Consensus definitions of fourteen severe acute toxicities during childhood lymphoblastic leukaemia therapy

Running title: Childhood ALL Toxicities – international consensus definitions

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ABSTRACT

Background: The high survival rate for childhood acute lymphoblastic leukaemia (ALL) is counterbalanced by the burden of toxicities, but reported frequencies vary widely across studies partly due to diverse toxicity definitions.

Method: Using Delphi method, 15 international childhood ALL study groups scrutinised ALL protocols to address 14 acute toxicities that are serious, but too rare to be addressed comprehensively within any single group or regarded to need consensus definitions for reliable incidence comparisons: hypersensitivity to asparaginase, hyperlipidaemia, osteonecrosis, asparaginase-associated pancreatitis, arterial hypertension, posterior reversible encephalopathy syndrome, seizures, depressed level of consciousness, methotrexate-related stroke-like syndrome, peripheral neuropathy, high-dose methotrexate related nephrotoxicity, sinusoidal obstructive syndrome, thromboembolism, and Pneumocystis jirovecii pneumonia.

Results: None of the ALL protocols addressed all 14 toxicities, no two protocols shared identical definitions of all toxicities, and no toxicity definition was shared by all protocols. Consensus definitions were obtained for all 14 toxicities.

Conclusion: In the overall evaluation of outcome of ALL therapy, these expert opinion-based definitions will allow reliable comparisons of acute toxicity frequencies and severities across treatment protocols and facilitate international research on aetiology, guidelines for treatment adaptation, preventive strategies, and development of consensus algorithms for reporting of ALL therapy outcome that balance toxicity and antileukaemic efficacy.

KEY WORDS: Acute lymphoblastic leukaemia, child, chemotherapy, Delphi method, toxicity.

INTRODUCTION

Acute lymphoblastic leukaemia (ALL) accounts for 25% of all childhood cancers and has leapt from being universally fatal two generations ago to having five year overall survival rates above ninety percent with the best contemporary treatment.[1] However, a substantial number of patients experience severe fatal or life-long toxicities.[2] The frequency of these toxicities vary widely across study protocols (webappendix pages 2, 5, 7, 8, 10, 11, 13, 15, 18, and 19), which reflects not only the treatment intensities, but also diverse toxicity definitions and strategies for toxicity capture and reporting, making meaningful comparisons of toxicity risks impossible.

The progressive intensification of ALL therapy in recent decades has led to a situation where, for good risk patients, the chance of treatment-related death may now equal the chance of leukaemic relapse.[3] Accordingly, trials no longer aim only to introduce more powerful antileukaemic agents, but in parallel focus on minimising toxicity. Evaluating the success of this approach depends on robust measurement of the toxicity burden within different arms of a trial, between different trials internationally, and between patient subsets defined by clinical features or germline DNA variants.[4]

Definitions for most organ toxicities already exist, and the United States National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE)[5] is widely used. However, many toxicities are described in very general terms in CTCAE, and the toxicity definitions were not developed to meet the specific needs associated with childhood ALL therapy. In addition, the toxicity grades that are currently captured and reported vary across protocols. Finally, various definitions are used for several toxicities (webappendix page 24), and consensus definitions across ALL protocols are lacking. Recognising the need for international collaboration on this issue, the Ponte di Legno consortium (PdL) established a toxicity working group (PTWG) to address serious adverse events associated with childhood ALL therapy. The PdL consortium aims to improve outcomes of childhood ALL.[1] It encompasses the Associazione Italiana Ematologia ed Oncologia

Pediatrica (AEIOP; Italy), the Berlin-Frankfurt-Münster study group (BFM; Germany), the German Co-operative Study Group for treatment of Acute Lymphoblastic Leukemia (COALL; Germany), the US Childrens Oncology Group (COG; USA), the Czech Working Group for Pediatric Hematology (CPH; Czech Republic), the Dutch Childhood Oncology Group (DCOG; Holland), the Dana Farber Cancer Institute consortium (DFCI; Boston, USA), the European Organisation for Research and Treatment of Cancer (EORTC; Belgium and France), the French Acute Lymphoblastic Leukemia study group (FRALLE; France), the Israel National Study (INS; Israel), the Japanese Pediatric Leukemia Study Group (JPLSG; Japan), the Nordic Society for Paediatric Haematology and Oncology (NOPHO; Denmark, Finland, Iceland, Lithuania, Norway, Sweden), St Jude Children's Research Hospital (SJCRH; USA), the Taiwan Pediatric Oncology Group (TPOG; Taiwan), and the United Kingdom Acute Lymphoblastic Leukaemia and Lymphoma Trial Group (UKALL; United Kingdom).

As a first step, the PTWG aimed to obtain consensus definitions of 14 prioritised acute toxicities. We report here the process and the final definitions that have been approved by the involved PdL ALL groups. These definitions will be crucial for future reliable comparison of toxicity data emerging from various ALL treatments, for collaborative research addressing risk factors including host genome variants, and for comparison of strategies for prevention or treatment of toxicities.

METHODS

Based on the need for international definitions for acute toxicities that are serious, but either too rare to be addressed comprehensively within any single ALL group or that need consensus definitions for reliable comparison of incidences and outcome, representatives from 15 PdL groups initially listed all acute toxicities that they regarded to be relevant for consideration by the PTWG (webappendix page 22, table A1). Following initial discussions, it was decided that toxicities that were almost universally reversible and in addition sufficiently common to be explored within a single ALL group, such as mucositis, bone-marrow and immune suppression, febrile neutropenia, skin rashes, hyperglycaemia, and several transient organ

failures should not be pursued by the PTWG. Among the remaining listed toxicities (webappendix page 22, table A1), “treatment-related mortality”, “invasive fungal infections” apart from Pneumocystis jirovecii pneumonia, and “transfer to intensive care unit” were deferred, since the former two either have been[6] or currently are being addressed by other international working groups, and the latter was regarded as being too influenced by local logistics and resources. Furthermore, toxicities that have multiple and complex causes (such as hepatic failure) were not regarded as candidates for PTWG consensus definitions, although they may be relevant for future prospective registration to quantify and qualify the burden of antileukaemic therapy. Finally, several toxicities that were serious but already defined and graded by CTCAE with definitions suitable for children with ALL were not addressed (webappendix page 22, table A1).

Search strategy and selection criteria

Since the pathogeneses and natural histories for most of the remaining 14 prioritised toxicities are poorly understood from a biological point of view, a Delphi process was chosen for obtaining expert opinion based consensus definitions (Figure 1).[7,8] For each of the 14 toxicities, ad hoc working groups (AWG), including a chair for each AWG, were established with initial representation of experts from at least three of the 15 involved ALL groups, but subsequently expanded after each face-to-face plenary PTWG meeting (webappendix page 22, table A1). Each AWG reviewed i) the current literature on their toxicity with special focus on ALL cohort publications, and ii) the toxicity sections of 13 treatment protocols currently used by PdL groups. In addition, co-author MK added information on the Japanese ALL protocols, as they were not available in English versions. AEIOP (Italy) and BFM (Germany and Austria) share almost identical ALL treatment protocols, including toxicity sections, which subsequently have been adopted by CPH (Czech) and INS (Israeli) groups. Each AWG’s results and considerations were debated within their collaborative ALL group and at three consecutive face-to-face plenary meeting including all AWGs during the International BFM annual meeting in Prague April 2014, the American Society of Hematology annual meeting in San Fransisco December 2014, and the International BFM annual meeting in Budapest May 2015 (Figure 1).

These face-to-face discussions were open to other individuals from the Ponte di Legno consortium, even if they were not directly involved in developing the final toxicity definitions. Based on discussions at these meetings and comments from the involved PdL ALL groups, the definitions (Table 1) and the webappendix were finalised. The definitions were then approved by all the groups.

RESULTS

Although the ALL protocols all have sections on treatment-related toxicities, none of the protocols address all of the 14 listed toxicities in this report, and when addressed they use various definitions (webappendix page 24, table A2). Furthermore, whilst one specific toxicity can be highlighted by one ALL treatment protocol with extensive description of that toxicity (e.g. posterior reversible encephalopathy syndrome (PRES)), other protocols may not mention that toxicity at all. Many protocols agree on individual toxicity definitions and grading, especially when CTCAE is applied, [5] but no two protocols share identical definitions of all toxicities, and no toxicity definition is shared by all protocols. Some protocols request data capture of any grade of a toxicity, whereas others only address the most severe grades. In addition, the consequence of occurrence of a specific toxicity varies by protocol from complete withdrawal of an antileukaemic agent (e.g asparaginase after pancreatitis) to no consequences, including acceptance of re-exposure, although not always specifically stated (see webappendix). Detailed discussion of the toxicities is presented in the webappendix, and a summary of some of the key disparities and discussion points are described below.

Hypersensitivity to asparaginase

Allergic reactions to asparaginase are frequent.[9,10] All protocols address hypersensitivity, but only a few address silent inactivation, and then with various definitions of trough levels and time-points for measurements, and none address allergic-like reactions (e.g. vomiting, stomach ache, or rash) without inactivation of asparaginase or indications for change in therapy (webappendix page 2). There was PTWG consensus that definitions of hypersensitivity and silent inactivation as well as allergy-like reactions were

needed, although each may pose practical clinical challenges. All but one group use pegylated asparaginase (Peg-Asp) as front-line therapy. Since Peg-Asp becomes inactivated in virtually all patients with and allergic reaction irrespective of its severity, [9] any degree of hypersensitivity should logically lead to a change to Erwinia asparaginase. [10] In addition to the definition of asparaginase hypersensitivity, the PTWG defined silent inactivation in patients without clinical allergy as trough asparaginase activity levels below lower level of quantification (LLQ, preferably measured in two independent samples), i.e. i) a day 7 asparaginase activity level <100 IU/L and/or a day 14 level <LLQ in case of biweekly PEG-Asp, and ii) a 48 hours post-dose level <LLQ in case of Erwinia asparaginase (2-3 times a week) (Table 1 and webappendix page 2).

Hyperlipidaemia

Both asparaginase and glucocorticosteroids can cause transient and occasionally severe hypertriglyceridaemia. This may lead to (albeit so far undocumented) toxic complications (e.g. thrombosis and cardiovascular late effects). [11] However, only a few protocols address this toxicity, mostly without a clear definition, and only one recommends routine monitoring of serum triglycerides for selected patients. There is PTWG consensus on defining severity of hypertriglyceridaemia based on levels, and also that routine monitoring should currently only take place as part of a research strategy.

Osteonecrosis

Osteonecrosis (ON) is a very common side effect of ALL therapy, and all protocols address although with diverse definitions [12] and guidelines for further glucocorticosteroid therapy, [12] and none clarify the role or interpretation/classification of imaging. [13] In spite of its limitations, all but one protocol used the CTCAE for clinical grading. There is PTWG consensus that MRI should be applied for confirmation of clinically symptomatic disease rather than for screening all patients, and that the latter should only be used currently within a research project.

Asparaginase-associated pancreatitis

Asparaginase-associated pancreatitis *(*AAP) has a low direct mortality, but is one of the most frequent causes of discontinuation of asparaginase therapy, which could increase risk of relapse. [14] All but one ALL protocol provide a definition of AAP with grading using either the CTCAE criteria or some modification of the Atlanta criteria, [15] i.e. i) abdominal pain suggestive of acute pancreatitis, ii) serum amylase at or above 2-3 times upper normal limit, and iii) imaging findings characteristic of acute pancreatitis, however varying as to whether two or three criteria should be fulfilled. Some protocols recommended measurements of both amylase and lipase, since the latter is more specific and sensitive. Protocols with extended use of asparaginase generally recommend truncation of asparaginase therapy only in cases of severe AAP.

Arterial hypertension

Arterial hypertension is common, especially during the first months of antileukaemic therapy. [16] However, none of the ALL protocols address arterial hypertension as an isolated phenomenon, instead mentioning it only in association with PRES. There was PTWG consensus that the American Academy of Pediatrics [17] and the CTCAE guidelines provide classifications of hypertension that are adaptable to its generally transient occurrence during ALL therapy (Table 1).

Posterior reversible encephalopathy syndrome

Although PRES is a clinico-radiological entity frequently seen during the first months of ALL therapy reflecting disturbances of cerebrovascular autoregulation and inconsistently characterised by headache, altered mental status, seizures, and visual disturbances, [18] seven protocols do not address it at all, and only one addresses it in detail. When addressed, all protocols apply the CTCAE grading used for any encephalopathy in spite of its limited usefulness for PRES. Except for postponing intrathecal therapy until symptoms resolve, no antileukaemic treatment modifications are recommended in any of the protocols.

The PTWG consensus definition of PRES addresses the essential clinical and imaging characteristics as well as supportive but non-mandatory findings.

Seizures

Seizures occur in approximately 10% of childhood ALL patients. [19] Most ALL protocols grade seizures clinically according to CTCAE, which does not require electroencephalography and excludes absence seizures which are anyway rare in childhood ALL. Seizures can occur both as an isolated symptom, together with various other CNS toxicities (e.g. intracranial haemorrhage or thrombosis, PRES, methotrexate (MTX) related stroke-like syndrome (MTX-SLS)), and second to electrolyte and metabolic disturbances, and infections. The PTWG decided not to include causation in the definition, but will address this complexity in registration of seizures in the future.

Depressed level of consciousness

The protocols provide grading for encephalopathy in general, but not specifically in the context of decreased consciousness or even coma, potentially reflecting the complexity of both classification of the toxicity itself and its multiple aetiologies such as infection, altered body temperature, electrolyte and metabolic disturbances, vascular or neurologic complications, and direct toxic effects of chemotherapy. The PTWG consensus definition is based on clinical findings only.

MTX-related stroke-like syndrome

MTX-SLS, which is characterised by focal neurological deficits or hemiparesis and often accompanied by disturbances in speech and/or affect, develops within two to three weeks after MTX administration and waxes and wanes over the subsequent hours to days. [20,21] All but one protocol provided grading for encephalopathy, although not specifically for MTX-SLS, using CTCAE or the US Eastern Cooperative Oncology Group criteria. Only five protocols address this syndrome, only one of these describes the

characteristic symptoms in detail, and only a few provide (various) guidelines for MTX re-exposure once the MTX-related neurotoxicity has resolved. Although MRI will not always be able to confirm MTX-SLS, it is included in the consensus definition due to the characteristic changes often seen, and its ability to distinguish between MTX-SLS and PRES.

Peripheral neuropathy

Peripheral motor and/or sensory neuropathy is common and generally caused by vincristine and in that case nearly always reversible. [22] No protocols recommend discontinuation of VCR except in cases of paralysis (occasionally caused by Charcot-Marie-Tooth disease), but several protocols recommend dose reduction in CTCAE grade 3-4 cases of paraesthesia or motor paralysis. This toxicity is addressed by all treatment protocols with the CTCAE grading, except for one group applying the Balis scale, [23] and the CTCAE grading was agreed upon by PTWG with minor modifications.

High-dose methotrexate related nephrotoxicity

All protocols that include administration of high-dose MTX (2.5-5.0 g/m^2) have clear, although diverse, guidelines for hydration, alkalinisation, and folinic acid rescue. They differ in their definition of delayed MTX elimination both with respect to MTX concentrations and time points from initiation of the MTX infusion. In cases of severely delayed elimination of MTX, less than half of the protocols include guidelines for the use of carboxypeptidase that enzymatically breaks down MTX to non-toxic metabolites. [24] Due to the very strong association between renal impairment and delayed MTX clearance, both parameters were included in the consensus definition.

Sinusoidal obstructive syndrome

The sinusoidal obstructive syndrome (SOS) or veno-occlusive disease is most commonly seen after haematopoietic stem cell transplantation and during 6-thioguanine containing maintenance therapy, but

rarely with 6MP-based maintenance therapy. [25] Although the general risks of hyperbilirubinaemia and elevations of aminotransferases during ALL therapy are mentioned in most of the ALL protocols, SOS is not included in CTCAE and only two of the ALL protocols specifically addressed SOS, with only one including a SOS definition. The PTWG consensus definition is based on combinations of at least three of five clinical findings and does not require imaging, although this may be of diagnostic benefit in selected cases.

Thromboembolism

The majority of the protocols address thromboembolic (TE) events, with all grading them according to CTCAE, but varying with respect to which grades are to be reported as severe adverse events. In cases of TE during asparaginase therapy, all six protocols that address the issue recommend re-exposure with asparaginase once the patient's clinical condition has stabilised and low molecular weight heparin has been instituted. [26] The PTWG consensus definition of TE incorporates both localisation and severity of symptoms.

Pneumocystis jirovecii pneumonia

The high risk of Pneumocystis jirovecii pneumonia (PJP) when PJP prophylaxis is not given during childhood ALL therapy is recognised in all protocols, but they differ in their dosage of prophylactic co-trimoxazole prescribed and in the required diagnostic criteria. [27] The PTWG consensus definition distinguishes between confirmed and probable PJP.

Discussion

"This is not the end, it is not even the beginning of the end, but it is, perhaps, the end of the beginning" (Winston Churchill, November 1942).

In childhood ALL, the term event-free survival traditionally encompasses five clear-cut events, namely death during induction, resistance to first-line therapy, relapse of ALL, non-leukaemic death during clinical

remission, and development of a second cancer. [1] While this composite measure of treatment outcome seemed sufficient, when life expectancy for children with ALL was poor, it falls short of current needs. Thus, while many patients with a late relapse or a second cancer have a fair chance of being cured by second line therapy, we cannot currently reverse their chronic toxicities. Each year thousands of children around the world are cured following ALL. However, many of them will have been burdened by severe acute toxicities that may cause permanent organ damage, such as osteonecrosis, chronic pancreatitis, thrombosis, and neurotoxicity, and even more will develop additional severe late effects that challenge their ability to establish and live a normal adult life. [28,29]

Although the cumulative risk of each of the 14 acute toxicities addressed in this report is in the order of five to ten percent or less, approximately half of all patients will be affected by at least one of these significant acute toxicities. [30] Thus, in the overall evaluation of ALL treatment protocols, there is a need for development of strategies to quantify the overall acute and long-term burden of therapy and balance it against event-free survival rates. This will require uniform reporting in ALL trials of both life-threatening and fatal toxicities as well as of toxicities that are associated with significant late effects.

If we are to develop evidence-based preventive interventions towards these, it requires i) consensus toxicity definitions for comparison of outcome across protocols, ii) common strategies for toxicity capture and registration, and iii) international collaboration to identify host genome variants and exposures (e.g. antileukaemic treatment, co-medication, food) associated with the risk of specific toxicities.

Not all toxicity definitions presented in table 1 are clear-cut, which primarily reflects their uncertain pathophysiology. Furthermore, several toxicities can involve overlapping symptoms, e.g. from the central nervous system, making precise classification challenging. In addition, guidelines for interventions can be directed towards the symptom (e.g. seizures or hypertension due to PRES) or the toxicity as such (e.g. MTX-

SLS). Accordingly, future registrations of certain organ toxicities should allow entry of both separate symptoms (e.g. seizures) and a putative syndrome (e.g. PRES).

The toxicity definitions listed in this report were developed after review of the existing literature, current ALL protocol, and use of the Delphi method to develop expert consensus. [7,8] These definitions are a starting point for developing evidence-based guidelines regarding optimal management and prevention strategies. Although the definitions are supported by the PdL ALL groups and should be widely applicable, their clinical and biological validity will emerge in parallel with their implementation and a deeper understanding of the pathogenesis of the toxicities, facilitated by relevant *in vitro* and animal models and international research collaboration.

The current CTCAE toxicity criteria are mostly clinical and their grading is generally based on a five grade scale (asymptomatic/mild; moderate/symptomatic rarely requiring intervention; severe/limiting activity of daily living but not life-threatening; life-threatening with urgent intervention needed; death). The CTCAE criteria benefit from their long history of use, and from the standardization of number of grades and uniformity of definitions. However, they are not specifically adapted to the administered anticancer therapy, and some toxicities (e.g. osteonecrosis and infertility) are never life-threatening or fatal, thus reducing the number of grades. Furthermore, the inclusion of medical intervention in several classifications is controversial, since it indicates that intervention is needed for a certain grade of toxicity, and the definition may on the other hand reclassify a patient, if it is decided to refrain from intervention due to local practice or patient preference rather than just toxicity severity. Finally, the definition of toxicity grades should also be coherent with re-exposure guidelines for ALL therapy (e.g. asparaginase in cases of mild AAP).

Due to national regulations some trial groups will be mandated to continue to register toxicities according to certain guidelines, such as the CTCAE (currently under revision) [5] in the US. These ALL groups will need to consider toxicity capture and registration strategies that cover both systems in order to allow future reporting of their data in a format that allow reliable comparison of the toxicity profile with ALL groups that use the PdL toxicity definitions.

The subsequent, but equally challenging, goal for the PTWG is now to develop common strategies for toxicity capture and registration, since targeting selected toxicities may favour their capture at the expense of non-targeted, but routinely registered, CTCAE graded toxicities, even though the latter toxicities may be equally important clinically.[31] In addition, the PTWG will address guidelines for drug re-exposures, explore the impact of host genome variants on toxicity risks, and develop consensus algorithms that balance toxicity and efficacy in composite evaluations of the outcome of ALL treatment. Thus, although many toxicities emerging during childhood ALL therapy can be far more difficult to capture than the classical five treatment failures, they are as critical to include in future registration and in intervention trials to improve the outcome of childhood ALL.

CONTRIBUTIONS

All authors equally contributed to the establishment of the PTWG and sharing of protocols, including toxicity sections. Authors are either representing their collaborative ALL group and/or have chaired an ad hoc toxicity working group under the PTWG. Kjeld Schmiegelow chaired PTWG and coordinated this work. All authors contributed in the data collection and interpretation. Kjeld Schmiegelow drafted the first version of the manuscript, which was subsequently revised and approved by all authors.

CONFLICTS OF INTEREST

All authors declared no conflict of interest.

LEGEND TO TABLE AND FIGURE

Table 1: * = Details on each toxicity are provided in the webappendix; ADL = Activity of daily living; APP = asparaginase-associated pancreatitis; CVL = Central venous line; CT = Computerised tomography; CTCAE.03 = National Cancer Institute Common Terminology Criteria for adverse events version 4.03; DBP = diastolic blood pressure; DWI = Diffusion weighted imaging; LLQ = Lower level of quantification; µM = micromolar; MRI = Magnetic resonance imaging; MTX = methotrexate; PEG = Pegylated; PJP = Pneumocystis jirovecii pneumonia; PRES = Posterior reversible encephalopathy syndrome; SBP = Systolic blood pressure; SOS = Sinusoidal syndrome; TE = Thromboembolism; UNL= Upper normal limit; US = Ultrasound.

Figure 1: Delphi process to reach consensus definitions for 14 toxicities. ALL = Acute lymphoblastic leukemia; AWG = Ad hoc toxicity working group; CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PTWG = Ponte di Legno Toxicity Working Group;

WEBAPPENDIX

Detailed document covering the 14 toxicities addressed by the Ponte di Legno Toxicity Working Group.

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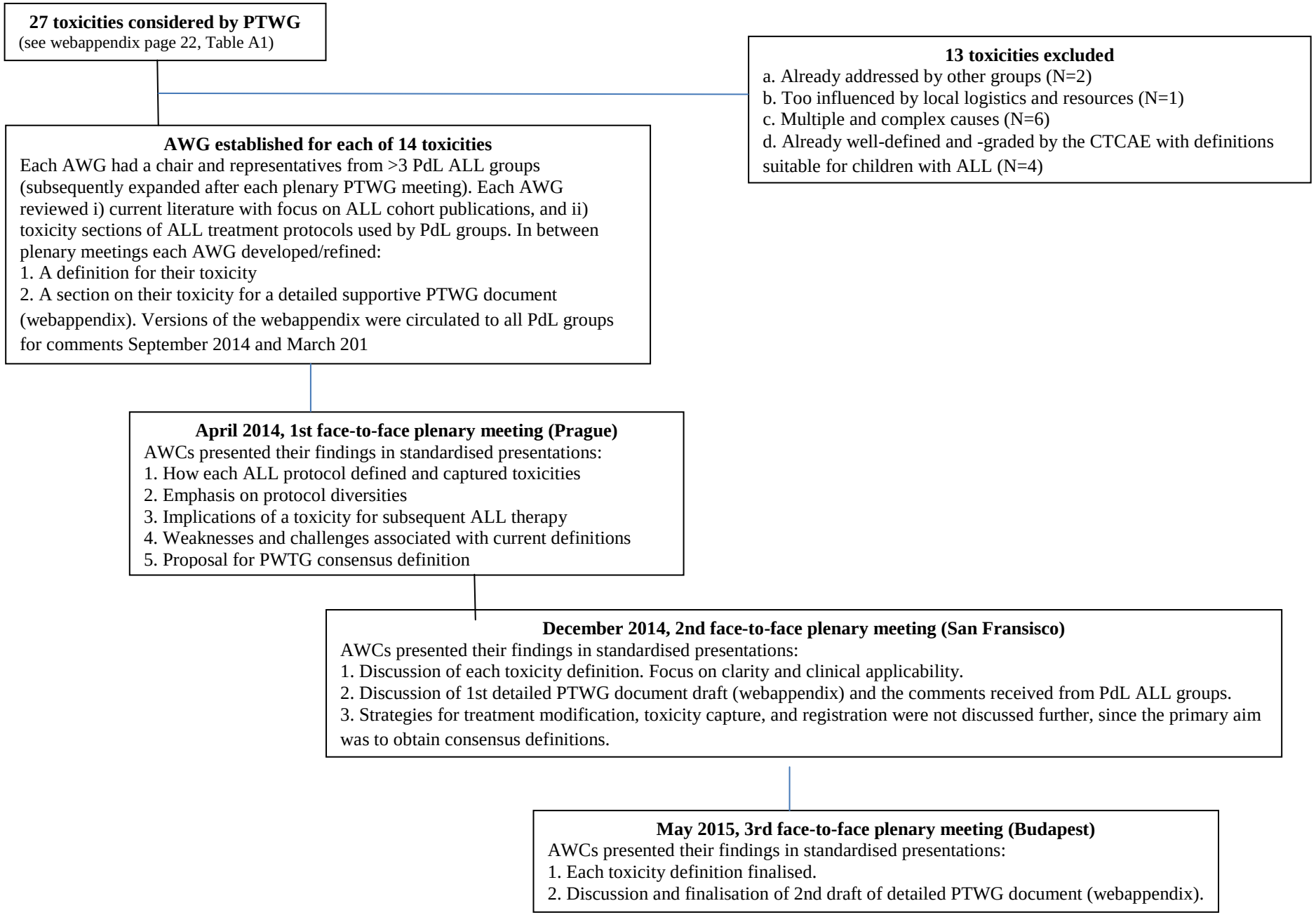
Table 1. Definitions and gradings of fourteen acute toxicities associated with treatment of childhood acute lymphoblastic leukaemia*

Toxicity	Consensus definition
Hypersensitivity to asparaginase	An adverse local or general response from exposure to Asparaginase characterised by flushing, rash, urticaria, drug fever, dyspnoea, symptomatic bronchospasm, oedema/angiooedema, hypotension and/or anaphylaxis. Grading: 1.Mild: transient flushing or rash, drug fever <38^{o} C, 2.Severe: drug fever >38^{o} C; allergy-related edema/angiooedema; dyspnoea and/or symptomatic bronchospasm with or without urticarial; and/or hypotension and anaphylaxis with indication for Asparaginase infusion interruption and parenteral medication (e.g. antihistamines, glucocorticosteroids).
Silent inactivation of asparaginase	No clinical allergy, but trough Asparaginase activity levels below lower level of quantification (preferably measured in two independent samples). In case of biweekly PEG-Asparaginase, a day 7 Asparaginase activity level <100 IU/L and/or a day 14 level <LLQ. In case of Erwinia Asparaginase (2-3 times a week) a 48 hours post-dose level <LLQ
Allergic-like reaction to asparaginase	Intolerance (e.g. vomiting, stomach ache, or rash) without inactivation of asparaginase, usually occurring later in the infusion than real Asparaginase allergy that in general occurs at the first drops. Note: Distinction between hypersensitivity and allergic-like reactions is critical, since clinical hypersensitivity (even mild) is closely associated with Asparaginase inactivation. Asparaginase activity measurements may distinguish and guide decision on switch to other Asparaginase preparations.
Hyperlipidemia	Triglycerides/cholesterol above UNL. Grading: 1.Mild: triglycerides/cholesterol <10 times UNL, 2.Moderate: triglycerides/cholesterol 10-20 times UNL, 3.Severe: triglycerides/cholesterol >20 times UNL. Note: Routine measurements only as part of research protocols. Dose modification based only on laboratory findings is not recommended.
Osteonecrosis	Osteonecrosis results from the temporary or permanent loss of the blood supply to the bones, which can cause pain, limitation in ADL, and may result in collapse of a articulating surface with enhanced pain and development of arthritis. It should be confirmed by magnetic resonance imaging (MRI). Grading: 1.Asymptomatic with findings only by MRI, 2.Symptomatic, not limiting or only slightly limiting self-care ADL. Lesions only outside joint lines in non-weight-bearing bones, 3.Symptomatic, not limiting or only slightly limiting self-care ADL. Lesions in weight-bearing bones or affecting joint lines in non-weight-bearing bones, 4.Symptomatic with deformation by imaging of one or more joints and/or significantly limiting self-care ADL.
Asparaginase-associated pancreatitis	At least two of three features must be fulfilled: i) abdominal pain strongly suggestive of pancreatitis, ii) serum lipase or amylase e3 times UNL, iii) characteristic imaging findings of pancreatitis (US/CT/MRI). Re-exposure should only be considered in mild cases. Grading: 1.mild: symptoms and enzyme elevations >3 times UNL that last <72 hours, 2.severe: symptoms and enzyme elevations above >3 times UNL that last $\geq$72 hours or haemorrhagic pancreatitis or pancreatic abcess or cyst, 3.death from pancreatitis.
Arterial hypertension	SBP and/or DBP e95th percentile for sex, age, and height on e3 occasions (3 consecutive days, or separate clinic visits if outpatient). Grading: 1.SBP/DBP in the 90th-95th percentile for age and/or BP exceeding 120/80 mmHg, 2.recurrent or persistent SBP/DBP above 95th UNL for age at three separate measurements or lasting more than 72 hours with monotherapy indicated, 3.recurrent or persistent SBP/DBP above 95th UNL for age at three separate measurements or lasting more than 72 hours and needing more than one drug or more intensive therapy than grade 2 for BP control, 4.life-threatening consequences, e.g. hypertensive crisis with transient or permanent neurologic deficit with urgent intervention needed, 5.death from hypertension.
Posteror reversible encephalopathy syndrome	PRES is a clinical diagnosis based on any combination of transient headache, confusion, seizures and visual disturbances in combination with characteristic, but transient, contrast-enhanced and DWI MRI findings (see webappendix page 9). Diagnosis can be supported by EEG findings, occurrence during early months of therapy, and presence of arterial hypertension. No grading.
Seizure	A disorder characterised by sudden, involuntary skeletal muscle contractions of cerebral/brainstem origin. Grading: 1.brief partial seizure, 2.brief generalised seizure, 3.multiple seizures despite medical intervention, 4.life-threatening, prolonged or repetitive seizures, 5.death from seizures.

Depressed level of consciousness	Abnormal changes in 1) level of arousal or 2) altered content of a patient's thought processes. 1) Quantified by Glasgow Coma Scale or the patient being alert (appear wakeful and aware of self and environment), lethargic (mild reduction in alertness), obtundated (moderate reduction in alertness with increased response time to stimuli), stuporous (deep sleep; arousal only by vigorous/repetitive stimulation and return to deep sleep when discontinued), or comatose (unconscious, sleep-like appearance and behaviorally unresponsive to all external stimuli). 2) Can involve simple capabilities (speech, calculations, spelling) and more complex modalities (emotions, behavior or personality) with confusion, disorientation, hallucinations, poor comprehension, or verbal expressive difficulty.
Methotrexate-related, stroke-like syndrome	Neurotoxicity occurring within 21 days of intravenous or intrathecal MTX with three characteristics that all need to be fulfilled: 1.new onset of one or more of paresis/paralysis; movement disorder or bilateral weakness; aphasia/dysarthria; altered mental status including consciousness (e.g. somnolence, confusion, disorientation, emotional lability); and/or seizures with at least one of the other symptoms, 2.either characteristic, but often transient, white matter changes indicating leukoencephalopathy on MRI or a characteristic clinical course with waxing and waning symptoms usually leading to complete (sometimes partial) resolution within a week, 3.no other identifiable cause. Note: Characteristic oval-shaped lesions of the subcortical white matter (mostly frontal or parietal) on MRI are best seen on diffusion-weighted (hyperintense) or apparent diffusion coefficient (hypointense) images. Can be graded 1-5 according to CTCAEv4.03 for “Encephalopathy”.
Peripheral neuropathy	Peripheral motor/sensory neuropathy, including pain and constipation, due to inflammation or degeneration of the peripheral motor/sensory nerves. Grading: 1.loss of deep tendon reflexes, slight paresthesia, numbness or pain that do not limit instrumental ADL or require treatment, 2.moderate symptoms somewhat limiting instrumental ADL, e.g. alters fine motor skills (ex. buttoning shirt) and/or paresthesia, numbness or pain that are controllable by non-narcotic medications, 3.severe symptoms limiting self-care ADL, including gait impairment, inability to perform fine motor tasks; and/or paresthesia, numbness or pain that require narcotics, 4.complete paralysis or life-threatening consequences (e.g. vocal cord paralysis) with urgent need for intervention or severe pain that is not controlled by narcotics, 5.death from peripheral neuropathy (e.g. vocal cord paralysis).
Severely delayed MTX clearance	Increase in plasma creatinine of $\geq$0.3 mg/dl (=26.5 µM) and/or a relative increase of 1·5 above a baseline value (measured within four days prior to hydration preceding high-dose MTX) together with plasma MTX concentrations at one or more time-points after initiation of the MTX infusion: 36 hours MTX >20 µM and/or 42 hours MTX >10 µM and/or 48 hours MTX >5 µM. Renal toxicity can be graded according to CTCAEv4.03.
Sinusoidal obstruction syndrome	Fulfilment of at least three out of five criteria: i) hepatomegaly, ii) hyperbilirubinaemia >UNL), iii) ascites, iv) weight gain of at least 5%, and v) thrombocytopenia (transfusion-resistant and/or otherwise unexplained by treatment, e.g. myelosuppression). Doppler ultrasound may document changes in hepatic portal venous flow and rule out alternative causes, but normal findings do not exclude sinusoidal obstruction syndrome. Grading: 1.mild: bilirubin <103 µM and weight gain <5%; 2.moderate: bilirubin 103-342 µM and/or weight gain $\geq$5% or ascites; 3.severe: bilirubin $\geq$342 µM and/or respiratory or renal failure or hepatic encephalopathy; 4.death due to SOS.
Thrombo-embolism	Venous and/or arterial TE. Confirmation by imaging or by autopsy is required for grade 2 and higher. Grading: 1. superficial thrombophlebitis or CVL-associated deep venous thrombosis with neither symptoms (e.g. pain, shortness of breath) nor objective signs (e.g. swelling, discoloration, collaterals); or causing only CVL dysfunction. Systemic anticoagulation not given, 2A. asymptomatic TE (including asymptomatic cerebral thrombosis). Systemic anticoagulation is usually given (not evidence-based), 2B. symptomatic DVT, systemic anticoagulation indicated, 3. symptomatic pulmonary embolism or cardiac mural thrombus without cardiovascular compromise or symptomatic cerebral sinovenous thrombosis or arterial ischaemic stroke; all grade 3 require systemic anticoagulation/antiaggregation, 4.life-threatening TE, including arterial insufficiency, haemodynamic or neurologic instability. Urgent intervention needed, 5.death due to TE.
Pneumocystis jirovecii pneumonia	1.Confirmed PJP: presence of PJ organisms[#] from a patient with fever, abnormal chest X-ray compatible with PJP infection, and/or hypoxaemia, 2.Probable PJP: pneumonia of undetermined origin (fever, PJP compatible chest X-ray, and/or hypoxaemia) and responding to empiric treatment with co-trimoxazole. [#]through cytological examination (Gomori-Grocott or Gram-Weigert staining), PJ specific PCR, or PJ immunofluorescence in a lung sample (broncho-alveolar lavage, bronchial aspiration, transbronchial biopsy, transthoracic needle aspiration, lung biopsy, or sputum)

Figure 1


27 toxicities considered by PTWG
(see webappendix page 22, Table A1)
13 toxicities excluded
a. Already addressed by other groups (N=2)
b. Too influenced by local logistics and resources (N=1)
c. Multiple and complex causes (N=6)
d. Already well-defined and -graded by the CTCAE with definitions suitable for children with ALL (N=4)
AWG established for each of 14 toxicities
Each AWG had a chair and representatives from >3 PdL ALL groups (subsequently expanded after each plenary PTWG meeting). Each AWG reviewed i) current literature with focus on ALL cohort publications, and ii) toxicity sections of ALL treatment protocols used by PdL groups. In between plenary meetings each AWG developed/refined:
1. A definition for their toxicity
2. A section on their toxicity for a detailed supportive PTWG document (webappendix). Versions of the webappendix were circulated to all PdL groups for comments September 2014 and March 201
April 2014, 1st face-to-face plenary meeting (Prague)
AWCs presented their findings in standardised presentations:
1. How each ALL protocol defined and captured toxicities
2. Emphasis on protocol diversities
3. Implications of a toxicity for subsequent ALL therapy
4. Weaknesses and challenges associated with current definitions
5. Proposal for PWTG consensus definition
December 2014, 2nd face-to-face plenary meeting (San Fransisco)
AWCs presented their findings in standardised presentations:
1. Discussion of each toxicity definition. Focus on clarity and clinical applicability.
2. Discussion of 1st detailed PTWG document draft (webappendix) and the comments received from PdL ALL groups.
3. Strategies for treatment modification, toxicity capture, and registration were not discussed further, since the primary aim was to obtain consensus definitions.
May 2015, 3rd face-to-face plenary meeting (Budapest)
AWCs presented their findings in standardised presentations:
1. Each toxicity definition finalised.
2. Discussion and finalisation of 2nd draft of detailed PTWG document (webappendix).

Supplemental material, table S1. Co-authors; childhood acute lymphoblastic leukaemia study group affiliation; funding sources

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AIEOP = Associazione Italiana Ematologia ed Oncologia Pediatrica; BFM = Berlin-Frankfurt-Münster study group; COALL = The German Co-operative Study Group COALL for treatment of acute lymphoblastic leukemia; COG = US Childrens Oncology Group; CPH = Czech Working Group for Pediatric Hematology; DCOG = Dutch Childhood Oncology Group; DFCI = Dana Farber Cancer Institute; EORTC = European Organisation for Research and Treatment of Cancer; INS = Israel National Study; JPLSG = Japanese Pediatric Leukemia Study Group; NOPHO = Nordic Society for Paeditric Haematology and Oncology; SJCRH = St Jude Children's Research Hospital; TPOG = Taiwan Pediatric Oncology Group; UKALL = United Kingdom Acute Lymphoblastic Leukaemia and Lymphoma Trial Group. None of the Funding Sources were involved in the writing of this manuscript or in the decision of its submission.

Webappendix to

Consensus definitions of fourteen severe acute toxicities

during childhood lymphoblastic leukaemia therapy

This document reflects consensus statements from 15 collaborative childhood acute lymphoblastic leukaemia groups. Some of the statements are well supported by published data, whereas others primarily reflect the need for common definitions to facilitate future comparisons of incidence and severity of acute toxicities across treatment protocols and various dosing strategies of antileukaemic agents. The definitions will facilitate collaborative international studies for understanding the pathogenesis of these acute toxicities (e.g. associations with patient characteristics including pharmacokinetics or host genome sequence variants) and for developing guidelines for prevention, capture, diagnosis, registration, re-exposure and follow-up after a given toxicity.

Hypersensititivity to asparaginase

Background:

Asparaginase (Asp) plays an important role in the treatment of childhood ALL. However, efficacy can be hampered by anti-Asp antibodies causing clinical allergies or silent inactivation. In both conditions the Asp activity levels will be non-therapeutic or zero (1). The hypersensitivity rate depends on the Asp preparation and the dosing, ranging from only a few percent in induction and up to 75% in intensification phases, when native E-coli is used in both induction and intensification (2,3,4,5). Contemporary protocols using pegylated (PEG)-Asp report lower hypersensitivity rates. Silent inactivation has been reported in 4-10% of patients (1,2,6).

Current guidelines in international ALL protocols:

Allergy (anaphylaxis and clinical allergy) is mentioned in all protocols and is graded mainly according to the United States National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (CTCAE) (7) in the majority of these. Anaphylaxis is not defined separately in most protocols, but this is probably neither a definition nor treatment issue. Only a few protocols have definitions of silent inactivation, and definitions differ somewhat (PEG-Asp: IBFM-AIEOP day 7 <100 U/l; DCOG day 7 <100 U/l and day 14 <20 U/l; DFCI 2 independent levels <25 U/l). Guidelines to switch preparations in case of a hypersensitivity reaction also differ across protocols. All but one protocol included use Peg-Asp as first-line therapy and both these and the single group using native E.coli Asp recommend switch to Erwinia asparaginase in case of allergic reaction or silent inactivation (if Asp activity measured). Subsequent presence of hypersensitivity to or inactivation of Erwinia asparaginase inactivation was addressed in three ALL protocols, of which one recommended substitution with one Vincristine dose and one week of glucocorticosteroids per dose of Peg-Asp missed, and the two others recommended different strategies of intensification of methotrexate (MTX)/6-mercaptopurine (6MP) maintenance therapy, and, if native E.coli Asp constituted the first-line Asp preparation, switch to Peg-Asp.

Considerations before new toxicity definition:

Discussion: All hypersensitivity reactions are important to define and register, since hypersensitivity to Asp is virtually always accompanied by inactivation of Asp (1). However, some patients have an 'allergic-like reaction' mimicking a clinical allergy, but without neutralisation of Asp activity. These patients might continue with the same preparation, if they have adequate Asp activity levels, and when it is clinically possible to administer the drug. Clinicians should be aware of this phenomenon. However, interpreting an Asp activity level in a blood sample taken just after a truncated intravenous infusion is challenging, since low levels can reflect both little Asp given prior to truncation of the infusion or inactivation. Anaphylaxis is included in the definition of an allergy (like in CTCAE) because the treatment modifications are the same.

Definitions: There is consensus on the clinical signs that define hypersensitivity. Since an Asp infusion will be truncated during an allergy reaction, and allergies often occur at the first drops when the plasma concentration is anyway still low, 'inactivation of Asp activity' is not included in the definition. In a continuous dosing schedule, a trough level measurement taken just before the dose leading to a hypersensitivity reaction can help distinguishing between allergy and allergic-like reactions. Not all groups have access to Asp activity measurements.

Grading of severity: The group agrees on the grading as proposed.

Consensus definition:

Definition of allergy to Asp:

An adverse local or general response from exposure to Asparaginase characterised by flushing, rash, urticaria, drug fever, dyspnoea, symptomatic bronchospasm, oedema/angiooedema, hypotension and/or anaphylaxis (accompanied by inactivation of Asp activity*).

** Trough level < LLQ before the 'allergic' dose. A post-infusion Asp activity level cannot be measured accurately, when an infusion is stopped after a few millilitres.*

Severity

mild:	transient flushing or rash or drug fever < 38^{o} C; or
severe:	drug fever >38^{o} C; allergy-related edema/angiooedema; dyspnoea and/or symptomatic bronchospasm with or without urticarial; and/or hypotension and anaphylaxis) with indication for Asp infusion interruption and parenteral medication (e.g. antihistamines, glucocorticosteroids).

Definition of allergic-like reaction:

An intolerance (e.g. vomiting, stomach ache, rash etc) usually occurring later in the infusion than real Asparaginase allergy that in general occurs at the first drops.

Note: Distinction between hypersensitivity and allergic-like reactions is critical but may be difficult, since clinical hypersensitivity (even mild) is closely associated with Asparaginase inactivation. Asparaginase activity measurements may distinguish and guide decision on switch to other Asparaginase preparation.

Definition of silent inactivation:

Patients without clinical allergy but with Asp activity levels, preferably measured in 2 independent samples, of:

PEGasp (biweekly schedule):	Day 7 < 100 and/or day 14 < LLQ
Erwinase (3x/week dosing schedule):	Day 2 < LLQ
General definition:	(trough) Asp activity level < LLQ

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Hyperlipidemia

Background:

Asp and steroids can cause transient, and occasionally severe, hyperlipidemia with additive effect if given concomitantly (1-5). Data regarding incidence of hyperlipidemia are very limited, and frequency of hyperlipidemia is likely to be underestimated due to lack of routine measurements. Furthermore, its clinical impact with respect to associated short and long-term toxicities is unknown.

Current guidelines in international ALL protocols:

In spite of the frequency of hypertriglyceridemia most protocols does not address this toxicity at all, none give a clear definition, and only one protocol recommend routine monitoring of serum triglycerides for selected patients, but then only in case of a family history of hyperlipidemia. Two of three protocols with extensive Asp exposure recommend withholding Asp until triglycerides are below 5 times or 10 times the upper normal limit (UNL), respectively, and one of these in addition recommended withholding glucocorticosteroid, if triglycerides were >5x UNL and rising or if they were >10x UNL.

CTCAE criteria:
Grade III: > 5 – 10 times UNL (> 500 – 1000 mg/dl)
Grade IV: > 10 times UNL (> 1000mg/dl)

Considerations before new toxicity definition:

The incidence of hyperlipidemia is unknown and may be underestimated as it is often self-limiting and only in rare cases causes severe acute toxicity. Virtually all long-term hyperlipidemia-associated toxicity reports reflect knowledge on adults with non-malignant disorders. In contrast, data on long term late effects associated with hyperlipidemia in childhood ALL are missing. The benefits of pharmacotherapy or treatment modification to avoid or treat hyperlipidemia in the childhood ALL setting is unknown, and potentially may carry a risk of reducing antileukaemic treatment efficacy.

Considerations before new toxicity definition:

Due to the lack of known associations with other toxicities including long-term sequelae, there is no indication for routine monitoring outside a research protocol and no indication for interventions based on laboratory findings only.
Grading of severity: The group agrees on the definitions and grading as proposed.

Consensus definition:

Triglyceride/cholesterol levels above the UNL.
Severity:
Mild: Triglycerides/cholesterol <10 times UNL,
Moderate: Triglycerides/cholesterol 10-20 times,
Severe: Triglycerides/cholesterol > 20 times UNL.

References:

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Osteonecrosis

Background:

Osteonecrosis (ON), defined as bone death resulting from poor blood supply, is a common but unclearly defined side effect of ALL therapy (1-18). Its reported frequency varies from less than 1% (1) to more than 70% (2). ON may cause significant short and long-term impairment in quality of life, as it can lead to joint articular surface collapse with debilitating arthritis and the potential need for surgical interventions, including arthroplasty. ON occurs in up to one third of adolescents and young adults with ALL. However, incidence reports have varied, perhaps given differences in whether reporting is based on clinical symptoms or radiological findings. While ON is most closely associated with corticosteroid exposure, the role of other agents, including Asp, is also being assessed. Glucocorticoids contribute to the development of ON by many mechanisms which include osseous lipocyte hypertrophy with resultant increased pressure within the bone which can lead to vascular collapse and then necrosis. Fat emboli, vasculitis or thromboemboli that cause vascular occlusion can also contribute and glucocorticoids can cause direct toxicity to osteocytes. Age is the strongest clinical predictor for ON with the highest incidence in female adolescents.

Current guidelines in international ALL protocols:

In spite of its limitations, all but one protocols used the CTCAE for clinical grading, except for one that applied the US Eastern Cooperative Oncology Group guidelines. Magnetic resonance imaging (MRI) is used for grading at SJCRH and being investigated in the current COG HR ALL study. Other groups use clinical grading systems. Treatment modifications for ON vary significantly:

- Most groups recommend no modification in corticosteroid therapy for asymptomatic ON with radiographic findings only.
- Some groups recommend no modification in corticosteroids during the Induction and Delayed Intensification phases of treatment.
- Some groups recommend omission of steroids for Grade 2 or greater symptomatic osteonecrosis after Delayed Intensification with a consideration for resuming steroid therapy, if symptoms later resolve and MRI findings improve or normalise
- Some groups recommend permanent discontinuation of that corticosteroids for any case of ON.

Considerations before new toxicity definition:

Definitions within protocols are largely descriptive, and most suggest confirmation by MRI. There is lack of data establishing the benefits of grading by MRI in addition to clinical symptoms. While some groups screen asymptomatic patients for ON with MRIs, most do not. There is consensus that MRI should be applied for confirmation of clinically symptomatic disease rather than for screening all patients. The latter should only be used within a research project.

Consensus definition:

Osteonecrosis results from the temporary or permanent loss of the blood supply to the bones, which can cause pain, limitation in ADL, and may result in collapse of a articulating surface with enhanced pain and development of arthritis. It should be confirmed by MRI. Grading:

1. Asymptomatic with findings only by MRI,
2. Symptomatic, but not limiting or only slightly limiting self-care ADL. Lesions only outside joint lines in non-weight-bearing bones,
3. Symptomatic, but not limiting or only slightly limiting self-care ADL. Lesions in weight-bearing bones or affecting joint lines in non-weight-bearing bones,
4. Symptomatic with deformation by imaging of one or more joints and/or significantly limiting self-care ADL.

References:

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Pancreatitis

Background:

Asp is an essential drug in the treatment of ALL, but has multiple side effects, including Asp associated pancreatitis (AAP) (1,2). AAP has a low mortality, but is one of the most frequent causes of discontinuation of Asp therapy, which may be associated with an increased relapse rate (3). With 6-7 months of continuous Asp therapy, the incidence of AAP is above 5% (1), with international reports on AAP during Asp therapy ranging 1-18% (3,6).

Current guidelines in international ALL protocols:

Most contemporary ALL protocols include definitions of AAP, although not all, and few distinguish between mild/moderate/severe/hemorrhagic AAP. The CTCAE criteria, although frequently used, are not suitable for AAP registration and grading. Several protocols define AAP with some modification of the Atlanta and United Kingdom Criteria (4,8) with at least two or three of i) Abdominal pain strongly suggestive of acute pancreatitis, ii) Serum amylase and/or lipase ≥3 (or 2) times the UNL (lipase is preferred over amylase due to greater specificity and sensitivity (7)), ii) Characteristic imaging findings of acute pancreatitis. The protocols varied as to whether amylase or lipase should be measured, whether enzymes should be ≥2 or 3 times UNL, and whether development of pancreatic cysts should be included in the definition or grading. Most protocols do not have guidelines regarding reintroduction of Asp.

Considerations before new toxicity definition:

Definition: There is consensus on following modified United Kingdom and Atlanta criteria (4,8).
Grading of severity: There is consensus on grading as proposed below.

Re-exposure: Guidelines must be adapted to the intensity of Asp treatment in the protocols, and the treatment day of occurrence of AAP (number of planned exposures remaining). "Asp heavy protocols" (such as DFCI) have shown increased relapse rate when Asp exposure is prematurely truncated (5), which has not been confirmed in less Asp intensive protocols (UKALL SR/IR) (6). Thus, re-exposure guidelines will be most relevant for protocols with long Asp exposure, but neither the risk of new episodes of AAP nor the benefits with respect to reduction of relapse rates has been sufficiently explored.

Toxicity consensus definition:

At least two of three features must be fulfilled: i) abdominal pain strongly suggestive of pancreatitis, ii) serum lipase or amylase ≥3 xUNL, iii) characteristic imaging findings of AAP (ultrasound, computed tomography, magnetic resonance imaging). Re-exposure should only be considered in mild cases. Grading:

1. mild: symptoms and amylase and/or lipase elevations above UNL for less than 72 hours,
2. severe: symptoms and amylase and/or lipase elevations above UNL last more than 72 hours, or haemorrhagic pancreatitis or pancreatic abcess or cyst,
3. death from pancreatitis.

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Arterial hypertension
This toxicity will in general be defined by national guidelines for arterial hypertension.

Background:
Hypertension in children with acute lymphoblastic leukaemia usually occurs during treatment with glucocorticosteroid and mostly resolves at discontinuation (1-8). Its incidence varies from 10% to 67% (2,5,6). Abnormal renal function and genetic polymorphisms are also considered predisposing factors (6). It can be associated with acute neurologic complication (Posterior reversible encephalopathy syndrome (PRES)). Some children present hypertension even after stopping chemotherapy; others can develop it as a late effect (isolated or part of a metabolic syndrome) (8). Hypertensive crisis rarely occur, and they can be symptomatic and complicated by neurological events (headache, seizures, haemorrhage) and require immediate intervention (aiming at reducing BP of 25% in about 8 hours).

The American Association of Pediatrics staging hypertension as
Prehypertension90th to <95th or if BP exceeds 120/80 mmHg
Stage 1 95th percentile to the 99th percentile plus 5 mmHg
Stage 2 >99th percentile plus 5 mmHg
Note: cuff size should be appropriate to the child's arm.

Consensus definition:
Hypertension is defined as average SBP and/or DBP that is greater than or equal to the 95th percentile for sex, age, and height on three or more occasions (3 consecutive days, or separate clinic visits if outpatient).

Grading:
1. SBP/DBP in the 90^{th}-95^{th} percentile for age and/or BP exceeding 120/80 mmHg,
2. recurrent or persistent SBP/DBP above 95^{th} UNL for age at three separate measurements or lasting more than 72 hours with monotherapy indicated,
3. recurrent or persistent SBP/DBP above 95^{th} UNL for age at three separate measurements or lasting more than 72 hours and needing more than one drug or more intensive therapy than grade 2 for BP control,
4. life-threatening consequences, e.g. hypertensive crisis with transient or permanent neurologic deficit with urgent intervention needed,
5. death from hypertension.

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Posterior reversible encephalopathy syndrome (PRES)

Background:

PRES, also named 'reversible posterior leukoencephalopathy syndrome, is a clinico-radiological entity based on disturbances of cerebro-vascular autoregulation and clinically characterised by headache, confusion (altered mental status), seizures and visual disturbances (1-5). In pediatrics, PRES is most commonly seen in pediatric hemato-oncology patients. Large cohort studies on its frequency are missing. In ALL patients, PRES occurs most commonly during induction or during the first 3-4 months of therapy. It may occur due to a number of causes, predominantly arterial hypertension, chemotherapy, and immunosuppression. On cranial MRI, areas of vasogenic edema (swelling) are predominantly seen, but not restricted to the posterior regions of the brain, and predominantly, but not exclusively, bilaterally. PRES is hypointense on T1-weighted and hyperintense on T2-weighted MRI revealing both patchy and confluent cortical and subcortical white matter lesions most commonly in parietal and occipital lobes or cerebellum and less commonly in basal ganglia, brainstem, and frontal lobes. In contrast to MTX-associated stroke-like syndrome, PRES is hyperintense on apparent diffusion weighted coefficient MRI images (DWI). EEGs usually show non-specific alterations sometimes with epileptiform discharges in posterior brain regions.

Current guidelines in international ALL protocols:

Detailed description and definition of PRES is only provided within the NOPHO protocol (adapted CTCAE).

Consensus definition:

Diagnosis of PRES is based on the essential and additional criteria below, but with no grading.

Essential criteria:

1) Clinical findings: any combination of headache, confusion, seizures and visual disturbances
2) Imaging findings: best imaging tool: contrast-enhanced MRI and DWI
   - Best diagnostic clue: patchy (and confluent) cortical (and subcortical) territory lesions
   - Most common location: cortex, subcortical white matter
   - Predilection: parietal and occipital lobes, cerebellum; less common: basal ganglia, brainstem, frontal lobes
   - Size: extent of abnormalities highly variable
   - Mass effect: minimal or none
   - Enhancement: minimal or none
   - MRI findings:
     T1WI: hypointense cortical / subcortical lesions
     T2WI: hyperintense cortical / subcortical lesions

On DWI images PRES is ususally normal or hyperintense.

Additional supportive findings:

1) Timing: usually during the first 3-4 months of therapy (mostly during remission induction therapy)
2) Presence of arterial hypertension
3) Complete resolution of clinical/imaging findings, although MR findings may persist in some patients
4) EEG: usually non-specific alterations, sometimes epileptiform discharges in the posterior region of the brain may be visible
5) Other causes reasonably ruled out

Treatment modifications:

As the pathophysiology of PRES is not clearly elucidated and PRES represents a multifactorial entity, recommendations concerning treatment modifications is difficult to establish beyond the already existing guidelines that include postponing intrathecals until almost complete normalisation of the MRI findings, freedom of clinical epilepsy and improvement of EEG abnormalities, and administration of anti-convulsant therapy (avoiding those inducing hepatic microsomal enzymes) and anti-hypertensive therapy.

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Seizures

Background:

Seizures are the commonest form of acute neurotoxicity during treatment for leukaemia and may be seen in up to 10% of children during treatment (1,2). Published data are limited, but a large series of 62 children with ALL or NHL from St Jude Children's Research Hospital (SJCRH) describes the characteristic features. Risk factors appear to be female sex and age <3 years (3). Seizures have a diverse aetiology - up to 60% are related to chemotherapy toxicity (predominantly MTX - either as part of a stroke-like syndrome (MTX-SLS) or occurring in isolation) with 10% due to intracranial haemorrhage, 8% to cerebral venous sinus thrombosis (CVST), 6% due to CNS infections and 16% unknown (3). Other reported causes include PRES, hyperviscosity and electrolyte imbalance. The first seizure can be complex partial (60%) or generalised tonic-clonic (40%). 25% occur in the first 6 weeks after diagnosis with 75% occurring within 18 months. In the SJCRH series 44/62 patients had controlled seizures and 18/62 uncontrolled at the last follow-up (3).

Current guidelines in international ALL protocols:

Most contemporary ALL protocols describe neurotoxicity and/or seizures as a potential side effect of MTX and/or ifosfamide, vincristine and cytarabine therapy. Grading is generally according to CTCAE: Grade 1 - brief partial seizure, Grade 2 - brief generalised seizure, Grade 3 - multiple seizures despite medical intervention, Grade 4 - life-threatening prolonged repetitive seizures, Grade 5 – death. Some protocols (e.g. DFCI 11-001) list seizures as an expected AE that does not require reporting (unless life-threatening), whilst others (e.g. AIEOP-BFM 2009) list all seizures as mandatory reportable AEs. Many protocols request all grade 2-4 events to be reported. Some protocols state that re-exposure is safe after MTX-related seizure, if full neurological recovery has occurred. In BFM-AIEOP 2009, ifosfamide-related seizures indicate discontinuation of that drug and replacement with cyclophosphamide.

Considerations before new toxicity definition:

Discussion: Since seizures can occur in isolation or as part of another recognized toxicity (CNS thromboembolism, PRES, MTX-SLS etc) they may be particularly prone to dual reporting or under-reporting. Since seizures are common they may be an important early indicator of increased neurotoxicity with new protocols/therapeutic agents and therefore this information should be captured, when possible and irrespective of grading.

Definitions: CTCAE defines a seizure as a disorder characterised by sudden, involuntary skeletal muscle contractions of cerebral or brainstem origin. This definition excludes absence seizures. An alternative definition comes from the the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE) who define a seizure as a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain (4). Both definitions have advantages and disadvantages. Since absence seizures are not typically seen during ALL therapy the CTCAE definition may be preferable, as it does not rely on having EEG evidence of seizure activity.

Grading of severity: Under CTCAE brief partial or generalized seizures are grade 1 and 2 respectively and therefore these would not be routinely reported in many ALL protocols, since they restrict reporting to Grade 2-5 or 3-5 events only.

Consensus definition:

Seizures are defined as a disorder characterised by sudden, involuntary skeletal muscle contractions of cerebral or brainstem origin. They are sub-classified according to partial vs. generalised and duration/response to therapy.

Severity: Grade 1 - brief partial seizure, Grade 2 - brief generalised seizure, Grade 3 - multiple seizures despite medical intervention, Grade 4 - life-threatening, prolonged or repetitive seizures, Grade 5 – death from seizures.

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Depressed level of consciousness

Background:

Decreased consciousness including coma has multiple aetiologies such as sepsis, electrolyte imbalance, vascular or neurologic events and direct toxic effects of chemotherapeutic agents (1-11). A decreased level of consciousness is more often described than coma. The frequency of depressed consciousness in various ALL protocols have not been determined, but the frequency of coma varies from 1% (10) to 4% (11), and it constitute between 5% (10) to 50% (11) of all registered neurotoxic events.

Aetiologies for coma/decreased consciousness in children and adolescents with ALL include:

1. Sepsis.
2. Encephalitis: viral, bacterial, fungal.
3. Progressive multifocal leukoencephalopathy.
4. Chemotherapy induced (1, 2, 5, 8, 6, 9, 13):
    - Cyclophosphamide, Fludarabine, Ifosfamide, cytarabine, Asp, MTX, Vincristine.
    - Cranial radiation.
5. Intracranial haemorrhage /thrombosis.
6. Posterior reversible encephalopathy syndrome.
7. Hypertensive encephalopathy.
8. IT MTX; acute and subacute leukoencephalopathy.
9. Accidental intrathecal Vincristine (6).
10. Electrolyte disturbance.
11. Direct effects of leukaemia on the nervous system.
12. Indirect effects of leukaemia on the nervous system: stroke or haemorrhage from hyperviscosity syndromes (7).
13. Hyperamoneamic encephalopathy (13).
14. Hyperglycemic-hyperosmolar non ketotic syndrome after therapy with prednisone or Asp (4).
15. Narcotic withdrawal.
16. Drug use/abuse.
17. Hepatic failure.
18. Hypothermia.

Current guidelines in international ALL protocols:

There is no reference to coma in any of the protocols, but most protocols address encephalopathy and decreased consciousness as one toxicity. Many protocols use the CTCAE classification, which defines “depressed level of consciousness” as:

A disorder characterised by decreased ability to perceive and respond.

Grade 1: Decreased level of alertness.

Grade 2: Sedation; slow response to stimuli; limiting instrumental ADL.

Grade 3: Difficult to arouse.

Grade 4: Life-threatening consequences.

Grade 5: Death.

Considerations before new toxicity definition:

There is no common definition of coma/depressed level of consciousness, or recommendation for evaluation, therapy and further exposure to the chemotherapy agent in any of the contemporary ALL protocols. Grading of the severity of the depressed level of consciousness seem be more appropriate than a simple classification of coma. Any re-exposure to potential toxic antileukaemic agents must include consideration of aetiology, concomitant drugs administered, chemotherapy given and planned, and the patients current medical condition.

Consensus definition:

Abnormal change in level of arousal or altered content of a patient's thought processes (12). The level of arousal is assessed by the Glasgow Coma Scale (GCS) where coma is classified GCS 3-8, moderate depression of consciousness as GCS 9-12, and minor depression of consciousness as GCS 13-15. An alert (conscious) patient has the appearance of wakefulness and awareness of self and environment.

Change in the level of arousal or alertness:

Grade A1: Lethargy - mild reduction in alertness

Grade A2: Obtundation - moderate reduction in alertness. Increased response time to stimuli.

Grade A3: Stupor - Deep sleep, patient can be aroused only by vigorous and repetitive stimulation. Returns to deep sleep when not continuously stimulated.

Grade A4: Coma (Unconscious) – Sleep-like appearance and behaviorally unresponsive to all external stimuli (Unarousable unresponsiveness, eyes closed).

Change in content (thought processes):

Grade B1: “Relatively simple” changes: e.g. speech, calculations, spelling.

Grade B2: More complex changes: emotions, behavior or personality, e.g. confusion, disorientation, hallucinations, poor comprehension, or verbal expression.

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Stroke-like Syndrome (SLS), Methotrexate-related

Background:

MTX is associated with a wide range of neurotoxicities including seizures, headaches and altered mental status. Amongst these a "stroke-like syndrome" (SLS) (also known as subacute MTX-related encephalopathy) is a well described, but poorly understood, entity. This typically includes focal neurological deficits or hemiparesis, often accompanied by disturbances in speech and/or affect, which can wax and wane over the course of hours to days. This subacute MTX-related encephalopathy develops within three weeks (usually between 2 and 14 days) after MTX administration and in most cases resolves completely over a few days. The incidence of SLS varies from <1%-15% in the literature (1-5) and appears to vary according to the scheduling and intensity of MTX and co-administration of other agents such as cyclophosphamide and Ara-C. It also appears to be commoner in children aged >10 years. Although most patients make a full recovery, there are also reports of persisting neurological deficits in some cases (2). MTX interferes with potentially neurotoxic amino acid and neurotransmitter pathways causing accumulation of homocysteine and its metabolites with strong excitatory effect on the N-methyl-D-aspartate receptor (NMDAR). These changes can be reversed by dextromethorphan, a non-competitive antagonist to NMDAR. Use of Dextromethorphan a non-competitive antagonist to NMDAR or aminophylline (more relevant for acute MTX-induced neurotoxicity) have both been advocated in small case series (6,7). However, the unknown pathophysiology of SLS, the transient nature of the symptoms, and rapid resolution in many patients without active treatment, make it difficult to assess the impact of these interventions. Further research is needed.

Current guidelines in international ALL protocols:

Most contemporary ALL protocols describe SLS and/or neurotoxicity as a potential side effect of MTX. However, formal definitions are not included in most trial protocols. Although neurotoxicity grading can be via CTCAE criteria, CTCAE does not list SLS as an adverse event. Thus, SLS could be classified as "Leukoencephalopathy", "Encephalopathy", "Stroke" or "Nervous system disorders – other". Most protocols state that re-exposure to MTX can be attempted (or discussed with trial coordinators) once the neurotoxicity resolves, although there are modifications in some protocols depending on whether or not toxicity occurred during high-dose MTX blocks.

Considerations before new toxicity definition:

SLS is a discrete entity which is clinically well characterised. However some overlap in symptoms may occur with PRES and radiological criteria for distinguishing between the two syndromes are not clearly defined. Recent DWI data suggest that the two syndromes may be distinguished by opposing effects on measured apparent diffusion co-efficient (ADC) values with PRES having increased values (due to vasogenic oedema) (3) and SLS reduced ADC values (due to cytotoxic oedema) (4,5), but this needs confirming in larger studies. Although seizures are a common feature of SLS, they can also occur without the rest of the SLS syndrome and may or may not have the same pathophysiology. Therefore, although seizures are listed amongst the neurological symptoms, an isolated seizure would not fulfill the diagnostic criteria for SLS.

Grading of severity: CTCAE grading is not particularly clinically useful and the subheading under which to record the toxicity is not clear. Some radiological criteria exist for leukoencephalopathy but their relevance in the SLS context is not established. Identifying predictors of a severe course or incomplete recovery is an important area for future research.

Consensus definition:

Patients must fulfil all 3 of the following criteria:

1. New onset of one or more of the following neurological symptoms/signs within 21 days of MTX therapy (intrathecal or intravenous):
   - Paresis/paralysis
   - Aphasia/dysarthria
   - Altered mental status- somnolence, confusion, disorientation, emotionally lability *etc*
   - Movement disorder
   - Loss of consciousness
   - Bilateral weakness
   - Seizures (isolated seizures without accompanying features from the list above and without criteria 2 and 3 below are excluded)
2. EITHER: Findings of characteristic white matter changes of leukoencephalopathy on MRI (see below)

   AND/OR: Characteristic clinical course with waxing and waning symptoms usually leading to complete resolution over 1-7 days (Note in severe cases only partial resolution may be seen in this time frame)

Characteristic MRI findings (best seen on T2-weighted images or ideally with DWI) include: oval shaped lesions of the subcortical white matter, often in the frontal, or parietal areas and often not conforming to a vascular territory. Lesions are generally hyperintense on DWI and hypointense on ADC.

3. No other identifiable cause.

Note that these changes (including DWI) may be transient and therefore missed if the scan is delayed for a few days after onset of symptoms, however subtle T2 and Fluid attenuation inversion recovery (FLAIR) abnormalities may remain in some cases.
Severity grading: CTCAE should continue to be used and all SLS recorded under “Encephalopathy” and graded 1-5.

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Peripheral neuropathy

Background:

Peripheral motor and/or sensory neuropathy is common and generally caused by vincristine and in that case nearly always reversible (1). This toxicity is addressed by all treatment protocols with the CTCAE grading, except for one group applying the Balis scale (1). Paralysis is considered as the most severe form of "peripheral neuropathy" or "paresthesias", mainly induced by vincristine or neralabine. There is no clear definition/grading system about paralysis due to CNS events. Paralysis during ALL treatment is common, but generally reversible, and has a low direct morality, although it may require many months for improvement and no effective medical treatment for paralysis. There is limited reporting regarding incidence of paralysis associated with ALL treatment. In recent reports, the incidence of grade 2-4 (CTCAE) vincristine-induced neuropathy was vary widely (2,3).

Current guidelines in international ALL protocols:

CTCAE criteria defines peripheral motor/sensory neuropathy in nervous system disorders as a disorder characterised by inflammation or degeneration of the peripheral motor/sensory nerves. Paresthesia, a symptom of sensory neuropathy, is defined as a disorder characterised by functional disturbances of sensory neurons resulting in abnormal cutaneous sensations of tingling, numbness, pressure, cold, and warmth that are experienced in the absence of a stimulus.
In COG protocol, BALIS pediatric scale of peripheral neuropathy is used for grading. Some protocols include constipation as peripheral neuropathy. Vocal cord paralysis was defined as severe neuropathy in a few protocols. In most protocols, there is no clear definition of paralysis due to CNS events. Most protocols do not have criteria for dose reduction of VCR because of paralysis, since it is generally reversible without life threatening event, except vocal cord paralysis. In a few protocols, dose reduction for paresthesis or motor paralysis is defined (DFCI, St. Jude).

Considerations before new toxicity definition:

Definition: The motor and sensory definition should be evaluated separately.
Grading of severity: Combine the BALIS scale (used in COG protocols) and CTCAE.
Re-exposure: Re-exposure is usually permitted if symptoms are improved.

Toxicity consensus definition:

Peripheral motor or sensory neuropathy (can include pain and constipation) due to inflammation or degeneration of the peripheral motor/sensory nerves. Grading:

1. loss of deep tendon reflexes, slight paresthesia, numbness or pain that do not limit instrumental ADL or require treatment,
2. moderate symptoms somewhat limiting instrumental ADL, e.g. alters fine motor skills (ex. buttoning shirt) and/or paresthesia, numbness or pain that are controlled by non-narcotic medications,
3. severe symptoms limiting self-care ADL, including gait impairment, inability to perform fine motor tasks; and/or paresthesia, numbness or pain that require narcotics,
4. complete paralysis or life-threatening consequences (e.g. vocal cord paralysis) with urgent need for intervention or severe pain that is not controlled by narcotics,
5. death from peripheral neuropathy (e.g. vocal cord paralysis).

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Severely delayed methotrexate clearance with renal toxicity

Background:

Although the use of alkalinisation and hydration with high-dose MTX (HDMTX) significantly reduces the risk for renal toxicity, approximately 2% of patients treated with HDMTX develop renal toxicity that compromises MTX clearance and results in excessive exposure (1;2). Plasma creatinine usually peaks within four days after initiation of the HDMTX infusion and returns to baseline after a few weeks (3). Higher doses of folinic acid are essential to limit toxicity in situations with excessive MTX exposure. In rare cases (<0.5% of all 5 g/m² HDMTX infusions) carboxypeptidase may be 'helpful' to degrade plasma MTX rapidly by enzymatic cleavage – independently of renal function (1;3). Caboxypeptidase has no immediate effect on MTX in the renal tubules that may be impeding renal function. Despite the availability of carboxypeptidase, diuresis and folinic acid rescue remain the mainstay of high dose MTX therapy. Even lower systemic MTX exposure can cause severe toxicity, if folinic acid is delayed more than 42 to 48 hours after initiation of the infusion (4-7). No prospective randomised studies have compared different folinic acid doses and schedules. However, several investigators suggest that excessive folinic acid may rescue the leukaemia cells and increase the risk of relapse. The assertion of this remains controversial (8;9).

Current guidelines in international ALL protocols:

Most ALL protocols using HDMTX 2.5-5 g/m² have guidelines that define the following plasma MTX concentrations as severely high and some suggest that carboxypeptidase may be used in such cases if available:

Plasma MTX conc.	ALL Protocol
24h MTX > 250 µM	NOPHO
36h MTX > 10-20 µM	BFM-AIEOP, NOPHO, UKALL
42h MTX > 5-10 µM	NOPHO, COG, St Jude, TPOG
48h MTX > 3-10 µM	COG, DCOG, UKALL

In protocols from BFM-AIEOP, DFCI, EORCT and Israel, no specific guidance is offered with regard to use of carboxypeptidase.

Considerations before new toxicity definition:

Patients with very high plasma MTX concentrations usually also have renal toxicity with increased serum creatinine. Few patients have an increase of more than 1.5-2.0-fold from baseline (1,10,11). The CTCAE defines renal toxicity as an increase in creatinine by > 0.3 mg/dl or a relative increase of 1.5-fold above baseline (12). In most ALL protocols the folinic acid dose is increased if plasma MTX is >1uM 42 hours after initiation of the HDMTX infusion because concentrations above this level are associated with increased toxicity (13-15). When the plasma MTX concentration is > 10 uM at 42-hour then the folinic acid dose has to be increased markedly to achieve a plasma tetrahydrofolate concentration of 1000 uM which is believed required to prevent serious toxicity (5;15).

Consensus definition*:*

An increase in plasma creatinine by >0.3 mg/dl or a relative increase of 1.5 above baseline together with severely high plasma MTX concentrations at one or more of the following time-points after initiation of the MTX infusion, independent of the MTX dose: 36h MTX >20 µM and/or 42h MTX >10 µM and/or 48h MTX >5 µM. The baseline plasma creatinine should be measured within four days prior to start of the hydration preceding the HDMTX infusion and be monitored until sufficient MTX clearance is confirmed.

Criteria for use of carboxypeptidase is not included in the consensus criteria (1,3,16).

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Sinusoidal obstruction syndrome (SOS)

Background:

Sinusoidal obstruction syndrome (SOS) also called veno-occlusive disease (VOD) is a well documented toxicity of 6-thioguanine (6TG), occurring in 206 (20%) of 1017 patients randomised to 6TG in the COG CCG-1952 trial, and in 82 (11%) of 748 randomised to 6TG in the ALL97 trial (1,2). However, rates of SOS may be influenced by scheduling and concomitant medication. In the CoALL92 trial no SOS was seen in either the 6-TG or 6MP arms (3). VOD appears to be very unusual during 6MP treatment (no cases occurred during 6MP treatment in CCG-1952 or UKALL97). Most ALL treatment trials and protocols have now replaced 6TG with 6MP. Most patients with mild 6TG-induced SOS tolerate the subsequent introduction of 6MP without suffering any further problems (4). Additive hepatotoxicity from Asp and MTX may be an important factor.

Current guidelines in international ALL protocols: (A summary from international ALL protocols)

Only two contemporary ALL protocols mention SOS/VOD at all, and only one of these includes a definition of VOD. NOPHO ALL 2008 defines veno-occlusive disease or SOS of the liver as painful hepatomegaly, ascites, weight gain >5%, thrombocytopenia, and retrograde portal venous flow. AIEOP-BFM ALL 2009 warns that patients with one variant TPMT allele (heterozygous genotype) are at a strongly elevated risk of developing hepatic VOD when exposed to 6TG. It states that "potential signs of VOD should be closely monitored in protocol IIB or protocol IIIB, particularly in patients with TPMT heterozygosity, in order to allow appropriate diagnostic and therapeutic measures to be introduced in a timely manner", but neither this trial, nor any others, makes any recommendations on when to modify or stop 6TG treatment. There is no specific definition of SOS/VOD in the CTCAE.

Consideration before new toxicity definition:

ALL protocols have now replaced 6TG with 6MP. Most patients with mild 6TG-induced SOS tolerate the subsequent introduction of 6MP without suffering any further problems (4).

Toxicity consensus definition:

Sinusoidal obstruction syndrome:

Fulfillment of at least three out of five criteria:

1. Hepatomegaly,
2. Hyperbilirubinaemia,
3. Ascites,
4. Weight gain >5%, and
5. Thrombocytopenia, otherwise unexplained and transfusion-resistant.

Doppler ultrasound may document changes in hepatic portal venous flow and rule out alternative causes, but normal Doppler findings do not exclude a diagnosis of VOD.

Grading:

Mild: Bilirubin <103 µM and weight gain <5%.
Moderate: Bilirubin 103-342 µM and either weight gain >5% or ascites.
Severe: Bilirubin >342 µM and respiratory or renal failure or hepatic encephalopathy.

Treatment Modifications:

If SOS fulfilling the above criteria occurs, hepatotoxic treatment (6MP/6TG, Asp, MTX etc) should be withheld until SOS has resolved. If SOS has occurred whilst the patient was taking 6TG, it may be possible to start 6MP as a substitute for 6TG, if the clinical features of SOS resolve.

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Arterial and venous thromboembolism (TE)

Background:

The incidence of TE in childhood ALL ranges between 2% (1) and 37% (2) with an overall average of symptomatic TE of 5% (3-5). This diversity in part reflects differences in definitions. TE is mostly located in the venous system as cerebral sinovenous thrombosis (CSVT) or central vein line (CVL)-associated deep venous thrombosis (DVT). Contributing factors to TE in ALL patients include administration of Asp and steroids, presence of CVL, inherited or acquired thrombophilia, infection, and possible other factors such as hyperlipidaemia (3,2,6,7). Older patients are more susceptible to TE (3). Mortality directly related to venous TE (VTE) in children is 2-9% (6,8,9). VTE impacts on the scheduled Asp treatment and may accordingly have negative influence on overall survival outcome in children with ALL.

Current guidelines in international ALL protocols:

Venous and/or arterial TE is graded according to CTCAE in the majority of treatment protocols. TE of CTCAE Grade e 3 is generally registered and only symptomatic TE considered clinically significant in the most of treatment protocols. TE definition is not specified in many of the treatment protocols.

Considerations before new toxicity definition and grading:

There is an agreement on the need to confirm TE by imaging, when TE is defined as a toxicity. The ad hoc working group (AWG) members agree to define Grade 1 as CVL-associated DVT without any symptoms (e.g., pain, shortness of breath, etc) or objective signs (e.g. swelling, discoloration, collaterals, etc) or causing only CVL dysfunction where no systemic anticoagulation is given or only endoluminal instillation of fibrinolytics is indicated. We propose do not register the Grade 1 as toxicity.

Difficulties in grading include different management of asymptomatic TE. Most members use systemic anticoagulation in asymptomatic TE, but some do not. Thus, asymptomatic and symptomatic TE should be graded separately (Grades 2A and 2B).

The proposed grading differs from CTCAE grading as we suggest asymptomatic (incidentally diagnosed) TE to be defined as Grade 2 vs. Grade 1 in CTCAE and cerebrovascular thrombosis as Grade 3 vs. Grade 4 in CTCAE.

Consensus definition:

Venous and/or arterial thromboembolism (TE). Confirmation by imaging or by autopsy is required by grade e 2.

Grading:

1. superficial thrombophlebitis or CVL-associated DVT without symptoms or objective signs or causing only CVL dysfunction. Systemic anticoagulation not given;
2. A. asymptomatic TE (including asymptomatic cerebral thrombosis). Systemic anticoagulation is usually given (not evidence-based);
   B. symptomatic DVT, systemic anticoagulation indicated;
3. symptomatic pulmonary embolism or cardiac mural thrombus without cardiovascular compromise or symptomatic cerebral sinovenous thrombosis or arterial ischaemic stroke; all grade 3 require systemic anticoagulation/antiaggregation;
4. life-threatening TE, including those with arterial insufficiency, hemodynamic or neurologic instability. Urgent intervention needed;
5. death due to TE.

References:

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Pneumocystis jiroveci Pneumonia

Background:

Pneumocystis Carinii, more recently reclassified as Pneumocystis Jiroveci (PJP), is a fungus commongly found in the environment. Whilst it rarely causes illness in healthy individuals, it may cause life-threatening or fatal pneumonia in the immunocompromised host, including patients with ALL (1-3). The definition of PJP infection, the prophylaxis regimen and treatment schedules vary across different international groups and support the development of a common definition and therapeutic strategy.

Current guidelines in international ALL protocols:

PJP is graded mainly according to CTCAE in the majority of the treatment protocols. There are no specific diagnostic criteria defined for PJP infection in ALL protocols. Patients receiving chemotherapy for ALL routinely receive prophylaxis against PJP with Co-trimoxazole, although the dose and schedule for Co-trimoxazole administration is variable across international study groups. Treatment for presumed PJP is generally with high dose Co-trimoxazole, however other agents are sometimes used by some centres in patients with severe cytopenias.

Considerations before new toxicity definition:

There are no specific definitions for PJP infection in international ALL protocols. The Infectious Disease Working Group of the EBMT have published definition of PJP in the context of haemopoietic stem cell transplantation. There are no definitions published by the HIV community. We favour a modified version of the EBMT definitions in which PJP is either unequivocally confirmed or deemed likely by clinical features.

Toxicity consensus definition:

Confirmed PJP infection: Presence of Pneumocystis Jiroveci (carinii) organisms identified through cytological examination (Gomori-Grocott or Gram-Weigert staining), PCR or immunofluorescence in a lung sample (broncho-alveolar lavage, bronchial aspiration, transbronchial biopsy, transthoracic needle aspiration, lung biopsy, or sputum) in a patient with fever or abnormal chest X-ray, or hypoxemia.

Probable PJP infection: Patients with pneumonia of undetermined origin (with fever and abnormal chest X-ray and/or hypoxemia compatible with PJP) and responding to empiric treatment with Co-trimoxazole.

References:

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Table A1. Childhood acute lymphoblastic leukaemia acute toxicities considered by the Ponte di Legno Toxicity Working Group (PTWG); outcome; and key members in the working committees for the toxicities reaching consensus definitions.

Toxicity	Results	Members (ALL group) in each ad hoc working committee
Hypersensitivity to asparaginase	Consensus definition by PTWG	Andishe Attarbaschi (BFM-Austria), Anja Möricke (BFM-Germany), Gabriele Escherich (COALL), Elizabeth Raetz (COG), Inge van der Sluis (DCOG, chair), Veerle Mondelaers (EORTC), Motohiro Kato (Japan), Birgitte Klug Albertsen (NOPHO), Hiroto Inaba (SJCRH), Der-Cherng Liang (TPOG), Jayashree Motwani (UKALL).
Hyperlipidemia	Consensus definition by PTWG	Deepa Bhojwani (SJCRH), Der-Cherng Liang (TPOG), Mike Gattens (UKALL), Inge van der Sluis (DCOG), Ester Zapotocka (Czech republic), Thomas Frandsen (NOPHO), Gabriele Escherich (COALL, chair).
Osteonecrosis	Consensus definition by PTWG	Andishe Attarbaschi (BFM-Austria), Arndt Borkhardt (BFM), Gabriele Escherich (COALL), Caroline Piette (EORTC), Riitta Niinimäki (NOPHO), Frederik Van Delft (UKALL), Rachael Hough (UKALL), Sima Jeha (SJCRH), Der-Cherng Liang (TPOG), Elizabeth Raetz (Chair).
Asparaginase-associated pancreatitis	Consensus definition by PTWG	Thomas Frandsen (NOPHO, chair), Motohiro Kato (Japan), Sima Jeha (SJCHR), Der-Cherng Liang (TPOG), Sujith Samarasinghe (UKALL),), Inge van der Sluis (DCOG), Elizabeth Raetz (COG), Ester Zapotocka(Czech Republic).
Arterial hypertension	Consensus definition by PTWG	Maria Caterina Putti (AIEOP, Chair), all groups contributed.
Posteror reversible encephalopathy syndrome	Consensus definition by PTWG	Andishe Attarbaschi (BFM-Austria), Inge van der Sluis (DCOG), Der-Cherng Liang (TPOG), Anja Möricke (BFM-Germany), Shlomit Barzilai (INS), Arja Harila-Saari (NOPHO), Bhojwani Deepa (SJCRH)
Seizure	Consensus definition by PTWG	Andishe Attarbaschi (BFM-Austria), Anja Möricke (BFM-Germany), Shlomit Barzilai (INS), Deepa Bhojwani (SJCRH), Motohiro Kato (Japan), Der-Cherng Liang (TPOG), Christina Halsey (UKALL, WG chair).
Depressed level of consciousness	Consensus definition by PTWG	Andishe Attarbaschi (BFM-Austria), Anja Moricke (BFM), Deepa Bhojwani (SJCRH), Hsi-Che Liu (TPOG), Shlomit Barzilai (INS, chair).
Methotrexate-related stroke-like syndrome	Consensus definition by PTWG	Christina Halsey (UKALL, WG chair), Andishe Attarbaschi (BFM-Austria), Anja Möricke (BFM-Germany), Gabriele Escherich (COALL), Paul Gaynon (COG), Inge van der Sluis (DCOG), Shlomit Barzilai (INS), Kjeld Schmiegelow (NOPHO), Deepa Bhojwani (SJCRH), Der-Cherng Liang (TPOG).
Peripheral neuropathy	Consensus definition by PTWG	Andishe Attarbaschi (Austria), Anja Möricke (BFM), Der-Cherng Liang (TPOG), Sujith Samarasinghe (UK), Hiroto Inaba (SJCRH), Motohiro Kato (Japan).
High-dose methotrexate related nephrotoxicity	Consensus definition by PTWG	Torben Stamm Mikkelsen (NOPHO, WG chair), Paul Gaynon (COG), Deepa Bhojwani (SJCHR/COG).
Sinusoidal obstruction syndrome	Consensus definition by PTWG	Christina Halsey (UKALL) (WG co-chair), Rod Skinner (UKALL) (WG co-chair), Andishe Attarbaschi (BFM-Austria), Gabriele Escherich (COALL), Thomas Frandsen (NOPHO), Der-Cherng Liang (TPOG), Anja Möricke (BFM-Germany), Inge van der Sluis (DCOG).
Thromboembolism	Consensus definition by PTWG	Ruta Tuckuviene (NOPHO, WG chair), Maria Caterina Putti (AIEOP), Andishe Attarbaschi (BFM-Austria), Anja Möricke (BFM-Germany), Caroline Piette (EORTC), Shlomit Barzilai (INS), Der-Cherng Liang (TPOG), Elizabeth Chalmers (UKALL), Motohiro Kato (Japan), Sima Jeha (SJCRH).
Pneumocystis jirovecii pneumonia	Consensus definition by PTWG	Rachael Hough (UKALL), Pat Brown (COG), Mette Levinsen (NOPHO), Sima Jeha (SJCRH), Ting-Chi Yeh (TPOG).
Treatment-related mortality	Addressed by other international working group[6]	Not addressed by PTWG
Invasive fungal infection	Addressed by other international working group	Not addressed by PTWG
Transferal to intensive care unit	Influences by logistics and local resources	Not addressed by PTWG
Severe local infections, including fasciitis	Multiple causes, new definition not attempted	Not addressed by PTWG
Severe dermatitis	Multiple causes, new definition not attempted	Not addressed by PTWG
Non-methotrexate related organ dysfunction	Multiple causes, new definition not attempted	Not addressed by PTWG
Other life-threatening events	Multiple causes, new definition not attempted	Not addressed by PTWG

Toxicities requiring laparotomy/laparoscopy	Multiple causes, new definition not attempted	Not addressed by PTWG
Miscellaneous other rare SUSARs	Multiple causes, new definition not attempted	Not addressed by PTWG
Heart failure or severe arrhythmia	Defined by NCI-CTCAEv4.03	
Hypoglycemia	Defined by NCI-CTCAEv4.03	
Psychosis	Defined by NCI-CTCAEv4.03	
Myopathy	Defined by NCI-CTCAEv4.03	

AIEOP = Associazione Italiana Ematologia ed Oncologia Pediatrica; BFM = Berlin-Frankfurt-Münster study group; COALL = The German Co-operative Study Group COALL for treatment of acute lymphoblastic leukemia; COG = US Childrens Oncology Group; CPH = Czech Working Group for Pediatric Hematology; DCOG = Dutch Childhood Oncology Group; DFCI = Dana Farber Cancer Institute; EORTC = European Organisation for Research and Treatment of Cancer; INS = Israel National Study; JPLSG = Japanese Pediatric Leukemia Study Group; NOPHO = Nordic Society for Paeditric Haematology and Oncology; SJCRH = St Jude Children's Research Hospital; TPOG = Taiwan Pediatric Oncology Group; UKALL = United Kingdom Acute Lymphoblastic Leukaemia and Lymphoma Trial Group.

Table A2: Overview of the 14 acute toxicities addressed in childhood ALL protocols.

Toxicity	**AEIOP**[a]	**BFM**[a]*	**COALL**[a]	**COG**[b] **All gr 4 reported**	**DCOG**[c] **All gr 3-4 reported**	**DFCI**[c] **All gr 3-4 reported**	**EORTC**[c] **All gr 3-4 reported**	**JPLSG**[c]	**NOPHO**[a]	**SJCRH**[d] **Extensive capture of gr 2-4**	**TPOG**[d]	**UKALL**[c]
Hypersensitivity to asparaginase	*As BFM*	*Modified CTC. All grades (details in protocol 2009)*	*CTC gr 4*	*CTC gr 3,4*	*CTC All grades*	*CTC All grades*	*CTC All grades*	*CTC All grades*	*CTC gr 3.4 that leads to ASP truncation*	*CTC gr 2-4*	*Allergy that leads to ASP truncation*	*CTC gr 2-4*
Silent inactivation of asparaginase	NONE	NONE	*Defined in Protocol 08-09*	NONE	*Details in protocol ALL11*	Defined in protocol 11-001	CTC gr 3,4 ("Other")	NONE	NONE	NONE	NONE	NONE
Allergic-like reaction to asparaginase	NONE	Targeted but not specifically defined	NONE	NONE	NONE	NONE	*CTC gr 1-4*	CTC All grades	NONE	*CTC gr 2-4*	NONE	CTC gr 3,4
Hyperlipidemia	NONE	NONE	NONE	NONE	NONE	>10x UNL	CTC gr 3,4 ("Other")	CTC All grades	*>5xUNL*	*CTC gr 2-4*	>5xUNL	CTC gr 3,4
Osteonecrosis	Not specifically defined	*ARCO staging*	CTC gr 2,3,4; but not specifically defined	*CTC gr 2,3,4*	CTC gr 3,4	*CTC All grades*	*CTC Not specifically defined*	CTC All grades	*CTC gr 2-4*	*CTC gr 2-4*	ECOG	CTC gr 3,4 *targeted reporting if symptomatic & radiologically confirmed*
Asparaginase-associated pancreatitis	*Defined as BFM*	*Abdominal pain & amylase/lipase >2xUNL*	CTC gr 2,3,4	*CTC gr 2,3,4 (amylase>2xUNL)*	CTC gr 2,3,4 (amylase>3xUNL >72h)	*CTC All grades (amylase>3 xUNL >72h)*	*CTC gr 3,4*	CTC All grades	*Abdominal pain & amylase/ lipase >3xUNL & imaging (2 of 3)*	*CTC gr 2-4 Severe: pain & amylase >3xUNL >72h*	CTC gr 2-4 Severe: as SJCRH	*CTC gr 3, 4 Details in protocol*
Arterial hypertension	NONE	NONE	NONE	CTC gr 4	CTC gr 2,3,4	CTC gr 3,4	CTCgr 3-4 ("Other")	CTC gr 4	CTC gr 4	CTC gr 2-4	CTC gr 4	*CTC gr 3,4*
Posteror reversible encephalopathy syndrome	CTC[a] All grades	*Only if MRI shows leukencephalo-pathy*	NONE	CTC gr 4	CTC gr 3,4	CTC gr 3,4	*CTC gr 1-4 as leukoence-phalopathy*	CTC gr 4	*Very detailed definition in protocol*	*CTC gr 2-4*	NONE	CTC gr 3,4 as leuko-encephalopathy
Seizure	NONE	*Any*	CTCAE gr 2,3,4	*CTC gr 2,3,4*	CTC gr 3,4	CTC *Reported if life-threatening*	*CTC gr 1-4*	CTC gr 4	*CTC gr 2-4*	*CTC gr 2-4*	ECOG	CTC gr 3,4 *Report if associated with it MTX*
Depressed level of consciousness	*As BFM*	*CTCAE gr 3,4*	NONE	*Only CTC gr 3-4 encephalopathy*	NONE Captured as CTC 'Other severe toxicity' gr 3,4	CTC gr 3,4	CTC gr 3-4 ("Other")	CTC All grades	*Only coma registered*	*CTC gr 2-4*	NONE	CTC gr 3,4
Methotrexate-related, stroke-	*CTC[a] All grades*	*Subacute neuro-toxicity with*	NONE	CTC *All grades of*	Captured as CTC 'Other	CTC gr 3,4	CTC gr 3-4	CTC gr 4	NONE	*CTC gr 2-4*	NONE	*CTC gr 3, 4 Targeted reporting*

like syndrome		*normalization <2w from it MTX*		*transient ischemic attacks*	severe toxicity' gr 3,4		("Other")					*Details in protocol*
Peripheral neuropathy	NONE	*Only peripheral paralysis registered*	NONE	Balis scale	CTC gr 3,4	CTC gr 3,4	*CTC gr 3-4*	CTC All grade	*Only peripheral paralysis registered*	*CTC gr 2-4*	NONE	CTC gr 3, 4
Severely delayed MTX clearance	*AE: h42>5µM h48>3µM*	*Normal (projected) clearance defined at h24, h36, h42, h48, h54*	NONE	NONE	NONE	CTC gr 3,4	CTC gr 3,4 ("Other")	*Concentration h42, h48, h66 captured.*	*h42 >10 µM*	*Research-based capture*[e]	h42 >10 µM	NONE
Sinusoidal obstruction syndrome	NONE	*CTC*	NONE	CTC gr 4	NONE Captured as CTC 'Other severe toxicity' gr 3,4	CTC gr 3,4	CTC gr 3,4 ("Other")	CTC gr 4	*Defined in protocol ALL2008*	*CTC gr 2-4*	NONE	CTC gr 3, 4
Thrombo-embolism	*AE=all DVT, CST, AT, TE*	*AE=all DVT, CST, other grade 4 thrombosis (e.g. pulmonary or aterial)*	NONE	*CTC gr 3,4*	CTC gr 3,4	*CTC All grades*	Only strokes CTC gr 1-4 targeted	CTC All grades	*Targeted but not specifically defined*	*CTC gr 2-4*	NONE	*CTC gr 3, 4 Details in protocol*
Pneumocystis jirovecii pneumonia	*AE only in case of LTI*	*NONE, only life-threatening infections registered*	NONE	CTC gr 4	NONE Captured as CTC 'Infection'	*CTC All grades*	CTC gr 3,4 ("infections")	NONE	*Targeted but not specifically defined*	*CTC gr 2-4*	NONE	CTC gr 3, 4

Summary of toxicity capture and definitions across protocols. Those that are specifically targeted (i.e. not part of the protocol's general AE reporting) are in italics. The capture, definition, and reporting strategies are detailed to various degrees in the protocols. All groups report toxic death (CTCAE grade 5); *=Austria, Czech Republic, and Israel use the BFM protocol and have identical toxicity strategies; AE=adverse event; ARCO=Association Research Circulation Osseous staging system; ASP=asparaginase; AT=arterial thrombosis; Balis=Balis scale for grading of peripheral neuropathy [23]; CST=cerebral sinus venous thrombosis; CTC=US National Cancer Institute Common Toxicity Criteria for Adverse Events; DVT=deep venous thrombosis; ECOG=US Eastern Cooperative Oncology Group criteria; gr=grades; h=hour; it=intrathecal; LTI=life-threatening infection; NONE=Not specifically captured; Other=CTC graded in group of "other" toxicities; TE=thromboembolisms; UNL=upper normal limit; [a]=CTC version not specified; [b]= CTC version 4 - COG protocols require routine reporting of all grade 4 non-hematologic AEs in addition to the targeted toxicities; [C]= CTC version 4; [d]=CTC version 3; [e]=captured as part of professor Mary Rellings research programme at St Jude Children's Research Hospital.
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