## Title

Acute Lymphoblastic Leukemia in Children and Adults: A Review of the Differences in Biology, Treatment, and Prognosis



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# Acute Lymphoblastic Leukemia in Children and Adults: A Review in the Differences in Biology, Treatment, and Prognosis

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**Abstract**

This paper analyzes the difference between Acute Lymphoblastic Leukemia (ALL) in adults and children. Specifically, it discusses the biological differences in the cancer subtypes seen between these two groups, how they affect the possible treatment options, and how these differences play a role in the disparity in prognostic outcomes. In addition, this paper also examines the disparity between adults and children has been hard to characterize and how the age differences play a role in risk management for Acute Lymphoblastic Leukemia.

## Introduction

Prior to the 1960s, ALL was viewed as a fatal disease without a cure.[1] Following the opening of St. Jude Children's Research Hospital, clinicians at the hospital began to use cranial radiation and intrathecal therapy to treat the occult central nervous system leukemia. Over the next decades, steroids and newly developed drugs were used to treat pediatric ALL, which spurred the formation of modern cancer cooperative study groups. By the 1990s, physicians applied molecular biology and a recently established system of risk classification when administering higher doses of therapy, which resulted in higher survival rates, especially for high-risk patients (Seibel, 2008). Acute lymphoblastic leukemia (ALL) is one of the most common neoplasms in children, and its prevalence in adults is comparatively rare (Chiaretti, 2013). Out of all the genetic subtypes of ALL, Philadelphia chromosome-positive ($Ph^+$) ALL, defined by the translocation caused by *BCR-ABL1* fusion, is known to be associated with poor clinical outcomes (Tasian, 2018).

There are specific biological differences that can affect the way that treatments affect children compared to an adult including specific chemotherapy doses. The genetic alterations also cause a variation in prognosis between adults and pediatric ALL, and the process of developing treatments has been slow and extremely complicated because of all the different types of genetic alterations that can occur. As a result of these variations in the prognosis of ALL, new risk management strategies are required in order to effectively stratify and treat patients (Bassan, 2020).

## Biological Differences

Acute lymphoblastic leukemia (ALL) is characterized by genetic alterations that block differentiation and promote the proliferation of lymphoid precursor cells. Although less common in adolescents, young adults, and adults than in children, survival rates and long-term prognosis for adults is inferior, making ALL a challenging disease to treat for adolescent and young adults (AYA) and adult populations. This is partly due to the lack of subtype-defining lesions observed in childhood ALL, making it difficult to identify subtypes within AYA and adult populations. Specifically, cytogenetic subtypes most prevalent in AYA and adult ALL have a poor prognosis (ex: Ph-like ALL, hypodiploidy, and IGH rearranged). This is largely due to the reduced prevalence of genetic subtypes associated with favorable outcomes (ex: ETV6-RUNx1) and a linked increase in subtypes associated with poor outcomes (ex: BCR-ABL1). For example, the prevalence of IGH rearrangements is particularly high in AYA and adult ALL and generally results in a poor prognosis. A subset of cases characterized by IGH to BCL2, MYC, and/or BCl6 rearrangement is largely identified in adults and associated with unfavorable outcomes (Bhojwani, 2015). However, the subset determined by the translocation of DUX4 to IGH is associated with excellent prognosis in both children and adults, with a slight peak in AYAs, despite secondary genetic alterations typically associated with poor outcomes. The rearrangement of IGH results in a negative prognosis, but the rearrangement of another IGH does not have the same issue. (Gröbner, 2018)

Another important difference between ALL in older adults versus children or adolescents is that ALL in older patients have a greater frequency of displaying high-risk genomic subgroups like the Philadelphia chromosome and Philadelphia-like chromosome ALL. A study was done on a group of 148 patients whose median age was 38 years old, the incidence of $PH^+$ ALL was 41% in adults that are aged 40 years or older, while this ratio in adults younger than 40 years old is

22% (Jain, 2017). In another study done to 83 patients with B-cell acute lymphoblastic leukemia (PH+ B-ALL), Ph-like ALL occurs commonly in adults. In this group, the median age of the patients is 46 years, ranging from 18 to 88 years old. In these groups of adults, the proportion of Ph-like ALL takes up to 46.6% of the cases in patients younger than the age of 40. However, the pattern for adults younger than the age of 40 is not as obvious (Tasian, 2016).

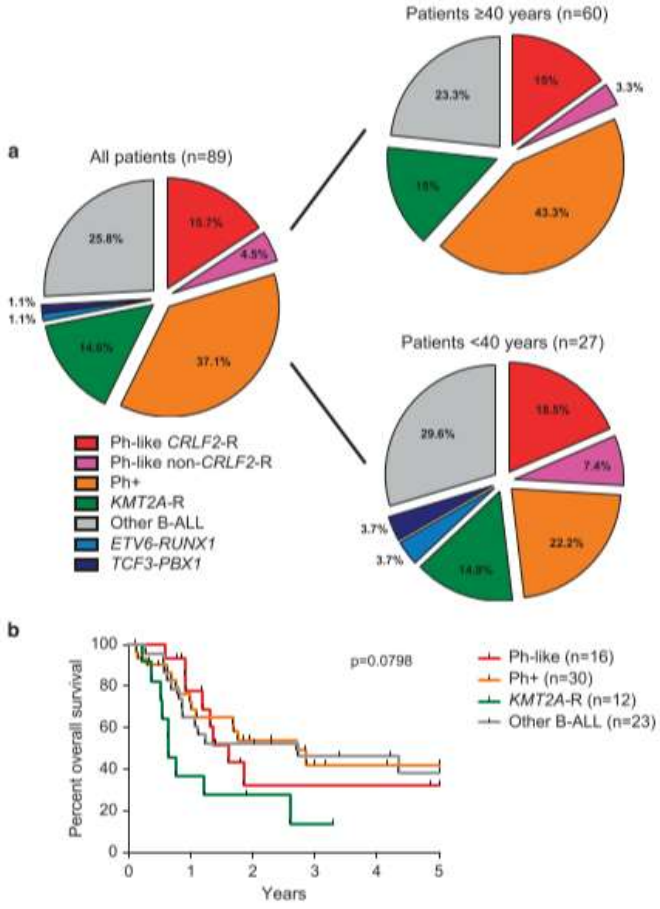


*Figure 1: Ph-like ALL occurs commonly in adults with B-ALL and is associated with poor outcomes. (a) Incidence of Ph-like and other genetic subtypes in adults with B-ALL with subset analyses of patients ⩾40 and o40 years of age. Age was not available for two patients. (b) Kaplan– Meier survival analysis with log-rank comparison test of patients with B-ALL for whom*

*outcomes data were available (n=81) with indicated P-value. When appropriate, survival was censored at last known clinical evaluation (Tasian, 2016).*

The biological differences that occur with ALL affect the difference in outcomes for children and adults. One of these is high hyperdiploidy which is the nonrandom gain of at least five chromosomes and is also associated with a favorable outcome. This is shown to occur in about 25% of children and only less than 5% of adults. Another difference is low-hypodiploid which often causes deletion of *IKZF2* and sequence mutations of *TP53* that are frequently inherited. Low-hypodiploid is correlated with very unfavorable outcomes and is present in less than 1% of children cases while being present in over 10% of adult cases (Roberts, 2018).

**Treatment Options**

Firstly, it is important to note the systematic differences in ALL treatments. Historically, there have been different clinical categorizations of 15 to 20-year-old patient age division under pediatric or adult treatment. Oftentimes, pediatricians refer this patient age group to pediatric academic medical centers where more than 90% of patients are under the age of 15 and are subjects in clinical trials (Sallan, 2006). Contrastingly, primary care doctors frequently refer 15 to 20-year-old patients to adult hospitals, instead of academic medical centers, where more than 90% of the patients are older than 40 years and the majority of patients are not enrolled in clinical trials (Sallan, 2006). Consequently, unlike 15 to 20-year-old ALL patients of internists, pediatric patients referred to academic medical centers receive maximum chemotherapy dosage administered in clinical trials.

Due to ALL being the most common childhood malignancy (25% of all childhood cancers), the majority of treatment strategies are designed for subtypes typically found in

children. Because adults lack subtype-defining lesions observed in childhood ALL, treatment of AYA and adult populations proved difficult until recent advancements in genomic analysis. Genome-wide profiling of RNA and DNA and next-generation sequencing (NGS) technologies have increased the ability to identify submicroscopic genetic alterations and sequence mutations, in turn defining new molecular subtypes commonly found in older populations (Roberts, 2018). The challenge remaining is determining how to implement this new genomic information into rapid, accurate diagnostic testing to facilitate the development of clinical trials that improve the outcome of AYAs and adults with ALL. In recent years, progress in the treatment of AYAs and adults with ALL was made by recognizing the group as a unique population separate from children, developing treatment protocols specifically for the age group, and increasing the availability of clinical trials to improve the understanding of ALL across the age spectrum.

When it comes to treatment options, there are many traditional treatments such as chemotherapy, but as time has progressed ALL has received more attention that has allowed for the development of more experimental treatments. One of these treatments is chimeric antigen receptor (CAR) T-cell therapy. This is targeted immunotherapy where T cells, which are types of white blood cells, are taken from the body and then engineered in order to attack tumor-specific antigens. This has led to outstanding results, such as 70%-90% MRD(minimal residual disease)-negative CR(complete remission) rates in single-institution trials, with multicenter trials having a respectable 60% CR rate (Gregory, 2019). However, compared to traditional methods of treatment, there is also the issue of neurotoxicity which can be induced by the CAR T-cell therapy, and the therapy can also affect regular B cells in the body. T cells also target these B cells, which are another kind of white blood cell, and lead to further depletion of them and a lack of their development, which can result in further issues.

Since adults have higher relapse rates, there are treatments that are more commonly used in adults than in children. An example of this is Nelarabine, which is a nucleoside analog that is FDA approved for the treatment of relapsed ALL patients who have failed two past treatments (Narayanan & Shami, 2011, p.99). In the study, it had a 31% CR rate in adults with a 1-year overall survival rate of 28%. However, it also has biological side effects such as neurotoxicity (Narayanan & Shami, 2011, p.99). Similarly, another treatment used to treat ALL is Clofarabine, which is a nucleoside analog that is also used by itself for pediatric patients with relapsed ALL. This treatment differs in adults in that it is often used in combination with first-line and salvage therapy (Narayanan & Shami, 2011, p.99). This is because since adults typically have stronger bodies, they can take this route of treatment sooner (Narayanan, 2012).

Chemotherapy is a commonly used treatment for many different types of cancer. For patients with ALL, research shows that the dosage and intensity of chemotherapy need to be specifically tailored to children and adults respectively. A study through the Pediatric Health Information Systems database sought to review health care outcomes in ALL pediatric (ages 10-14) and AYA patients (ages 15-29) that were in the hospital from the beginning of 1999 and end of 2014 (Gupta, 2021). A level of toxicity was measured relevant to ICD-9 data. The results of the study showed that AYA patients with ALL had a much higher chance of being in the ICU compared to pediatric patients with ALL but the length of the stay, as well as the mortality rate between the two groups, showed no significant difference. This showed that AYA patients showed to have much higher toxicities from the chemotherapy drugs regularly used for pediatric patients with ALL.

**Prognosis**

Studies have shown that although acute lymphoblastic leukemia is less common in AYAs than in children, the prognosis is bleaker. It has been discovered that the decline in survival rate as age increases can be connected to a reduced amount of specific genetic alterations. Being able to properly identify these genetic alterations is important in beginning to understand how to approach the treatment of patients with ALL. Because of the wide range of genetic variants that can cause ALL, this cancer is extremely difficult to treat, which is reflected in the survival rate in adults.

One cause for the difference in the prognosis of children and adults may be related to how ALL in adults begins in multipotent stem cells, whereas in children it begins with mature lymphoid committed progenitor cells (Plasschaert, 2004). Philadelphia chromosome (Ph)-positive ALL's translocation is found in the stem cell compartment, which furthers the reasoning behind adult ALL originating in multipotent stem cells, due to the higher occurrence of Ph-ALL in adults. Another difference between adult and childhood ALL may be the result of how multipotent stem cells frequently divide to produce more stem cells which can transform into controlled amounts of other cell types with focused roles.[1] Multipotent stem cells have been found to be more impervious to chemotherapy in comparison to committed progenitors.

The joint causes of an increased probability of high-risk ALL subtypes and a decreased tolerance for cancer treatment has resulted in a worse prognostic outcome in adults with ALL. The 5-year survival of CLRF2+ ALL, a very common subtype of Ph-like ALL, has an extremely low survival rate of less than 20% (Jain, 2017). Another study found that the median survival rate of ph-like ALL is 1.6 years, which is also lower in comparison to other types of ALL that are present in the study (Tasian, 2016). Besides the general overall survival rate, the 5-year overall survival among people who achieved complete remission is still significantly worse in

the older group - the OS for older groups is 30% compared to 44% of the younger group (Sive, 2012). In the aspects of treatment, there are significantly more incidences of drug reductions, omissions, or delays in the older group in phase 1 - such rates for the older group is 30%, compared to the 15% in the younger group).


*Figure 2: . Survival of patients by age at entry to study showing (A) overall survival and (B) event-free survival in all patients and (C) overall survival in those who acheived complete remission.*

Among the age groups of acute lymphoblastic leukemia patients, adults have experienced the least amount of treatment progression and improvement. Limited treatment options and opportunities to be included in clinical trials in comparison to children have become a factor for adults having the poorest prognosis among all age groups with ALL. The complete remission (CR) rates of adults are 75 to 89%. Moreover, the long-term disease survival rates are 28 to 39%. The CR and long-term disease-free survival rates of children with ALL are much higher than that of adults. Children with ALL have a CR rate of 95% and a long-term disease-free survival rate of 63 to 83% (Plasschaert, 2004).

**Additional Important Factors**

ALL is a heterogeneous disease, meaning that it has multiple etiologies. Because ALL has several root causes, comparing the effects of the disease between children and adults and differentiating treatment approaches by primary care doctors and pediatricians can be inefficacious. For instance, when researchers compared the percentages of complete remissions between adolescents and adults, they found that the time to enter the end-stage is reported at the end of approximately 1 month of multiagent chemotherapy in pediatric trials while the same data is recorded following 2 months of treatment in several adult trials (Sallan, 2006). This variability is substantial because they found that in 12 of the pediatric trials, the difference between complete remission in 1 month or 2 months determined life or death for most slow-responding subjects.

With ALL, it is important to manage the risks of patients. This is primarily due to ALL being a fast disease and having biological differences when looking at the different age groups. As a result, when looking at patients, there is a need for risk stratification in order to ensure that patients would be properly put into the categories in which they belong. In a study done in 2008 to 2012, patients were stratified into certain groups depending on data obtained via sensitive molecular probes. The collection of data was done at weeks 10, 16, and 22, and patients were then put into certain categories based on if they had standard, high risk, or very high risk, which would then lead to them having certain kinds of treatments (Bassan, 2020). This is important as in the future, there can be more clear categories on the types of stratification and as a result the treatment which patients get.

Acute lymphoblastic leukemia patients of varying age groups may experience an overall effect on their prognoses due to the medical resources accessible to them. Among children with ALL, 90% are long-term survivors due to rigorous treatment plans carried through for them by a

team. The medical team may be located at a specialized pediatric oncology center led by a pediatric hematologist, who has an ample amount of experience with types of leukemia. Adults with ALL often do not have the choice to be treated by a specialized hematologist. The treatment plans of children with ALL are rigorous, such that each treatment is given on schedule and at the maximal dosage. There is certainty that a child's treatment plan can be carried out strictly following a schedule. Another life-altering medical resource that is a scarce option to AYA and adults is clinical trials. Children diagnosed with ALL have the option of participating in clinical trials; however, adolescent, young adult, and adult patients have limited opportunities to take part in clinical trials (Neaga, 2021).

**Conclusion**

There is evidence that suggests that compared to pediatric ALL, adult ALL has a higher frequency of high-risk genomic subgroups like Philadelphia chromosome-positive ALL and Philadelphia chromosome-like ALL. In addition, as a result of higher rates of hyperdiploidy and lower rates of hypodiploid in children, children have greater biological advantages for favorable outcomes than adults do. Because treatment for individuals varies greatly between children and adults, there needs to be more extensive research done on how the current treatments can be altered as well as future treatment developments to better the prognosis for both children and adults with ALL. Homogenizing referral patterns for young adult patients must be considered to maximize the benefits of chemotherapy for adult patients. While work should be done to improve the prognosis for both children and adults with ALL, our findings suggests a stronger need to focus on developing treatments for adults due to the greater frequency of high-risk subytpes and unfavorable treatment outcomes. It is obvious that adults are at a disadvantage both in terms of survival rates and the positive responses to drugs compared to children with ALL.

Establishing clinical trials with adult ALL patients is a vital step in advancing ALL knowledge and approaches.

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