Severe toxicity free survival: physician-derived definitions of unacceptable long-term toxicities following acute lymphocytic leukaemia

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5-year overall survival rates have surpassed 90% for childhood acute lymphocytic leukaemia, but survivors are at risk for permanent health sequelae. Although event-free survival appropriately represents the outcome for cancers with poor overall survival, this metric is inadequate when cure rates are high but challenged by serious, persistent complications. Accordingly, a group of experts in paediatric haematology–oncology, representative of 17 international acute lymphocytic leukaemia study groups, launched an initiative to construct a measure, designated severe toxicity-free survival (STFS), to quantify the occurrence of physician-prioritised toxicities to be integrated with standard cancer outcome reporting. Five generic inclusion criteria (not present before cancer diagnosis, symptomatic, objectifiable, of unacceptable severity, permanent, or requiring unacceptable treatments) were used to assess 855 health conditions, which resulted in inclusion of 21 severe toxicities. Consensus definitions were reached through a modified Delphi process supplemented by two additional plenary meetings. The 21 severe toxicities include severe adverse health conditions that substantially affect activities of daily living and are refractory to therapy (eg, refractory seizures), are without therapeutic options (eg, blindness), or require substantially invasive treatment (eg, cardiac transplantation). Incorporation of STFS assessment into clinical trials has the potential to improve and diversify treatment strategies, focusing not only on traditional outcome events and overall survival but also the frequencies of the most severe toxicities. The two major aims of this Review were to: prioritise and define unacceptable long-term toxicity for patients with childhood acute lymphocytic leukaemia, and define how these toxicities should be combined into a composite quantity to be integrated with other reported outcomes. Although STFS quantifies the clinically unacceptable health tradeoff for cure using childhood acute lymphocytic leukaemia as a model disease, the prioritised severe toxicities are based on generic considerations of relevance to any other cancer diagnosis and age group.

Lancet Haematol 2021; 8: e513–23

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Introduction

Childhood cancer 5-year overall survival rates now surpass 80%; therefore, a research focus on long-term therapy-related toxicities is important.[1,2] Outcomes have previously been measured by overall survival and event-free survival, with events encompassing resistant disease, relapse, second malignant neoplasms, and death. However, detailed information regarding the rates of other severe toxicities is needed to address and further improve the quality of life among survivors.

In childhood acute lymphocytic leukaemia, the most common childhood cancer, the 5-year event-free survival now exceeds 85% and overall survival exceeds 90%, 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 acute lymphocytic leukaemia therapy, including a dramatic decrease in the use of radiotherapy, anthracyclines, and alkylating drugs, 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's Common Terminology Criteria for Adverse Events (CTCAE)[7] and, over the past 5 years, by international consensus definitions to enable 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.

The Ponte di Legno Working Group (PdL)—which represents 17 major childhood acute lymphocytic leukaemia study groups and institutions across North America, Europe, Japan, Taiwan, and Australia—[9] launched an initiative in May, 2019, to prioritise physician-derived severe toxicities for future reporting of severe toxicity-free survival (STFS) alongside the other reported outcome events.

The two major aims of this Review were to: prioritise and define unacceptable long-term toxicity for patients with childhood acute lymphocytic leukaemia, and define how these toxicities should be combined into a composite quantity to be integrated with the traditionally reported outcomes.

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See Online for appendix

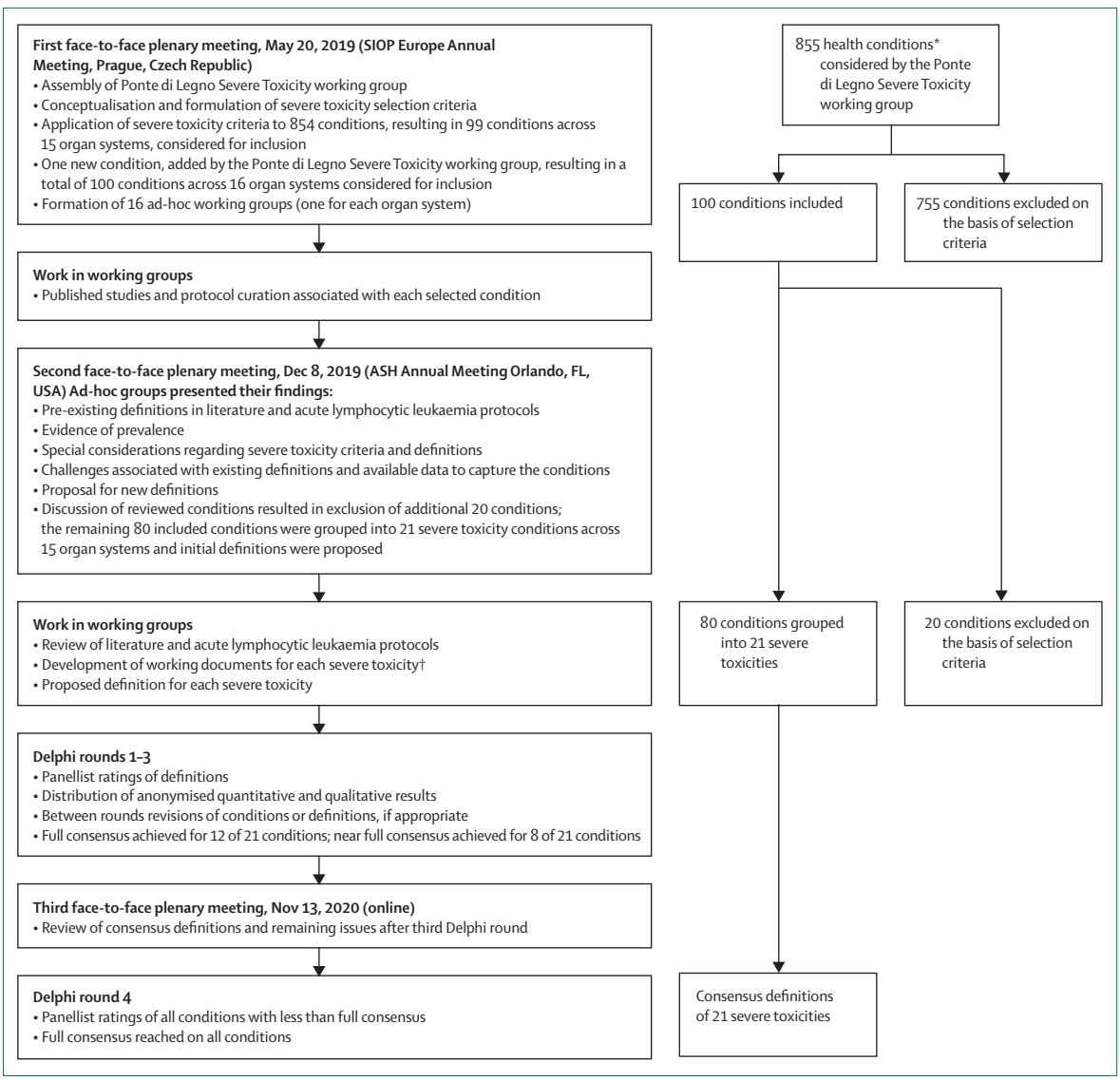

Figure: **Process leading to consensus definitions of prioritised severe toxicities**
SIOP=International Society of Paediatric Oncology. ASH=American Society of Hematology. *The 855 health conditions are listed in the appendix (pp 5–47). †Working documents for each severe toxicity are listed in the appendix (pp 53–78).

Methods

Defining severe toxicities

Unacceptable severe toxicities were defined as health conditions perceived by the treating physicians to represent an unacceptable tradeoff for disease control. More specifically, this definition was interpreted as severe and permanent physical or mental health issues that substantially affected self-care and 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 severe toxicities; or with no curative therapy available. After the selection of health issues, an iterative Delphi process guided by existing evidence and expert opinion was done over an 18-month period until a final consensus on the definitions of each severe toxicity was reached (figure).

Selection of severe toxicities

The five generic severe toxicity selection criteria are listed in the panel. 855 health conditions were reviewed (appendix pp 5–47), including all 837 conditions in the 5th 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 Severe Toxicities Working Group (STWG). To allow future use of the severe toxicities definitions and the STFS measure for other cancers, all conditions were evaluated irrespective of their frequency

and relevance for childhood acute lymphocytic leukaemia. During the initial plenary meeting, we excluded 755 health conditions using the generic selection criteria. Ad-hoc working groups, which included a chair and representation of paediatric haematology–oncology 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 published studies and the toxicity sections of 13 acute lymphocytic leukaemia 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 severe toxicities across 15 organ systems (figure). External specialists within the relevant organ areas were consulted regarding all definitions before commencing the consensus process.

Consensus definitions

Initial definitions for each severe toxicity were developed by the ad-hoc working groups and subsequently evaluated using 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 acute lymphocytic leukaemia group. The proposed definitions were evaluated for clarity and precision within the frame of the five generic criteria during each round. Consensus for each definition was 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 panellists. Preliminary definitions were circulated to principal investigators of the 17 PdL acute lymphocytic leukaemia groups after the second Delphi round, with feedback integrated into subsequent rounds. Full consensus was reached after four rounds (figure, appendix pp 48–52).

Panel: **Generic criteria for selection of physician-derived severe toxicities**

Not present before diagnosis of acute lymphocytic leukaemia

- Not present before the cancer diagnosis; only conditions occurring during or after cancer diagnosis are included.

Symptomatic

- To ensure equal probability of capturing the condition across different protocols using different screening strategies, the condition must be symptomatic and expected to lead to a clinical diagnosis without use of routine screening.
- Compensated cardiac failure detected by routine echocardiogram is not included, whereas severe, symptomatic cardiac failure is included.

Objective

- The condition must be uniformly classifiable across different patients and by different observers.
- Chronic pain, nausea, or fatigue, which are subjective, are not included, although these conditions can represent a substantial burden to the survivor.

Unacceptable severity

- The condition must be so severe, that it is considered an unacceptable tradeoff for disease control—ie, had the condition been predictable at acute lymphocytic leukaemia diagnosis, it would probably have led to a change in anticancer therapy.
- Physical and mental conditions that substantially affect self-care and instrumental activities of daily living or posing substantial threat of early mortality fulfil this criterion.
- This consideration mirrors current actions (eg, 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 (eg, re-exposure to asparaginase following asparaginase associated pancreatitis).

Permanent or correctable only by unacceptable treatments

- The condition must be anticipated to be permanent and present at severe toxicity capture or have been corrected by a treatment, which in itself is considered unacceptable—ie, radical and invasive, as specified in the individual definitions.
- Acute events are not included, but sequelae such as severe cognitive deficits following cerebral haemorrhage 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 growth hormone replacement is not considered an unacceptable treatment.

Results

Consensus definitions of the 21 prioritised severe toxicities are shown in the table. A brief context is provided for each condition, with incidences among survivors of acute lymphocytic leukaemia provided if available. Working documents with additional background, supporting references, and considerations from plenary discussions are found for each severe toxicity in the appendix (pp 53–78).

Hearing loss

Treatment-related hearing loss can result from platinum-based chemotherapy and cranial irradiation (>30 Gy), thus it is not relevant to contemporary acute lymphocytic leukaemia therapy.[13] Rarer causes of hearing loss include leukemic infiltration, infection, and haemorrhage into the cochleae, or supportive therapy such as aminoglycosides.[14–17] Treatment with a cochlear implant was considered unacceptable because speech development and sound experience remain challenging with a cochlear implant despite technical improvements.[18] By contrast, correction with other hearing aids was considered acceptable as these improve sound experience and speech 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 small subset of patients with acute lymphocytic leukaemia.[19] Blindness emerging during acute lymphocytic leukaemia 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

	Consensus definitions	Additional notes
Hearing loss	Permanent bilateral hearing loss emerging during anticancer therapy and defined as need for cochlear implant (completed or planned), or >40 dB hearing loss at ≤2 kHz.	..
Blindness	Untreatable blindness emerging during anticancer therapy, defined as visual acuity of <20/200 or a corresponding visual field loss to <10° in the stronger eye with the best possible correction.	..
Heart failure	Permanent, symptomatic cardiac dysfunction emerging during or after anticancer therapy and defined by a decrease in left ventricular ejection fraction to a value <40% or fractional shortening to <20% and one of the following. Age 0–1 years: marked tachypnoea or diaphoresis with feeding or prolonged feeding times with growth failure or tachypnoea, retractions, grunting, or diaphoresis at rest.* Age 1–17·9 years: marked dyspnoea on exertion or at rest.* Age ≥18 years: marked dyspnoea, palpitations or anginal pain on exertion or at rest.†	Screening of patients with echocardiography is generally not required for inclusion as a severe toxicity, but echocardiographic measures are included in this definition because we expect that all patients with symptoms will be identified and have one done. Echocardiographic parameters are provided because international surveillance guidelines accept its use as the primary surveillance tool for cardiotoxicity. It is expected that a repeat echocardiograms will be done at least 1 week apart to confirm cardiac dysfunction.
Coronary artery disease	Coronary artery disease emerging during or after anticancer therapy and resulting in myocardial infarction or requiring angioplasty (balloon or stent) or coronary bypass surgery (completed or planned).	..
Arrythmia	Arrhythmia emerging during or after anticancer therapy, requiring a pacemaker or an implantable cardioverter defibrillator (completed or planned).	Known underlying predisposing condition likely to explain the arrhythmia is reported at time of severe toxicity data capture.
Heart valve disease	Heart valve dysfunction emerging during or after anticancer therapy and requiring surgical valve replacement (completed or planned).	..
Gastrointestinal failure	Gastrointestinal failure emerging during anticancer therapy, resulting in permanent (at time of evaluation) need of parenteral nutrition, or placement of a permanent PEG tube due to physical inability to eat or swallow, or placement of a permanent stoma (completed or planned).	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: symptomatic (typical symptoms include fatigue, gum bleeding, epistaxis, itching, and icterus in all age groups in addition to impaired growth and delayed puberty in children), decompensated liver disease including cirrhosis and portal hypertension that is not responsive to pharmacologic and endoscopic management (patients reaching resolution after ligation and sclerotherapy for varices are excluded, patients receiving a shunt are included because shunts are intended for refractory disease, most often as a bridge to liver transplant) and is persisting for >12 months; or, any hepatobiliary failure requiring liver transplantation (completed or planned).	..
Insulin dependent diabetes	Permanent insulin dependent diabetes emerging during anticancer therapy.	Insulin dependent diabetes is treatable; however, is included because of the substantial 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 (completed or planned).	..
Pulmonary failure	Chronic lung failure (including pulmonary fibrosis and bronchiolitis obliterans) emerging during or after anticancer therapy and requiring daily oxygen supplement or lung transplantation (completed or planned).	..
Osteonecrosis	Osteonecrosis occurring during or after anticancer therapy and requiring total joint arthroplasty (completed or planned) or resulting in grade 4 toxicity according to the Ponte di Legno Toxicity Working Group Criteria (ie, symptomatic with deformation by imaging of one or more joints or substantially affecting 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, or contractions affecting self-care and instrumental ADL or causing substantial facial disfigurement and defined as follows: lower limb amputation (proximal to ankle); upper limb amputation (proximal to wrist); scoliosis, kyphosis, or lordosis affecting ADL, or requiring spinal surgery; scarring or contractions affecting range of movement that affects ADL; scleroderma caused by graft-versus-host disease affecting ADL; amputation of nose; amputation of one or both eyes; and complete facial palsy.	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 haematopoietic stem-cell transplantation.
Cognitive dysfunction	Any substantial impairment of neurocognitive functions (eg, executive function [planning and organisation], sustained attention, memory [particularly visual sequencing, temporal memory], processing speed, visual-motor integration, fine motor dexterity, diminished performance on IQ tests, and learning deficits), emerging during or after anticancer therapy, that severely restricts participation in school, vocational training, practice, career, or other key activities of instrumental ADL.	As evaluated by the physician, since uniform and objective neurocognitive evaluation is not done across study groups.
Seizures	Seizures emerging during anticancer therapy that require neurosurgical intervention (completed or planned) to reach 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 reach sustained seizure freedom).	..

(Table continues on next page)

	Consensus definitions	Additional notes
(Continued from previous page)		
Psychiatric disease	Any psychiatric or mental health disorder, emerging during anticancer therapy, that is severe enough to require ongoing mental health input (psychology or psychiatry), and is not adequately controlled (ie, the condition severely restricts participation in school, vocational training, practice, or career, or other instrumental ADL) by medical, mental, or other therapeutic interventions.	As evaluated by the physician because uniform and objective evaluation is not done across study group. Cases with any known psychiatric disease before acute lymphocytic leukaemia diagnosis are excluded.
Paralytic, neuropathic, myopathic and movement disorders	Paralytic, neuropathic (eg, paraesthesia, numbness or pain), myopathic (eg, generalised muscle weakness caused by rhabdomyolysis) or movement disorders (eg, ataxia) emerging during anticancer therapy that substantially affects ADL, which includes impaired gait to a degree necessitating wheelchair or other instrumental aid or substantially impaired upper or lower limb function (ie, severely restricting age-appropriate instrumental and self-care ADL).	..
Vocal cord paralysis	Permanent vocal cord paralysis, either unilateral or bilateral, emerging during anticancer therapy, requiring tracheostomy or ventilatory support or leading to substantially reduced ability or inability to produce speech sounds.	..
Cytopenia	Profound and permanent cytopenia in one or more haematopoietic cell lines, without evidence of haematopoietic recovery, emerging during anticancer therapy, and requiring HSCT (completed or planned).	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.
Immunodeficiency	Permanent immunodeficiency emerging during anticancer therapy and requiring HSCT (completed or planned).	Cases with known underlying primary immune deficiency, identified at any timepoint before data capture are included and the underlying condition is reported at time of severe toxicity data capture. Severe leukopenia requiring HSCT is classed as cytopenia.
Second malignant neoplasm and benign CNS tumours	Second malignant neoplasms or benign CNS tumours emerging during or after anticancer therapy.	Non-melanoma skin cancers are not included. Known underlying cancer prone syndromes are reported at time of severe toxicity data capture.

ADL=activities of daily living. HSCT=haematopoietic stem-cell transplantation. PEG=percutaneous endoscopic gastrostomy. STFS=severe toxicity-free survival. *Equating to more than class 3 as per the modified Ross Classification system for children aged 0–17·9 years. †Equating to class 3 or more as per the New York Heart Association Failure Scale for adults.

Table: **Consensus definitions of the 21 prioritised severe toxicities**

reversible encephalopathy syndrome. Cataract is a more common ocular morbidity among survivors of acute lymphocytic leukaemia;[19–21] however, blindness is only expected to result in low-income countries where access to efficient treatment can be difficult because of cost and insufficient availability.

Cardiac conditions

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 incidence at 20 years from acute lymphocytic leukaemia diagnosis is reported to be 0·31%–0·40% for severe heart failure, 0·19%–0·27% for coronary artery disease, 0·05%–0·12% for arrhythmias, and 0·02%–0·09% for heart valve disease, 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 currently no clear evidence of a decline in cardiovascular disease among survivors of acute lymphocytic leukaemia.[25,26]

Severe grades of these cardiovascular conditions can impose unacceptable limitations on ADL, and their definitive treatments (eg, heart transplantation, angioplasty or bypass surgery, heart valve replacement, pacemaker, and implantable cardioverter defibrillator) 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, which is suspected to also be applicable to arrhythmias and heart valve disease.[31,32]

Gastrointestinal failure

The majority of gastrointestinal toxicities occurring secondary to chemotherapy, immunotherapy, radiation, and infection or inflammation are transient. However, enterocolitis and typhlitis occur in up to 7% of patients with childhood acute lymphocytic leukaemia depending on treatment intensity,[33] conferring risk of complications such as permanent stomas or dependence on total parental nutrition, although this complication 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 thioguanine as the maintenance therapy

For the **Ross Classification system** see *Pediatric Cardiol* **33:** 1295–300

For the **New York Heart Association Failure Scale** see https://www.heart.org/en/health-topics/heart-failure/what-is-heart-failure/classes-of-heart-failure

thiopurine drug[34] and is associated with chronic liver conditions such as splenomegaly, thrombocytopenia, portal hypertension, and oesophageal 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 is frequent during therapy and typically induced by corticosteroids and asparaginase, whereas permanent pancreatogenic insulin dependent diabetes (type 3c) is more likely to result from asparaginase associated pancreatitis. Asparaginase associated pancreatitis occurs in approximately 7% of patients with childhood acute lymphocytic leukaemia who are receiving extensive asparaginase therapy, and in 9% of those who need insulin second to asparaginase associated pancreatitis 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 substantially increased compared with age-matched and sex-matched controls.[38] Some insulin dependent diabetes cases occurring during anticancer therapy might not be therapy related, but the proportion of non-treatment-related cases is expected to be negligible as incidence rates of insulin dependent diabetes among children with acute lymphocytic leukaemia are many times higher than in the paediatric 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 survivors of childhood cancer depending on cancer type, treatment regimen, length of follow-up, definitions of toxicities, and assessment methods.[42] The most nephrotoxic therapies (eg, cisplatin or ifosfamide) and irradiation to the kidney bed, are not used in acute lymphocytic leukaemia therapy. However, renal failure can result from tumour lysis syndrome and (rarely) from high-dose methotrexate, cyclophosphamide, and antibiotics (eg, aminoglycosides and vancomycin).[42] The highest risk among survivors of acute lymphocytic leukaemia is found among those undergoing haematopoietic stem-cell transplantation (HSCT) due to total body irradiation, graft-versus-host disease, and its associated treatment, and infectious complications (eg, BK virus).

Pulmonary failure

Symptomatic pulmonary late effects are uncommon following acute lymphocytic leukaemia therapy, except following total body irradiation and high-dose alkylating drugs used for conditioning before HSCT or as a consequence of graft-versus-host disease. Studies published within the past 5 years have suggested an increased pulmonary-cause standardised mortality ratios among survivors of childhood leukaemia, but rates and absolute excess risk were very low and has decreased during the treatment era among survivors of childhood cancer.[43,44]

Osteonecrosis

The prevalence of symptomatic osteonecrosis among children and young adults with acute lymphocytic leukaemia ranges from 2%–16%, with a peak incidence in adolescence.[45–47] The primary therapy-related risk factor is corticosteroid exposure, and 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 patients 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 might be required. Most cases occur during therapy, but a substantial 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 graft-versus-host disease, can all result in permanent and substantial effects on self-care and instrumental ADL, and severe physical disfigurements that can cause emotional distress.[48,49] The prevalence of such cases among survivors of acute lymphocytic leukaemia is unknown but expected to be rare, compared with other childhood cancer subtypes (eg, survivors of sarcoma).

CNS disorders

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

Seizures develop in approximately 10% of patients with acute lymphocytic leukaemia during therapy,[53] secondary to drug-induced neurotoxicity, infections, electrolyte derangements, and other metabolic disturbances, and up to one-third of those who develop seizures have uncrontrolled 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 (eg, cytarabine, methotrexate, and dexamethasone), with long-term declines observed in those treated with cranial irradiation. Additionally, acute complications (eg, 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 have moderate to severe effects on attention, memory, processing speed, executive function, fine motor dexterity, and performance on IQ tests.[56,57] Objective characterisation of cognitive function with neuropsychological evaluation is likely to be done in patients who are symptomatic, but systematic screening is not required for STFS inclusion.

Psychiatric episodes, including psychosis, can occur during acute lymphocytic leukaemia therapy second to corticosteroid exposure but are almost always transient.[58] However, survivors are at increased risk for persistent psychological maladjustment, anxiety, and depression that occurs during or after therapy.[59] The cause of these psychiatric events is multifactorial, and associations with specific treatment exposures are unknown.

Paralytic, neuropathic, and movement disorders

Despite distinct underlying pathogenesis, paralytic, neuropathic, myopathic, and movement disorders are grouped into one severe toxicity category since their clinical presentations are overlapping, and the exact cause could be difficult to discern. Disabling paralytic and movement disorders can result from CNS toxicities, and from peripheral motor neuropathy, typically related to vinca alkaloid exposure, whereas myopathy can result from steroids or rhabdomyolysis. A study of more than 4000 survivors of childhood acute lymphocytic leukaemia found substantial weakness or inability to move arms or legs at a statistically significant rate ratio of 5·0 compared with siblings.[60]

Vocal cord paralysis

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

Cytopenia

Chemotherapy-induced cytopenia almost always resolves spontaneously, but some intensive myelotoxic exposures (eg, high-dose alkylating drugs and total body irradiation) can induce permanent bone marrow failure and cytopenia.[61] Insufficient bone marrow repopulation following HSCT can occur because of 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.

Immunodeficiency

Persistent severe immunodeficiency following cessation of chemotherapy is rare,[62] but this might change with the increased use of immunotherapies such as chimeric antigen receptor T-cell therapy. Notably, immunodeficiencies emerging during acute lymphocytic leukaemia therapy in the absence of targeted immunotherapy are most likely to represent underlying primary (rather than therapy induced) immunodeficiencies. Diagnosis of such non-tretament-related cases can be unreliable, even with whole genome or exome sequencing; therefore, they cannot be systematically excluded from STFS.

Second malignant neoplasms and benign CNS tumours

The cumulative incidence of second malignant neoplasms following childhood acute lymphocytic leukaemia 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-times increase in risk compared with the general population.[64] Most cases, primarily haematological malignancies in non-irradiated patients, occur within 10 years from diagnosis of acute lymphocytic leukaemia, but a substantial proportion are diagnosed after more than 15 years.[65] Although 5-year overall survival has improved for most second malignant neoplasm subtypes, is it below that of relapsed acute lymphocytic leukaemia as a competing event.[65] Important therapy-related risk factors include the use of alkylating drugs, topoisomerase-2 inhibitors (eg, epipodophyllotoxins and anthracyclines), and 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

Infertility, which is associated with high dose alkylating drugs and total body irradiation, is regarded as an unacceptable toxicity. However, infertility is asymptomatic before puberty and before parenthood has been attempted. Systematic screening for infertility is not routinely done; therefore, infertility was excluded from STFS. Future consensus strategies for screening to capture infertility will allow its inclusion.

Substantially reduced final height resulting from prepubertal cranial and spinal radiation therapy can be unacceptable, but was excluded because evaluation requires systematic data regarding patient height standard deviation scores at diagnosis and severe toxicity 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) because of 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 were excluded on the basis of the same subjectivity considerations.

Discussion

More than 1 million survivors of childhood cancer are estimated to live in Europe and the USA, of which survivors of acute lymphocytic leukaemia represent the largest diagnostic group. Survival is accompanied by risks of severe and permanent adverse health conditions, which can greatly affect ADL, and reduce quality of life and overall life expectancy, making cancer a chronic disease in a subset of patients.[66,67] Event-free survival is an excellent outcome metric for cancers associated with poor survival, but is inadequate 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 acute lymphocytic leukaemia. The 21 severe toxicities included in this Review are considered to be of such a severity that acute lymphocytic leukaemia therapy would probably have been modified if the toxicity had been predictable. This is not just a philosophical deliberation but parallels the strategy already taken—eg, in patients with Down syndrome (avoidance of anthracyclines and high-dose methotrexate)[68] and when limiting re-exposure to asparaginase in patients with asparaginase-associated pancreatitis.[69]

The total health-related burden resulting from cancer and cancer treatment is characterised by a continuum-spanning objective, well defined conditions (eg, heart failure) to intricate, difficult to define, and subjective disorders (eg, chronic fatigue); and from permanently disabling disorders to transient and mild conditions with low overall effect. Importantly, the prioritised severe toxicities only represent 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 severe toxicities and requires the inclusion of patient-reported experiences relating not only to physiological but also psychosocial and socioeconomic outcomes.[70,71] The severe toxicity strategy is, however, considered an initial important step towards capturing the overall quality of survival as it allows for the subsequent evaluation of survivor quality of life related to the severe toxicities. As these severe toxicities are individually rare, the consensus-based capture across international study groups is suggested as a necessary preliminary activity. Future comprehensive and complex targets should also include lower grade, but equally burdensome, chronic, or subjective somatic late effects (eg, fatigue, pain, and quality of life) and overall measures of ability to do ADL, as directed by the survivors.[72] The STFS concept is flexible and can be expanded as evidence is published, suggesting that the strength of the 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 severe toxicities are rare among survivors of acute lymphocytic leukaemia 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 (eg, breast cancer, Hodgkin lymphoma, and thyroid cancer). The combined cumulative incidence of the 21 severe toxicities will not be reliably quantified until captured systematically. However, based on reported data for the most common severe toxicities (eg, second malignant neoplasms, osteonecrosis, and post-pancreatitis insulin dependent diabetes), they are likely to be present in up to 5% of survivors of acute lymphocytic leukaemia, which is substantial considering current overall mortality rates being below 10%.[4] Notably, variation in clinical practices (eg, regarding cardiac catheterisation or valve replacement) could affect regional rates of individual severe toxicities.

In this Review, we aimed to include only uniformly objectifiable conditions as severe toxicities; however, the definitions of psychiatric disease and cognitive dysfunction include assessments made by the physician, which leads to some subjectivity. Uniform psychiatric and neurocognitive evaluations would be preferable; however, as these assessments are not done systematically in patients with acute lymphocytic leukaemia, we suggest the proposed definitions to be a compromise between having a gold standard or no standard. The cause of some severe toxicities (eg, blindness) includes cancer itself, however, as early diagnosis and therapeutic approach is expected to moderate the risk of long-term sequelae, and as causality can be impossible to discern, the inclusion of such conditions does not compromise the purpose of the STFS quantification.

5 years following diagnosis is suggested as the initial time for evaluation because 5-year severe toxicity data are expected to be available in all cohorts, which enables comparisons. However, additional later time points are also recommended (eg, every 5 years). The severe toxicity 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

Search strategy and selection criteria

No systematic search was done. Working groups established for each organ system reviewed published studies for existing evidence and definitions of relevance for the prioritised toxicities. The toxicity sections of 13 acute lymphocytic leukaemia treatment protocols currently used by major childhood acute lymphocytic leukaemia study groups and institutions groups across North America, Europe, Japan, Taiwan, and Australia were also reviewed. External specialists within the relevant organ areas were consulted regarding all definitions.

overall survival and event-free survival. Optimally, known toxicity-prone genotypes should also be registered at the time of data capture as this would clarify the extent to which the severe toxicities are restricted to genotypically well defined patient subsets. Currently, data capture of even the most severe long-term toxicities varies among acute lymphocytic leukaemia study groups regarding outcome definitions, data capture logistics, and the follow-up period. Some acute lymphocytic leukaemia groups have access to national population-based health registers (eg, the Danish National Patient Registry); however, implementation of a uniform registration beyond the acute lymphocytic leukaemia treatment protocol period, typically limited to 5–10 years after acute lymphocytic leukaemia diagnosis, is generally absent. The proposed STFS concept could motivate a uniform toxicity capture strategy reaching beyond this time-point. As a next step, the PdL STWG will apply the STFS concept to four acute lymphocytic leukaemia cohorts that represent European and North American survivors. When results are available, we will approach the large international acute lymphocytic leukaemia consortia, the International Society of Paediatric Oncology, and patient-led and parent-led organisations to promote application of the STFS concept.

The analysis of toxicity data routinely collected in clinical trials relies on frequency tables. We call on future trials to account for time to occurrence of severe toxicity conditions and to consider them as additional events in a composite endpoint that extends the traditional overall survival and event-free survival. An approach that can account for censored data, such as the Kaplan-Meier 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 severe toxicities, which can be presented as STFS (with death being the only competing risk) and the mean cumulative number of severe toxicities occurring at a given age or interval from acute lymphocytic leukaemia diagnosis. These measures can be presented for both individual and grouped severe toxicities. Second, the compiled measure of STFS and event-free survival, which will show the proportion of survivors without traditional events and without severe toxicities conditions at any given time point (appendix p 79).

Beyond the observational outcomes, severe toxicity measures could also accelerate investigations of risk factors that can ultimately improve personalised therapy and further reduce the risk of unacceptable toxicities. Modifications of treatment are already done in patient groups with specific toxicity-prone genomic profiles, such as patients with TPMT or NUDT15 deficiency, or Down syndrome,[74,75] and one ongoing trial is currently investigating dose-reductions in relation to other such genotypes (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 severe toxicity data alongside traditional treatment outcomes will provide essential information regarding life-long risks to patients and their families, enable reliable comparisons of diverse treatment strategies, and promote research on risk factors and preventive measures aimed at reducing the most severe toxicities of therapy without compromising cure.

Contributors

All authors contributed equally to the establishment of the Ponte di Legno Severe Toxicities Working Group (STWG). All authors contributed to the Delphi process and are either representing their collaborative acute lymphocytic leukaemia group or have chaired an ad-hoc severe toxicity working group under the STWG, or both. KS chaired the STWG and LAJ coordinated this Review. 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. All authors have access to all the data presented in this Review and LAJ and KS verified all the data.

Declaration of interests

ER reports grants from Pfizer and has been on a data and safety monitoring board for Celgene, outside the submitted work. KS reports personal fees from Jazz Pharmaceuticals, Servier, Amgen, and Medscape, and personal fees and grants from Servier, outside the submitted work. All other authors declare no competing interests.

Acknowledgments

The study presented in this Review was funded by the Danish Cancer Society and the Danish Childhood Cancer Foundation. The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and final responsibility to submit for publication. We thank all who have contributed to discussions, scrutinising of literature, development of working documents and initial definitions. All contributors are mentioned in the appendix (pp 2–3). All authors have access to all the data presented in this Review.

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