Crisis management in the treatment of childhood acute lymphoblastic leukemia: putting right what can go wrong (emergency complications of disease and treatment)

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The improvement in overall survival in children with acute lymphoblastic leukemia (ALL) over the last 5 decades has been considerable, with around 90% now surviving long term. The risk of relapse has been reduced to such an extent that the risk of treatment-related mortality is now approaching that of mortality caused by relapse. Toxicities may also lead to the suboptimal delivery of chemotherapy (treatment delays, dose reductions, dose omissions), potentially increasing relapse risk, and short- and long-term morbidity, adding to the "burden of therapy" in an increasing number of survivors. Thus, the need to reduce toxicity in pediatric ALL is becoming increasingly important. This work focuses on the risk factors, pathogenesis, clinical features, and emergency management of the life-threatening complications of ALL at presentation and during subsequent chemotherapy, including leucostasis, tumor lysis syndrome, infection, methotrexate encephalopathy, thrombosis, and pancreatitis. Potential strategies to abrogate these toxicities in the future are also discussed.

Learning Objectives

- To understand the importance of reducing toxicity if additional improvements in high-quality, long-term survival in pediatric acute lymphoblastic leukemia are to be achieved
- To gain a greater understanding of the risk factors, presentation, and immediate management of the life-threatening complications of pediatric ALL chemotherapy and to also learn how these toxicities could be reduced in the future

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Introduction

Since the first description of pediatric acute lymphoblastic leukemia (ALL) in the 1920s, outcomes have improved[1,2] from an invariably fatal disease to one with event-free survival rates of 73% to 87% at 5 years (Table 1). Contemporary protocols allocate stratified chemotherapy of different intensities according to risk factors present at diagnosis (including age, white count, involvement of the cerebrospinal fluid, and cytogenetics) and response to early therapy (determined by minimal residual disease assessment after induction and sometimes, also after consolidation). The risk of relapse has considerably reduced over time[1,2]; current relapse rates are 8% to 19% at 5 years, of which around 23% to 67% are salvageable, leading to overall long-term survival rates of around 90% at 5 years (Table 1).

As a result of these advances, the risk of treatment-related mortality is now approaching that of the mortality associated with relapse,[3] with induction death rates of 1.0% to 2.8% and death in complete remission rates of 2.3% to 5.3% (Table 1). Specific toxicities may also lead to subsequent delays,[4] omissions, or dose reductions of different agents, thereby potentially compromising the efficacy (relapse prevention) of treatment. In addition, toxicities are a source of immediate and sometimes, ongoing morbidity, adding to the "burden of therapy" in an increasing number of long-term survivors of ALL.[3] For these reasons, reduction in the toxicity of pediatric ALL protocols is becoming an increasingly pressing issue. This work focuses on the immediate management of the life-threatening complications of acute leukemia or its treatment. Although addressing nonlife-threatening and late treatment–related complications, such as avascular necrosis, neurocognitive effects, and secondary malignancies, is equally important, these will not be discussed in detail here because of space constraints.

What goes wrong?

The risk of an individual patient experiencing a specific toxicity is determined by genetic and acquired risk factors (Table 2). There are a number of rare syndromes that predispose to both the development of ALL and also, overall treatment–related mortality or particular side effects when exposed to ALL therapy[5]; these include Down syndrome, Li Fraumeni syndrome, and ataxia telangiectasia (Tables 2 and 3). Specific polymorphisms and acquired risk factors may also predispose to individual toxicities.

The overall risk of a child developing at least one serious adverse event during first-line ALL therapy is around 30% to 50% (Table 1), but varies with age. The etiology and management of life-threatening

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Table 1. Outcomes of contemporary pediatric protocols

Trial	No. of patients	Years of recruitment	Age, y	Overall survival, %	Event-free survival, %	Toxicity Induction death, %	Death in remission, %	Proportion of patients with at least 1 serious adverse event, %	Relapse risk, %
UKALL2003[15]	3126	October 2003 to June 2011	1-24	89 at 5 y	87 at 5 y	1.5	2.3	37.2 (30.6 ages 1-9 y)	8.8 at 5 y
IC-BFM 2002[42]	5060	November 2002 to November 2007	1-17	82 at 5 y	74 at 5 y	2.8	5.3	—	19 at 5 y
NOPHO ALL2008[4]	1162	July 2008 to April 2013	1-45	—	88 ages 1-9 y, 79 ages 10-17 y, 73 ages 18-45 y at 5 y	1.1	3.3	49.8 (44.5 ages 1-9 y)	8.2 at median 4 y
St. Jude's Total Therapy XV[43]	498	June 2000 to October 2007	1-18	93 at 10 y	86 at 10 y	—	2.3	—	11.6 at 10 y
DFCI 05-001[44]	551	April 2005 to February 2010	1-18	91 at 5 y	85 at 5 y	2.0	—	—	8.9
DCOG 9[45]	859	January 1997 to November 2004	1-18	86 at 5 y	81 at 5 y	1.0	2.7	—	15.8
COG[2]	21626	January 1990 to December 2005	0-22	90 at 5 y	—	—	1.6	—	Death after relapse 7.22 at 5 y

COG, Children's Oncology Group; DCOG, Dutch Childhood Oncology Group; DFCI, Dana-Farber Cancer Institute; IC-BFM, International Berlin-Frankfurt-Münster Study Group; NOPHO, Nordic Society of Paediatric Haematology and Oncology.

complications of ALL and its treatment are summarized in Table 3. Determining the exact frequency of different toxicities and comparing these across the different study group protocols are very challenging, because each uses different definition criteria, data capture procedures, and reporting strategies.[6]

Leucostasis

Leucostasis arises in patients with a high circulating white cell count caused by increase blood viscosity and reduced deformability of blast cells, which causes ischemic injury to vital organs, primarily the central nervous system (CNS), lungs, and kidneys,[7] and is often compounded by hyperuricemia caused by tumor lysis. The clinical features range from mild visual disturbance, headache, cough, or dyspnea to coma, acute respiratory distress syndrome, or renal failure. The incidence of hyperleucocytosis is around 5% to 10% of newly diagnosed children with ALL,[8] with leucostasis being more likely in those with a high white count ($>200 \times 10^9$/L), males, those with a T-cell immunophenotype, infants, and those with *KMT2A* or *BCR-ABL* rearrangements.[8,9] The risk of leucostasis is lower in ALL compared with acute myeloid leukemia.

Historically, leucostasis was associated with a high mortality of up to 20%. More recently, the outcome has markedly improved with hydration, judicious blood product support (avoidance of red cell transfusions until the white count is below 100×10^9/L and platelet transfusions to reduce the risk of CNS bleeding), early institution of cytoreduction with steroids with or without low-dose chemotherapy (vincristine), and aggressive treatment of coexistent sepsis or tumor lysis. Leucopheresis has been previously used to reduce the circulating white count quickly. However, it may increase the risk of hypocalcemia, catheter-related thrombosis or malfunction, and coagulopathy without reducing the frequency or severity of the complications of leucostasis; leucopheresis is, therefore, not generally used in children with ALL.[8]

Tumor lysis syndrome

Tumor lysis syndrome (TLS) occurs when there is simultaneous destruction of a large number of rapidly dividing tumor cells, which causes the sudden release of intracellular metabolites. This results in an acute metabolic disturbance, which may include hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia, or uremia. These abnormalities can develop spontaneously and be present at diagnosis or may develop within 12 to 72 hours after initiation of chemotherapy. Tumor lysis may be asymptomatic but can cause seizures, cardiac arrhythmias, acute renal failure, and death. Patients with preexisting renal impairment or a high tumor burden (white cell count $>100 \times 10^9$/L, large mediastinal mass, high urate, and high lactate dehydrogenase) are at greatest risk. All patients with ALL should be considered to be at risk of TLS irrespective of white cell count and should receive prophylactic Allopurinol (a xanthine oxidase inhibitor) and hyperhydration before and for a few days after starting treatment. Patients with a white count above 100×10^9/L should receive prophylactic Rasburicase (recombinant urate oxidase) on initiation of therapy (after excluding glucose 6 phosphate dehydrogenase (G6PD) deficiency, because these patients can develop methemoglobinemia and hemolysis). The prophylactic use of Rasburicase in those with a white count $<100 \times 10^9$/L but with a high lactate dehydrogenase[10] is more controversial, and it may be reasonable to reserve this for situations in which TLS develops, despite prophylactic Allopurinol and hyperhydration.[11] Immediate supportive care of TLS, including hyperhydration, correction of electrolyte abnormalities, antiepileptics and renal support if necessary, is essential.

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Table 2. Risk factors for toxicity

Etiology and risk factors
Inherent
Syndromes[5]
Down syndrome (increased risk of gastrointestinal toxicity and infections)
Li Fraumeni (increased risk of induction death, death in remission, and second malignancies)
Ataxia telangiectasia (increased risk of toxic death, cyclophosphamide-induced cystitis, and second malignancies)
Polymorphisms
GSTP1, MTHFR, SHMT1 (methotrexate encephalopathy)[22]
RGS6, UKL2, ASNS, CPA2 (pancreatitis)[31,33]
TPMT, NUDT15 (6-mercaptopurine toxicity)[46,47]
Acquired
Age (discussed below)
Preexisting comorbidities
Obesity (particularly avascular necrosis)
Regimen intensity, including allogeneic transplant
Presence of central venous catheter (line-related infection, thrombosis)
Exposure to specific drugs

Infection

Infections are the most frequent complications of ALL chemotherapy and constitute the greatest cause of treatment-related mortality. Medical Research Council (MRC) Working Party on Leukaemia in Children UK National Acute Lymphoblastic Leukaemia (ALL) Trial, UKALL2003, the 5-year cumulative incidence of infection-related mortality was 2.4% and accounted for 30% of all deaths and 64% of treatment-related deaths.[12] Bacterial and fungal infections are most frequently seen during the intensive phases of treatment when neutropenia is more likely, whereas viral infections are seen throughout the treatment course, often increasing toward the end of therapy.[12,13] The risk of opportunistic infection with *Pneumocystis jiroveci* is greatest between days 50 and 120 after diagnosis but may occur throughout therapy.[14]

In UKALL2003, 68% of infection-related deaths were caused by bacterial infection (64% gram negative), and 20% were caused by fungal infection. Viral infections, sufficiently severe to be reported as "serious adverse events," were seen in 5% of patients and resulted in 12% of infection-related deaths.[12,15] The risk factors for infections and infection-related mortality include Down syndrome, age (infants and adolescents are at higher risk than patients ages 1-9 years old), higher-intensity regimens, and failure to achieve neutrophilia after dexamethasone pulses.[12,13,15] The risk of treatment-related mortality, primarily caused by sepsis, may be around sevenfold higher in children with Down syndrome compared with non–Down syndrome children (21.6% at 5 years vs 3.3%, $P < .00005$),[16] with the greatest risk being immediately after glucocorticoid therapy.[17]

Management of infections requires prompt recognition and early institution of antimicrobial therapy determined by local bacterial prevalence and resistance patterns. There are no consensus recommendations on antimicrobial prophylaxis or replacement immunoglobulin infusions in children receiving chemotherapy for ALL other than routine prophylaxis for *Pneumocystis* Jiroveci. Trimethoprim-sulfamethoxazole is now universally recommended, albeit with different schedules, and it is highly effective at preventing this life-threatening opportunistic infection.[18]

The use of Fluoroquinolone prophylaxis in children receiving chemotherapy for ALL is highly controversial. Although it may reduce the risk of bacterial infections[19] and is recommended in some adult ALL guidelines,[20] this potential benefit must be weighed against the risk of development of antibiotic-resistant organisms and *Clostridium difficile* infections. Additional efficacy and safety data are required before antibiotic prophylaxis can be routinely recommended in children receiving chemotherapy for ALL. Similarly, the use of azoles in preventing fungal infections is complicated by the potential for interaction with vincristine. Until randomized, prospective evaluations of antimicrobial prophylaxis answer these questions definitively, clinicians must rely on a high index of suspicion of infection (even in afebrile patients during dexamethasone blocks and those in lower-intensity phases of treatment, such as maintenance chemotherapy), with rapid access to the hospital and prompt administration of antimicrobials. Patients with Down syndrome should be monitored especially closely and may be the best candidates for antimicrobial prophylaxis and replacement immunoglobulin.

Methotrexate neurotoxicity

The use of intrathecal methotrexate has provided effective CNS-directed therapy, such that craniospinal irradiation with its associated long-term complications is generally no longer required.[21] Asymptomatic leucoencephalopathy is demonstrable in around 20% of children undergoing contemporary chemotherapy for ALL.[22] However, the incidence of symptomatic methotrexate leucoencephalopathy is around 4% to 8% and more likely in those over the age of 10 years old, those receiving higher-intensity regimens, and during treatment blocks where there is concomitant administration of cytarabine and cyclophosphamide (eg, delayed intensification).[15,22,23]

Methotrexate neurotoxicity typically occurs around 2 to 14 days after exposure to oral, intrathecal, or high-dose intravenous methotrexate. Clinical features include headache, seizures, change in affect, speech disturbance, cerebellar syndrome, stroke-like syndrome, altered conscious level, and rarely, death. The classical waxing and waning nature of the neurological signs helps to distinguish it from other differential diagnoses, including thrombosis, hemorrhage, and infection. The immediate management is to exclude these alternative diagnoses (magnetic resonance imaging/venogram classically shows increased white matter signal on T2 weighted images with or without electroencephalogram), control seizures, correct electrolyte imbalances, and protect the airway, depending of the conscious level. Generally, the neurological abnormalities will fully resolve within hours or a few days (usually up to 9 days) spontaneously. In severely affected individuals, folinic acid, aminophylline, and dextromethorphan may be considered; small case series suggest potential benefit of these agents,[24,25] although definitive data are lacking.

In general, >80% of patients may be safely re-exposed to methotrexate without additional toxicity, although a small number of patients may have recurrent or long-term significant neurological deficits.[22,23] In these rare patients, the balance between additional exposure to methotrexate and potential exacerbation of neurological injury needs to be carefully weighed against replacement of methotrexate with intrathecal hydrocortisone and cytarabine and a potential higher risk of CNS relapse.

The mechanism of methotrexate encephalopathy remains poorly understood but may be caused by disruption of the folate homeostatic mechanisms in the CNS with or without direct neuronal injury.[22] Genome-wide single-nucleotide polymorphism studies are beginning to find interesting polymorphisms in genes enriched for neuronal

Table 3. Specific toxicities

Toxicity	Etiology/risk factors	Management
At presentation		
Fever	Usually disease related and resolves on initiation of ALL therapy	Infection screen
	May be caused by infection (impossible to distinguish from disease related and may be present as a result of neutropenia and immune dysregulation)	Broad spectrum antibiotics until fever resolved and infection excluded
Leucostasis	Hypoxia in vital organs as a result of increased blood viscosity and microvasculature damage	Maintain euvolemia
		Avoid red cell transfusions until white count reduced
	More likely in infants, males, high white count, T-cell disease, and *KMT2A* or *BCR-ABL* rearrangements	Platelet transfusion to reduce risk of CNS bleeding
		Early cytoreduction (steroids with or without vincristine)
		Management of concomitant tumor lysis or sepsis
		Leucopheresis no longer generally used
		Beware: pseudohyperkalemia
TLS	Sudden tumor cell death with release of intracellular cytokines	Hyperhydration
		Correction of metabolic abnormalities
		Management of seizures, arrhythmias, and renal insufficiency
	More likely in those with preexisting renal impairment or high tumor burden	Prevention: Allopurinol if white count $<100 \times 10^9$/L, Rasburicase if white count $>100 \times 10^9$/L (beware: check G6PD)
Compression of superior vena cava and/or large airways	Mediastinal mass composed of blasts, primarily seen in T-cell ALL	Nurse in semiupright position
		Avoid imaging requiring the patient to lay flat, because this may result in cardiac arrest
		Immediate administration of corticosteroids and early initiation of chemotherapy
Disseminated intravascular coagulation	Rapid release of procoagulants resulting in uncontrolled systemic activation of coagulation pathways; this may cause (1) microvascular thrombosis and multiorgan dysfunction and (2) hemorrhage because of consumption of clotting factors and platelets	Initiation of all chemotherapy
		Replacement of coagulation factors (eg, fibrin concentrate, fresh frozen plasma) if there is bleeding and to cover procedures (eg, bone marrow biopsy, lumbar punctures)
		Management of thrombosis is rarely required (eg, LMWH)
During chemotherapy		
Infection	Down syndrome, age (infants and adolescents at higher risk than children ages 1-9 y), female sex, higher-intensity regimens, failure to achieve neutrophilia after dexamethasone pulses, and white race	Early recognition of sepsis, rapid access to expert care, and early institution of antimicrobials
		Intravenous immunoglobulin may be considered for those with hypogammaglobulinemia or recurrent infections
Methotrexate encephalopathy	Mechanism poorly understood? CNS folate homeostasis disruption	Supportive care with control of seizures, correction of electrolytes, maintenance of airway
	More common with children >10 y, more intensive regimes, concomitant administration of cyclophosphamide and cytarabine	Exclude CNS thrombosis, hemorrhage, or infection
		Folinica acid, aminophylline, or dextromethorphan may be effective in severe cases
		Reexposure to methotrexate safe $>80\%$ but avoid concomitant administration with cyclophosphamide or cytarabine

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Table 3. (continued)

Toxicity	Etiology/risk factors	Management
Thrombosis	Prothrombotic state because of a combination of the leukemia itself, host factors, and exposure to asparaginase; other risk factors include increasing age, presence of a central venous catheter, concomitant administration of anthracycline and prednisolone, and inherited thrombophilic syndromes	LMWH Caution around procedures Reexposure to asparaginase is safe once thrombosis symptoms have resolved and the patient is fully anticoagulated Insufficient evidence currently exists for thromboprophylaxis in newly diagnosed patients Deferring insertion of a central venous catheter until the end of induction should be considered where possible
Pancreatitis	Pathophysiology is unknown Asparaginase is the primary etiology Higher cumulative dose or duration of asparaginase exposure, older age, concomitant steroid and anthracycline administration, severe hypertriglyceridemia, and genetic predisposition (*RGS6*, *UKL2*, *ASNS*, and *CPA2* genes)	Fluid resuscitation, analgesia, and antibiotics for infected pancreatic necrosis ? Octreotide to reduce pancreatic inflammation
Veno-occlusive disease (VOD) of the liver (sinusoidal obstruction syndrome)	Pathophysiology unknown Risk factors include thiopurine exposure, thiopurine methyltransferase polymorphisms, hemopoietic stem cell transplantation Small hepatic vessel thrombi classically lead to acute VOD with painful hepatomegaly, ascites, hyperbilirubinemia, thrombocytopenia, multiorgan failure, and a high risk of mortality The use of thiopurines may result in chronic veno-occlusive disease, which presents with disproportionate thrombocytopenia and evidence of chronic portal hypertension	Supportive care, including careful fluid balance (to prevent fluid overload but ensuring adequate intravascular volume to prevent renal injury), small volume ascetic taps, hemodialysis, intensive care unit support Defibrotide
Neutropenic enterocolitis (typhlitis)	Pathophysiology is unknown Transmural inflammation primarily of the cecum; the ascending and transverse colon may also be involved	Supportive care with intravenous fluids, parenteral nutrition, gut rest, correction of electrolyte imbalance, analgesia, and broad spectrum antibiotics Omit chemotherapy and consider the use of granulocyte colony stimulating factor (GCSF) The role of surgery is controversial and generally avoided unless typhlitis is complicated (eg, by perforation, bowel necrosis, uncontrolled bleeding, or abscess formation)

development pathways, which may also be linked to migraine, autism, attention deficit disorder, and Alzheimer disease.[22]

Thrombosis

Symptomatic thrombosis during treatment of ALL is a significant complication, with an incidence of around 4% to 6%; 54% of these events occur in the CNS, and 28% are related to central venous catheters.[26] The pathogenesis of thrombosis is poorly understood and likely contributed to by the leukemia itself, host factors, and chemotherapy (in particular, asparaginase exposure). Asparaginase causes reduced synthesis of many proteins involved in the coagulation and fibrinolytic pathways, and thrombotic events in children with ALL primarily occur during the asparaginase-containing intensive blocks of therapy (particularly induction), with events being more likely the longer the duration of asparaginase exposure.[26] Other risk factors include increasing age, presence of a central venous catheter, concomitant administration of anthracycline and prednisolone, and inherited thrombophilic syndromes.[26] The management of thrombosis is complicated by the presence of coexisting hemorrhage (in CNS thrombosis), the need for frequent procedures (lumbar punctures and bone marrow aspirates), and intermittent thrombocytopenia caused by chemotherapy. Low–molecular weight heparin (LMWH) is the most commonly used anticoagulant, and it is omitted around the time of procedures, is dose-reduced or omitted during periods of thrombocytopenia, and may be delayed if there is CNS hemorrhage secondary to thrombosis. Asparaginase can usually be safely administered after the clinical symptoms have resolved and the patient is fully anticoagulated.[27,28] LMWH is generally continued until at least 3 weeks after the last dose of pegylated asparaginase is given and for a variable period thereafter determined by the site of thrombosis. There are no data to suggest that prophylaxis with low-dose warfarin, LMWH, or antithrombin replacement is effective in preventing thrombosis in this context. However, prospective randomized clinical trials of thromboprophylaxis (for example, using intermediate-dose LMWH, LMWH with antithrombin replacement, or nonvitamin K antagonist oral anticoagulants) are much needed.

Pancreatitis

Pancreatitis is a severe complication of asparaginase therapy, occurring in 1.5% to 10% children receiving ALL chemotherapy.[29] Presenting features include abdominal pain, nausea and vomiting, fever and back pain arising between 6 and 14 days after asparaginase administration; this ranges in severity from a mild self-limiting illness to a fulminant form, with systemic inflammatory response syndrome, failure of pancreatic function, and multiorgan failure, with around one-third of patients requiring admission to the intensive care unit. The diagnosis is confirmed using raised biochemical markers (pancreatic amylase and lipase) and imaging (ultrasound, computerized tomography, or magnetic resonance imaging scans). Immediate management includes fluid resuscitation, analgesia, and antibiotics for infected pancreatic necrosis. Octreotide may be useful in decreasing pancreatic inflammation, although experience in children is limited.[30] Long-term complications can arise, particularly after severe pancreatitis, including pseudocyst formation in 25% to 28% of patients, recurrent abdominal pain in 7%, and exogenous insulin dependency in 8%.[31,32] Risk factors for the development of pancreatitis include a higher cumulative dose or duration of asparaginase exposure, older age, concomitant steroid and anthracycline administration, severe hypertriglyceridemia, and genetic predisposition (*RGS6*, *UKL2*, *ASNS*, and *CPA2* genes).[29-34] Re-exposure to asparaginase may be possible in children who have, within 48 hours from the onset of symptoms, resolution of their symptoms, amylase and lipase levels below 3 times the upper limit of normal, and no pancreatic pseudocysts

or necrosis on ultrasound.[30,32] However, for the majority of patients, additional exposure to asparaginase is contraindicated; it is unclear whether this impacts on subsequent relapse risk.[32,35]

Impact of age on toxicity

Since the mid-2000s, the upper age limit of many pediatric ALL studies has increased in response to the observation that adolescents and young adults have a 10% to 15% superior event-free survival when treated on pediatric rather than adult ALL protocols.[36-40] The treatment of children, adolescents, and young adults on the same protocol in prospective trial settings has facilitated detailed study of the impact of age on the frequency of different toxicities.[4,15] In patients treated on the UKALL2003,[15] the risks of death in remission, treatment delays, infections, thrombosis, and psychosis increased with increasing age; age had no impact on some complications, including vincristine-related neuropathy, line-related thrombosis, and line-related sepsis, implying that other risk factors (genetic polymorphisms or presence of central venous catheter, respectively) are more dominant risk factors for these toxicities. Interestingly, avascular necrosis was primarily restricted to patients ages between 10 and 20 years old, suggesting the importance of an interplay between steroid and asparaginase exposure and host factors present in the peripubertal patient (such as rapid bone growth and changes in sex hormones). A final group of toxicities appeared to be more common in patients ages 10 years old or older compared with younger patients, with no increasing risk in the young adults compared with adolescents. These include pancreatitis, mucositis, methotrexate encephalopathy, and hyperglycemia and were not solely accounted for by differences in treatment regimen.

What next?

The improvement in overall survival in pediatric ALL is a great success story. The reduction in relapses is now exposing the high morbidity and mortality associated with current chemotherapy regimens. Successive trials have facilitated a reduction in the use of hemopoietic stem cell transplantation, largely obviated the need for cranial radiotherapy, and enabled the safe de-escalation of some regimens for patients with low-risk disease.

As we become more sophisticated in our ability to define those at low, intermediate, and high risks of relapse[41] and novel agents (such as inotuzumab, blinatumomab, and chimeric antigen receptor T cells [CAR]) with different mechanisms of action become available, we are presented with new opportunities to reduce toxicity. Additional de-escalation of conventional chemotherapy for low-risk patients with an expected event-free survival in excess of 95% should be possible, because these patients are likely overtreated at present. For those with extremely poor–risk disease, intensive chemotherapy with allogeneic transplant or use of CAR T cells in first-line therapy seems to be justified. Intermediate-risk patients may benefit from the incorporation of newer agents alongside conventional chemotherapy, with the potential for increased efficacy without undue toxicity, given the different mechanisms of action and different toxicity profiles of these agents.

It is also clear that gaining additional understanding of the pathogenesis and risk factors for specific rare toxicities in a rare disease, such as pediatric ALL, will necessitate international collaboration to agree on definition sets for the most important toxicities, explore the pharmacogenetic basis for complications, and ask randomized

supportive care questions with the aim of reducing both short- and long-term toxicities.[6]

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