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Review

Closing the gap: Novel therapies in treating acute lymphoblastic leukemia in adolescents and young adults

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ABSTRACT

Acute lymphoblastic leukemia (ALL) is one of the most common cancer diagnoses identified in adolescents and young adults (AYAs). Although most children with ALL are cured of their disease, AYAs have experienced much worse outcomes over time, with event-free survival ranging from 30 to 45%. This survival disparity is likely due to differences in tumor biology, treatment-related toxicities, and nonmedical issues. This review summarizes these differences as well as focusing on the various trials that have demonstrated superior outcomes with pediatric protocols in AYAs with ALL. Even with the widespread use of these protocols, a treatment gap remains, and novel therapies are one way to address this problem. Still, these therapies also have significant toxicities and unique issues that need to be tested further, especially in the AYA population. The development of more AYA-specific trials will be an important way to examine novel therapies and interventions designed to reduce treatment-related toxicities and improve long-term outcomes.

1. Introduction

Approximately 70,000 adolescents and young adults (AYAs), defined by the National Cancer Institute (NCI) as patients between the ages of 15 and 39 years, are diagnosed with cancer each year [1]. Acute leukemia is the fifth most common neoplasm within this population and among this group, acute lymphoblastic leukemia (ALL) is seen most frequently [2].

Although > 80–90% of children with ALL are cured of their disease, outcomes historically have been much poorer for AYAs, with event-free survival (EFS) ranging from 30 to 45% [3–5]. While outcomes have continued to improve for patients younger than age fifteen, survival for AYAs with ALL appeared to plateau in the 1990s [6,7]. There are multiple medical and nonmedical reasons that can account for this disparity in outcomes. Most significant is that ALL in AYAs has different biology from ALL in children, as leukemia cells in older patients typically have more genetic alterations. A recent discovery is the characterization of Ph (Philadelphia)-like ALL, in which the leukemia cells are Ph negative by PCR but have a gene expression profile similar to what is seen in Ph-positive-ALL [8,9]. Also, AYAs have been shown to have greater treatment-related toxicities and differences in drug metabolism when compared to children [10,11]. Additionally, young adults have unique practical and psychosocial issues that may contribute to poor outcomes.

Even with these challenges, survival for AYAs with B-cell precursor ALL has begun to show some improvement in recent years [12,13]. One reason for this change is the recognition that AYAs often have better outcomes when treated with pediatric-inspired regimens, consisting of the Berlin-Frankfurt-Munster (BFM) backbone, central nervous system (CNS) prophylaxis, and a prolonged maintenance phase [12]. This is in contrast to the typical “adult” regimens that may include intensive use of daunorubicin, cytarabine, and cyclophosphamide followed by allogeneic hematopoietic stem cell transplantation (HSCT) in first remission [4,14].

While the utilization of pediatric-based regimens has improved survival for AYAs with ALL, a substantial treatment gap still exists when compared to children. This review will summarize the differences in tumor biology and outcomes between children and AYAs with ALL, and describe the unique toxicities and psychosocial issues seen in this population. We will also report on recent clinical trials attempting to address these problems, as well as propose new studies that focus on testing novel therapies and target specific needs of this underserved population. The goal is to demonstrate that while some progress has been made recently in improving survival for AYA patients with ALL, more can be done to design AYA-specific trials that focus on reducing treatment-related toxicities and improving long-term outcomes.

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Table 1
Distribution of genetic alterations among different age groups with B-cell precursor acute lymphoblastic leukemia. NR = not reported. Ph = Philadelphia [9,17,18].

Acute lymphoblastic leukemia subtype	Children	Adults	Adolescents (16–20 years)	Young adults (21–39 years)	Older adults (> 60 years)
Hyperdiploidy	25%	7%	11%	3%	NR
Hypodiploidy	1%	2%	1%	< 1%	NR
MLL rearrangement	8%	10%	5%	16%	13%
ETV6-RUNX1	22%	2%	4%	2%	< 1%
Ph chromosome	3%	25%	6%	22%	31%
Ph-like	12%	20%	21%	27%	24%
Other	22%	23%	36%	23%	31%

2. Understanding the treatment gap

2.1. Tumor biology

A number of biological factors exist in ALL for AYAs that helps to explain the poor results seen in this population. The main difference is the increased prevalence of specific genetic alterations, such as a higher proportion of patients with BCR-ABL1, MLL, and IGH translocations, and iAMP21, that predict a poor prognosis [9,15,16]. Similarly, there are fewer patients with genetic alternations that portend a favorable prognosis including hyperdiploidy and ETV6-RUNX1 translocation [9,16,17]. More recently, researchers have identified the Ph-like signature, that has a similar gene expression pattern to Ph-positive ALL without expression of the BCR-ABL1 fusion protein [8,9]. This pattern of gene expression has been observed in up to 21–27% of AYAs with ALL, and has been associated with poor prognosis [18]. In addition, older children and young adults comprise the largest age group with unspecified chromosomal abnormalities, which may also explain their reduced survival [16]. Differences in tumor biology are summarized in Table 1.

Besides the differences in the genetic abnormalities seen in these patients, AYAs have been shown to have greater treatment-related toxicities when compared with younger children, including higher rates of infections, steroid-induced osteonecrosis and hyperglycemia, and asparaginase-related thrombosis and pancreatitis [10,11]. Drug metabolism may also differ in these older patients, which may increase the risk of treatment-related toxicities and decrease the effectiveness of certain chemotherapeutic agents [19]. Further, leukemia cells from AYAs, in vitro, have been shown to be more resistant to chemotherapy than those tested in patients less than ten years of age [20].

2.2. Practical and psychosocial challenges

In contrast to the medical issues that may lead to poor outcomes in this population, there are also unique practical and psychosocial challenges that occur in this age group. Practical issues include variation in referral patterns by primary care providers, insurance barriers, and transportation problems that prevent AYAs from accessing the proper medical care that they need [21,22]. In addition, AYAs have unique psychosocial needs that include inadequate family support, young children to care for, and higher rates of anxiety and depression [23,24]. These are significant problems that can lead to noncompliance and may contribute to their inferior outcomes.

2.3. Treatment and outcomes

Due to the differences described above, survival in AYAs with ALL is significantly worse when compared with children. Further, an additional contributor to this survival difference is the fact that AYAs are frequently treated differently from the way children are managed. Unlike children that are almost always treated according to national protocols, AYA patients are much less likely to be enrolled on clinical trials. Yet patients who participate in clinical trials have been shown to have better outcomes [25]. The protocols used for children typically follow the BFM model, utilizing induction chemotherapy, interim maintenance and delayed intensification phases, as well as a prolonged maintenance phase. Asparaginase is a frequent component of therapy, as its depletion of asparagine and glutamine, amino acids that are essential for lymphocytes, is thought to be especially critical in treating ALL [26]. Allogeneic HSCT is typically only recommended for high-risk patients, primarily patients who are found to be MRD (minimal residual disease)-positive following both induction and consolidation [26].

In contrast to the treatment of children with ALL, AYA patients have frequently been treated using adult ALL protocols that often use fewer doses of asparaginase and may not include a lengthy maintenance phase. While the perception has been that intensive therapies used in pediatric protocols such as asparaginase are too toxic for older adolescents and young adults, multiple studies have shown that these therapies are well-tolerated and efficacious in these patients [27,28]. As opposed to the infrequent use of allogeneic HSCT in pediatric populations, this procedure is often favored in AYAs with ALL. Yet the cumulative incidence of non-relapse mortality in patients aged greater thirteen years or older who have undergone allogeneic HSCT is as high as 28% [29]. Conversely, a meta-analysis that compared studies that treated AYA patients with ALL with either a pediatric-inspired regimen or a conventional adult chemotherapy regimen found that the cumulative rate of non-relapse mortality among patients that received a pediatric regimen was only 7% [30].

In the past decade, there have been several retrospective trials comparing the treatment of AYAs with ALL with either an adult or pediatric-based regimen. The results have demonstrated consistently better clinical outcomes for patients treated on pediatric protocols when compared with similar patients treated with adult regimens. The largest of these trials compared patients treated on either pediatric Children's Cancer Group (CCG) treatment regimens or adult Cancer and Leukemia Group B (CALGB) regimens. After seven years of follow-up, patients on the pediatric protocol revealed EFS of 63% and overall survival (OS) of 67% as opposed to EFS of 34% and OS of 46% for patients treated on the adult regimen [31]. Other studies have corroborated these findings as described in detail in Table 2. A common theme across these studies is that patients treated on pediatric protocols were exposed to more prednisone and vincristine primarily due to a longer maintenance phase, and to more frequent use of asparaginase. For example, in FRALLE-93, patients received a cumulative amount of asparaginase up to twenty times greater than patients treated on LALA-94 [32]. Also, patients on pediatric protocols were exposed to lower doses of anthracyclines, cyclophosphamide, cytarabine, and etoposide. Further, CNS-directed therapy was given more frequently in pediatric protocols [31].

While these studies were performed primarily in adolescents aged twenty years and younger, recent trials suggest that these regimens may be broadened to the greater AYA population. Some trials have successfully treated young adults up to age forty, [28,37,38] while others have demonstrated tolerability up to fifty-five years of age [39,40]. Although some studies have reported higher rates of side effects due to steroids and asparaginase, these appear to be balanced by reduced rates of relapse [41]. Adult protocols also may have significant toxicity, such as hyper-CVAD that results in high rates of fever and neutropenia,