LEUKEMIA & LYMPHOMA SOCIETY®

HEALTHCARE PROFESSIONALS

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providing the latest information

Facts About **Pediatric Acute Leukemia**

Introduction

Acute leukemias represent a substantial proportion of pediatric cancers. Early diagnosis and treatment is critical to optimize outcomes among children and adolescents. Although clinical outcomes have improved considerably for young patients with acute lymphoblastic leukemia (ALL) in recent decades, outcomes in acute myeloid leukemia (AML) lag behind, underscoring the need for further therapeutic innovations. Accordingly, well-designed and forward-thinking clinical trials are essential to further improve long-term survival. Beyond initial treatment, survivors of childhood and adolescent acute leukemias are growing in number, increasing the need for healthcare providers to be well-versed in the long-term follow-up of these patients, who are at increased risk of late effects in a variety of organ systems and second primary malignancies, as well as psychosocial, financial, and healthcare access issues. To help ensure that children and adolescents with leukemia receive the best possible care, this fact sheet has been developed to provide essential knowledge regarding diagnosis, treatment, clinical trials, and long-term management, as well as key resources to help patients and families along this lifetime healthcare journey.

Overview of Childhood and Adolescent Leukemias

Leukemias account for a substantial proportion of all cancer in children and adolescents. According to data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program, an estimated 129,221 children and adolescents younger than 20 years in the United States (US) are living with or in remission from any type of cancer, of which 42,211 are leukemias (about one-third).[1] The acute leukemias collectively represent the most prevalent type of blood cancer among US children and adolescents, **(Table 1)**. Acute lymphoblastic leukemia (ALL) is the most prevalent blood cancer type in this age group, accounting for 35,416 cases, or about 84% of all leukemias, while acute myeloid leukemia (AML) accounts for 4,467 cases, or about 11% of all leukemias.

Table 1. Approximate US Prevalence of Major Blood Cancer Types in Children and Adolescents Younger than 20 years (as of January 1, 2019)

Type	Prevalence*
Leukemia	**42,211**
Acute Lymphoblastic Leukemia (ALL)	35,416
Acute Myeloid Leukemia (AML)	4,467
Acute Monocytic Leukemia (AML-M5)	476
Chronic Leukemias**	1,026
Non-Hodgkin Lymphoma	**7,406**
Hodgkin Lymphoma	**4,365**
Chronic Myeloproliferative Disorders	**448**
Myelodysplastic Syndromes	**435**
Myeloma	**23**

Source: SEER*Explorer: An interactive website for SEER cancer statistics [Internet]. Surveillance Research Program, National Cancer Institute. Accessed July 28, 2022. Available from https://seer.cancer.gov/explorer/.

* Based on prevalence estimates for individual disease categories. For Chronic Myeloproliferative Disorders and Myelodysplastic Syndromes, data are limited to ≤18 years since diagnosis.

** Chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), and chronic myelomonocytic leukemia (CMML).

Mortality

Despite progress in therapy and supportive care, mortality due to acute leukemias remains a significant concern. Prognosis has improved for young patients with ALL, such that the current estimated 5-year survival rate is 92% for children with lymphoid leukemias, but just 76% among adolescents. Unfortunately, outcomes are still lagging in pediatric AML, with estimated 5-year survival rates of 68% and 67%, respectively, in children and adolescents.[2]

Demographics

ALL is most often diagnosed in early childhood, with a peak in incidence between 2 to 5 years of age. By contrast, AML cases occur throughout childhood, though diagnoses are somewhat more common between birth and 2 years, and again during adolescence.[3] While ALL is slightly more common in male vs female children and adolescents (38.4 and 30.2 per 1 million, respectively), AML incidence is about the same (7.9 and 8.0 per million, respectively). Racial/ethnic differences in incidence have not been observed in AML, but in ALL; i.e., ALL is more common in Hispanic and White children and adolescents (44.9 and 34.2 per million, respectively) than in Black children and adolescents (18.3 per million).[4]

Risk factors

Some genetic factors and conditions may increase the risk of developing acute leukemias in childhood. Specific conditions linked to both ALL and AML include Down syndrome (DS), Li-Fraumeni syndrome, neurofibromatosis, Bloom syndrome, and Fanconi anemia.[5,6] Other accepted risk factors for ALL include prenatal X-ray exposure, high-dose radiation treatment, and prior chemotherapy.[5] The sibling of a child with leukemia has a slightly elevated risk of leukemia. By contrast, leukemia risk is increased by 2- to 4-fold in the fraternal twin of a child with a leukemia diagnosis, while the identical twin of a leukemia patient has an approximate 1 in 5 chance, of also being diagnosed, with an even higher risk reported in the first year of life.[5,7]

Down syndrome is a significant risk factor for leukemias in childhood. About 2–3% of children with DS receive a leukemia diagnosis, as compared to 0.05% of children without DS.[5,8] The cumulative risk of AML in children with DS is greatest before the age of 4 or 5, while the age distribution of ALL is similar in children with or without DS.[5,8,9]

Diagnosis and Risk Stratification

Signs and symptoms

The early recognition of acute leukemias, along with timely referral to a specialist (i.e., a pediatric hematologistoncologist), is critical to ensuring prompt evaluation and appropriate treatment. However, recognition can be challenging due to symptoms that are often non-specific and therefore overlooked. Many patients will present with recurrent fever, bone pain, swollen lymph nodes, or abdominal swelling. Patients may have symptoms suggestive of anemia (such as fatigue, weakness, and pale skin), neutropenia (infections or fever), or thrombocytopenia (easy bruising and bleeding).[10] Loss of appetite and weight loss may occur. Leukemia cutis, which presents as red or violet papules, nodules, or plaques on the skin, is present in some patients.[11] Gingival hyperplasia (i.e., overgrowth of gums) can form rapidly and may be the first sign of AML in some individuals.[12]

Differential diagnosis

The workup of suspected acute leukemia should include consideration of other potential diagnoses that may be confused with leukemia, including neutropenia, drug-induced cytopenia, viral suppression, immune thrombocytopenic purpura, and autoimmune hemolytic anemia. Others may include aplastic anemia, juvenile idiopathic rheumatoid arthritis, rheumatic fever, Evans syndrome, splenic sequestration, osteomyelitis, and transient erythroblastopenia of childhood.[13,14]

Diagnostic workup

A number of tests and procedures may be performed in the diagnostic workup of a pediatric patient with suspected acute leukemia. A complete blood count (CBC) with differential is useful to identify abnormalities in cell counts and determine the presence of blasts. The presence of blasts in blood or bone marrow is required for a leukemia diagnosis. Chest radiographs (X-rays) are usually performed and may reveal mediastinal masses, among other findings.[15] A lumbar puncture can help detect leukemic blasts in the cerebrospinal fluid.[10]

Bone marrow aspiration and biopsy is also central to a definitive diagnosis. Morphologic analysis of marrow and leukemic blasts under a microscope helps to distinguish different types of leukemia based on factors such as nucleus-to-cytoplasm ratio or cell features such as nuclear

indentation.[13] Flow cytometry and immunohistochemistry is also useful in determining the precise leukemia subtype based on specific proteins found in or on cells.[16] Cytogenetic testing is performed to identify chromosomal abnormalities (e.g., translocations or gains); fluorescence in situ hybridization (FISH) can be used to identify an array of chromosomal abnormalities, including some not detectable with standard cytogenetic tests. Molecular testing is increasingly important in the diagnostic workup to identify genomic alterations that may affect prognosis or treatment decision making. From the date a sample is taken, it may take a few days to weeks to receive the test results. In patients with AML, tests may reveal mutations in genes such as *FLT3*, which are associated with poor outcomes, whereas mutations in *NPM1* and *CEBPA* are associated with more favorable prognosis.[17] In ALL, genomic alterations tend to cluster by subtype; e.g., *IKZF1* deletions and mutations are often seen in patients with Philadelphia chromosomepositive (Ph+) ALL and Ph-like (BCR-ABL1-like) ALL, while *TP53* mutations often occur in patients with low hypodiploid ALL.[5]

Prognostic factors and risk-based treatment

Acute Lymphoblastic Leukemia (ALL)

Specific prognostic factors related to patient characteristics, disease characteristics, and treatment response have been identified. Prognostic risk groups have been identified based on groupings of these factors; e.g., the Children's Oncology Group (COG) has stratified children with ALL based on a subset of factors including age, white blood cell (WBC) count, immunophenotype, cytogenetics, and genomic alterations, among other factors. Risk-based treatment assignment allows for more intensive therapy to be allocated to children with a lower probability of favorable long-term outcomes, while sparing treatment-related toxicity for children predicted to have good outcomes.[5]

Age is strongly linked to prognosis in pediatric ALL, with the best disease-free survival (DFS) seen among young children between the ages of 1 and 10 years, in contrast to pediatric patients who are younger (under 1 year) or older (over 10 years of age).[5] In an analysis of Surveillance Epidemiology and End Results (SEER) data, survival was found to peak among children diagnosed at 1–4 years, with a steady decline at older ages of diagnosis, plus the lowest survivorship overall in infants.[18] In studies, rates of survival among Black and Hispanic children with ALL is generally lower than in White children with ALL, a finding that is at least partially explained by differences by race in the prevalence of favorable/unfavorable ALL subtypes, rates of treatment adherence, and genomic variations related to ancestry.[5]

Leukemia-specific factors that impact prognosis include immunophenotype, as well as cytogenetics and genomic abnormalities. Most children with B-ALL have the common immunological subtype with blast cells positive for CD10 but negative for surface and cytoplasmic immunoglobulins (common ALL), which carries a favorable prognosis.[5] A number of genomic alterations have been associated with more or less favorable prognosis in B-cell ALL. In the COG AALL0331 trial, favorable cytogenetics including the ETV6-RUNX1 fusion and simultaneous trisomies of chromosomes 4, 10, and 17 were found to predict cure.[19] By contrast, poor-prognosis features include hypodiploidy, the Philadelphia chromosome, *KMT2A* gene rearrangements, and intrachromosomal amplification of the *AML1* gene (iAMP21).[5]

Response to therapy assessed by conventional means or measurable residual disease (MRD) is associated with prognosis in pediatric patients with ALL. In particular, MRD has emerged as an important predictor of relapse. In a COG study, early response to induction treatment, based on the level of MRD as measured by flow cytometry, was the most important prognostic variable for outcome in children with ALL.[20]

Acute Myeloid Leukemia (AML)

Similar to what is observed in ALL, prognostic factors for AML have been identified that relate to patient characteristics, underlying disease, and response to treatment. Prognostic risk factors have been used by cooperative clinical trial groups to stratify patients with pediatric AML and assign treatment. Recent clinical trials by COG have incorporated cytogenetics, molecular markers and MRD following treatment to classify patients as low- or high-risk.[21,22]

Age, race/ethnicity, body mass index (BMI), and a diagnosis of DS have all been implicated as patient-related prognostic factors in children with AML. More specifically, older age has conferred a worse prognosis in multiple studies, though survival differences may hinge on risk of toxicity-related mortality, which is increased among older patients.[23] With regard to race and ethnicity, White children generally have had higher rates of overall survival versus Hispanic and/or Black children, in clinical trials, though the potential sociological and biologic causes of these disparities remain understudied.[24] Higher BMI is associated with higher mortality and poorer event-free survival versus lower BMI in studies of pediatric AML, similar to studies of pediatric ALL.[25] Of note, while a diagnosis of DS confers a high risk of subsequent AML, the prognosis of these patients is quite good with regard to overall survival rates of approximately 80%, as compared to less than 35% for children without DS.[26]

Response to therapy, including MRD status, is also predictive of clinical outcome in pediatric AML. In a recent systematic review, MRD positivity during treatment emerged as the most powerful factor in prognosis in pediatric AML with respect to both relapse and overall survival; however, MRD negativity did not exclude possibility of relapse.[27]

Leukemia-related risk factors in pediatric AML include WBC count, leukemia subtype, CNS disease, immunophenotype, and cytogenetic or molecular features of the disease. A number of genetic aberrations are associated with both favorable and unfavorable prognosis in pediatric AML. Leukemia subtypes with abnormalities linked to favorable prognosis include AML with mutated *NPM1*, AML with biallelic mutations of *CEBPA*, and core-binding factor (CBF) AML, which is associated with chromosomal rearrangements involving genes that include *RUNX1, RUNX1T1, CBFB,* and *MYH11*.[28] Genetic factors linked to unfavorable prognosis include specific mutations (e.g., presence of a *FLT3* internal tandem duplication [*FLT3*-ITD] mutation) and chromosomal abnormalities such as 5q deletion and monosomy 7.[6]

Treatment of Pediatric Leukemia

Treatment of Pediatric B-cell ALL

For children with newly diagnosed ALL, standard therapy consists of chemotherapy for remission induction, followed by consolidation/intensification and maintenance therapy, and intrathecal chemotherapy. Treatment is also needed to address clinical or subclinical disease at extramedullary sites, i.e., the central nervous system (CNS) and testes. For the CNS, treatments may include additional intrathecal chemotherapy, systemic chemotherapy, or radiation. Although radiation may be used to treat testicular involvement, a strategy of aggressive conventional chemotherapy with no radiation has led to good outcomes in studies and is used in clinical practice.[5,28]

For patients with Philadelphia chromosome-positive (Ph+) ALL, standard treatment includes use of a tyrosine kinase inhibitor (TKI) such as imatinib or dasatinib plus chemotherapy, sometimes followed by hematopoietic stem cell transplantation (HSCT) in first complete response (CR).[30] Based on available evidence, use of a TKI plus intensive chemotherapy is likely to extend overall survival in children with Ph+ ALL.[31]

The optimization of chemotherapy regimens for pediatric ALL over many decades has led to CR rates of 90% to 100% and potential cure rates exceeding 85%.[32,5] Systemic induction chemotherapy typically includes 3 drugs: vincristine, asparaginase, and a corticosteroid (prednisone or dexamethasone). A fourth drug (an anthracycline, either daunorubicin or doxorubicin) may be included, usually for higher-risk patients.[5] The great majority of patients (>95%) will achieve CR to induction chemotherapy within 4 weeks of treatment. If residual disease (i.e., MRD) is found despite standard induction and consolidation, therapy may be further intensified or given for a longer duration.[33] In addition, blinatumomab is a bispecific CD19-directed CD3 T-cell engager that is approved by the U.S. Food and Drug Administration (FDA) for the treatment of adults and children with B-cell precursor ALL that is in first or second remission with MRD.[34] Of note, blinatumomab was investigated as a frontline therapy for children with ALL in the COG AALL1731 study, which compares the bispecific agent to conventional chemotherapy and showed significantly improved disease-free survival.[35,84]

Following CR, patients proceed to several months of post-induction therapy, which varies depending on protocol, and then maintenance therapy (along with CNS-directed treatment). The most common approach is initial consolidation with cyclophosphamide, low-dose cytarabine, and mercaptopurine, followed by an interim maintenance phase that includes high-dose methotrexate; reinduction with treatment similar to those used initially; and maintenance with mercaptopurine and low-dose methotrexate, often with the addition of vincristine plus corticosteroid pulses.[36,37] New treatment approaches are under study in this setting; currently recruiting patients is COG AALL1732, a phase 3 study of inotuzumab ozogamicin and post-induction chemotherapy in treating patients with newly diagnosed high-risk B-cell ALL (NCT03959085).

Patients with relapsed ALL will require further therapy. For patients with extramedullary relapse, treatment may include additional intrathecal chemotherapy in the case of a CNS relapse, and radiation in the event of testicular relapse. For children with ALL in first bone marrow relapse, usual treatment consists of reinduction cytotoxic chemotherapy with a multidrug regimen, followed by post-reinduction therapy for patients who experience a second CR. However, the specific treatment approach may depend on timing of relapse (early vs late). Although definitions of early relapse vary (i.e., occurring within 36 months of initial diagnosis per COG, or within 6 months of completing primary therapy per the Berlin–Frankfurt–Münster [BFM] group[38]), early relapsing B-cell ALL is associated with a poorer prognosis; as such, these patients may receive more aggressive chemotherapy or undergo allogeneic transplant.[5,33]

Further therapy for relapsed/refractory B-cell ALL may include options such as blinatumomab, inotuzumab, or the chimeric antigen receptor (CAR) T-cell therapy tisagenlecleucel.[39] Blinatumomab, a bispecific CD19-directed CD3 T-cell engager, is indicated for the treatment of adults or children with relapsed or refractory CD19-positive B-cell precursor ALL (note that blinatumomab is also approved for adults and children with ALL who have MRD in first or second CR).[85] Inotuzumab, a humanized anti-CD22 monoclonal antibody, is FDA approved for the treatment of adults with relapsed/refractory B-cell ALL, is considered a treatment option for pediatric ALL on the basis of available clinical trial data in adults and younger patients.[39–42]

CAR T-cell Therapy in Pediatric ALL

Chimeric antigen receptor (CAR) T-cell therapy has emerged as a treatment option for pediatric and young adult patients with relapsed/refractory ALL. More specifically, tisagenlecleucel (tisa-cel) is a CD19-directed, genetically modified autologous T-cell immunotherapy that is approved for the treatment of B-cell precursor ALL that is refractory or in second or later relapse in patients up to 25 years of age.[43]

One-time treatment with tisa-cel involves the collection of the patient's T cells, which are re-engineered, expanded ex vivo, and then infused into the patient following a course of lymphodepleting therapy.[44] In clinical trials, tisa-cel has demonstrated high rates of response and encouraging durability of response in pediatric and young adult patients with relapsed/refractory ALL. In a pivotal trial (ELIANA), the overall remission rate following tisa-cel infusion was 81% at 3 months.[45] In an updated report on ELIANA, out of 65 patients with CR or CR with incomplete blood count recovery, 29 were still in response, with durations of response up to 29 months and ongoing, and overall survival not reached.[46]

Although CAR T-cell therapy is generally well tolerated, it is associated with cytokine release syndrome, which is potentially life-threatening, and neurotoxicity, referred to as immune effector cell-associated neurotoxicity syndrome (ICANS). Severe CRS can be treated with tocilizumab, an interleukin-6 inhibitor.[5] In the ELIANA study,[46] grade 3 or 4 CRS occurred in 48% of patients and was reversible in all cases, and 13% of patients experienced grade 3 neurological events.

For more detailed information on this important treatment strategy, please refer to the LLS fact sheet for HCPs on CAR T-cell Therapy.

Treatment of Pediatric AML

For children with newly diagnosed AML, treatment typically starts with an induction phase that may include chemotherapy, immunotherapy, targeted therapy (i.e., a *FLT3* inhibitor), and supportive care. Intrathecal chemotherapy may be used to treat CNS disease seen at diagnosis or as prophylaxis (i.e., to prevent later development of CNS disease).[6] In patients achieving remission, treatments may include chemotherapy, targeted therapy, and HSCT. Although overall survival rates remain suboptimal in childhood AML, the use of currently accepted treatment regimens results in CR rates of 85% to 90%.[6]

Chemotherapy for most pediatric AML patients includes an anthracycline (usually daunorubicin) plus cytarabine, sometimes given with other drugs such as etoposide. Alternative regimens may help reduce exposure to anthracyclines, which are associated with late cardiotoxicity.

Immunotherapeutic approaches may improve clinical outcomes beyond what can be achieved with chemotherapy alone. Accordingly, patients with newly diagnosed AML may also receive gemtuzumab ozogamicin, an antibodydrug conjugate (a CD33-directed monoclonal antibody linked to the cytotoxic agent calicheamicin). In the COG trials AAML03P1 and AAML0531, gemtuzumab ozogamicin was well tolerated, safe in combination with intensive chemotherapy, and effective as shown by reduced relapse risk and improved event-free survival, with favorable outcomes demonstrated even in infants under 1 year of age.[48] Some evidence suggests that the clinical benefit of gemtuzumab ozogamicin may be correlated to the level of CD33 expression on the leukemic cell surface.[86] Gemtuzumab ozogamicin has been incorporated as part of treatment for all patients in AAML1831, a recent phase 3 randomized trial of the COG (NCT04293562).

Targeted therapies may also provide additional clinical benefit; in particular, therapies targeting *FLT3* mutations have been extensively studied in AML, including midostaurin, sorafenib, and gilteritinib. Midostaurin is FDA approved for treatment of adults with newly diagnosed, *FLT3* mutation-positive AML in combination with chemotherapy,[50] while gilteritinib, a highly potent and selective *FLT3* inhibitor, is approved for adults who have relapsed/refractory AML with a *FLT3* mutation.[51] Sorafenib, a multikinase inhibitor, does not have a specific approval in AML, but has been evaluated in both adult and pediatric patients with newly diagnosed AML. In the COG AAML1031 trial, sorafenib was evaluated in combination with conventional induction chemotherapy and as single-agent maintenance therapy in children with high allelic ratio *FLT3*-ITD-positive AML. Sorafenib was

relatively well tolerated and appeared to provide a clinical benefit, suggesting it may improve outcomes in this patient population.[48]

A *FLT3*-targeting strategy is currently under study as part of the aforementioned COG phase 3 trial, AAML1831; i.e., gilteritinib is added for patients with *FLT3* mutations (NCT04293562). Gilteritinib was selected for this trial based on promising results in adults with newly diagnosed or relapsed/refractory *FLT3*-mutated AML.[52,53]

Recurrent or progressive AML remains a clinical challenge. Although many children can achieve a second remission with treatment similar to their initial induction therapy, the prognosis is unfavorable.[6] Reinduction chemotherapy in this setting often consists of highdose cytarabine given in combination with other agents including fludarabine and idarubicin, mitoxantrone, asparaginase, or etoposide. In a randomized trial, the addition of liposomal daunorubicin to fludarabine, cytarabine, and granulocyte colony-stimulating factor (FLAG) improved early treatment response overall and improved survival in patients with core-binding factor (CBF) AML.[55] In a more recent, phase 1/2 study, CPX-351 followed by FLAG given for pediatric AML in first relapse demonstrated manageable toxicity, with response rates superior to historical data.[55]

Pediatric AML patients may also receive immunotherapeutic or targeted treatment following relapse. Gemtuzumab ozogamicin is specifically indicated not only in newly diagnosed, CD33-positive AML in adults and pediatric patients 1 month and older, but also in relapsed or refractory CD33-positive AML in adults and pediatric patients 2 years and older.[56] Although experience with the *FLT3* inhibitors midostaurin and gilteritinib in relapsed pediatric AML is currently limited, some data is available for sorafenib in this setting.[58]

Additional Treatment Options for Pediatric Acute Leukemia

Importance of Clinical Trials

Despite recent progress in chemotherapy optimization, supportive care, and the introduction of novel therapeutics, rates of relapse and survival remain suboptimal in pediatric acute leukemia. This gap underscores an unmet need for clinical trials to study new therapeutic approaches for younger patients involving chemotherapy, targeted therapy, or novel strategies such as chimeric antigen receptor (CAR) T-cell therapy for relapsed/refractory AML (NCT03971799).[59] In contrast to what has been seen with CAR T-cell therapy in patients with ALL, the development of a safe and effective therapy has been more difficult in AML. This is in part because of the immunosuppressive tumor microenvironment of AML, which dampens responses to CAR T cells, but also due to a relative lack of tumor-associated antigens, making it challenging to target leukemic cells.

Nevertheless, novel CAR T cell therapies remain under study in a number of clinical trials enrolling patients with AML, raising hope that the therapeutic armamentarium will expand in the future.

According to the World Health Organization, clinical trials in children are important to the development of age-specific and empirically-verified therapies for this unique patient population, which has distinct developmental and physiological differences from adults.[60,61] However, only about 5% of oncology drugs have been approved for first use in children, and the gap between first-in-human and first-in-child trials of FDA-approved oncology drugs is 6.5 years.[62] Accordingly, participation in available clinical trials is critical.

Healthcare providers should encourage participation in studies of the COG, as well as The Leukemia & Lymphoma Society (LLS) PedAL, a paradigm-changing approach to pediatric drug development (described below). Patients and their families can be directed to the LLS Clinical Trial Support Center (CTSC), a free service through which LLS Clinical Trial Nurse Navigators guide individuals throughout the entire clinical trial process (www.LLS.org/CTSC).

About LLS PedAL

LLS PedAL (www.LLS.org/dare-to-dream/pedal) is a global precision medicine master trial that is actively accruing patients across 19 countries on the PedAL Screening Trial as well as two therapeutic subtrials. This is the first comprehensive, international study to systematically and prospectively collect vital information on children with relapsed leukemia.

To implement this strategic initiative, LLS has partnered with COG for North American, Australian, and New Zealand participation, and with COG, European and Japanese partners. Working together with these collaborators, LLS intends to identify and validate underlying drivers of pediatric leukemia, and match patients to the most promising targeted therapies based on their unique genetic information. PedAL funded the development of GEARBOx (Genomic Eligibility Algorithm at Relapse for Better Outcomes), which is a specialized trial search tool. It is now active and healthcare providers can use it at no cost. GEARBOx will be improved continuously based on user feedback going forward.

LLS has also partnered with the University of Chicago Data for the Common Good (D4CG) to create the International Acute Myeloid Leukemia Consortium (INTERACT) Pediatric AML Data Commons. By consolidating pediatric cancer data from multiple institutions into a single data set, D4CG has established a common language to define and analyze the data, and has made data from completed clinical trials in 12 countries available to researchers worldwide.

Hematopoietic Stem Cell Transplantation

The use of allogeneic hematopoietic stem cell transplant (HSCT) may increase the chances of cure in children with acute leukemia, though its use is limited by acute and long-term complications.[63]

Due to improvements over time, rates of survival following transplantation appear to be comparable regardless of whether the stem cell source is matched related, matched unrelated, haploidentical donor, or cord blood.[64,65]

In patients with ALL, HSCT may be reserved for patients with high-risk features who are in first CR or who have relapsed/refractory disease, for whom the procedure has been shown to improve clinical outcomes.[63] According to pediatric ALL clinical practice guidelines from the National Comprehensive Cancer Network (NCCN), it is reasonable to consider HSCT in first CR for certain patients (e.g., those with unfavorable cytogenetics or MRD), among other settings.[39] In guidelines from the American Society for Transplantation and Cellular Therapy (ASTCT), allogeneic transplantation is considered for pediatric ALL patients in first CR with high-risk features and for patients in second CR.[66]

In pediatric AML, allogeneic HSCT has frequently been used as a consolidation strategy for patients in first remission, with long-term remissions of 60% to 70% for children with HLA-matched donors.[6] Although HSCT in first CR was historically reserved for children with HLA-identical sibling donors, contemporary protocols rely on risk assessments including disease characteristics and response-related factors, with HSCT typically employed only for patients with high-risk features.[67] In the setting of relapsed AML, the use of allogeneic HSCT (preferably after a second CR has been achieved) provides the best chance of cure.[67] The previously mentioned ASTCT guidelines describe allogeneic transplantation as a standard for pediatric patients with AML in first CR with high-risk features, for all patients with second or later CR, and for patients who are not in remission.[66]

Side Effect Management

Common side effects of chemotherapy may include alopecia, mucositis, nausea and vomiting, and diarrhea, as well as cytopenias that may lead to bleeding and bruising, fatigue, and increased risk of infections. Specific drugs routinely used in acute leukemias may have characteristic toxicity profiles; e.g., daunorubicin can cause severe myelosuppression and myocardial toxicity.[68] Although chemotherapy side effects are usually (but not always) limited to the treatment period, some supportive measures during treatment may include the use of antiemetics to address nausea and vomiting and the use of growth factors in the case of cytopenias.[33]

The side effects of other treatments for acute leukemia depend on the type of therapy. Radiation, when used, may cause nausea and fatigue, as well as short-term side effects in the treated area, including sunburn-like skin reactions (that may be managed with mild soaps or other skin care products[69]) or alopecia. The use of HSCT is associated with an increased risk of infections, graftversus-host disease, and other serious complications, with reported rates of transplant-related mortality that have improved over time but are still significant.[70] HSCT is also associated with side effects such as mucositis and nausea/vomiting (due to chemotherapy given during the preparative regimen) that may be ameliorated with standard supportive care measures including mouth rinses and antiemetics.

Immunotherapeutic treatments have characteristic side effect profiles that require special management approaches in some cases. Notable toxicities associated with CAR T-cell therapy include CRS and neurotoxicity, i.e., ICANS, along with B-cell aplasia, cytopenias, and infections. Management of CRS and neurotoxicity begins with supportive care but could escalate to pharmacologic therapy if response is inadequate, while B-cell aplasia may be treated with intravenous immunoglobulin (IVIG) replacement therapy. Tocilizumab (with or without a corticosteroid) is a treatment for CRS, while neurotoxicity is managed with corticosteroids and supportive care.[71] Blinatumomab is also associated with CRS and neurologic adverse events that should be promptly managed and minimized (e.g., through dose-escalation strategies).[72] Gemtuzumab treatment is associated with increased risk of hepatotoxicity and hepatic veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS), particularly after HSCT; expert recommendations for managing these and other serious adverse events (including tumor lysis syndrome) have been published.[73]

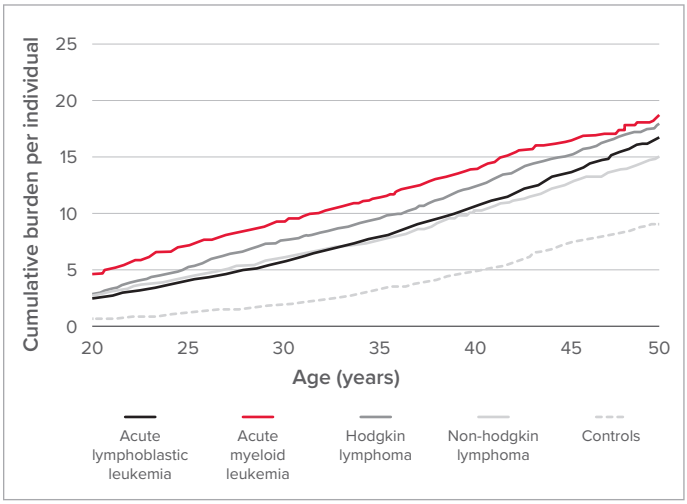
Targeted therapies also have toxicities that may need to be managed. In pediatric AML, sorafenib-related dermatologic adverse events (including hand-foot syndrome and skin rash) are common and may be exacerbated by concurrent medications and may require supportive care, and it is possible that alternate dosing strategies may be explored to minimize these toxicities.[73] In children with Ph+ ALL, the TKIs imatinib and dasatinib have generally mild side effects such as diarrhea, nausea, fatigue, skin rash, and muscle pain. Patients also may experience edema of the hands and feet and cytopenias.[33]

Long-term and Late Effects and Survivorship Care

There are nearly 500,000 survivors of childhood and adolescent cancers in the United States.[75] Survivors of pediatric leukemia require close monitoring over time due to adverse effects that persist beyond the initial treatment period, or manifest months or even years after treatment. An estimated 60% to 90% or more of pediatric cancer survivors develop chronic health conditions, and between 20% to 80% experience life-threatening complications.[76]

In results of the St. Jude Lifetime Cohort Study[76] including more than 5,500 childhood cancer survivors (35% of whom had survived acute leukemia), the excess burden of disease related to curative therapies was found to be excessive, and especially so among survivors of AML **(Figure 1)**. Findings of this study underscore the importance of active clinical management for these high-risk patients.

Figure 1. Cumulative Burden of Chronic Health Conditions in Childhood Cancer Survivors and Community Controls in the St. Jude Lifetime Cohort Study



Source: Bhakta et al, Lancet. 2017.

Survivors may experience a range of long-term and late effects encompassing a wide variety of organ systems. For example, cardiac system involvement may be seen among individuals who were treated with anthracyclines, particularly at higher doses.[77] Individuals may also experience impacts on fertility and growth/development, depending on the treatments previously used to treat the cancer.

Risk is also increased for emotional and psychosocial issues such as stress, anxiety, depression, and symptoms typically associated with post-traumatic stress disorder; educational difficulties, including those related to memory problems; and socioeconomic challenges related to accessing and paying for long-term follow-up care.[79]

Cognitive late effects are likely to have the strongest impact on a student's academic journey, reading to a decline in academic performance or slowed progression of learning. Learning difficulties may be related to the cancer or the treatment itself. Students may experience attention and focus difficulties that mimic ADHD and may even be misdiagnosed as such. They can experience difficulty with concentration, slowed processing speed, and executive dysfunction, impacting activities such as planning, organizing, and problem solving. Visual-spatial deficits can make nonverbal skills difficult and may impact handwriting. Slowed processing or nonverbal skill deficits may affect social skills, as students may have difficulty reading and interpreting social cues and may have inappropriate or untimely responses. Early detection of cognitive late effects is crucial to ensuring timely intervention. Children who are diagnosed and treated at younger ages appear to be at greatest risk for cognitive late effects, possibly due to the fact that the young brain is at a critical stage of development during treatment.

Survivors of pediatric leukemias are also at increased risk of subsequent cancers.[80] In an analysis of SEER data through 2014, the most common secondary malignant neoplasms among pediatric leukemia survivors were thyroid cancer, sarcoma, astrocytoma, lymphoma, salivary gland carcinoma melanoma, and breast cancer, with more than three-fourths of cases occurring within 20 years of the initial leukemia diagnosis.[81] The prevalence of late effects is variable and may depend on factors such as age and treatment intensity. Recent evidence suggests that risk-adapted therapy may be reducing the overall prevalence of late morbidity and mortality among some acute leukemia survivors.[82]

Despite the importance of active management, clinical application of best practices can be complex and challenging, particularly for primary care providers, from whom survivors receive the majority of their ongoing care.[83] General and subspecialty healthcare providers all play an increasingly important role in the ongoing care of childhood cancer survivors.[83] Accordingly, the COG has developed specific guidelines for long-term follow-up of these individuals (available at www.survivorshipguidelines.org).

It is recommended that primary care providers work collaboratively with oncology subspecialists to develop an individualized long-term follow-up plan and coordinate survivorship care, using the COG guidelines as a guide.[83]

Relevant resources from LLS include a Survivorship Workbook that collects all the important information that patients and families will need throughout diagnosis, treatment, follow-up care, and long-term management (available for children and adolescents and young adults). Another useful resource for long-term follow-up is the Screening Recommendations Generator. Developed by Passport for Care®, this tool can be used by survivors or caregivers to receive information on the potential late effects associated with treatments, recommended followup screenings, and more. Visit www.passportforcare.org for more information.

Resources for Patient/Caregiver Education and Support

LLS Resources

Childhood Blood Cancer: A dedicated resource from LLS to help parents and guardians navigate multiple challenges associated with blood cancers in children and young adults. Topics include treatment options, what to tell your child, caring for your child during treatment, helping siblings cope, and more.

www.LLS.org/ChildhoodCancer

Stars Will Twinkle, The Sun Will Shine: *A 3-book trilogy* that follows Olivia and her family as Olivia is diagnosed with leukemia, goes to the hospital for treatment, and returns to school. Also available in Spanish. To order a copy of this trilogy, call an Information Specialist at (800) 955-4572.

www.LLS.org/booklet/stars-will-twinkle-sun-will-shine

Stars Will Twinkle, The Sun Will Shine: *An animated movie* about Olivia as she is diagnosed with leukemia, goes to the hospital for treatment, and returns to school.

https://www.LLS.org/children-and-young-adults/childhood-blood-cancer/stars-will-twinkle

Caregiver Workbook – Caring for Kids and Adolescents: An informational series covering 14 topics.

www.LLS.org/FamilyWorkbook

Medi-Teddy: Teddy bear that fits over IV and feeding tube bags to conceal the contents.

www.LLS.org/booklet/medi-teddy

LLS Coloring for Kids™ App: Free LLS Coloring for Kids™ mobile app.

www.LLS.org/ColoringApp

The Stem Cell Transplant Coloring Book: Features pictures and activity pages depict the experiences of Sam and Serena, two young stem cell transplant patients.

www.LLS.org/sites/default/files/2022-02/PS51_Stem_Cell_Coloring_Book_12.21_1.pdf

LLS Booklets: Download or order these free informational resources:

- *Acute Lymphoblastic Leukemia (ALL) in Children and Teens* https://www.LLS.org/booklet/acute-lymphoblastic-leukemia-all-children-and-teens
- *Acute Myeloid Leukemia in Children and Teens* www.LLS.org/booklet/acute-myeloid-leukemia-children-and-teens
- *Pediatric Resources booklet* www.LLS.org/booklet/pediatric-resources
- *Learning & Living With Cancer* www.LLS.org/booklet/learning-living-cancer
- *Side-Effect Management: Effects of Childhood Cancer Treatment on Learning* www.LLS.org/booklet/side-effect-management-effects-childhood-cancer-treatment-learning
- *Fertility and Cancer* www.LLS.org/booklet/fertility-and-cancer

Survivorship Workbook – Navigating Life During and After a Blood Cancer Diagnosis: Patients and caregivers can bring this workbook to appointments to collect important information from diagnosis through long-term management.

www.LLS.org/managing-your-cancer/survivorship-workbook

A School's Guide For Children With Cancer: This guide helps the school and larger community to assist young people with cancer in maintaining continued involvement in school and other normal life activities.

www.LLS.org/booklet/schools-guide-children-cancer

A Parent's Guide to School and Childhood Cancer: This guide helps parents be the mobilizing force behind their child's education plan.

https://www.LLS.org/booklet/parents-guide-school-and-childhood-cancer

Other Resources

The COG Family Handbook, New Diagnosis Guide, and KidsCare App: The handbook and guide provide families with reliable information about treatment, support, and follow-up care, plus focused information to be used at the time of diagnosis. The app includes the handbook and guide content, plus journaling, one-touch dialing, appointment tracking, among other features.

www.childrensoncologygroup.org/cog-family-handbook

COG Survivorship Guidelines – Health Links for Patients: A complementary set of patient education materials called "Health Links" are designed to enhance patient follow-up visits and broaden the application of the authoritative COG long-term follow-up guidelines for clinicians.

www.survivorshipguidelines.org

NCCN Guidelines for Patients – ALL: A step-by-step guide to cancer care options, based on the treatment guidelines used by healthcare providers and designed to help patients discuss cancer treatment with doctors.

www.nccn.org/patients/guidelines/content/PDF/ped_all_patient.pdf

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We're Here to Help

LLS is the world's largest voluntary health organization dedicated to funding blood cancer research, education and patient services. LLS has regions throughout the United States and Canada. To find the region nearest to you, visit our website at www.LLS.org/ChapterFind or contact

The Leukemia & Lymphoma Society
1201 15th Street N.W., Suite 410,
Washington, D.C. 20005
Phone Number: (800) 955-4572
(M-F, 9 a.m. to 9 p.m. ET)
Website: www.LLS.org

LLS offers free information and services for patients and families touched by blood cancers as well as for healthcare professionals. The resources listed below are available to you and your patients and are meant to be a compliment to the HCP team and an additional source of support.

Consult with an Information Specialist. Information Specialists are highly trained social workers and nurses who assist through treatment, financial, and social challenges. They offer up-to-date disease and treatment information. Language services are available. For more information, please:

- Call: (800) 955-4572 (M-F, 9 a.m. to 9 p.m. ET)
- Visit: www.LLS.org/IRC
- Email or Live chat: www.LLS.org/InformationSpecialists

Clinical Trials Support Center (CTSC). Work one-on-one with an LLS clinical trial nurse navigator who will personally assist throughout the entire clinical trial process. A nurse navigator will help identify potential clinical trials and overcome the barriers to enrollment (navigators help HCPs and patients). For more information about this free service, please:

- Call an Information Specialist: (800) 955-4572 to be referred to the CTSC
- Visit: www.LLS.org/CTSC
- Complete a referral form for your patient at: www.LLS.org/CTSCreferral

Nutrition Consultations. Nutrition Education Services Center (NESC) provides one-on-one *free* nutrition education and consultations to patients and caregivers of all cancer types with registered dietitians who have expertise in oncology nutrition.

- Visit: www.LLSnutrition.org

Free Information Booklets. LLS offers free education and support publications that can either be read online or downloaded. Free print versions can be ordered. For more information, please:

- Visit: www.LLS.org/booklets

Información en Español. (LLS information in Spanish) Para mayor información por favor:

- Visite: www.LLS.org/espanol

LLS Community. LLS Community is an online social network and registry for patients, caregivers, and healthcare professionals. It is a place to ask questions, get informed, share your experience, and connect with others. To join:

- Visit: www.LLS.org/community

LLS Regions. LLS offers community support and services in the United States and Canada including the *Patti Robinson Kaufmann First Connection Program* (a peer-to-peer support program), in-person support groups, and other great resources. For more information about these programs or to contact your region, please:

- Call: (800) 955-4572
- Visit: www.LLS.org/ChapterFind

Patti Robinson Kaufmann First Connection® Program. A free peer-to-peer support program that connects patients and their loved ones to a trained peer volunteer who has gone through a similar experience.

- www.LLS.org/FirstConnection

Childhood Blood Cancer Resources:

- www.LLS.org/ChildhoodCancer

LLS Dare to Dream Project, LLS Children's Initiative:

- www.LLS.org/DaretoDream

Resources for Healthcare Professionals: Webinars, Podcasts, In-person Education Programs, Videos, and Fact Sheets:

- www.LLS.org/CE (free accreditation)
- www.LLS.org/HCPpodcast
- www.LLS.org/HCPvideos
- www.LLS.org/HCPbooklets
- www.LLS.org/StayingConnected (free online course on the effects of childhood and AYA cancer treatment to help improve the learning experience during and after treatment)

Resources for your Patients:

- www.LLS.org/programs
- www.LLS.org/EducationVideos
- www.LLS.org/podcast

Additional Resources

Children's Oncology Group (COG)

www.childrensoncologygroup.org

The Children's Oncology Group (COG), a National Cancer Institute supported clinical trials group, is the world's largest organization devoted exclusively to childhood and adolescent cancer research. The COG unites more than 10,000 experts in childhood cancer at more than 200 leading children's hospitals, universities, and cancer centers across North America, Australia, New Zealand, and Europe in the fight against childhood cancer. COG provides important information for children and their families from the time of diagnosis, through treatment and following cure.

The National Cancer Institute (NCI)

www.cancer.gov
(800) 422-6237

The National Cancer Institute, part of the National Institutes of Health, is a national resource center for information and education about all forms of cancer. The NCI also provides a clinical trial search feature, the PDQ® Cancer Clinical Trials Registry, at www.cancer.gov/clinicaltrials, where healthcare professionals and patients can look for clinical trials.

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