Increasingly, adolescent and young adult (AYA) patients with acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL) are being treated with pediatric-inspired regimens to improve both the quantity and quality of survival. In the United States, the cooperative groups sponsored by the National Cancer Institute (NCI) studying adult patients with cancer were able to successfully develop, enroll, and complete a trial focused on AYA patients with newly diagnosed ALL. Three adult cooperative groups were able to collaborate on this effort and double the survival of their AYA patients, as described herein. Now, through the National Cancer Treatment Network (NCTN), they have developed a successor trial (Alliance A041501) that has opened as well.

However, this remarkable accomplishment has not reached the vast majority of AYA patients with ALL and LBL who are not being treated with a pediatric type of regimen, despite the sentinel observation on this topic published a decade ago and numerous comparisons in favor of the pediatric regimen reviewed herein. This disparity is becoming increasingly important as the incidence of ALL and LBL in AYAs in the United States is increasing at a greater rate than in younger or older persons. Their optimal treatment has been increasingly debated as pediatric regimens have become more widely used in the age group. This review compares the basic features of pediatric and adult chemotherapy regimens for ALL and LBL, recognizes and describes the challenges of the pediatric regimen, and suggests strategies to facilitate its adoption for AYAs with ALL and LBL.
Figure 1. Annual Incidence and New Cases in the United States of Adolescents and Young Adults (AYAs) With Acute Lymphoblastic Leukemia and Lymphoblastic Lymphoma (ALL/LBL), 2000 to 2014

A and B. Shown in A are incidence data from the Surveillance, Epidemiology, and End Results (SEER) 18 data set on which the estimated numbers of new cases in B are based. The age range of the AYAs was 15 to 39 years. Average percentage change (APC) represents the mean percentage change of logarithmic values, with APC values and P values for incidence provided by SEER and calculated by us for new case numbers. The International Classification of Diseases-Oncology, Third Edition codes used for ALL and LBL are available in the eTable in the Supplement.

The importance of Ph-like ALL is that an increasing number of tyrosine kinase inhibitors effective against the subtype are available and being added to pediatric regimens.\(^5\) The survival cliff between ages 17 and 21 years has also been attributed to the transition of patients from pediatric to adult treatment sites during this age span.\(^7\) Extending the slope of the pediatric linear survival trend for patients aged 1 to 17 years into the adult age range suggests that current pediatric regimens could increase the 5-year survival rate in those aged 20, 25, 30, and 35 years by absolute amounts of 21%, 18%, 14%, and 11%, respectively (Figure 2B).

Comparison of Outcomes

Concurrent outcome comparisons of pediatric and adult treatment regimens for ALL have consistently demonstrated, in 13 countries on 4 continents, the superiority of the pediatric regimen for AYAs (Table).\(^2,8-21,23-33\) Thirteen of 16 comparisons favor the pediatric regimen,\(^7,8,21,23,24\) albeit none are prospective randomized trials. In addition, all of 9 noncomparative reports have similar results for the pediatric regimen (Table).\(^25-33\)

There are only 2 exceptions. The first exception is no reported difference in a comparison from The University of Texas MD Anderson Cancer Center\(^24\) that, other than a report from Mexico,\(^18\) is the only single-institution comparative study in the Table. In that comparison,\(^24\) the adult regimen (hyper-cyclophosphamide, vincristine, doxorubicin, and dexamethasone [hyper-CVAD]) included 6 patients who underwent allogeneic stem cell transplant after achieving remission, 5 of whom were alive at the time of analysis. For reasons not provided, 11 patients receiving the pediatric regimen also underwent stem cell transplant in first remission, 4 of whom died of transplant complications. Without censoring of the patients who received transplants, there was no significant difference in the continuous complete remission rate or overall survival.

The greater number of deaths after transplant among the patients...
receiving the pediatric regimen was not addressed. The pediatric regimen also had a higher central nervous system (CNS) relapse rate (8.5% isolated and 14.2% isolated and concurrent with marrow relapse) than reported by others using a similar regimen.²⁵⁻²⁷,³⁴,³⁵ Also, the strong effect of asparaginase on CNS leukemia in all pediatric regimens is missing in hyper-CVAD.

The second exception is a comparison in Finland¹⁴ that had a similar event-free survival (EFS) for their pediatric and adult regimens but a better overall survival for their pediatric regimens. However, both the pediatric and adult regimens contained asparaginase, with the mean total dose of asparaginase actually higher in the adult regimens than in the pediatric regimens (50 000 vs 40 000 IU/m²).³⁶

A meta-analysis²⁶ of 11 of the above-cited reports of pediatric vs adult regimen comparisons,²⁻²⁸,¹⁴,¹⁶,¹⁸,²⁹ comprising 2489 patients, concluded that the pediatric regimens have statistically significant superior rates of complete remission and relapse-free, event-free, and overall survival rates. The relative risk of nonrelapse mortality was comparable.³⁶

In the United States, the C10403 study²⁸ was a national, Intergroup phase 2 trial of a pediatric regimen in 318 adults aged 17 to 39 years with either T-cell or B-precursor Ph chromosome-negative ALL, of whom 296 are fully evaluable. At a median follow-up of 28 months for surviving patients, the EFS was more than double that of the prior experience. The EFS of 59 months had a lower 95% CI of 38 months, for surviving patients, the EFS was more than double that of the prior experience. The EFS of 59 months had a lower 95% CI of 38 months, which allowed rejection of the trial’s basic null hypothesis that, based on the prior Intergroup experience, the median EFS would have been at most 32 months.

As a result, pediatric regimens are increasingly being used to treat adults with ALL (Table).³⁷⁻³⁹ The largest pediatric regimen-based experience to date is of 1529 patients aged 15 to 35 years treated by the German Multicenter Group for Adult ALL.⁴⁰ Their 5-year overall survival rates were 73%, 69%, and 60% for patients aged 15 to 17 years, 18 to 25 years, and 26 to 35 years, respectively. In Canada,⁴¹ there was a significant increase in survival during 1986 to 2009 among the patients with ALL aged 20 to 29 years, which was primarily attributed to pediatric regimens, in contrast to the same age group in the United States treated with adult regimens, in whom no increase occurred. In 51 adolescents aged 15 to 18 years, the Dana-Farber Cancer Institute (DFCI) Acute Lymphoblastic Leukemia Consortium⁴² reported a 5-year 78% EFS with a pediatric regimen, leading to the consortium’s adoption of this regimen for patients aged 18 to 50 years.

A 2013 meta-analysis⁴³ concluded that in AYAs with ALL allogeneic hematopoietic stem cell transplant (HSCT) in first remission was superior to chemotherapy regimens without HSCT. However, the chemotherapy comparators in that report were limited to “traditional adult-intensity chemotherapy regimens,” for which results were published 20 to 30 years ago and not to current pediatric-inspired regimens.⁴⁴ As concluded in a follow-up correspondence, “the more appropriate conclusion to be drawn is the importance of using more effective, conventional, pediatric-inspired ALL treatment regimens in the adolescent and young adult population”⁴⁵ rather than the “regimens historically used for adults.”

In summary, all but 2 of 25 comparisons of outcomes with pediatric and adult regimens for ALL and LBL in AYAs and 1 meta-analysis favor the pediatric regimen. Why then, hasn’t the pediatric regimen been adopted more widely in the US?
Table. Pediatric and Adult Therapy Regimen Outcomes in AYAs With ALL or LBL

<table>
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<tr>
<th>Report</th>
<th>Clinical Trial</th>
<th>Age, y</th>
<th>No. of Patients</th>
<th>Follow-up, y</th>
<th>EFS, DFS, or CCR, %</th>
<th>Overall Survival, %</th>
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<td>DFS 35</td>
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Abbreviations: ALL, acute lymphoblastic leukemia; AYA, adolescents and young adults; CCR, continuous complete remission; DFS, disease-free survival; EFS, event-free survival; hyper-CVAD, hyper-cyclophosphamide, vincristine, doxorubicin, and dexamethasone; LBL, lymphoblastic lymphoma; NA, not available; ±R, with or without rituximab.

* Median age.

b Pediatric-like.
Challenges of the Pediatric Regimen

Multiphasic Complexity and Intricacy
Considering the strong data on outcome, treatment-related mortality, and toxicity in general favoring pediatric-inspired regimens for AYAs, why have they not been more widely adopted in the medical oncology setting?

Figure 3 shows the history of the pediatric regimen from the perspective of the national randomized clinical trials conducted in North American children with newly diagnosed ALL. In the United States, at least 160 regimens for ALL were evaluated during the last half-century in phase 3 trials conducted by the Children’s Cancer Group and the Pediatric Oncology Group. Since 2000, the Children’s Oncology Group has conducted 10 randomized controlled trials in patients newly diagnosed as having ALL. Not shown are regimens studied by the St Jude Children’s Research Hospital, the Dana-Farber Cancer Institute Acute Lymphoblastic Leukemia Consortium, and in Europe by the following cooperative pediatric groups: International Berlin-Frankfurt-Münster (IBFM), United Kingdom Acute Lymphoblastic Leukemia (UKALL), French Acute Lymphoblastic Leukemia Study Group (FRALLE), Italian Association of Pediatric Hematology and Oncology (AEIOP), and Programa para el Tratamiento de Hemopatías Malignas Spanish Cooperative Group (PETHEMA). In contrast, less than 10 randomized controlled trials have been conducted to date in adult patients. Therefore, contemporary pediatric regimens have evolved into more complex, intricate, multiphasic, risk-based regimens. In contrast, adult treatment regimens have remained simple and easier to administer, with minor incorporation of risk or biological factors.

An element of particular importance on pediatric regimens is the phase of delayed intensification that was pioneered by the Berlin-Frankfurt-Münster Cooperative Group. It applies the Norton-Simon principle of cancer therapy by re-treating the patient with induction and consolidation therapy again (reinduction/reconsolidation) after an interim phase that allows recovery from the initial therapy. Delayed intensification was confirmed in a large phase 3 randomized trial to be a critical component of ALL therapy, substantiated in other trials, and found applicable to AYA patients with ALL, including the C10403 trial. Other than the intensive therapy enabled by HSCT after remission induction, no adult regimen to date has incorporated a delayed-intensification phase at a similar time after diagnosis.

Outpatient Management
The pediatric regimens were also designed to be delivered in the outpatient setting, allowing children and adolescents to be at home with their families as much as possible. This patient-centered strategy requires a robust clinic infrastructure to support the care of outpatients who require frequent interaction with the medical system. With the exception of a recent finding supporting the use of high-dose intravenous methotrexate in children with high-risk B-precursor ALL during an interim phase of treatment, none of the pediatric regimens require hospitalization after the initial admission for newly diagnosed cancer, staging, and initiation of therapy.

Asparaginase
Asparaginase contributes more to the overall chemotherapy regimen benefit than its numerical value of “one in so many drugs” in combination chemotherapy regimens. For the pioneering prospective randomized trial of asparaginase in children with ALL, the asparaginase-containing regimen had a 10-year to 20-year overall
survival rate that was 34% higher with asparaginase, despite it being
the only difference in the regimen of 8 antileukemia drugs.50 A Pe-
diatic Oncology Group study51 that also randomized asparaginase
had an 8-year overall survival that was 53% greater with asparagi-
nase compared with the control 9-drug regime. Some in vitro ex-
periments suggest that lymphoblasts from adult patients may be
more resistant to asparaginase than those obtained from pediatric
patients.52 No significant differences were observed between
B-precursor and T-cell lymphoblasts.53

Asparaginase causes more hepatic dysfunction, pancreatitis,
and coagulopathies in AYAs than in younger patients.23,53,55 In most
cases, hyperbilirubinemia occurs with the first dose and not subse-
quent doses.54 A lower dose and longer intervals between doses of
asparaginase prevent drug-limiting hyperbilirubinemia.27 Several
review articles have addressed this challenge and offer practical
guidelines for prevention and management of asparaginase toxici-
ties in AYAs.53,55-58

In adult ALL, a lesser experience has nonetheless suggested sig-
nificant benefit from asparaginase. In a Cancer and Leukemia Group
B trial,59 the 22 patients who had less asparaginase depletion had a
lower overall survival (hazard ratio [HR], 2.37; 95% CI, 1.38-4.09;
P = .002) and disease-free survival (HR, 2.21; 95% CI, 1.19-4.13;
P = .01) than 63 patients who did achieve asparaginase depletion.
In a multi-institutional study60 of 95 adult patients with T-cell ALL or
T-cell LBL with a median age at diagnosis of 32 years (age range, 17-75
years), those who received asparaginase had statistically improved
relapse-free survival (HR, 2.65; P = .01) and overall survival (HR, 2.30;
P = .02), differences that remained statistically significant after ad-
justing for covariates of age, sex, and white blood cell count at di-
agnosis. Overall survival was greater in asparaginase-treated pa-
tients younger than 40 years (HR, 3.4; 95% CI, 1.2-9.5) than in older
adults. In another multi-institutional study,61 adults with early
T-cell precursor ALL had a statistically significant better progression-
free survival and overall survival if they received asparaginase. With
regard to progression-free survival, only the inclusion of aspara-
ginase with induction was associated with outcome, while all other
covariates failed to show any significance, including cytogenetics sta-
tus, histology, marrow or peripheral blast burden, chemotherapy
choice, or allogeneic transplant in complete remission or at any
time.61

Therefore, the benefit to toxicity ratio of asparaginase in AYAs
with ALL or LBL is favorable. Learning how to prevent and manage
its toxicity is a distinct challenge for oncologists who are not fami-
lar with it. As experienced nationwide on the C10403 trial, in Eu-
rope by many of the adult-treating groups in the Table, and particu-
larly by the Dana-Farber Cancer Institute Acute Lymphoblastic
Leukemia Consortium in the United States and Canada that uses pro-
longed intensive asparaginase,27 adult-treating oncologists have
successfully managed asparaginase therapy in their patients.

Hematopoietic Stem Cell Transplant
With the notable exception of Ph chromosone-positive ALL, pedi-
atriatric regimens have not required allogeneic HSCT.44 In contrast, many
adult patients with ALL treated on an adult regimen receive HSCT dur-
ing initial remission if they have a matched, available donor. Being able
to avoid the toxicities, late adverse effects, and financial cost of HSCT
substantially favors the pediatric regimen. Another factor favoring the
pediatric regimen is that young AYA recipients are more suscep-
tible to allogeneic HSCT-induced acute graft-vs-host disease than
either younger or older patients.62

Collaboration
The challenge of the pediatric regimen lies in becoming knowledge-
able and comfortable with its complexity. Adult-treating oncologists
benefit from the collaboration with and support of pediatric oncolo-
gists and their staff in applying a pediatric regimen, as well as from or-
ganizational modifications of their ambulatory clinics to support ef-
ective and manageable delivery of the pediatric regimen.63 That the
 collaboration is critical is evidenced by the comparison of the mortal-
ity rate of pediatric and young AYA patients with that of patients hav-
ing ALL at Children’s Oncology Group (COG) vs non-COG institu-
tions.64 The mean death rates in the non-COG centers were clearly worse
than those at COG institutions, with almost twice the death rate within
1 year after diagnosis and increasingly worse from 5 to 9 years after
diagnosis. The AYAs treated at specialty or NCI-designated cancer
centers likely have improved outcomes due to the familiarity of these
centers with ALL management in this age group.

US ALL Treatment Trial Accruals—The Accrual Cliff

For NCI-supported clinical trials since 2000, Figure 4 shows the es-

dimated accrual proportion of patients with ALL participating in clini-
cal trials (blue curves) and its associated “accrual cliff” between ages
15 and 30 years. Since 2010, the accrual cliff has shifted upward in
AYAs younger than 30 years (upward arrows), in contrast to a de-
creased proportion in older patients. The trend in AYA patients is a
notable accomplishment for the age group that historically has had
less than 10% of those diagnosed as having cancer referred to or ini-
tially seen at academic medical centers and the lowest referral rate of
all ages up to 70 years.65

The NCI Community Clinical Oncology Program66 did not con-
tribute to the improvement, with their AYA accruals decreasing
during 2009 to 2013. The successor NCI Community Oncology Re-
search Program67 is expected to reverse the trend. In the greater
San Francisco Bay area of California, no adult patients treated be-
fore 2008 by adult-treating oncologists received a pediatric
regimen.68 Between 2008 and 2012, while the C10403 protocol was
open to accrual, 31% of AYA patients in the San Francisco Bay area
treated by adult oncologists received pediatric regimens.68 Mean-
while, the national accrual cliff in those aged 17 to 21 years is just as
steep since 2010 as it was during the prior decade (Figure 4).

The age-related survival cliff and accrual cliff, as well as a “refer-
ral cliff,” coincide (Figures 2 and 4). This overlap suggests a strong
cause-effect relationship, with the lack of clinical trial activity likely
representing a primary factor for the survival deficit.67 Strategies to im-
prove clinical trial participation by AYAs with cancer include the fol-
lowing: increasing availability of clinical trials specifically designed for
them, reducing clinical trial regulatory requirements, centralizing all
national cancer clinical trial accruals and data management, optimiz-
ing the efficacy of central institutional review boards having reduced
local review board management, liberalizing clinical trial eligibility cri-
teria, using social media to inform patients with cancer and their fami-
lies, increasing health insurance coverage of clinical trial expenses, and
providing funds to offset patient travel expenses and meals and addi-
tional staff time for minority recruitment.69,70
Since 2012, the National Comprehensive Cancer Network (NCCN) has recommended either a clinical trial or pediatric-inspired regimen for newly diagnosed Ph chromosome-negative ALL in AYAs.71 The clinical trial recommendation for AYAs was based in part on the likelihood that a clinical trial would be based on pediatric therapy.71 In 2016, the NCCN added hyper-CVAD plus rituximab to its AYA ALL guidelines but specified that it was for CD20-positive ALL only and that the pediatric regimens for all forms of Ph chromosome-negative ALL were “preferred.”72 In 2017, the guidelines expanded hyper-CVAD to all Ph chromosome-negative AYAs and added a pediatric-inspired University of Southern California regimen, with the specification that both were based on data from single institutions as opposed to the pediatric regimens that were based on data from multi-institutional or cooperative group studies.73

Where Should an AYA With ALL Be Treated?

Optimally, for the reasons stated herein and as recommended up front by the NCCN, AYAs with ALL should be referred to a center with an available clinical trial. As described in the Challenges of the Pediatric Regimen section, the challenges faced by adult-treating oncologists in transitioning to a pediatric regimen require pediatric oncologists and their staffs and the cooperative groups to educate, train, and provide close support to their medical oncology colleagues. Ideally, an AYA patient with ALL should be comanaged by the pediatric and adult services and, in certain circumstances, be transferred to a pediatric or AYA oncology service. Ultimately, an AYA oncology discipline with specific training, including fellowship programs, may provide a sufficient number of AYA oncologists to optimize management of a complex pediatric regimen.

Conclusions and Recommendations

The progress in treating AYAs with ALL and LBL is due to multiple factors. These include the following: the change that has occurred with recognition of this patient population, the knowledge and application of biological underpinnings of AYA ALL and LBL, the collaboration between the cooperative groups in the NCTN, and the development of protocols to address important treatment issues and subgroups. The survival cliff and accrual cliff and other data presented herein provide the rationale to treat AYAs with newly diagnosed ALL on either a pediatric-inspired regimen or an approved national clinical trial designed for this patient group, such as the Alliance A041501 trial.1 If not available in the AYA’s community, referral to a specialized center with access to these trials should be arranged.73 For the survival of AYAs with ALL and LBL to continue to improve, clinical trial development and accrual for this age group will need continued improvement.74 The new trials for Ph-like ALL, such as the AALL1131 trial,75 are particularly promising because this form of ALL predominates in AYAs.

Not included in this narrative review is a description of the better quality of life during and after therapy on the pediatric regimen than on the hyper-CVAD regimen, as indicated by hospitalization time, readmission for treatment complications, and late adverse effects, such as infertility and second malignant neoplasms. This quality-of-life advantage will be the subject of another review article.
TREATMENT REGIMENS FOR ADOLESCENTS AND YOUNG ADULTS WITH PH CHROMOSOME-NEGATIVE ALL

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**REFERENCES**


17. Hayakawa F, Sakura T, Yujiri T, et al. Japanese Adult Leukemia Study Group (JALSG). Markedly improved outcomes and acceptable toxicity in adolescents and young adults with acute lymphoblastic leukemia following treatment with...
53. Rizzoli C, Putti MC, Colombini A, et al. Rationale for a pediatric-inspired approach in the adolescent...


