



Optimal therapy for adolescents and young adults with acute lymphoblastic leukemia-current perspectives

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Abstract

Adolescents and young adults (AYA) with acute lymphoblastic leukemia (ALL) have worse prognosis than children. Differing biology of ALL may account for some of this disparity in outcome, with AYA patients having far lower incidence of good risk cytogenetic abnormalities, and higher proportion of patients with genetic lesions associated with inferior survival such as Ph-like ALL. Actual chemotherapy may also contribute to differences in outcome. Retrospective studies have shown that AYA patients treated on pediatric-based regimens had higher survival than those treated with adult regimens; the superiority of pediatric protocols has also been proven in several prospective comparative trials. Increase in rate of enrollment of AYA patients in clinical trials may further improve outcome. Cure based on chemotherapy may further limit the role of allogeneic hematopoietic cell transplantation (HCT) in AYA patients. The unique biology of AYA ALL may allow for novel methods of targeted therapy, while immunotherapy, the efficacy of which has been proven for both children and adults, may also play a major role in the treatment of relapsed/refractory ALL.

Key Words Acute lymphoblastic leukemia, Adolescents, Young adults, Ph-like ALL

INTRODUCTION

The biology of acute lymphoblastic leukemia (ALL) and response to therapy are different when comparing pediatric and adult patients. The adolescent and young adult patient population may represent a unique age-based subgroup that is distinct from both children and older adults. Appropriate treatment of this subgroup may allow for significant improvement in survival when compared with historical cohorts. This review summarizes recent studies on ALL in the AYA population to determine the current status of ALL therapy in this age cohort, and possibly to conclude upon means of further improving outcome.

The definition of the AYA patient group differs significantly according to clinical study. The broadest age group that may be termed AYA includes adolescents and adults up to the age of 40. Many studies in ALL, however, focus on patients who are 15-20 years old at the time of diagnosis [1-3]. In South Korea, the age-standardized incidence rate (ASR) of cancers in the AYA population, defined as patients who are 15-29 years old, is 279.9/million, with ASR for ALL at 3.9/million [4].

BIOLOGY OF ALL IN AYA PATIENTS

Differences in the biology of the leukemic blast between children and AYA patients may partly explain disparities in patient survival. In terms of recurrent cytogenetic abnormalities, those associated with favorable prognosis such as high hyperdiploidy and *ETV6-RUNX1* have a lower incidence in AYA patients compared with younger children [5]. In contrast, *BCR-ABL1* which is associated with lower survival is diagnosed with greater frequency with increasing age. Intrachromosomal amplification of chromosome 21 (iAMP21) is another cytogenetic abnormality that is found more commonly in adolescents than in children and has been associated with poor outcome [6, 7].

The proportion of patients with a non-recurrent cytogenetic abnormality, the prognostic implications of which are unclear, is highest in the AYA group [5]. Some of these patients may be categorized as Philadelphia chromosome-like ALL (Ph-like ALL), characterized by a gene expression profile similar to Ph+ ALL but without the defining translocation. One study on a large number of precursor B-cell (pre-B) ALL patients showed that the incidence of

Ph-like ALL increased from 10% in children with standard risk ALL to 21% in adolescents and 27% in young adults. Importantly, patients with Ph-like ALL had inferior survival compared with non-Ph-like ALL patients [8]. A recent study also showed that *DUX4* fusions, in which the *DUX4* gene on chromosome 4q is translocated to the *IGH* locus on chromosome 14, and *ZNF384* and *MEF2D* fusions comprise about 30–40% of AYA patients with Ph- Pre-B ALL, allowing for classification of patients lacking established genetic abnormalities [9].

Early T cell precursor (ETP)-ALL is a subtype of T-cell ALL with an immature phenotype defined as CD1a(-), CD8 (-), CD5 weak, and expression of one or more myeloid or stem cell markers [10]. Although overall consensus is lacking, children with ETP-ALL have been reported to have non-inferior outcome compared with other T-cell ALL patients [11]. However, a study based on adolescent and adult patients showed that those with ETP-ALL had significantly lower rates of complete remission (CR) and overall survival (OS) than patients with other T-cell ALL, indicating that the ETP-ALL phenotype has prognostic relevance, although this study included patients who were much older than the young adult age group [12].

Overall, the lower incidence of cytogenetic abnormalities associated with favorable outcome, combined with the higher proportion of patients with poor risk genetic features such as Ph+ and Ph-like ALL in AYA patients contribute to their inferior survival compared with children. Recently reported recurrent genetic features such as *DUX4*-rearranged ALL allow for accurate diagnosis of AYA patients with hitherto unclassified genetic abnormalities. Also, although further studies are needed to draw definite conclusions, ETP-ALL phenotype may act as a poor prognosis feature in older T-cell ALL patients.

TREATMENT OF AYA PATIENTS

Comparison of pediatric and adult protocols

Many multi-institutional studies have compared the outcome of AYA ALL when treated with either a pediatric-based or adult-based chemotherapy regimen. In this context, a pediatric regimen refers to one incorporating multiple doses of asparaginase, with greater exposure to vincristine and steroids, intensive central nervous system (CNS) prophylaxis, and a prolonged maintenance phase based on anti-metabolite therapy. In contrast, an adult regimen such as hyper-fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone (hyper-CVAD) utilizes greater doses of cyclophosphamide and anthracycline and, as a result, is more myelotoxic.

One of the largest earlier studies retrospectively compared the outcome of 321 AYA patients aged 16–20 years old who were treated on either the Children's Cancer Group (CCG) trials or the adult Cancer and Leukemia Group B (CALGB) protocols [3]. The study found a significantly higher 7-year event-free survival (EFS) rate for patients treated with CCG

regimens than for patients treated with CALGB regimens (63% vs. 34%, $P < 0.001$). Of note, 18–20 year old patients treated with the adult regimen had much lower survival than those treated with a pediatric regimen, although 16–17 year old patients had comparable outcome regardless of treatment type.

Overall, of 25 studies comparing pediatric and adult ALL treatment of AYA patients, all but two showed superior survival for patients treated with a pediatric regimen [13]. The advantage of pediatric-based therapy for AYA patients was also proven in a meta-analysis of 11 comparative studies, with patients treated with pediatric regimens having a lower rate of relapse, similar non-relapse mortality, and higher EFS than patients treated with adult regimens [14]. Also, a recent Korean study based on 1,168 AYA patients showed that OS of pediatric treatment recipients was significantly higher than those who received adult treatment [15]. Importantly, the study also showed that the majority of AYA patients (65%) received pediatric-based therapy for ALL.

Prospective study of pediatric regimens

The efficacy of pediatric-based ALL therapy for AYA patients, evident in retrospective comparisons of pediatric and adult treatment groups, resulted in adoption and prospective evaluation of pediatric therapy in these patients by adult hematologists. The Japan Adult Leukemia Study Group reported the outcome of treating 139 Ph- ALL patients (age 15–24 yr) with a pediatric regimen; the 5-year disease-free survival (DFS) and OS rate was 67% and 73% respectively [16]. The DFS was higher for recipients of pediatric therapy compared with a cohort of patients given adult-based therapy, irrespective of risk group.

A recent study reported the outcome of the implementation of the Nordic Society of Pediatric Hematology and Oncology (NOPHO) ALL2008 in 1,509 patients aged 1–45. The study found a greater proportion of high risk ALL in older patients due to increased incidence of T-cell ALL, *KMT2A* rearrangements, and post-induction minimal residual disease (MRD) [17]. The 5-year EFS of patients aged 18–45 was 74%. Treatment of young adult patients with a pediatric-based regimen was safe, with no significant difference between pediatric and adult patients with regards to rates of induction death. In terms of the specific adverse events, adult patients experienced a significantly higher incidence of thrombosis compared with children [18]. The rate of avascular necrosis was highest among 10–14 year old patients, but was also increased in older adults compared with younger children.

Also, results from the recently reported prospective CALGB 10403 study, based on 295 patients diagnosed at age 17–39, showed estimated 3-year EFS and OS of 59% and 73% respectively. The median EFS duration of 78.1 months was significantly longer than that of a historical cohort [19]. As was found for the NOPHO ALL2008 study, implementation of a pediatric protocol in adults was safe, with a 3% rate of treatment-related mortality.

In contrast to these studies which reported improved outcome of AYA patients treated with pediatric regimens, a study by the MD Anderson Cancer Center showed comparable outcomes for patients treated with pediatric and adult regimens. In this study, 208 AYA patients up to the age of 40 received either the pediatric augmented Berlin-Frankfurt-Münster (BFM) therapy or the adult hyper-CVAD therapy, resulting in CR rate of 93% and 98%, and 5-year complete remission duration rate of 53% and 55% respectively. The 5-year OS rates for the two treatment arms were both 60% [20]. The study found that although outcomes for the different treatment strategies were similar, the resulting toxicities were different, with the augmented BFM notable for asparaginase-related complications such as hyperbilirubinemia, hypofibrinogenemia, pancreatitis and thrombosis, while hyper-CVAD caused more myelosuppression and subsequent episodes of infection and bleeding.

Overall, several prospective studies indicate improved survival of AYA patients by adoption of pediatric regimens by adult hematologists. Still, the proportion of AYA patients treated with pediatric regimens remains unclear. One nationwide study of AYA patients in Australia found that 82% of ALL patients were treated with pediatric regimens regardless of treatment site, indicating that many adult hematologists had adopted pediatric therapy [21]. A recent study, however, pointed to the potential for persistent disparity in outcome of AYA patients between pediatric and adult medical centers. The study found that AYA patients (age 15–21 years old) who received pediatric therapy at an adult center had significantly higher survival than those who received adult therapy, but still lower than patients who were treated at a pediatric center [22].

A key method of ensuring that pediatric regimens are implemented accurately is to increase the number of AYA patients who are enrolled in clinical trials of ALL. A population-based study from the United States showed a recent increase in clinical trial enrollment for AYA patients (age 15–39 years old) with various cancers including ALL [23]. Further efforts to fully utilize pediatric regimens in the context of a clinical trial may contribute to improved outcome of AYA patients.

Hematopoietic cell transplantation (HCT) for AYA patients

The role of allogeneic HCT as a means of consolidation in first CR in pediatric ALL is diminishing, while it still remains a fundamental component of therapy for adult patients [24]. Indications for HCT in AYA patients remain unclear, although adverse cytogenetic features such as *BCR-ABL1*, *KMT2A* rearrangement and hypodiploidy, and post-induction MRD may be widely accepted criteria for HCT. Whether broader application of HCT in first CR results in superior outcome compared to pediatric-based chemotherapy remains unclear, although one retrospective study showed a similar relapse rate for the two treatment strategies, with lower treatment-related mortality (TRM) and increased OS for patients treated with pediatric chemotherapy [25].

A recent population-based study of allogeneic HCT for

AYA ALL patients in first CR reported that 28.5% of eligible patients underwent HCT in first CR resulting in 84% two-year OS [26]. Although rate of relapse-free survival (RFS) was higher in patients who received allogeneic HCT compared with those treated with chemotherapy only, the OS between the two groups was similar possibly due to increased TRM associated with HCT. Similarly, a nationwide study on allogeneic HCT for AYA ALL patients in first CR or beyond reported lower OS compared with children due to a higher rate of TRM, although rates of relapse were similar [27]. Overall, several studies consistently underscore the potential for greater TRM in AYA HCT recipients; more extensive use of pediatric chemotherapy for AYA may limit and clearly define the indications for allogeneic HCT in first CR.

Treatment of subgroups and novel therapy

Concurrent use of tyrosine kinase inhibitors (TKI) has markedly improved the outcome of Ph+ ALL. The Children's Oncology Group (COG) trial AALL0622 incorporated dasatinib into chemotherapy for patients aged 1–30 years, using the TKI from day 15 of remission induction, while reserving allogeneic HCT for a minority of patients based on MRD and matched sibling donor availability [28]. Cranial irradiation was limited to patients with CNS leukemia. The study reported EFS and OS rates of 60% and 86% overall, results comparable to patients treated with imatinib in the previous COG AALL0031 trial, all of whom received cranial irradiation [29].

As the incidence of Ph-like ALL is greater in the AYA population than among children, therapy targeting the kinase-activating lesion of this ALL subtype may be more relevant for the older patient population. In terms of the actual target, *CRLF2* rearrangements with or without *JAK* mutations, *JAK2* rearrangements and other mutations activating the JAK-STAT pathway have a greater incidence in AYA patients, whereas *ABL1* class rearrangements are more important in children [8]. Case reports have shown that treating adolescent patients with *ABL1* class rearrangement or activating *JAK2* mutation, who previously showed poor response to conventional chemotherapy, with imatinib or ruxolitinib respectively resulted in MRD(-) remission as a bridge to successful allogeneic HCT [30, 31].

Immunotherapy with chimeric antigen receptor (CAR) T-cells has significantly improved the outcome of patients who fail initial chemotherapy. The phase 2 trial of single infusion CAR T-cell therapy resulted in 50% EFS at 12 months for children and young adults with relapsed/refractory pre-B ALL, with the EFS maintained at this level beyond 12 months [32]. However, the median age at treatment for the 75 patients was 11 years, with the oldest patient reported to be 23 years old. Hence, the patients treated in this cohort did not encompass the broader definition of young adults up to the age of 30, or even 40. In contrast, the study of CAR T-cell therapy in adults, with a median age at infusion of 44 years, showed a much lower EFS at 12 months, with the survival rate continuing to fall beyond one year post-infusion [33].

Whether CAR T-cell therapy alone without further treatment may be curative, or whether this mode of immunotherapy may act as bridge to curative consolidation with allogeneic HCT in AYA patients, and whether expected therapeutic benefit may differ according to age sub-brackets within the broad definition of AYA require further investigation.

CONCLUSION

Lower rates of enrollment in clinical trials contributed to the inferior outcome of AYA patients with ALL compared with children. Increase in therapy of AYA patients within the auspices of clinical trials, and the wider use of pediatric-based regimens for the treatment of these patients may result in significant improvements in outcome. Utilization of more effective chemotherapy may limit and clearly define subsets of patients who may benefit from allogeneic HCT in first CR, a treatment modality reported to result in a higher rate of TRM for AYA patients than for children. The unique biology of ALL in AYA patients offers the chance for targeted therapy, as has been shown for patients with Ph-like ALL. Finally, although immunotherapy such as CAR T-cell therapy has proven to be extremely effective in leading to CR, its role within the long-term treatment strategy for relapsed/refractory AYA patients requires further study.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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