction of remission is typically followed by postremission CNS-directed systemic and intrathecal therapy (continuing the TKI) and allogeneic SCT in CR1 if a donor is available.\textsuperscript{87} This remains our current recommendation for the AYA patient with Ph\textsuperscript{+} ALL, based in part, on historical data (prior to TKIs) demonstrating that long-term survival for Ph\textsuperscript{+} ALL was only possible with allogeneic transplant.\textsuperscript{88} The power of achieving major or complete molecular remissions with the addition of a TKI to frontline therapy has resulted in prolonged DFS, even in patients who did not undergo allogeneic SCT in CR1.\textsuperscript{89} Several contemporary trials suggest that excellent DFS can be achieved (70\% to 75\%) with or without transplant if patients achieve molecular remissions following TKI (dasatinib or nilotinib), plus low-dose chemotherapy and intrathecal prophylaxis.\textsuperscript{84,90,92} Importantly, these studies still require longer follow up, but suggest that achievement of molecular remissions is a goal of treatment in Ph\textsuperscript{+} ALL and may obviate the need for allogeneic transplant for achievement of long-term survival. Interestingly, although not specifically designed or powered to evaluate the role of allogeneic transplant, a study by the COG group demonstrated no difference in EFS among 65 pediatric patients (aged 1 to 21 years) with Ph\textsuperscript{+} ALL who received imatinib plus intensive chemotherapy vs allogeneic BM transplant.\textsuperscript{83} Thus, the treatment of Ph\textsuperscript{+} ALL is rapidly evolving and, in addition to the transplant question, future studies may also evaluate the role of newer, more potent TKIs including ponatinib in frontline therapy,\textsuperscript{93} their impact on achievement of molecular remissions, and the importance and duration of TKI maintenance therapy, including their role following transplant.

\textbf{Patient 4}

\textbf{A 27-year-old single mother, living apart from her immediate family, has been diagnosed with precursor B-cell ALL and is currently receiving maintenance therapy on the C10403 regimen. She recently lost her job, does not have health insurance, and has not been taking prophylactic medications because of cost. She missed several appointments because of lack of childcare for her 2-year-old daughter and forgot to take her oral methotrexate for the past several weeks. Depressed about her health, she worries about who will help take care of her daughter if her disease relapses.}

Nonadherence to treatment regimens and missed appointments are a significant challenge in the AYA population. This is especially true with complicated and prolonged ALL regimens, where the majority of treatment is administered as an outpatient. Clinical trials of AYA patients with leukemia and lymphoma suggest that up to 63\% of AYA patients have difficulties adhering to oral treatment regimens.\textsuperscript{84,95} Factors that affect treatment adherence include emotional factors (such as depression and self-esteem), patient health beliefs, and family environment. Although evidence-based interventions are lacking, several strategies have been suggested to improve treatment adherence, including anticipatory guidance, frequent monitoring of adherence, and interventions such as increasing availability of psychosocial support, modifying communication style, and allowing flexibility in treatment.\textsuperscript{94,95} Several groups are now exploring whether medication timing reminders and communication using electronic-based methods (eg, texting and web-based approaches) will facilitate treatment compliance and enhance patient satisfaction. We also encourage patients to keep a treatment diary, so that we can review and address ongoing concerns.

It has been suggested that AYAs face significantly greater challenges accessing health care due to insurance issues, including prescription drug coverage for crucial outpatient medications.\textsuperscript{96} Young adults with cancer are more likely to present with advanced stage or metastatic disease, be undertreated, and die after a diagnosis of cancer, relative to those who are insured.\textsuperscript{97} In countries with other health care systems and more comprehensive insurance coverage, this may be less of an issue, and, in the United States, we hope that the implementation of the Affordable Care Act will result in fewer uninsured AYAs and improvement in these statistics. Perceived social support from family, friends, and health care providers is an important predictor of mental health and symptom distress.\textsuperscript{98} Support groups can also be a useful resource for adolescent and adult oncology patients and, although there is limited evidence,\textsuperscript{99} we have found them to be beneficial. A psychologist in our clinic also meets with our patients regularly and helps determine when a referral to psychiatry
is warranted. Although the data are inconsistent, some studies have shown that mental health, depression, and anxiety are worse in AYA oncology patients at the time of diagnosis than in the general population.100 This improves as time progresses, but it highlights the importance of good psychological support for these patients.

Given the complexity of ALL treatment and the significant psychosocial and socio-economic challenges, we believe these patients are optimally treated in a supportive outpatient setting with expertise in management of the “whole” patient. At our institution, we have created an AYA cancer clinic that is composed of both pediatric and adult practitioners, as well as the resources and expertise to address the specific issues of a young adult with cancer. Prior to each clinic, we conduct a multidisciplinary meeting with nurses, physicians, pharmacists, social workers, physical therapists, and psychologists to discuss the patient, identify any issues, and determine the best plan of management for the patient. Even though these multidisciplinary teams have already become the standard of care in some countries,101,102 we believe this approach should become the standard for all AYA patients.

Conclusion

The future for AYAs with ALL is bright. Survival rates of 70% or greater are being reported in the recent AYA focused trials, and new targeted therapies individualized to optimize response and minimize toxicity are entering the clinic. Given the tremendous biological heterogeneity of this relatively rare disease and the complexity of the treatment approach, further improvements in survival will be achieved quickly if we can commit to offering these young adults enrollment on novel clinical trials and can provide the multidisciplinary expertise that will facilitate successful treatment outcomes. It “takes a village” to successfully treat ALL; and the AYA with ALL should be able to partake in the best scientific and supportive expertise that we have to offer!

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Authorship

Contribution: E.C. wrote the manuscript, and W.S. wrote the manuscript and supervised the project.

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How I treat acute lymphoblastic leukemia in older adolescents and young adults

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