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Severe Toxicity Free Survival: Physician-derived definitions of unacceptable long-term toxicities following acute lymphoblastic leukemia

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Abstract

Five-year survival rates have surpassed 90% for childhood acute lymphoblastic leukemia (ALL), but survivors are at risk for permanent health sequelae. While event-free survival appropriately represents the outcome for cancers with poor survival, this metric falls short when cure rates are high but challenged by serious, persistent complications. Accordingly, an expert group consisting of pediatric Hematologists/Oncologists, representative of 17 international ALL study groups, launched an initiative to construct a measure, designated Severe Toxicity Free Survival (STFS), to quantify the occurrence of physician-prioritized toxicities to be integrated with traditional cancer outcome reporting. Five generic inclusion criteria (not present prior to cancer diagnosis, symptomatic, objectifiable, of *unacceptable* severity, permanent or requiring unacceptable treatments) were used to filter 855 health conditions yielding inclusion of 21 Severe Toxicities (STs). Consensus definitions were reached through a modified Delphi process supplemented by two additional plenary meetings. The 21 STs include severe adverse health conditions that significantly limit activities of daily living and are refractory to therapy (*e.g.,* refractory seizures), are without therapeutic options (*e.g.,* blindness), or require substantially invasive treatment (*e.g.,* cardiac transplantation). Incorporation of STFS assessment into clinical trials has the potential to better assess diverse treatment strategies, focusing not only on traditional outcome events and overall survival but in addition the frequencies of the most severe toxicities. Although STFS quantifies the clinically unacceptable health tradeoff for cure using childhood ALL as a model disease, the prioritized STs are based on generic considerations of relevance to any other cancer diagnosis and age group.

INTRODUCTION

Childhood cancer five-year survival rates now surpass 80%, so a focus on long-term therapy-related toxicities is paramount.[1,2] Traditionally, outcomes have been measured by overall survival (OS) and event-free survival (EFS), with events encompassing resistant disease, relapse, second malignant neoplasms (SMN), and death. However, more detailed information regarding the rates of other severe toxicities is needed to address and further improve the quality of life among survivors.

Using childhood acute lymphoblastic leukemia (ALL), the most common childhood cancer, as a prototype, the five-year EFS and OS now exceed 85% and 90%, respectively, following the best available contemporary therapy.[3] However, the compiled risk of severe and permanent adverse effects, such as end organ dysfunction and severe cognitive impairment, approaches or even surpasses those of resistant disease and relapse.[4–6] Decades-long awareness of treatment-related morbidity has prompted stepwise modifications of ALL therapy, including a dramatic decrease in the use of radiotherapy, anthracyclines, and alkylating agents, contributing to a marked reduction in late mortality among 5-year survivors of childhood cancer.[5] Nevertheless, the risk of long-term severe toxicities persists.

Acute toxicities are monitored as part of cancer treatment trials and typically defined according to the US National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE)[7] and, more recently, by international consensus definitions to facilitate reliable comparisons between cohorts.[8] Yet, these definitions contain no guidance about severe long-term toxicities that would be beneficial to integrate into an overall measure of treatment outcome.

Accordingly, the Ponte di Legno consortium (PdL), which represents 17 major childhood ALL study groups and institutions across North America, Europe, Japan, Taiwan, and Australia,[9] launched an initiative in May 2019 to prioritize physician-derived Severe Toxicities (STs) for a future reporting of Severe Toxicity Free Survival (STFS) alongside the traditionally reported outcome events.

METHODS

The two major aims were to 1) prioritize and define *unacceptable* long-term toxicity for patients with childhood ALL, and 2) define how these should be combined into a composite quantity to be integrated with traditional events in outcome evaluation. Unacceptable STs were defined as health conditions perceived by the treating physicians to represent an unacceptable tradeoff for disease control. More specifically, this was interpreted as severe and

permanent physical or mental health conditions significantly limiting self-care and instrumental activities of daily living (ADL); being either refractory to medical management, curable only by radical, invasive treatments, which in themselves carry a risk of long-term STs, or with no curative therapy available. After the selection of conditions, an iterative Delphi process guided by existing evidence and expert opinion was performed over an 18-month period until a final consensus of ST definitions was reached (Figure 1).

Selection of Severe Toxicities

The five generic ST selection criteria are listed in Panel 1. A total of 855 health conditions were reviewed (appendix pp.5–47), including all 837 conditions in the fifth version of CTCAE,[7] 17 additional conditions from the St Jude Children's Research Hospital modification of the CTCAE version 4.03,[10] and one condition (physical deformation) added by the PdL ST working group (STWG). To allow future use of the ST definitions and the STFS measure for other cancers, all conditions were evaluated irrespective of their frequency and relevance for childhood ALL. During the initial plenary meeting, 755 health conditions were excluded based on the generic selection criteria. Ad-hoc working groups, which included a chair and representation of pediatric Hematologist/Oncologist experts from at least two other PdL groups, were established for each of the 16 organ systems covering the remaining 100 health conditions (appendix p.4). Each group reviewed literature and the toxicity sections of 13 ALL treatment protocols currently used by the PdL groups for existing evidence and definitions of relevance for the 100 conditions. The synthesis of these data and plenary discussions in the STWG formed the basis for an iterative selection process, ultimately yielding 80 potential health conditions, grouped into 21 STs across 15 organ systems (Figure 1). External specialists within the relevant organ areas were consulted regarding all definitions before commencing the consensus process.

Consensus definitions

Initial definitions for each ST were developed by the ad hoc working groups and subsequently evaluated in a modified Delphi process (appendix pp.48–52).[11] The Delphi panel of 21 experts included chairs of all ad hoc working groups and at least one representative from each PdL ALL group. The proposed definitions were evaluated for clarity and precision within the frame of the five generic ST criteria during each round. Consensus for each definition was *a priori* defined as 100% consensus without a prespecified number of Delphi rounds to achieve this.[12] Definitions not reaching full consensus were revised after each round by the ad-hoc working groups according to the anonymous comments provided by Delphi panelists. Preliminary definitions were circulated to principal investigators of the 17 PdL ALL

groups after the second Delphi round, with feedback integrated into subsequent rounds. Full consensus was reached after four rounds. (Figure 1, appendix pp.48–52).

Role of the funding source

The funders of the study had no role in the study design, the collection, analysis, and interpretation of data, in the writing of the report, or in the decision to submit the paper for publication. All authors had full access to all the data in the study and accept responsibility to submit for publication.

FINDINGS

Consensus definitions of the 21 prioritized STs are shown in Panel 2. A brief context is provided for each condition below, with incidences among ALL survivors provided when available. Working documents with additional background, supporting references, and considerations from plenary discussions are found for each ST in the appendix pp. 53–78.

Hearing loss

Hearing loss can result from platinum-based chemotherapy and cranial irradiation (>30 Gy), thus of limited relevance for contemporary ALL therapy.[13] Rarer causes of hearing loss include leukemic infiltration, infection, and hemorrhage into the cochleae; or supportive therapy such as aminoglycosides.[14–17] Cases treated with a cochlear implant were considered unacceptable since speech development, sound experience, and educational achievements remain a challenge with a cochlear implant despite technical improvements.[18] In contrast, correction with other hearing aids was considered acceptable as these facilitate a higher quality sound experience and thus normal language development.

Blindness

Increased risk of blindness among childhood cancer survivors is associated with radiation to the eye, the temporal lobe, and the posterior fossa, of relevance for a limited subset of ALL patients.[19] Blindness emerging during ALL therapy can, however, also result from ocular damage caused by leukemic infiltration and retinal bleeds, infections, or cortical damage due to anoxia, bleeding, thrombosis, infections, or posterior reversible encephalopathy syndrome. Cataract is a more common ocular morbidity among ALL survivors;[19–21] however, blindness is only expected to result in low-income countries where access to efficient treatment is limited.

Cardiac conditions: heart failure, arrhythmia, coronary artery disease, heart valve dysfunction

Heart failure is largely attributable to anthracyclines, anthracenediones, and radiation; coronary artery disease to cardiac irradiation and tyrosine kinase inhibitors; arrhythmias to alkylators, anthracyclines, tyrosine kinase inhibitors, (viral) myocarditis and any form of myocardial damage; and valvular disease to cardiac irradiation and endocarditis.[22–24] The cumulative incidences of severe heart failure, coronary artery disease, arrhythmias, and heart valve disease at 20 years from ALL diagnosis were recently reported to be 0·31–0·40%, 0·19–0·27%, 0·05–0·12%, and 0·02–0·09%, respectively, depending on the decade of treatment.[25] Although marked reductions in the use of anthracyclines and chest irradiation have reduced cardiac mortality,[5] there is no clear evidence of a decline in cardiovascular disease among ALL survivors yet.[25,26]

Severe grades of these cardiovascular conditions can impose unacceptable limitations on ADL, and their definitive treatments (heart transplantation, angioplasty or bypass surgery, heart valve replacement, pacemaker, and implantable cardioverter defibrillator [ICD]) are in themselves associated with life-long risks of serious complications and repeated invasive procedures.[27–30]

Therapy-related heart failure and coronary artery disease can progress substantially over time.[31,32] Although less certain, this is suspected to also be true for arrhythmias and heart valve disease.

Gastrointestinal failure

The vast majority of gastrointestinal toxicities occurring secondary to chemotherapy, immunotherapy, radiation, and infection/inflammation are transient. However, enterocolitis and typhlitis occur in up to 7% of childhood ALL patients depending on treatment intensity,[33] conferring risk of complications such as permanent stomas or dependence on total parental nutrition, although this is expected to be rare.

Hepatic failure.

Hepatotoxicity can result from chemotherapy, immunotherapy, radiation, transfusion-acquired hepatitis, transfusion-acquired iron overload, and cholestasis from prolonged parenteral nutrition. Sinusoidal obstruction syndrome has been observed in 10–20% of patients receiving 6-thioguanine as the maintenance therapy thiopurine drug[34] and is associated with chronic liver conditions such as splenomegaly, thrombocytopenia, portal hypertension, and

esophageal varices potentially requiring liver transplantation.[35] The prevalence of severe and long-term hepatobiliary sequelae is otherwise low.

Insulin dependent diabetes

Transient insulin dependent diabetes mellitus (IDDM) is frequent during therapy and typically induced by corticosteroids and asparaginase, whereas permanent pancreatogenic IDDM (type 3c) is more likely to result from asparaginase associated pancreatitis (AAP). AAP occurs in approximately 7% of childhood ALL patients receiving extensive asparaginase therapy, and 9% of those needing insulin second to AAP have persistent insulin dependence.[36,37] The risk profile of type 3c diabetes is considered the same as type 1 and 2 diabetes, and although diabetes-related mortality and incidence of cardiovascular disease have decreased with improved diabetes treatment, they remain significantly increased compared to age- and sex-matched controls.[38] Some IDDM cases occurring during anticancer therapy may not be therapy-related, but the proportion of "false positive" cases is expected to be negligible since incidence rates of IDDM among children with ALL are many fold higher than in the pediatric background population,[39,40] unless the prevalence of obesity is high.[41]

Renal failure

Prevalence of long-term renal toxicities ranges from 0 to 84% in childhood cancer survivors depending on cancer type, treatment regimen, length of follow-up, definitions, and assessment methods.[42] The most nephrotoxic therapies, *e.g.*, cisplatinum, ifosfamide, and irradiation to the kidney bed, are not used in ALL therapy. However, renal failure can result from tumor lysis syndrome and (rarely) from high-dose methotrexate, cyclophosphamide, and antibiotics, *e.g.*, aminoglycosides and vancomycin.[42] The highest risk among ALL survivors is found among those undergoing hematopoietic stem cell transplantation (hSCT) due to total body irradiation (TBI), graft-versus-host disease (GvHD), and its associated treatment, and infectious complications (*e.g.*, BK virus).

Pulmonary failure

Symptomatic pulmonary late effects are uncommon following ALL therapy, except following TBI and high dose alkylating agents used for conditioning before hSCT or as a consequence of GvHD. Recent studies have indicated increased pulmonary cause standardized mortality ratios among childhood leukemia survivors, but rates and absolute excess risk were very low and furthermore decreasing with increasing treatment era among childhood cancer survivors as a whole.[43,44]

Osteonecrosis

The prevalence of symptomatic osteonecrosis among childhood and young adult ALL patients ranges from 2–16%, with a peak incidence in adolescence.[45–47] The primary therapy-related risk factor is corticosteroid exposure, while host-related factors include host genome variants, female sex, adolescent age, and elevated body mass index. Osteonecrosis can result in articular collapse accompanied by severe pain and loss of function, and approximately 20% of cases undergo joint-preserving surgery or joint replacement.[45] Longevity of a replaced joint is uncertain in this population, and revisions or future invasive surgical procedures may be required. Most cases occur during therapy, but a significant proportion are diagnosed after treatment cessation.[47]

Amputation and physical deformation

Amputations and surgical removal of infected tissue; asymmetrical spinal irradiation or surgery resulting in severe scoliosis, lordosis or kyphosis; severe scarring and contractions caused by infections and surgery; and scleroderma secondary to chronic GvHD, can all result in permanent and significant limitations of self-care and instrumental ADL, as well as severe physical disfigurements causing emotional distress.[48,49] The prevalence of such cases among contemporary ALL survivors is unknown but expected to be rare, compared with other childhood cancer subtypes, *e.g.*, sarcoma survivors.

Central nervous system disorders: seizures, cognitive dysfunction, and psychiatric disease

Acute central nervous system (CNS) toxicities, such as drug-induced encephalopathy or stroke-like syndrome, cerebrovascular complications, and cerebral infections, occur in 3–13% of childhood ALL patients, conferring risk of long-term neurological conditions, including seizures and cognitive dysfunction.[50–52]

Seizures develop in approximately 10%of ALL patients during therapy,[53] secondary to drug-induced neurotoxicity, infections, electrolyte derangements, and other metabolic disturbances, and up to one third experience uncontrolled seizures years following therapy,[54] carrying risk of sudden unexplained death in epilepsy and potentially resulting in neurosurgical intervention. Cognitive dysfunction is associated with cranial irradiation and CNS directed drugs (*e.g.,* cytarabine, methotrexate, and dexamethasone), with long-term declines observed in those treated with cranial irradiation. In addition, acute complications such as cerebral venous thrombosis or invasive CNS infections infer risk of severe and permanent cognitive deficits. Although risk has decreased with the omission of prophylactic cranial

irradiation,[55] an estimated 5–10% of survivors treated with chemotherapy only experience moderate to severe deficits across domains of attention, memory, processing speed, executive function, fine motor dexterity, IQ performance.[56,57] Objective characterization of cognitive function with neuropsychological evaluation is likely to be performed in symptomatic patients, but systematic screening is not required for STFS inclusion.

Psychiatric episodes, including psychosis, can occur during ALL therapy second to corticosteroid exposure but are almost always transient.[58] Yet, survivors are at increased risk for persistent psychological maladjustment, anxiety, and depression occurring both during and after therapy.[59] The etiology is multifactorial, and associations with specific treatment exposures are uncertain.

Paralytic, neuropathic, and movement disorders

Despite distinct underlying pathogenesis, paralytic-, neuropathic-, myopathic-, and movement disorders are grouped into one ST category since their clinical presentations are overlapping, and the exact etiology may be difficult to discern. Disabling paralytic and movement disorders can result from CNS toxicities, as well as from peripheral motor neuropathy, typically related to vinca alkaloid exposure, whereas myopathy can result from steroids or rhabdomyolysis. A study of >4,000 childhood ALL survivors found significant weakness or inability to move arm(s) or leg(s) at a significant rate ratio of 5·0 compared with siblings.[60]

Vocal cord paralysis

Vocal cord paralysis leading to dysphonia, aphonia, and ultimately tracheotomy during ALL therapy is extremely rare.[52] Severe cases requiring prolonged ventilatory support and unilateral cordectomy have, however, been described, mostly among infants and patients with Down syndrome.

Cytopenia

Chemotherapy-induced cytopenia almost always resolves spontaneously, but some intensive myelotoxic exposures, *e.g.,* high-dose alkylating agents and TBI, can induce permanent bone marrow failure and cytopenia.[61] Insufficient bone marrow repopulation following hSCT can occur due to host versus graft reactions, excessive myelotoxic drug exposure, and infections. The burden of unintended, permanent cytopenia requiring hSCT is comparable with that of relapse or resistant disease.

Immune deficiency

Persistent severe immunodeficiency following cessation of chemotherapy is rare,[62] but this might change with the increased use of immunotherapies such as CAR T. Of note, immune deficiencies emerging during ALL therapy in the absence of targeted immunotherapy most likely represent underlying primary rather than therapy-induced immune deficiencies. As a reliable diagnosis of such cases, even with whole genome or exome sequencing, may not be recognized, they cannot be systematically excluded from STFS.

Second malignant neoplasms and benign central nervous system tumors.

The cumulative incidence of SMN following childhood ALL diagnosed between 1962 and 1998 is 4·17% at 15 years, rising to 10·85% at 30 years.[63] Among those treated after 1983, the cumulative incidence is much lower; 1·18% at 10 years, although representing a more than 7-fold increase in risk compared to the background population.[64] Most cases, primarily hematologic malignancies in non-irradiated patients, occur within 10 years from ALL diagnosis, but a significant proportion are diagnosed after more than 15 years.[65] Although 5-year survival rates have improved for most SMN subtypes, they are below those of relapsed ALL as a competing event.[65] Important therapy-related risk factors include the use of alkylating agents, topoisomerase-2 inhibitors (epipodophyllotoxins and anthracyclines), as well as irradiation. The true contribution from an underlying cancer predisposition syndrome is likely to be revealed as a growing number of patients are offered extensive germline DNA sequencing.

Important excluded conditions

Although infertility, primarily associated with high dose alkylating agents and TBI, is regarded an unacceptable toxicity, the condition is “asymptomatic” prior to puberty and in cases where parenthood has not been attempted; and since systematic screening is not performed, the condition was excluded. Future consensus strategies for screening to capture infertility will allow its inclusion.

Significantly reduced final height resulting from pre-pubertal cranial and spinal radiation therapy may be unacceptable but was excluded since evaluation requires systematic data regarding patient height standard deviation scores at diagnosis and ST capture, parental height, and adjustments according to ethnicity and national standards.

Chronic pain can be a disabling and unacceptable burden but was excluded (apart from disabling neuropathic pain) due to the subjective nature and influence of personal, societal, and cultural factors, thereby challenging meaningful comparisons between cohorts.

Sexual dysfunction, fatigue, and general measures of health-related quality of life (QoL) were excluded based on the same subjectivity considerations.

DISCUSSION

More than one million childhood cancer survivors are estimated to live in Europe and the US today, of which ALL survivors represent the largest diagnostic group. Survival is accompanied by risks of severe and permanent adverse health conditions, which may limit ADL, QoL, and overall life expectancy, thus making cancer a chronic disease in a subset of patients.[66,67] EFS is an excellent outcome metric for cancers with a poor survival but falls short when cure rates are high. Accordingly, the STFS measure was developed to quantify the physician-defined unacceptable health tradeoff for disease-free survival in the frame of childhood ALL. The 21 included STs are considered to be of such a severity that ALL therapy would likely have been modified if the toxicity had been predictable. This is not just a philosophical deliberation but parallels the strategy already taken, e.g., in patients with Down syndrome (avoidance of anthracyclines and high-dose methotrexate)[68] and when limiting re-exposure to asparaginase in patients with AAP.[69]

The total health-related burden resulting from cancer and cancer treatment is characterized by a continuum spanning objective, well-defined conditions (*e.g.*, heart failure) to intricate, difficult to define, as well as subjective disorders (*e.g.,* chronic fatigue); and from permanently disabling disorders to transient and mild conditions with low overall impact. Importantly, the prioritized STs describe the tip of the iceberg and represents only the objectively most severe end of this spectrum. However, they are also considered the conditions most likely to drive research that will frame changes in the treatment of an otherwise life-threatening cancer. Evaluation of the overall quality of survival exceeds the mere presence or absence of the 21 STs and requires the inclusion of patient-reported experiences relating not only to physiological but also psychosocial and socioeconomic outcomes.[70,71] The ST strategy is, however, considered an initial critical step towards capturing the overall quality of survival as it facilitates the subsequent exploration of survivor experiences related to the STs. As these are individually rare, the consensus-based capture across international study groups is suggested as a necessary preliminary activity. Future more comprehensive (but also more complex) targets should also include lower grade, but equally burdensome, chronic, and/or subjective somatic

late effects such as fatigue, pain, QoL, and overall measures of ability to perform ADL, as directed by the survivors.[72] The ST concept is flexible and can be expanded as evidence arises, indicating that the strength of the ST concept lies not only in the 21 selected consensus definitions but in a decision to capture and report such outcome data as a routine part of treatment evaluation.

Several of the STs are rare among ALL survivors but are included for the construct to be exhaustive and furthermore applicable to other cancer diagnoses and age groups, not least those with high cure rates, such as most childhood cancers and several adult cancers (*e.g.,* breast cancer, Hodgkin lymphoma, thyroid cancer). The combined cumulative incidence of the 21 STs will not be reliably quantified until captured systematically. However, based on reported data for the most common STs such as SMN, osteonecrosis, and post-pancreatitis IDDM, they are likely to be present in up to 5% among ALL survivors, which is substantial considering current overall mortality rates being below 10%.[4] Of note, variation in clinical practices, e.g. regarding the indication for cardiac catheterization or valve replacement, may influence regional rates of individual STs.

We aimed to include only uniformly objectifiable conditions as STs, however the definitions of psychiatric disease and cognitive dysfunction include assessments made by the physician, thus imposing some subjectivity. Uniform psychiatric and neurocognitive evaluations would be preferable; however, as these are not performed systematically across ALL groups, we suggest the proposed definitions to be a compromise between having a gold standard or no standard. Of note, the etiology behind some STs, *e.g.,* blindness, includes cancer itself, however since early diagnosis and therapeutic approach is expected to moderate the risk of long-term sequelae, and since causality can be impossible to discern, the inclusion of such conditions does not compromise the ST purpose.

Five years post-diagnosis is suggested as the initial time for evaluation since 5-year ST data are expected to be available in all cohorts, thus facilitating comparisons. However, additional later time points are also recommended (e.g., every five years). The ST capture strategy includes registration of the 21 health conditions, their timing of onset, and subsequent follow-up on top of the traditional events included in OS and EFS. Optimally, known toxicity-prone genotypes should also be registered at the time of data capture, as this would clarify the extent to which the STs are restricted to genotypically well-defined patient subsets. At present, data capture of even the most severe long-term toxicities varies across ALL study groups regarding outcome definitions, data capture logistics, and the follow-up period. Some groups have access to National population-based health registers; however, implementation of a

uniform registration beyond the ALL treatment protocol period, typically limited to five to ten years post ALL diagnosis, is generally absent. The proposed ST concept could motivate a uniform toxicity capture strategy reaching beyond this time-point. As a next step, the PdL STWG will apply the ST concept to four ALL cohorts representing European and North American survivors. When results are available, we will approach the large international ALL consortia across the globe, International Society of Paediatric Oncology (SIOP), and patient- and parent organizations to promote a wider application.

While the analysis of toxicity data routinely collected in clinical trials relies on frequency tables, we propose to account for time to occurrence of ST conditions and to consider them as additional events in a composite endpoint that extends the traditional OS and EFS. An approach that can account for censored data, such as the Kaplan-Meyer estimator for the cumulative probability of occurrence of the composite endpoint, would be appropriate, whereas other methods, such as the method of mean cumulative count,[73] should be considered for the description of multiple and potentially recurring conditions occurring in the same patient. Thus, the analysis will consider two general outcomes. First, the cumulative incidence of STs, which can be presented as STFS (with death being the only competing risk) in addition to the mean cumulative number of STs occurring at a given age or interval from ALL diagnosis. Both measures can be presented for individual as well as grouped STs. Second, the compiled measure of ST-EFS, which will illustrate the proportion of survivors without traditional events *and* without ST conditions at any given time point (appendix p.79).

Beyond the observational outcomes, ST measures may also accelerate investigations of risk factors that can ultimately improve personalized therapy and further reduce the risk of unacceptable toxicities. Modifications of treatment are already performed in patient groups with specific toxicity-prone genomic profiles, such as patients with low activity thiopurine methyltransferase, nudix hydrolase 15 deficiency, or Down syndrome,[74,75] and ongoing trials are currently investigating dose-reductions in relation to other such genotypes (*ClinicalTrials.gov, NCT03117751*). Heterogeneity in toxicity profiles necessitates multi-institutional collaborations investigating and validating genetic findings for these to have clinical application.

In conclusion, a global decision to routinely report ST data alongside traditional treatment outcomes will provide essential information regarding life-long risks to patients and their families, facilitate reliable comparisons of diverse

treatment strategies, and promote research into risk factors and thus preventive measures aimed at reducing the most severe toxicities of therapy without compromising cure.

Author contributions

All authors contributed equally to the establishment of the PdL STWG. All authors contributed to the Delphi process and are either representing their collaborative acute lymphoblastic leukemia group or have chaired an ad-hoc ST working group under the STWG, or both. KS chaired the STWG and LAJ coordinated this report. All authors contributed to the data collection and interpretation. LAJ drafted the first version of the manuscript, which was subsequently revised and approved by all authors.

Declaration of interest.

ER reports grants from Pfizer and other from Celgene, outside the submitted work. KS reports personal fees from Jazz Pharmaceuticals, personal fees from Servier, personal fees from Amgen, personal fees from Medscape, personal fees and grants from Servier, outside the submitted work. All other authors declare no competing interests.

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ONE FIGURE LEGEND AND TWO PANELS

Figure 1. Process leading to consensus definitions of prioritized Severe Toxicities.
SIOP=International Society of Paediatric Oncology; ; ST=Severe Toxicity; ASH=American Society of hematology; ALL=acute lymphoblastic leukemia. *Appendix pp.5–47. †Appendix pp.53–78.

#	Severe Toxicity selection criteria	Explained
I	**Not present prior to diagnosis of ALL**	**Not present prior to the cancer diagnosis.** Only conditions occurring during or (in some cases) after cancer diagnosis are included.
II	**Symptomatic**	**To ensure equal probability of capturing only burdensome conditions across protocols, the condition must be symptomatic and expected to lead to a clinical diagnosis without use of routine screening**. As an example, compensated cardiac failure detected by routine echocardiogram is not included, whereas severe, symptomatic cardiac failure is.
III	**Objective**	**The condition must be uniformly classifiable across different patients and by different observers.** Conditions such as chronic pain, nausea or fatigue, which are subjective, are thus not included, even though these conditions can represent a significant burden to the survivor.
IV	**Unacceptable severity**	**The condition must be so severe, that it is considered an *unacceptable* tradeoff for disease control, *i.e.*, had the condition in question been predictable at ALL diagnosis, it would likely have led to a change in anticancer therapy in the specific case. Physical and mental conditions significantly limiting self-care and instrumental ADL or posing significant threat of early mortality fulfill this criterion.** This consideration mirrors current actions, *e.g.,* as reduction of anthracycline use in patients with Down Syndrome, reduction of thiopurine doses in patients with *TPMT* deficiency, or concerns related to re-exposure after severe drug-induced toxicity, *e.g.,* re-exposure to asparaginase following asparaginase associated pancreatitis.
V	**Permanent or correctable only by unacceptable treatments.**	**The condition must be anticipated to be permanent and present at ST capture or have been corrected by a treatment, which in itself is considered unacceptable, *i.e.*, radical and invasive, as specified in the individual definitions.** Acute events are not included but sequelae such as severe cognitive deficits following cerebral hemorrhage or amputation of a limb following severe infections, are. Organ transplantation is an example of an unacceptable treatment since it is itself associated with risk of severe mortality and morbidity, whereas *e.g.,* growth hormone replacement is not considered an unacceptable treatment.

Panel 1. Generic criteria for selection of physician-derived Severe Toxicities.
Abbreviations: ST=Severe Toxicity; ALL=acute lymphoblastic leukemia; TPMT=thiopurine methyltransferase

Consensus definitions	
Hearing loss Permanent bilateral hearing loss emerging during anticancer therapy and defined as indication for cochlear implant (performed or planned) and/or above 40 dB hearing loss at 2 kHz and below.	
Blindness Untreatable blindness emerging during anticancer therapy and defined as visual acuity of less than 20/200 or a corresponding visual field loss to less than 10° in the better eye with the best possible correction.	
Heart failure Permanent, symptomatic cardiac dysfunction emerging during or after anticancer therapy and defined as: A) - Age 0–1 years: Marked tachypnea or diaphoresis with feeding and/or prolonged feeding times with growth failure OR tachypnea, retractions, grunting or diaphoresis at rest.* - Age 1–17·9 years: Marked dyspnea on exertion or at rest.* - Age ≥ 18 years: Marked dyspnea, palpitations or anginal pain on exertion or at rest.† AND B) - Decrease in left ventricular ejection fraction to a value below 40% and/or fractional shortening to less than 20% (normal reference value for two-dimensional echocardiogram). * *Equating to: ≥ Class 3 as per the modified Ross grading system for children aged 0–17·9* *†Equating to ≥ Class III as per New York Heart Association Failure Scale for adults*	**Note** Screening of patients with echocardiography is generally not required for inclusion as a ST, but echocardiographic measures are included in this definition, since we expect that all patients with symptoms will be identified and have one performed. Echocardiography parameters are provided, since international surveillance guidelines accept its use as the primary surveillance tool for cardiotoxicity. Furthermore, it is expected that a repeat echo will be performed at least one week apart in order to confirm cardiac dysfunction.
Coronary artery disease Coronary artery disease emerging during or after anticancer therapy and resulting in myocardial infarction and/or requiring angioplasty (balloon and/or stent) or coronary bypass surgery (performed or planned).	
Arrythmia Arrhythmia emerging during or after anticancer therapy, requiring, a pacemaker or an implantable cardioverter defibrillator (performed or planned).	**Note** Known underlying predisposing condition likely to explain the arrhythmia is reported at time of ST data capture.
Heart valve disease Heart valve dysfunction emerging during or after anticancer therapy and requiring surgical valve replacement (performed or planned).	
Gastrointestinal failure Gastrointestinal failure emerging during anticancer therapy, resulting in permanent (at time of evaluation) need of parenteral nutrition, and/or placement of a permanent PEG tube due to physical inability to eat/swallow and/or placement of a permanent stoma (performed or planned).	**Note** Underlying conditions include critical reduction in gastrointestinal tract mass and all other conditions leading to the described gastrointestinal failure.
Hepatic failure Severe and permanent hepatobiliary failure emerging during or after anticancer therapy, and defined as any of the following: A. Symptomatic*, decompensated liver disease including cirrhosis and portal hypertension that is not responsive to pharmacologic and endoscopic management† and is persisting for more than 12 months.	

OR B. Any hepatobiliary failure requiring liver transplantation (performed or planned). * Typical symptoms include fatigue, gum bleeding, epistaxis, itching, and icterus in all age groups in addition to impaired growth and delayed puberty in children. † Patients achieving resolution after ligation and sclerotherapy for varices are excluded. Patients receiving a shunt are included since shunts are intended for refractory disease, most often as a bridge to liver transplant.	
Insulin dependent diabetes Permanent insulin dependent diabetes emerging during anticancer therapy.	**Note** This condition is treatable, however is included due to the significant risk of cardiovascular disease and end-organ failure.
Renal failure Permanent loss of kidney function emerging during anticancer therapy that requires dialysis or renal transplantation (planned or performed).	
Pulmonary failure Chronic lung failure* emerging during or after anticancer therapy and requiring daily oxygen supplement or lung transplantation (performed or planned). *Including pulmonary fibrosis and bronchiolitis obliterans	
Osteonecrosis Osteonecrosis occurring during or after anticancer therapy and requiring total joint arthroplasty (performed or planned) and/or resulting in Grade 4 toxicity according to the Ponte di Legno Toxicity Working Group Criteria ("Symptomatic with deformation by imaging of one or more joints and/or substantially limiting self-care activity of daily living) at the time of STFS data capture.	
Amputation and physical deformations Amputation of extremities, severe spinal deformation, and disabling scleroderma/scarring/contractions limiting self-care and instrumental ADL or causing significant facial disfigurement and defined as follows: - Lower limb amputation, proximal to ankle - Upper limb amputation, proximal to wrist - Scoliosis, kyphosis or lordosis limiting ADL* and/or requiring spinal surgery - Scarring or contractions limiting range of movement resulting in limited ADL* - Scleroderma caused by graft versus host disease limiting ADL* - Amputation of nose - Amputation of one or both eyes - Complete facial palsy * instrumental and self-care ADL	**Note** Conditions are included if emerging during anticancer therapy. Scleroderma caused by chronic graft versus host disease and fulfilling the definition is included at any time point after hematopoietic stem cell transplantation
Cognitive dysfunction Any significant impairment of neurocognitive functions*, emerging during or after anticancer therapy, that severely restricts participation in school, vocational training, practice and career and/or other key activities of instrumental ADL *such as executive function (planning and organization), sustained attention, memory (particularly visual sequencing, temporal memory), processing speed, visual-motor integration, fine motor dexterity, diminished IQ, and learning deficits.	**Note** As evaluated by the physician, since uniform and objective neurocognitive evaluation is not performed across study groups.
Seizures	

Seizures, emerging during anticancer therapy, and requiring neurosurgical intervention (performed or planned) to achieve control, or that fulfil the International League Against Epilepsy definition for drug-resistant epilepsy*. *namely the failure of adequate trials of two tolerated and appropriately chosen and used anti-epileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom.	
Psychiatric disease Any psychiatric/mental disorder, emerging during anticancer therapy, that is severe enough to require ongoing mental health input (psychology/psychiatry), and is NOT adequately controlled* by medical, mental, or other therapeutic interventions. * *i.e.*, the condition severely restricts participation in school, vocational training, practice and career and/or other key activities of daily living.	**Note** As evaluated by the physician, since uniform and objective evaluation is not performed across study group. Cases with any known psychiatric disease prior to ALL diagnosis are excluded.
Paralytic, neuropathic, myopathic and movement disorders Paralytic, neuropathic (*e.g.,* paresthesia, numbness or pain), myopathic (*e.g.,* generalized muscle weakness caused by rhabdomyolysis) or movement disorders (*e.g.,* ataxia) emerging during anticancer therapy, and significantly limiting activities of daily living (ADL). This includes impaired gait to a degree necessitating wheelchair or other instrumental aid and/or significantly impaired upper or lower limb function (*i.e.*, severely limiting age-appropriate instrumental and self-care ADL).	
Vocal cord paralysis Permanent vocal cord paralysis, either unilateral or bilateral, emerging during anticancer therapy, requiring tracheostomy and/or ventilatory support or leading to significantly reduced ability or inability to produce speech sounds	
Cytopenia Profound and permanent cytopenia in one or more hematopoietic cell lines, without evidence of hematopoietic recovery, emerging during anticancer therapy, and requiring hematopoietic stem cell transplantation (performed or planned).	**Note** Myelodysplastic syndromes are captured as second malignant neoplasms. Known underlying predisposing condition likely to explain the cytopenia is reported at time of STFS data capture.
Immune deficiency Permanent immunodeficiency emerging during anticancer therapy and requiring hematopoietic stem cell transplantation (performed or planned).	**Note** Cases with known underlying primary immune deficiency, identified at any time point prior to data capture are included and the underlying condition is reported at time of ST data capture. Severe leukopenia requiring hematopoietic stem cell transplantation is registered as “Cytopenia”.
Second malignant neoplasm and benign CNS tumors Second malignant neoplasms (SMN) or benign CNS tumors emerging during or after anticancer therapy.	**Note** Nonmelanoma skin cancers are not included. Known underlying cancer prone syndromes are reported at time of ST data capture.

Panel 2. **Consensus definitions of the 21 prioritized Severe Toxicities**

Abbreviations: ST=Severe Toxicity; PEG=percutaneous endoscopic gastrostomy; ADL=activities of daily living; ALL=acute lymphoblastic leukemia

First face-to-face plenary meeting, May 20th, 2019, SIOP Europe Annual Meeting (Prague, Czech Republic)
- Assembly of Ponte di Legno Severe Toxicity working group
- Conceptualization and formulation of ST selection criteria
- Application of ST criteria to 854 conditions, resulting in 99 conditions across 15 organ systems, considered for inclusion
- One new condition added by the Ponte di Legno Severe Toxicity working group, resulting in a total of 100 conditions across 16 organ systems considered for inclusion
- Formation of 16 ad-hoc working groups; one for each organ system

Work in working groups
- Published studies and protocol curation in relation to each selected condition

Second face-to-face plenary meeting, Dec 8, 2019, ASH Annual Meeting (Orlando,FL, USA)
Ad-hoc groups presented their findings:
- Preexisting definitions in literature and ALL protocols
- Evidence of prevalence
- Special considerations regarding severe toxicity criteria and definitions
- Challenges associated with existing definitions and available data to capture the conditions
- Proposal for new definitions
- Discussion of reviewed conditions resulted in exclusion of additional 20 conditions. The remaining 80 included conditions were grouped into 21 ST conditions across 15 organ systems and initial definitions were proposed.

Work in working groups
- Review of literature and ALL protocols
- Development of working documents for each ST†
- Proposed definition for each ST

Delphi rounds 1-3
- Panelist ratings of definitions
- Distribution of anonymized quantitative and qualitative results
- Between rounds revisions of conditions/definitions if appropriate
- Full consensus achieved for 12/21 conditions; near full consensus achieved for 8/21 conditions

Third face-to-face plenary meeting, November 13th, 2020, online
- Review of consensus definitions and remaining issues after third Delphi round

Delphi round 4
- Panelist ratings of all conditions with less than full consensus
- Full consensus achieved for all conditions