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Acute therapy-related toxicities in pediatric acute lymphoblastic leukemia

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Abstract

Most children diagnosed with acute lymphoblastic leukemia (ALL) will achieve remission and be cured of their disease. However, this high cure rate comes at the cost of acute and chronic treatment-related toxicities. In fact, a similar number of children die from either ALL itself or the toxicities associated with its treatment. Therapy-related toxicities, whether acute or chronic, can impact treatment efficacy, overall survival (OS), and the patient's quality of life.

This review focused on six major acute toxicities of ALL therapy, venous thromboembolism, osteonecrosis, neurological sequels, delayed MTX elimination, asparaginase-associated pancreatitis, and toxicities of the new biological therapies. Most of these severe acute toxicities of ALL treatment can be mitigated through tailored therapy adaptations for individual patients and careful incorporation of immunotherapy. These adaptations will soon become a central component of contemporary pediatric ALL protocols and ultimately improve patients’ OS and Wellness.

Summary

While the remarkable cure rate of ALL is a significant achievement, it is accompanied by both acute and chronic treatment-related toxicities. Personalized treatment approaches, which consider individual characteristics, risk factors, and genetic polymorphisms, in addition to the incorporation of immunotherapy, are crucial. These adjustments will help reduce the short- and long-term toxicities associated with conventional chemotherapy and improve survival and quality of life for ALL patients.

Introduction:

The improved overall survival (OS) of children with Acute lymphoblastic leukemia (ALL), exceeds today's 90% with the best contemporary treatment (1). However, a substantial number of patients suffer from severe, fatal, or lifelong toxic effects (2,3). As most children will be cured of their disease, trials no longer aim only to introduce more powerful antileukemic drugs but rather focus on minimizing treatment-related toxicities.

Therapy-related toxicities may involve numerous organs with various severity, may be acute or chronic, and have an impact on therapy modification, OS, and quality of life.

This review will focus on six major acute toxicities of ALL therapy, their clinical characteristics, pathophysiology, risk factors, treatment, and prevention options. These toxicities include venous thromboembolism (VTE), osteonecrosis (ON), neurological sequels; MTX stroke-like syndrome (MTX SLS) and posterior reversible encephalopathy syndrome (PRES), MTX-related nephrotoxicity with delayed MTX elimination (DME), asparaginase-associated pancreatitis AAP), and toxicities of the new biological therapies. Despite their enormous importance, the infectious toxicities deserve a separate chapter and will not be discussed here.

1. Thromboembolism in children with ALL

a. Epidemiology and manifestations

Thromboembolism (TE) is a well-recognized serious complication in ALL therapy, with a prevalence of clinically significant thrombosis in up to 15% (4,5). The thrombotic events are mainly venous and over 50% of symptomatic VTE events are in potentially life-threatening sites. Cerebral sinus vein thromboses (CSVT) are

described in 20-44%, pulmonary embolism in 5-3%, and deep vein thrombosis (DVT) of the limbs or right atrial (considered central catheter-related) accounted for 70% of all VTEs. (4,6). The most common symptoms of CSVT are hemiparesis, seizures, decreased consciousness, and severe headaches. Younger children may present with moderate headache, or irritability (4). Most events occur during therapy's induction or delayed intensification phase, in temporal proximity to asparaginase and corticosteroid therapy (4). VTE may lead to modification of further chemotherapy and indeed, reduced overall survival (OS), and event-free survival (EFS), have been described in children with ALL and thrombosis (7)

b. Pathogenesis and risk factors:

VTE results from a combination of the disease, patient, and treatment-related factors. The main **disease-related risk factors** are increased formation of thrombin, factors VIII, IX, von Willebrand factor (vWF), and alpha-2-macroglobulin during active leukemia, in addition to a reduction in the natural coagulation inhibitors protein C & S (5), and increased interaction of procoagulant molecules and inflammatory cytokines synthesized by the malignant cells with the vascular endothelium (8).

Several **patient-related risk factors** for VTE in ALL have been identified, including inherited thrombophilia, (9) high-risk ALL group, older age (4), hypertriglyceridemia (4,10) mediastinal mass (11), obesity (12), and non-O blood group (13). No single nucleotide polymorphisms (SNP) reached genome-wide significance. The SNPs most strongly associated with thrombosis are: rs2874964 near RFXAP, rs55689276 near the α globin cluster in non-European ancestry, rs2519093, in ABO,(14), ALOX15B (rs1804772) and KALRN (rs570684) genes (15).

Treatment-related thrombosis: Any cancer therapy may increase the pro-thrombotic risk, by activating platelets and monocyte-macrophage tissue factor (16). However, the main hypercoagulability in children with ALL is associated with the use of **asparaginase** which compromises hepatic protein synthesis and reduces the levels of plasminogen, antithrombin (AT), protein C, S, and vWF (17). Most ALL protocols have replaced native E. coli-asparaginase with the long-acting PEG-asparaginase, which may have a stronger thrombogenic effect (4). **Corticosteroids** also contribute to the hypercoagulable state by elevating multiple clotting factors, vWF, plasminogen activator inhibitor 1, and anti-plasmin (5). Another therapy-related risk factor is the **central venous line (CVL)**, accounting for more than two-thirds of VTEs in children in general (18). Among pediatric oncology patients, an elevated risk has been reported with external CVL (19), left-sided (18), and peripherally inserted central catheters (PICCs) (20).

c. **Sequel of VTE**

The most significant sequels post-VTE occur among patients with CVST, and permanent neurological disability has been described in up to 35%. The most common are epilepsy, motor deficits, and cognitive disabilities including attention and perception problems (19). DVT of the limbs may lead to post-thrombotic syndrome (21).

d. VTE therapy and thromboprophylaxis

The ASH guideline suggests using either low-molecular-weight heparin (LMWH) or vitamin K antagonists in pediatric patients with symptomatic DVT or PE (22). Due to interactions of vitamin K antagonists with chemotherapy drugs, anticoagulation with LMWH has been the drug of choice for VTE in children with cancer for decades. However, pain at the injection site reduces adherence to therapy (23). In addition, recurrent VTEs occur despite LMWH therapy, which might imply sub-optimal activity, maybe due to AT deficiency (4). Direct oral anticoagulants (DOAC), an attractive therapeutic option for children with cancer, have recently been evaluated in pediatric clinical trials and demonstrated the noninferiority of Rivaroxaban (24) and dabigatran (25) over LMWH, leading to their recent approval for pediatric use in the United States and Europe. Still, good-quality data regarding the outcome of children with cancer-associated thrombosis treated with DOACs are limited (16). Bleeding risk, VTE resolution, and recurrence in children are currently unknown. In addition, their pharmacokinetics necessitate a longer anticoagulation pause before invasive procedures, administration with food, and increases the potential drug interactions.

Considering the rarity of VTE in children compared to adults, thromboprophylaxis is currently suggested to be considered in selected high-risk patient groups (9, 23, 26). Most physicians still use LMWH for VTE prophylaxis, but further studies on DOACs may promote their implantation in pediatric anticoagulant therapy and prevention.

2. Osteonecrosis

Osteonecrosis (ON) is one of the seriously debilitating and long-lasting complications of ALL therapy in children, significantly impacting their quality of life.

a. Epidemiology and clinical manifestations:

The severity of osteonecrosis ranges from asymptomatic bone injury limited to radiological findings, to severe pain with permanent disability and deformative bone changes. Weight-bearing joints are mainly affected (27) and most children have multifocal involvement (28). The reported prevalence of radiologically proven symptomatic osteonecrosis in children with ALL ranges between 1– 17 % with adolescents at highest risk (29-31). The most affected joints are the knees (45-88%),

hip (35-67%), ankle (13-44%), and shoulder (13-24%) (28, 32, 33). Most events occur within 2-3 years of ALL therapy initiation and then reach a plateau (29, 33).

b. Pathogenesis:

The presumed pathogenesis is diminished blood supply to the bones with failure to deliver essential nutrients, leading to apoptosis of osteocytes, intramedullary lipocytes proliferation, and destruction of bone architecture. During revascularization, bone resorption by osteoclasts results in demineralization, trabecular thinning, and mechanical failure (34, 35). Multiple factors may act synergistically in the development of osteonecrosis in children with ALL, and corticosteroids play a major role (36). Corticosteroids induce osteoclasts' and osteoblasts' apoptosis, decrease bone turnover and density, and cancellous bone formation (34,37). Furthermore, corticosteroids drive the marrow mesenchymal stem cells toward lipoid differentiation at the expense of osteogenesis leading to increased intramedullary pressure and reduced blood flow (36). In addition to corticosteroids, Asparaginase and MTX have been traditionally presumed contributors to the development of ON in children with ALL, however, their role in the absence of steroids is doubtful.

c. Risk Factors:

Several risk factors for the development of ON among children with ALL have been identified. The most agreed upon is **older age**, adolescents during their growth spurt are at the highest risk (28, 31-33) due to rapid bone growth and epiphyseal closure, increasing intramedullary pressure (30). **Female gender** is another significant risk factor (31,33,38) and possible mechanisms are earlier growth plate closure through puberty, gender-associated altered lipid metabolism (31), and female bone expansion into the medullary space leading to thinner bones (39). Other risk factors are **high-risk ALL** (29,33), perhaps due to more intense steroid therapy, **hyperlipidemia,** peak values, or prolonged exposure (33,40,41). The proposed pathogenesis is increased blood viscosity and intraosseous pressure due to accumulations of fat cells in the intramedullary tissue. (34). **Bone pain at ALL diagnoses,** especially at the knees or hips, was reported as an additional risk factor for ON at those sites. A possible explanation may be a local ischemic injury with vulnerability to future additional stress. (33). A higher prevalence of ON was reported among patients of Asian ethnicity (28) and Caucasian background (27), and a lower prevalence in children of Arabic origin (33). Several genetic risk factors for ON in children with ALL such as polymorphisms in the plasminogen activator inhibitor-1 (PAI-1) gene, thymidylate synthase, antifolate, steroid hormone response, glutamate receptor, and adipogenesis pathways have been reported (32).

d. Therapy:

Despite the detrimental consequences of ON in children with ALL, there is no consensus or recommendations regarding an optimal therapy since high-quality studies are lacking. The numerous therapeutic options include bisphosphonate, prostacyclin analogs, statins, anticoagulation or anti-hypertension treatment, hyperbaric oxygen, and surgical interventions such as human bone morphogenetic protein, fresh osteochondral allografting, core decompression and joint replacement (33, 35). Most of these treatments are more effective if introduced during the early stages of ON and offer mainly pain relief without resolution of bone pathology. Once ON occurs, the resolution rate among survivors is low and more than half of the affected patients suffer from persistent physical disabilities (28,33).

e. Prevention:

Reducing treatment-related ON is feasible by discontinuous instead of continuous steroid scheduling, or by reducing the duration of steroid therapy (35,32). Considering the potential negative effect on survival, this approach is recommended only to patients at the highest risk of ON, mainly older age and female gender (32).

3. Neurotoxicity

3.1 Methotrexate-Induced Stroke-Like Syndrome

a. **Epidemiology and Clinical Manifestations**

Methotrexate-induced stroke-like syndrome (MTX SLS) is a significant complication of ALL therapy. Clinical manifestations typically include sudden onset of neurological symptoms such as hemiparesis, aphasia, seizures, and altered mental status. The condition is termed "stroke-like" due to its resemblance to ischemic stroke (42,43). The onset of SLS usually occurs within 3 weeks after systemic or intrathecal (IT) MTX administration. MRI findings, particularly diffusion-weighted imaging (DWI), have been instrumental in identifying characteristic changes such as focal or diffuse hyperintensity of the periventricular or subcortical white matter on T2-weighted images. Restricted diffusion on the ADC map suggests cytotoxic edema (43-45).

b. **Pathogenesis**

The pathogenesis of MTX SLS is not entirely understood, but it is thought to involve direct neurotoxic effects on the central nervous system (CNS). Several mechanisms have been suggested. MTX acts by inhibiting dihydrofolate reductase, which decreases tetrahydrofolate, a key factor in DNA synthesis and repair. This depletion may result in neurotoxicity, especially in rapidly dividing cells within the CNS (2, 44). Elevated homocysteine levels may cause direct damage to the vascular

endothelium. Moreover, homocysteine metabolites are also excitatory agonists of the N-methyl-D-aspartate (NMDA) receptor, and excessive activation of this receptor has been linked to neurotoxicity and seizure activity (46).

c. **Risk Factors**

Specific risk factors for MTX SLS are not yet established. However, co-administration of cytarabine and cyclophosphamide alongside IV high-dose MTX or IT MTX treatment may play a role. These drugs promote neurological complications in high-dose regimens. Older age was proposed as another risk factor, but this may reflect increased exposure to courses of intensive chemotherapy (47). Polymorphisms in genes related to MTX and folate metabolism, such as methylenetetrahydrofolate reductase (MTHFR), have been associated with an increased risk of adverse CNS effects. Genome-wide association studies have identified potential genetic variants that could elevate the risk for MTX SLS in the SHMT1, ABCG2, and ABCB1 genes involved in the folate pathways and ATP-binding (48).

d. **Treatment and Prevention**

Various drugs can mitigate the biochemical effects of MTX. Folic acid supplementation and leucovorin rescue have effectively reduced SLS in patients re-exposed to high-dose MTX. Aminophylline, an adenosine antagonist, and dextromethorphan, which blocks NMDA receptors, have also been used as secondary prophylaxis (49-51). Supportive care measures, such as anti-seizure medications and close monitoring of neurological function, are essential components of the treatment strategy. Importantly, spontaneous resolution happens in most cases, and re-challenge is recommended according to scheduled doses of MTX but should be deferred during co-administration of IV cyclophosphamide and cytarabine (42).

3.2 . Posterior Reversible Encephalopathy Syndrome (PRES)

a. **Epidemiology and Clinical Manifestations**

Posterior reversible encephalopathy syndrome (PRES) is a neurological disorder marked by a rapid onset of headaches, seizures, altered mental status, and visual disturbances. In children with ALL, it occurs, particularly during induction chemotherapy and after hematopoietic stem cell transplantation (52-54). The exact prevalence of PRES among children with ALL is unclear and ranges between 4.7% in a single-center study (52) to 0.9% in a population-based study (55). The clinical manifestations are non-specific and may overlap with other neurological complications of ALL like MTX SLS, convulsions, and encephalopathy (53,56).

b. **Pathogenesis**

The mechanisms underlying PRES in children with ALL are not fully understood. One hypothesis suggests that endothelial dysfunction leads to a blood-brain barrier breakdown, resulting in fluid accumulation and edema in the brain (57, 58). Another theory implicates chemotherapeutic agents, such as cyclophosphamide, L-asparaginase, vincristine, and methotrexate, which may directly affect the brain's blood vessels or trigger an inflammatory response contributing to endothelial dysfunction (52, 54).

c. **Risk Factors**

Older age and T-cell immunophenotype increase the risk of PRES in children with ALL. In addition, CNS involvement was suggested to be associated with early PRES and high-risk block treatment with late PRES (53). Other risk factors are hypertension, specific chemotherapeutic agents as described above, pre-existing brain abnormalities, and renal dysfunction (52,54,57, 59). The role of genetics in PRES is not fully understood, and further research is needed to identify specific genetic risk factors. A genome-wide association study on neurotoxicity in children with ALL excluded patients with PRES from the analyses due to their genomic inflation (60).

d. **Treatment and Prevention**

Early diagnosis of PRES and prompt management of the underlying cause are crucial for a good prognosis. This typically includes withholding or adjusting the chemotherapy agents suspected of triggering PRES, and lowering blood pressure to a safe range. Supportive care, including anti-seizure medications, pain management, and close monitoring of neurological function, is also recommended. Due to the unclear pathogenesis of PRES, preventative recommendations were not established. However, strategies such as careful blood pressure monitoring, neurological symptoms, and potential risk factors during ALL treatment, are important for early detection. Maintaining adequate hydration may help prevent blood vessel dysfunction, and alternative chemotherapy regimens with a lower risk of PRES may be considered in some cases (52,53, 57).

4. MTX-related nephrotoxicity

a. <u>Epidemiology and clinical manifestations:</u>

One of the fundamental drugs included in most contemporary pediatric ALL treatment protocols is high-dose methotrexate (HDMTX; 1-5 g/m^2), which was proven to decrease central nervous system (CNS) relapse and improve OS (61). Nevertheless, up to 4% of the treated patients develop renal toxicity with severely delayed MTX elimination (DME) (62-64). The risk of severe DME is highest with the first HDMTX infusion (63). The Ponte di Legno Toxicity Working Group (PTWG) has

defined DME as an increase in plasma creatinine of >0.3 mg/dl or of 1.5-fold above baseline, together with severely elevated plasma MTX concentrations at one of the time points after MTX initiation: 36h MTX >20 µM/l, 42h MTX >10 µM/l, 48h MTX >5 µM/l. (2) DME may lead to cessation of HDMTX therapy and thus may hamper the efficacy of treatment and increase the rate of relapse. Some patients can be re-challenged with HDMTX (65), but no evidence-based re-exposed guidelines exist. Additional symptoms, such as vomiting and diarrhea shortly after the MTX administration, have been reported, but most patients with DME are initially asymptomatic and present with non-oliguric renal dysfunction. An abrupt rise in serum creatinine during or shortly after MTX infusion implies the development of renal dysfunction and can result in significantly elevated plasma MTX concentrations. (66,67).

b. Pathogenesis:

MTX enters the cell via the reduced folate carrier and undergoes polyglutamation which retains it inside the cell. MTX blocks methionine, thymidine, purine, and pyrimidine synthesis by inhibiting dihydrofolate reductase (DHFR). The critical factor of MTX cytotoxicity is the duration of exposure. Prolonged exposure to MTX and its metabolite; 7-hydroxy-methotrexate (7-OH-MTX), can result in acute renal, central nervous system, gastrointestinal and liver toxicity, bone marrow suppression, and even life-threatening (62,66). The presumed etiologies of MTX-induced renal dysfunction are the precipitation of MTX and its metabolites in the renal tubules, leading to arteriolar vasoconstriction and reduced renal perfusion, or uptake of MTX into the renal tubules with direct tubular toxicity (62,66). Nephrotoxicity may result from elevated oxidative stress within the kidneys, inflammation, mitochondrial dysfunction, and increased apoptosis (68). Decreased MTX solubility or renal extraction induces prolonged exposure to high MTX levels and leads to nephrotoxicity, which in turn increases the risk of other systems' toxicities, such as myelosuppression, mucositis, hepatitis, and dermatitis (67).

c. Risk factors:

The most significant risk factor for DME is acidic urine pH. More than 90% of MTX and its metabolites, 7-OH-MTX and DAMPA are cleared by the kidneys, and their solubility is poor at acidic pH. Hyperhydration before and after MTX infusion and urine alkalinization increase MTX solubility and urine extraction. (67). Inhibition of renal tubular secretion, MTX transport and elimination, or decreased GFR may be induced by co-administered drugs such as probenecid, salicylates, sulfisoxazole, penicillins, nonsteroidal anti-inflammatory agents, gemfibrozil, amphotericin, aminoglycosides, dasatinib, radiographic contrast dyes, proton-pump inhibitors, levetiracetam, chloral hydrate, and even food or beverages containing licorice, and

thus consequently increase MTX toxicity. (62,67,69). Additional risk factors are effusions and fluid collections which may serve as reservoirs of MTX and hypoalbuminemia which may lead to increased free plasma MTX levels and third-spacing fluids (70). Several SNPs in the genes, ABCB1, ABCC2, MTHFR, and most significantly in the SLCO1B1 gene, appear to play significant roles in MTX metabolism and clearance (71).

d. Therapy:

Early recognition of renal dysfunction, manifested by increasing serum creatinine, leading to urgent intervention, is crucial to prevent irreversible toxicity. Highly effective pharmacologic intervention that includes the combination of hyperhydration and high-sustained LCV dosage before and after systemic glucarpidase (carboxypeptidase-G2) administration significantly decreases the development of grade 4 and 5 toxicity (66,72).

Glucarpidase is a recombinant bacterial enzyme that rapidly hydrolyzes MTX into its inactive metabolites: DAMPA and 7-OH-MTX. Treatment with glucarpidase at a dose of 50 units/kg, is indicated and FDA-approved for patients with severe DME and should be given within 96 hours after the start of MTX. Due to its large molecular size, glucarpidase does not enter cells nor cross the blood-brain barrier. Thus, LCV should be given before and renewed 2 hours after glucarpidase administration. Afterwards, plasma MTX levels should be monitored using a specific high-pressure liquid chromatography (HPLC) method, and not by an Immunoassay method that does not distinguish between MTX and its metabolite. A potential rebound of MTX due to its release from tissue stores, obligates prolonged monitoring of MTX concentrations and LCV administration.

LCV provides a source of intracellular tetrahydrofolates that enter the folate cycle downstream of DHFR, inhibited by MTX. However, LCV competes with MTX for cellular uptake and polyglutamylation and is less effective at high MTX concentrations. LCV rescue usually starts 24–42 hours after the start of the HDMTX infusion and must not be delayed beyond 42–48 hours (66). Alternative therapies of hemodialysis or hemodiafiltration can only temporarily clear free plasma MTX and are recommended in addition to high-dose LCV rescue, just in the absence of glucarpidase (66). Thymidine, which counteracts the effects of MTX, has not been confirmed as beneficial in DME (72).

e. Prevention:

Urine alkalinization and fluid hyperhydration to maximize MTX solubility in urine, avoidance of competitive drugs, frequent monitoring of serum creatinine, and plasma MTX levels, and adequate LCV rescue, reduced the risk of DME (66).

5. Asparaginase-associated pancreatitis

a. Epidemiology, Pathogenesis & Clinical manifestations:

Asparaginase is a fundamental drug in the treatment of ALL. It depletes the amino acid asparagine through its deamidation and increases the cure rate by inducing apoptosis of malignant lymphoblasts lacking asparagine synthetase (73,74). Still, organs with a high protein metabolism like the liver and the pancreas may be injured, and genetic variability might play a role. One of the serious adverse events of asparaginase is asparaginase-associated pancreatitis (APP) described in up to 18% of patients (2,75). AAP often results in the truncation of asparaginase therapy, which might increase the risk of relapse (76). AAP is a sudden inflammation of pancreatic parenchyma that develops between 3 and 10 days after the last asparaginase dose, with clinical and imaging findings resembling acute pancreatitis from other causes (77). The assumed pathophysiology involves an elevation in Ca^{2+} levels triggering the activation of proteolytic pancreatic enzymes leading to pancreatic autodigestion (11). The PTWG graded and defined AAP based on the Atlanta criteria, with at least two of three obligatory features: abdominal pain strongly suggestive of pancreatitis; serum lipase or amylase ≥ 3 times UNL; and characteristic imaging findings of pancreatitis. Grade 1; Mild AAP: symptoms and enzyme elevations ≥ 3 times UNL for less than 72 h, grade 2; severe AAP: symptoms or enzyme elevations ≥ 3 times UNL for more than 72 h, or hemorrhagic pancreatitis, pancreatic abscess, or cyst, and grade 3; death from pancreatitis (2).

The most common symptoms of AAP are abdominal pain, nausea, and vomiting, some suffer from fever, back pain, hypotension, and even SIRS (75,77). In most cases, AAP is reversible and characterized by modest, generalized pancreatic edema without pancreatic failure or systemic complications. However, up to 20% might suffer from severe complications such as pseudocysts, hemorrhage or abscess, a need for assisted ventilation, prolonged use of insulin therapy, and even death. Severe complications are more common among patients with pseudocysts, older children, and those with severe AAP, and may persist (77,78). The long-term sequels of APP are more common after pseudocysts and may include chronic pancreatitis with exocrine pancreatic insufficiency, type 3c Diabetes Mellitus, and chronic abdominal pain (75).

b. Risk Factors:

The following risk factors for APP have been found, age≥ 10 years (76,79) treatment intensity, native American ancestry (80), and obesity (81). In addition, several gene mutations and SNPs were associated with AAP: SNP rs281366 in the ULK2 gene, rs17179470 in RGS6, (82), rs4726576 and rs10273639 (77) rs199695765 in the CPA2 (carboxypeptidase A2) gene(80), rs3809849 in the MYBBP1A gene, rs11556218 in IL16 and rs34708521 in SPEF2 (83), rs213950 in the CFTR gene and rs3832526 in the ASNS gene- asparaginase pathway polymorphisms (84), rs4726576 and rs10273639- in Trypsin-encoding PRSS1-PRSS2 genes (85).

c. Therapy:

Therapy is primarily supportive by providing fluid replacement, pain relief, parenteral nutrition as needed, and close monitoring. Early enteral nutrition is essential to secure nourishment during severe acute disease. No treatment is currently available to reverse pancreatic damage (78). Pharmacological interventions for treatment and prevention are controversial and include octreotide, a somatostatin analog that inhibits exocrine pancreatic enzyme production and may lessen the damage to the surrounding tissue (86], and galactose and pyruvate that may protect from AAP-induced necrosis by preventing asparaginase from depleting adenosine triphosphate (ATP) (89).

d. Re-exposure

Re-exposure, when appropriate, is recommended due to lower PFS and OS in patients with reduced asparaginase therapy (74,76). However, this must be done with caution considering the severity grading. A second episode of AAP was reported in 46– 63% of the re-exposed patients, and 23% of the events were severe. No risk factors for a second AAP event were found and its severity or complications were not correlated with the first event's severity (77,78). Future incorporation of gene testing to identify risk factors before asparaginase therapy might reduce the risk of 2^{nd} AAP.

6. Immunotherapy-Associated Toxicities in Pediatric Acute Lymphoblastic Leukemia

The advent of immunotherapy has dramatically altered the landscape of pediatric ALL therapy. Agents such as blinatumomab, inotuzumab ozogamicin, and chimeric antigen receptor T-cell therapy (CAR-T) have demonstrated remarkable efficacy in achieving durable remissions and improving OS with reduced treatment toxicities (88). However, these therapeutic advancements are accompanied by a spectrum of new adverse

events, with cytokine release syndrome (CRS) and neurotoxicity emerging as the most critical safety concerns.

CRS is a complex, systemic inflammatory response triggered by the uncontrolled release of pro-inflammatory cytokines, including interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) (89). This hyperinflammatory state can lead to a cascade of pathophysiological events, including endothelial dysfunction, vascular leakage, and organ damage (90,91). Clinically, CRS manifests as a spectrum of symptoms ranging from mild flu-like illness to life-threatening multiorgan dysfunction. Common initial symptoms are fever, chills, fatigue, myalgias, and nausea. As CRS progresses, patients may develop more severe symptoms such as hypotension, tachycardia, dyspnea, and acute respiratory distress syndrome. The severity of CRS is often correlated with tumor burden, and patients harboring higher disease burden are at increased risk for severe CRS (88).

Blinatumomab, a bispecific CD19/CD3 T-cell engager, and chimeric antigen receptor (CAR T) cell therapy have revolutionized the treatment of pediatric ALL while demonstrating efficacy in relapsed/refractory ALL as well as in frontline therapy (88,92,93). Although the toxicities of these drugs are generally milder than those with conventional chemotherapy regimens, the development of CRS can lead to a robust life-threatening hyperinflammatory cytokine storm that requires prompt intervention (88,92). Additionally, their neurotoxicity poses a significant concern. The direct oncolytic and bystander effects of Blinatumomab and CAR T cells on the central nervous system contribute to an immune effector cell-associated neurotoxicity syndrome (ICANS), which can manifest as encephalopathy, cognitive impairment, confusion, headache, dizziness, tremor, and seizures (94,95). Additionally, two clinical trials in pediatric ALL patients reported acute kidney injury and electrolyte abnormalities as serious complications following the CAR-T treatment (96,97). The management of CRS and neurotoxicity associated with these immunotherapies requires a multidisciplinary approach involving hematologists, oncologists, intensivists, and neurologists. Early recognition and prompt intervention are crucial to preventing progression to severe complications. Supportive care measures, including intravenous hydration, oxygen supplementation, and vasopressor support, are essential components of the management. Tocilizumab, an interleukin-6 receptor antagonist, has emerged as a valuable therapeutic option for the treatment of CRS [98]. Corticosteroids are commonly used for both CRS and neurotoxicity, although their efficacy and safety profile in these settings warrant further investigation.

Inotuzumab ozogamicin, an antibody-drug conjugate targeting CD22, represents another therapeutic option for pediatric ALL. While inotuzumab ozogamicin has demonstrated efficacy in certain patient populations, its toxicity profile differs from that of blinatumomab and CAR T-cell therapy. The incidence of CRS and neurotoxicity is

generally lower, and other toxicities such as febrile neutropenia, infections, and hepatotoxicity can be more prominent (99). Furthermore, the risk of sinusoidal obstruction syndrome following HSCT after inotuzumab ozogamicin therapy is a critical safety consideration.

Discussion and summary

The excellent cure rate of ALL comes with the cost of acute and chronic treatment toxicities. Principally, every organ may be affected and injured by ALL intensive therapy. This review focused on six systems involved in major treatment toxicities: the nerve system including PRESS and MTX SLS, the bony system with AVN, the vascular system with VTE, the kidneys with DME, the gastrointestinal system with pancreatitis, and finally, the toxicities of the new immunotherapies. Several other acute toxicities such as infections, hepatotoxicity, typhlitis, mucositis, psychiatric, pulmonary, ocular, and musculoskeletal injuries, in addition to long-term toxicities including cardiac, endocrine, cognitive, metabolic, and quality of life, notwithstanding their importance, were out of the scope of this review.

Most of the severe acute toxicities of ALL treatment can be reduced by patients-adjusted dose intensity and targeted therapy, considering the germline and somatic mutations, and the leukemia risk-based stratification. A comprehensive understanding of the risk factors for each toxicity, the clinical manifestations, preventive strategies, and early intervention, will further optimize therapy outcomes. Patients' tailored therapy adaptations, considering individual gene polymorphism with incorporation of immunotherapy into frontline ALL therapy, would hopefully enable reducing the short and long-term toxicities of conventional chemotherapy, and further improve OS and quality of life for ALL patients.

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Legend to Figure 1: The six major acute toxicities of ALL therapy:

Six major acute toxicities of pediatric ALL therapy: venous thromboembolism (VTE), avascular necrosis (AVN), neurological toxicities: MTX stroke-like syndrome (MTX SLS), and posterior reversible encephalopathy syndrome (PRES), delayed MTX elimination with renal injury (DME), asparaginase associated pancreatitis (AAP), cytokine release syndrome (CRS) and neurotoxicity of immunotherapies.

Toxicity tree of pediatric Acute Lymphoblastic Leukemia Therapy