

# Blood consult: Therapeutic strategy and complications in the adolescent and young adult with acute lymphoblastic leukemia

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## Case presentation

A 21-year-old woman was diagnosed with B lineage acute lymphoblastic leukemia (ALL) after presenting to a community-based medical oncologist with fatigue, fevers, and pancytopenia (white blood cell count  $2.3 \times 10^3/\mu\text{L}$ , hemoglobin 8 g/dL, platelets  $42 \times 10^3/\text{L}$ ). She was transferred to a regional children's hospital to institute therapy. Cytogenetics showed 55, XX, +4, +6, +10, +14, +17, +18, +21, +21[8]/46, XX[7]. Fluorescence in situ hybridization confirmed the presence of trisomies of chromosomes 4, 10, and 17 and was negative for *ETV6-RUNX1* [t(12;21)] or *BCR-ABL1* [t(9;22)(q34;q11)] fusion. A lumbar puncture performed before therapy showed no malignant cells. She began 4-drug induction therapy (vincristine, prednisone, daunorubicin, PEG-asparaginase) and intrathecal chemotherapy following the Children's Oncology Group (COG) protocol AALL0232.<sup>1</sup>

She was discharged home after day 8 chemotherapy, with plans to continue treatment with her community medical oncologist in consultation with the pediatric oncology team. During subsequent outpatient visits, she reported severe fatigue and weakness, making it difficult for her to return to her third-floor walk-up apartment, and she became dependent on her parents to carry out activities of daily living. She demonstrated hyperglycemia requiring insulin therapy throughout induction and progressive hyperbilirubinemia (chemotherapy doses were modified appropriately). In the final week of induction, she presented with severe nausea, sharp right-upper-quadrant abdominal pain, total bilirubin 6.1 mg/dL (direct bilirubin 4.2 mg/dL), and sequential labs demonstrated rising lipase. With a broad differential, including asparaginase-induced hepatotoxicity and/or pancreatitis, steroid-induced fatty liver disease, gallstones, and cholangitis, she was admitted to receive supportive care for the remainder of induction therapy.

Bone marrow evaluation at end induction showed remission with no blasts by morphology; flow cytometry minimal residual disease testing showed 0.012% leukemia cells. Still facing difficulties with mobility, fatigue, and malnutrition, she was discharged home to start consolidation therapy as an outpatient. To date, she has completed consolidation, interim maintenance with high-dose methotrexate, and delayed intensification treatment, during which she again experienced significant hyperglycemia.<sup>1</sup> Most treatment has been administered by her community-based medical oncologist in collaboration with the pediatric oncology team.

## Discussion

### What makes AYA ALL patients unique and how do these features differ between patients 15 to 21 years old and 22 to 39 years old?

Adolescent and young adult (AYA) patients 15 to 39 years of age with ALL are recognized as a unique patient subset. In this discussion, patients 15 to 21 years old will be referred to as older adolescents, and those 22 to 39 years old as young adults. A complete understanding of the clinical and psychosocial aspects of AYA ALL patients is challenging because they are underrepresented in clinical trials and their treatment is divided between pediatric and adult oncologists. Because of this, outcomes for this population are often absorbed into larger age-group analyses. Paradoxically, older adolescents are viewed as high risk by pediatric oncologists and a favorable risk subset by medical oncologists. Multiple studies have demonstrated important differences in sentinel genetic lesions that underlie ALL, frequency of clinical complications, pharmacokinetics, and pharmacodynamics of chemotherapy in AYA patients compared with younger children and older adults with ALL (Table 1).<sup>2,3</sup> Acknowledging and anticipating these differences are critical to develop appropriate treatment strategies for AYA ALL patients.

**Table 1. Clinical features and common complications of AYA patients with ALL**

Features	Complications
Treatment toxicity	Steroid-induced hyperglycemia, avascular necrosis Asparaginase-induced fatigue, weakness, pancreatitis, thrombosis Liver dysfunction
Cytogenetic abnormalities	Increased prevalence of high-risk features Ph <sup>+</sup> ALL ( <i>BCR-ABL1</i> ) <i>iAMP21</i> <i>MLL</i> rearrangements Decreased prevalence of lower-risk features High hyperdiploidy and/or trisomies of chromosomes 4 and 10 <i>ETV6-RUNX1</i>
Social	Poor medical compliance Underinsured Low enrollment in clinical trials

AYA indicates adolescent and young adult; and ALL, acute lymphoblastic leukemia.

Our case demonstrates some of the common complications that AYA patients experience early in therapy. Corticosteroids induce hyperglycemia and contribute to profound fatigue and weakness, both of which may be exacerbated by asparaginase therapy that can contribute to hyperbilirubinemia and/or pancreatitis.<sup>4</sup> This increase in complications contributes to lower event-free survival and overall survival in older adolescents compared with younger children with ALL, although the outcome gap has narrowed significantly in recent years.<sup>5-7</sup> Nachman et al reported that death as a first event accounted for 18.3% of total events in older adolescents as opposed to 11% in children 1 to 9 years of age.<sup>6</sup> Compared with younger children with ALL, AYA patients have increased rates of corticosteroid-related diabetes mellitus, avascular necrosis of bone, and asparaginase-related pancreatitis and thromboembolism.<sup>6,7</sup> Less data are available to identify common treatment complications in young adults, although studies suggest increased hematologic toxicity and infections compared with rates seen in older adolescents.<sup>8</sup>

The presence or absence of specific sentinel genetic lesions is commonly used for risk stratification in pediatric ALL. Genetic alterations associated with a better prognosis are found less frequently in AYA patients compared with children, including high hyperdiploidy (chromosome number > 51), favorable chromosome trisomies (4 and 10,  $\pm 17$ ), and  $t(12;21)(p13;q22)$ . Conversely, adverse prognostic features, including intrachromosomal amplification of chromosome 21, *MLL* translocations, and the Philadelphia chromosome ( $Ph^+$  ALL), are more common in older adolescents.<sup>3</sup> Favorable genetic features become much less common and unfavorable features, especially  $Ph^+$  ALL, much more common in young adults, contributing to the inferior outcome of this group compared with older adolescents.<sup>9</sup> Our patient had hyperdiploidy with favorable chromosome trisomies, which is associated with outstanding outcomes in pediatric ALL trials, although the prognostic significance is not as well defined in AYA ALL.

#### How and where should AYA ALL patients be treated?

Because older adolescents can be treated by either pediatric or adult oncology teams, several retrospective outcome comparisons have been performed in North America, the United Kingdom, France, The Netherlands, and Finland.<sup>2</sup> The largest study compared older adolescents treated in North America on Children's Cancer Group and the adult Cancer and Leukemia Group B (CALGB) trials from 1988 to 2001.<sup>10</sup> The 7-year event-free survival/overall survival for Children's Cancer Group patients was 63%/67% versus only 34%/46% ( $P < .001$ ) in CALGB trials. Differences of similar magnitude in favor of pediatric ALL regimens have been seen in multiple other studies.<sup>2</sup>

Although it is not obvious why treatment with pediatric protocols resulted in improved outcomes, some common features of pediatric treatment strategies may help explain the disparity. Pediatric protocols are typified by dose-intensive use of nonmyelosuppressive chemotherapy agents, including vincristine, glucocorticoids, and asparaginase.<sup>9</sup> They include earlier and more frequent central nervous system-directed therapy with higher cumulative intrathecal chemotherapy doses. Pediatric protocols also include longer antimetabolite-based maintenance cycles. In contrast, adult regimens more frequently include blocks of high-dose intermittent myelosuppressive chemotherapy.<sup>9,10</sup> Finally, patients treated on pediatric protocols are

more likely to adhere to cycle start dates and have shorter times between cycles. Together, these features may contribute to the improved outcomes for older adolescents treated on pediatric regimens. It is also possible that patients treated by pediatric oncologists are more likely to reside with their parents and have a better social support network than "emancipated" adolescents treated by medical oncologists. It is notable that our patient resides with her mother, and family assistance has been critical to her complex care needs. Importantly, the major United States adult cooperative groups are now testing one arm of COG AALL0232 in ALL patients 16 to 39 years old on the intergroup trial C10403 (<http://www.cancer.gov/clinicaltrials/CALGB-10403>).

Although these comparisons were not randomized, there is general consensus that pediatric ALL therapies are superior for older adolescents. Because of this, a number of groups have started to use pediatric-based or "inspired" ALL regimens in young adults (or even older) with very encouraging early results (reviewed by Schafer and Hunger<sup>2</sup>). For example, Ribera et al demonstrated that young adults treated primarily by adult oncologists, but according to pediatric regimens, showed identical improved outcome as older adolescents treated by pediatric oncologists.<sup>8</sup> Therefore, the debate should focus less on what facility AYA patients are treated in and more on the treatment regimen.

#### What is the optimal treatment strategy for AYA ALL patients?

The patient presented to a medical oncologist and was referred to our center, based on demonstrated better outcome for AYA ALL patients treated on pediatric protocols.<sup>2,10</sup> Our collaborative goal has been to deliver as much care as possible through the medical oncology office, located closer to her home. This approach has been quite successful and exemplifies how academic pediatric and community-based medical oncologists can collaboratively provide care to young adults. She is receiving therapy according to the recent COG AALL0232 trial, which showed outstanding results.<sup>1</sup> Treatment included a 4-drug induction with 28 days of prednisone, an augmented 8-week consolidation phase, 4 courses of high-dose methotrexate with leucovorin rescue during an 8-week interim maintenance phase, a single delayed intensification phase, and maintenance treatment extending until approximately 27 months after diagnosis.<sup>1,11</sup> Although many adult centers have considered allogeneic stem cell transplantation a primary part of therapy for AYA ALL patients, the results of pediatric trials have established that there is no role for routine use of stem cell transplantation in older adolescents without adverse prognostic features.<sup>2,5,6,7</sup>

Whereas older adolescents are treated in both pediatric and adult centers, young adults are almost always treated by medical oncologists. The very encouraging results of pediatric-type ALL regimens in these patients provide a strong argument that young adults with ALL should be referred initially for treatment to a center experienced with such regimens. Treatment of AYA ALL patients across the entire age spectrum is complex. Anticipating, recognizing, and promptly treating complications are vital to achieving successful outcomes.<sup>4</sup> To accomplish this, it is important to have a comprehensive approach to care that includes professionals from social work, nutrition, endocrinology, physical therapy, and psychiatry. Continued collaboration between pediatric and medical oncologists is needed to design,

implement, and enroll AYA ALL patients in clinical trials to optimize outcomes.

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## Authorship

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