Chapter 12
Late Effects of Therapy of Acute Lymphoblastic Leukemia

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Abbreviations

AAP	asparaginase-associated pancreatitis
ALL	acute lymphoblastic leukemia
BMD	bone mineral density
CCSS	Childhood Cancer Survivor Study
CIPN	chemotherapy induced peripheral neuropathy
CNS	central nervous system
CTCAE	United States National Cancer Institute Common Terminology Criteria for Adverse Events
HD	high dose
hSCT	hematopoietic stem cell transplantation
MetS	metabolic syndrome
MRI	magnetic resonance imaging
MTX	methotrexate

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NMDAR	N-methyl-D-aspartate receptor
ON	osteonecrosis
OS	overall survival
PEG	polyethylene glycol
PRES	posterior reversible encephalopathy syndrome
PTWG	Ponte di Legno Toxicity Working Group
QoL	quality of life
RCT	randomized controlled trial
SLS	stroke-like syndrome
SOS	sinusoidal obstruction syndrome
STFS	severe toxicity free survival
TBI	total body irradiation
TE	thromboembolism
UNL	upper normal limit

Introduction

The best contemporary chemotherapy for childhood acute lymphoblastic leukemia (ALL) yields 5-year overall survival (OS) rates above 90%, which reflects intensified chemotherapy with treatment stratification directed by the mutational landscape of the leukemic clone and the early response to chemotherapy, better use of conventional antileukemic agents, introduction of molecularly targeted drugs, refined strategies for hematopoietic stem cell transplantation (hSCT), and improved supportive care [1, 2]. However, the high cure rate has come at a price [3–5]. All patients encounter severe acute toxicities during therapy, mostly infections but frequently also severe organ dysfunctions [6], and a significant proportion of survivors are burdened by late effects [7]. Whereas high-throughput, cost-effective technologies have revolutionized our insight into the mutations driving ALL pathogenesis and drug resistance [8], our biological understanding of late effects remains limited, thus hindering further personalized therapy to reduce their incidence. This partly reflects their individual relative rarity (requiring multi-institutional and international research), complex pathogenesis, and uncertain associations with potential risk factors, including germline DNA variant profiles [9, 10].

The Toxicity Scenario

Toxicities have traditionally been defined and graded according to the United States National Cancer Institute Common Terminology Criteria for Adverse Events [11], although some research groups (e.g., St. Jude LIFE [12] and the PTWG [13]) have adapted these to better address toxicities relating to childhood cancer in general or to childhood ALL patients specifically. Several of the late effects are long-term consequences of acute toxicities that occurred during chemotherapy (e.g., insulin-dependent diabetes pancreatitis) [14], while others may emerge after discontinuation of therapy (e.g., osteonecrosis or second cancers) [15, 16].

Pattern of Late Effects

Parallel to changes in antileukemic therapy, the pattern of late effects has changed dramatically over the last decades [7]. Hematopoietic stem cell transplantation (hSCT) and prophylactic and therapeutic cranial irradiation are used less frequently with the latter being completely eliminated in many first-line protocols [17], while the use of glucocorticosteroids (including dexamethasone) and asparaginase has been intensified. Consequently, second cancers in the central nervous system (CNS), cognitive disturbances, reduced growth, and hypothalamic/pituitary dysfunction have become rarer, while osteonecrosis, musculoskeletal dysfunction, and endocrine disturbances have become more frequent (Fig. 12.1). The long-term impact on late effects of the more recently introduced immunotherapies, including chimeric antigen receptor modified T cells, is yet to be determined [18, 19].

Many late effect studies only address subsets of patients, one or a few specific late effects, are cross-sectional, or emerge from single institutions with limited study power. Since survival has become the most likely outcome for a child with

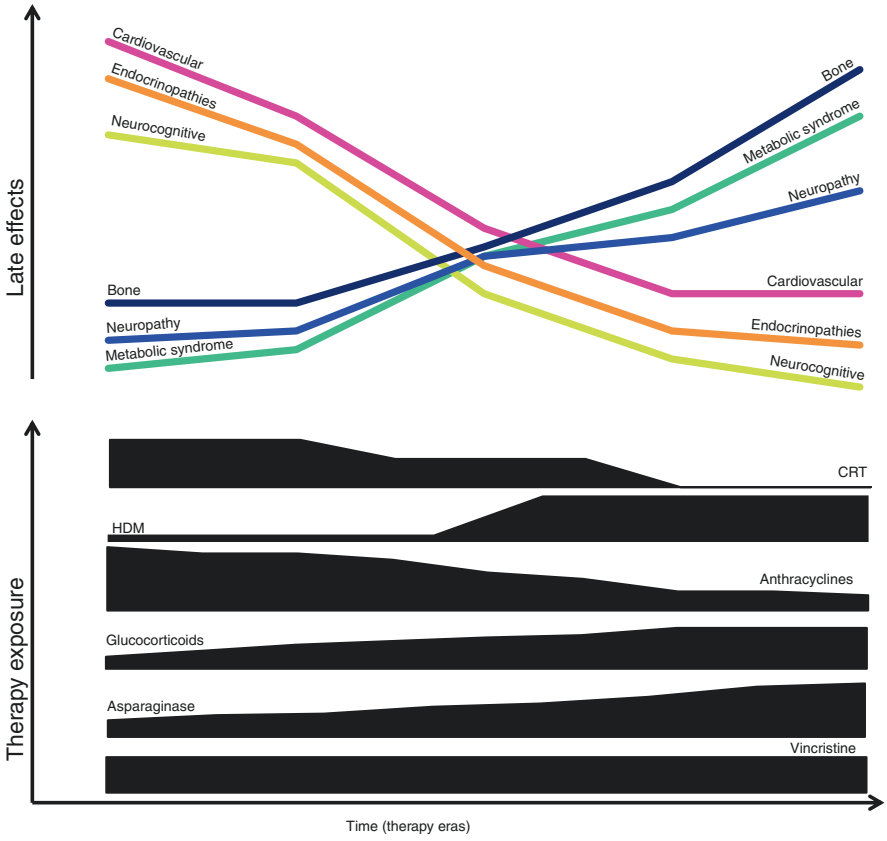

Fig. 12.1 Temporal changes in therapy exposure and late effects. *CRT* cranial radiation therapy, *HDM* high-dose methotrexate

ALL, systematic, longitudinal follow-up is of paramount importance. However, only a few very large (>10,000 patients), multi-institutional childhood cancer survivor cohort studies exist such as the US Childhood Cancer Survivor Study (www.ccss.stjude.org), the Nordic Adult Life after Childhood Cancer in Scandinavia (www.aliccs.org), and the British Childhood Cancer Survivor Study [20].

Severe Toxicity Free Survival

As survival rates are high for children with ALL, there is a need for supplementing traditional outcome measures (OS and EFS with events encompassing resistant disease, relapse and second malignancies) with severe and persisting late effects to reflect not only survival but also the cost of cure. Until recently, no international consensus have existed to guide a standardized capture of even the most severe late effects. Addressing this issue, the Ponte di Legno consortium, representing 17 major ALL childhood study groups and institutions across North America, Europe, Japan, Taiwan, and Australia, recently published a prioritized list and consensus definitions of 21 severe toxicities proposed to be captured and reported as an integrated part of the outcome evaluation of treatment protocols [21]. The measure of severe toxicity free survival (STFS) focuses on the most serious and objective late effects, while subsequent and more comprehensive (but also more complex) targets should include the lower-grade (equally burdensome), chronic, subjective late effects such as fatigue, pain, self-reported quality of life (QoL), and overall measures of the ability to comply with routine activities of daily living.

Late Deaths

Case-control and cohort studies of childhood cancer survivors have shown that even 15 years after cessation of therapy, the majority of deaths are caused by cancer or its treatment and only approximately 20% by non-neoplasia-related causes with an absolute excess risk of 6.2 per 1000 person-years [22, 23]. Importantly, for 5-year survivors of childhood ALL, the 15 years cumulative risk of recurrence has dropped from 10.2% in the 1970s to 2.2% for patients diagnosed in the 1990s parallel to the refinement and intensification of treatment, whereas the risk of death from health-related causes has stayed almost unchanged at 2–3% [24]. Accordingly, the life expectancy gap for 5-year ALL survivors compared to controls has dropped from 14.7 years in 1970–1979 to just 8 years in more recent years.

Second Malignant Neoplasm

In nationwide population- and register-based Nordic studies, the overall standardized incidence rate of second primary cancers is 3.3 times that of the background population, being increased in all age groups, even after the age of 70 years. Still,

the reported frequency of second cancer (SMN) after ALL therapy is in the order of only 2% and dominated by second myeloid neoplasia. Importantly, the frequency of SMN is generally underestimated due to insufficient duration of follow-up. Thus, in a large international study of 642 childhood ALL survivors with SMN, 80% of hematological malignancies (3/4 being therapy-related acute myeloid leukemia (AML) and myelodysplasia (MDS)) occurred within 5 years from diagnosis of ALL, 80% of CNS tumors (except meningiomas) and sarcoma had occurred 12 years from diagnosis, while 16 years had to pass before 80% of carcinomas had been diagnosed (and even later for non-thyroid carcinomas) [16]. Patients with CNS tumors or therapy-related myeloid neoplasia had 5-year overall survival rates in the order of only 20%, but in contrast to CNS tumors, myeloid neoplasias demonstrated clear improvement in survival over time (34.1% ± 6.3% for AML and 48.2% ± 10.6% for MDS diagnosed after 2000) and were furthermore positively associated with the lag time from ALL diagnosis (10% drop in death hazard per year of interval). Importantly, 5-year survival rates were above 90% for patients with meningioma, Hodgkin lymphoma, thyroid carcinoma, basal cell carcinoma, and parotid gland tumor and were almost 70% for non-Hodgkin lymphoma, i.e., very similar to their primary counterparts. Development of solid tumors is associated with cyclophosphamide exposure, whereas AML/MDS are associated with topoisomerase II inhibitor exposure and higher starting doses of methotrexate/mercaptopurine for maintenance therapy. The role of germline DNA variants is only beginning to emerge.

The Overall Burden of Antileukemic Therapy

According to the largest, prospective, clinical follow-up study among childhood ALL survivors, the 30-year-old survivor will have experienced an average of 5.7 recurring or chronic health events compared to only 2.0 in matched controls (at age 50 years, these figures have risen to 16.7 and 9.3, respectively) [7]. As the long-term morbidities we see today echo protocols used decades ago, further prospective, longitudinal research is needed to reveal the true burden of current childhood ALL regimens.

Endocrine Late Effects

Risk of hospital contact for endocrine disorders has been evaluated among >30.000 1-year Nordic childhood cancer survivors, revealing that survivors of leukemia and CNS tumors are the ones at highest risk [25]. The leukemia survivors were at significantly elevated risk for hospital contact relating to pituitary disorders, testicular dysfunction, and other disorders of puberty, reflecting therapy regimens using substantial amounts of cranial and testicular irradiation, which is becoming abandoned today.

Growth

Cranial and spinal irradiation causes the highest risk for reduced final height, as spinal irradiation inhibits vertebral growth directly resulting in reduced sitting height (larger impact with younger age), whereas cranial irradiation compromises growth via the hypothalamic-pituitary axis resulting in growth hormone deficiency, precocious puberty, and hypothyroidism [26]. Height reduction after cranial irradiation is dose-dependent and most consistently reported after doses ≥24 Gy, whereas no lower safe threshold has been determined [27]. Similarly, growth hormone deficiency has been reported more consistently after treatment with >24 Gy cranial irradiation than after doses of 18 Gy. The odds rate of clinical short stature below −2 SD is proportional to the extent of irradiation being 2.8 (95% confidence interval (CI) 1.9–4.0) for spinal irradiation, 2.9 (CI 2.0–4.2) for cranial irradiation, 8.0 (CI 3.7–17.4) for total body irradiation (TBI) in association with hSCT, and 10.6 (CI 4.25–25.3) for cranial irradiation and TBI [28].

Growth suppression from chemotherapy alone is frequently seen during treatment but is typically followed by subsequent catch-up growth and achievement of adult height within the normal range [26, 27, 29]. Risk factors associated with reduced final height in both irradiated and non-irradiated survivors include female gender and younger age at diagnosis [28, 29]. Importantly, most studies of final adult height reflect protocols used during the 1970s–1990s, and follow-up of more recently treated patients is needed.

Thyroid Dysfunction

TBI and craniospinal irradiation with scatter to the thyroid gland can cause hypo- and, more rarely, hyperthyroidism. Although the risk of hypothyroidism 15 years from ALL diagnosis is reported at only 1.6% (CI 1.1–2.1), the rate is significantly increased compared with siblings [30]. Importantly, survivors treated with cranial irradiation or chemotherapy only do not seem to be at increased risk of thyroid dysfunction [27, 30, 31].

Metabolic Syndrome

Although the applied definitions vary, several studies have reported increased rates of obesity, disproportional alterations in body composition (sarcopenic obesity), hypertension, dyslipidemia, and metabolic syndrome (MetS) among childhood ALL survivors [27, 29, 32–34]. One of the largest studies with 784 ALL survivors found MetS in 33% of adult survivors [35]. When compared to matched community controls ($N = 777$), survivors had a higher risk of MetS (relative risk [RR] 1.43, 95% [CI] 1.22–1.69), hypertension ([RR] 2.43, 95% [CI] 2.06–2.86), dyslipidemia ([RR]

1.40, 95% [CI] 1.23–1.59), obesity ([RR] 1.47, 95%[CI] 1.29–1.68), and insulin resistance (1.64, 95%[CI] 1.44–1.86). Risk factors include female gender, cranial irradiation, and older age at evaluation [33, 35]. The dysmetabolic effects of cranial irradiation is likely mediated by hypothalamic-pituitary dysregulation of leptin sensitivity and growth hormone deficiency [27, 32, 33]. Although radiotherapy is gradually being omitted from frontline childhood ALL protocols, it has been replaced by intensified glucocorticosteroid therapy and extended asparaginase exposure, thus replacing one risk factor for MetS by others [32, 36].

Corticosteroids can alter substrate oxidation and energy expenditure by suppressing growth hormone and inducing leptin resistance [27, 32, 37]. L-asparaginase reduces insulin secretion and plasma insulin levels while increasing insulin resistance, thereby acting synergistically with corticosteroids. In addition, asparaginase can cause acute pancreatitis (AAP) ultimately leading to insulin-dependent diabetes (type 3c). In a Nordic ALL cohort of 1285 patients exposed to 30 weeks of pegylated asparaginase, 6.8% developed AAP of whom 8% had persisting need of insulin therapy at a median follow-up of 4.6 years [38, 39]. In a study from the St. Jude Lifetime cohort including 1044 survivors with mean age at follow-up of 33.97 years, 7.5% were found to have type 2 diabetes mellitus (T2DM) compared to 3.8% in matched controls [40]. In that study, body mass index (BMI) $\geq$30 kg/m^2, older age, and drug-induced diabetes mellitus during ALL therapy were all associated with T2DM. Since dysmetabolic adverse effects generally emerge early during ALL therapy and furthermore are modifiable, they should be targeted throughout therapy and follow-up. There has been a lack of randomized clinical trials testing dietary and physical interventions to prevent or reduce MetS [41]; however such studies are now being performed.

Puberty and Fertility

In a large US-Canadian study of almost 11,000 5-year survivors of childhood cancer treated in 1970–1999 (median follow-up of 8 years (IQR 4–12)) and 4000 sibling controls, 38% of survivors reported a pregnancy, and 83% of these reported at least one live birth compared to 62% and 90% among siblings, respectively [42]. The most significant drugs associated with reduced likelihood of pregnancy were alkylating agents.

Male

Cranial irradiation disturbs the hypothalamic-pituitary-gonadal axis and can lead to pubertal disturbances, while antileukemic agents, especially alkylators, may cause testicular damage with the germinal epithelium being more sensitive than Leydig cells [43]. Thus, biopsy studies have found spermatogonia in only 50% of

seminiferous tubuli and pathological sperm concentrations in patients with normal or only slightly reduced sex hormone levels [44, 45]. The most detrimental effects with azoospermia, Leydig cell insufficiency, and need for testosterone replacement are seen following direct testicular irradiation in cases of testicular relapse or as part of TBI [46]. Cranial irradiation does not seem to cause a higher frequency of oligospermia or azoospermia when compared to chemotherapy only [47].

In survivors treated with chemotherapy only, Leydig cell function is rarely impaired, and survivors generally achieve normal puberty [44] with levels of gonadotropins and testosterone being similar to those of controls [46]. Cyclophosphamide is one of the most gonadotoxic antileukemic agents used; however risk of impaired sperm quality is considered to be low in survivors exposed to <8 mg/m^2 [46, 47]. Survivors treated with high doses of cyclophosphamide and/or testicular radiation have small chances of fathering a child unless using stored semen samples. However, for the remaining male ALL survivor population, risk of impaired fertility seems to be comparable to the background population [48]. According to the International Guideline Harmonization Group, survivors treated with one or more potentially gonadotoxic agents should be made aware of risk of testosterone deficiency and impaired spermatogenesis, those treated with irradiation exposing the testes to 12 Gy or more should be monitored for pubertal development, and those being exposed to cyclophosphamide and/or testicular radiation exposure should be offered semen analysis [49].

Females

In general, female ALL survivors who were premenarchal at diagnosis should expect to maintain ovarian function and achieve normal puberty (>90% achieve menarche within normal age range) [50, 51], unless exposed to high-dose alkylating agents and/or irradiation exposing the ovaries [52, 53].Thus, spinal irradiation with exposure of the ovaries and alkylating agents significantly increases the risk of premature ovarian failure and impaired fertility [54, 55]. One self-report study of fertility among 182 long-term ALL survivors indicated reduced fertility if treated with cranial radiation at any dose around the time of menarche [48]; however, ovarian dysfunction was not clinically validated. Two Danish studies examined ovarian function 10 years apart in 100 survivors of childhood cancer (47 with ALL) and found that survivors in spite of a reduced antral follicle count (AFC) in their mid-20s had a high chance of preserved ovarian function at least until their mid-30s, with more than 50% having achieved at least one live birth [56, 57]. However, as survivors generally had significantly lower AFC than age-matched controls, survivors may have a shortened reproductive span.

Risks relating to contemporary ALL therapy without spinal irradiation and with reduced doses of alkylating agents are more uncertain. Only a few clinical studies have investigated ovarian function in post-pubertal survivors treated with chemotherapy and no spinal irradiation at pre-pubertal age, finding subtle signs of ovarian

insufficiency in some [58] and normal function in others [59]. International guidelines recommend systematic evaluations for signs indicating risk of premature menopause in post-pubertal survivors treated with potentially gonadotoxic chemotherapy and/or irradiation potentially exposing the ovaries [52].

Bone Morbidity

Osteoporosis

Although a few, small studies have reported little or no risk of osteoporosis among ALL survivors [60, 61], nearly all studies show that bone mineralization density (BMD) is frequently reduced. Risk factors include leukemia-related low BMD present at diagnosis [27], inadequate diet including lack of D-vitamin and calcium, low level of weight-bearing physical activity, intensive glucocorticosteroid and high-dose methotrexate exposure, and/or cranial irradiation. If patients fail to achieve expected normal peak bone mass during and following cessation of therapy, it is likely that reduced BMD and risk of osteoporotic fractures persist throughout life. Thus, a large St. Jude Lifetime Cohort study of 845 survivors found osteoporosis and osteopenia in 6% and 24%, respectively, at 31 years of age [62]. High-dose (≥24Gy) cranial or craniospinal irradiation was the strongest predictor of reduced BMD, while the cumulative dose of glucocorticoids was associated with significantly lower BMD in female survivors only. Importantly, 67% of those with osteoporosis improved by one or more BMD categories over a period of median 8.5 years, although the only provided advice consisted of physical activity and vitamin D and calcium supplementation. The clinical significance of low BMD has been emphasized in a prospective study of 186 ALL patients, finding that 16% had vertebral fractures at diagnosis and 26% had at least one low-trauma bone fracture within 4 years from diagnosis [63]. Significant risk factors predicting low-trauma fractures included corticosteroid exposure, low BMD z-score at diagnosis, and vertebral fracture at diagnosis. By 6 years follow-up, nearly 25% of patients had persistent vertebral deformity following vertebral fracture, more frequently affecting older children and cases with most severe vertebral collapse. Importantly, 23% had no or only partial vertebral body reshaping. Adults with vertebral deformity have been shown to be at high risk for chronic back pain and reduced mobility, but similar studies among childhood cancer survivors are lacking.

Osteonecrosis

Osteonecrosis (ON) is one of the most common and debilitating toxicities with potentially long-term impact on daily function and QoL. A marked rise in the incidence of ON coincided with the introduction of dexamethasone for delayed

intensification. The overall incidence of clinical ON is reported as high as 17.6%, however with varying frequencies reflecting the proportion of adolescents (who are at highest risk), the antileukemic treatment regimens, and also the methodology for toxicity capture [64]. Prospective studies including only symptomatic cases report incidences of 10–16% among patients aged 10–15 years and 15–20% among patients aged >15 years [64]. Of note, the interval between diagnosis of ALL and of ON increases with older age [15]. The most common joints affected are knees (45–88% of cases) and hips (35–67%), followed by ankles (13–44%), shoulders (13–24%), and elbows (3–15%). Affection of multiple joints is seen in 29–90% of cases [64]. The underlying pathology of ON is poorly understood but is thought to reflect hypoperfusion caused by microvascular clotting (intraluminal obliteration), increased marrow pressure (extraluminal obliteration), and direct damage to the endothelial and smooth muscle cells in the nurturing arteries, caused by chemotherapy agents and systemic inflammation. In addition, chemotherapy, such as glucocorticoids, is thought to have a direct toxic effect on osteocytes and compromising normal osteogenesis. The strongest risk factors for ON is female sex and adolescent age, but also occurrence of hyperlipidemia [65], glucocorticoid exposure (cumulative dose and exposure time), cranial and gonadal irradiation, and race. The significance of obesity, BMI, and leukemic bone infiltration is so far insufficiently validated [64, 66]. Trials implementing shortening of continuous exposure to dexamethasone found a reduced occurrence of ON, however also significantly better EFS among the high-exposure patients with high incidence of ON [64]. Many ON cases occur after cessation of therapy, not least in the older patients [15], but few studies have addressed long-term incidence and impact of ON on QoL among childhood ALL survivors. One self-report study among 20-year survivors found a cumulative incidence of 0.2% in individuals aged <10 years at diagnosis and of 2.8% in patients ≥16 years at diagnosis, compared to 0.03% among siblings [66]. Studies among adults with ON indicate that lesions involving ≥30% of the articular surface are the most likely to cause joint collapse with need of arthroplasty surgery [67]; however long-term follow-up studies among children are lacking.

Teeth

Long-term dental abnormalities such as tooth agenesis, arrested root development, microdontia, and enamel dysplasia can occur in as many as 34–94%, not least among survivors treated with TBI and/or cranial irradiation and with age below 5 years being a significant risk factor [68, 69]. Even very low radiation doses (1–3 Gy) can permanently damage ameloblasts and halt tooth development, and cranial radiation may also cause craniofacial developmental disturbances due to deficient mandibular development. Still, few studies have addressed the long-term dental outcome among survivors treated with chemotherapy only. In one study of 111 survivors not receiving irradiation, 28–45% was found to have microdontia,

disturbed root development, or enamel hypoplasia [70]. Diagnosis at or before 5 years of age and cumulative doses of anthracyclines >120 mg/m^2 (potentially reflecting the impact of severe mucositis and altered oral microbiome) were strongly associated with more severe dental aberrations, whereas survivors diagnosed with ALL above the age of 5 years experienced caries in their permanent dentition.

Neurotoxicity

Neurocognitive Effects

Significant proportions (16–50%) of childhood ALL survivors have impaired neurocognitive performance across a range of domains, which is associated with reduced chance of educational achievements and employment [71–73]. Neurocognitive impairment is predominantly found in non-verbal domains such as attention, visual perception, memory, and concept formation, while verbal skills are mostly spared [74]. Cranial irradiation has the most significant impact on brain morphology and neurocognitive outcome. Although there is a positive correlation between the dose of irradiation and degree of neurotoxicity, no lower safe limit has been defined. Furthermore, the neurotoxicity is enhanced, when irradiation is combined with neurotoxic chemotherapy, probably reflecting radiation-induced increased blood-brain barrier permeability. Even with decreasing use of irradiation, late neurotoxicity is reported in up to 10–30% of survivors [74, 75]. A meta-analysis of 10 studies, including a total of 509 survivors treated with chemotherapy only, concluded that compared to controls, at mean 8 years from diagnosis, survivors had moderate deficits in several neurocognitive domains including working memory, information procession speed, and fine motor functioning, with intelligence being most affected (IQ deficits of 6–8 points) [76]. Neurocognitive performance has rarely been evaluated longitudinally; however one study found that the pattern of affected neurocognitive domains changed over time and that degree and type of neurocognitive impairment at the end of therapy could not predict later impairment [77]. The three most neurotoxic chemotherapeutic agents responsible for late neurocognitive deficits are cytarabine, corticosteroids, and methotrexate given intrathecally or as high dose intravenously. The exact underlying pathophysiological pathways are not fully understood. Animal models have suggested that nucleoside analogs have a presynaptic depressant effect in neuronal tissues in addition to a direct toxic and apoptotic effect [74]. Antifolate disruption of normal folate physiology within the CNS causes direct neurotoxicity, including demyelination. Younger age at treatment is associated with Late effects of therapy neurotoxicity Neurotoxicity increased neurotoxicity of both CNS-directed chemotherapy and irradiation, potentially reflecting disturbed myelination in the maturing brain [73]. Intrathecal liposomal cytarabine could be less neurotoxic than methotrexate [78]. Corticosteroids are thought to exert deleterious effects on hippocampus, acting synergistically with the excitatory neurotransmitters which are seen elevated in cases of acute neurotoxicity.

Abnormalities are found in up to 78% of survivors, when systematic cerebral imaging is performed [74]; however no substantial longitudinal studies exist that describe persistence versus resolution over time. Findings include calcifications, atrophy, leukoencephalopathy, focal perfusion defects, and changes in glucose metabolism. Radiologic findings sometimes parallel histological abnormalities including demyelination, necrosis, and astrocytosis and can correlate with cerebral spinal fluid biomarkers of brain injury. However, correlations between imaging findings and neurocognitive outcome have in general not been found, although one study of 190 ALL survivors did find a significant association between screening-positive leukoencephalopathy during therapy and poorer neurocognitive performance at 5 years follow-up [79].

Peripheral Neuropathy

Chemotherapy-induced peripheral neuropathy (CIPN), experienced by most patients during treatment, is mainly caused by vincristine (VCR), and other antileukemic and supportive care drugs (such as antifungal azoles, increasingly used over the last decades) can modulate VCR pharmacokinetics and thus enhance both central and peripheral neurotoxicities. VCR exerts its antineoplastic effect by binding to mitotic β-tubulin, thereby disrupting mitotic microtubule aggregation in leukemic cells, leading to mitotic arrest and cell death. One β-tubulin subtype is found exclusively in neuronal axons, and the neurotoxic effect of VCR stems, in part, from the drug binding to these, causing demyelination [80], axonal degeneration, and compromised axonal transport [81]. Chemotherapy-induced peripheral neuropathy involves both small and large fibers resulting in sensory, motor, and autonomic nerve dysfunction. Sensory symptoms include hypo-, hyper-, and paresthesia, thermal hypoesthesia, and neuropathic pain with the affected area presenting with a "stocking and glove" type distribution, reflecting how longer axons are affected first. Motor dysfunction presents as distal muscle weakness and atrophy, while autonomic nerve dysfunction can result in orthostatic hypotension, constipation, and sexual dysfunction. At the time of therapy cessation, around 30% will have clinical findings, such as depressed tendon reflexes [82]. With time, symptoms resolve in most patients; however persisting neuropathy can be found among survivors even years off therapy, and some studies have suggested that CIPN can emerge several years after cessation of chemotherapy, known as the coasting effect [83, 84]. Two to 10 years post therapy, neuropathic symptoms are reported among 30–60% of survivors, while clinical signs of neuropathy are found in 10–41%, nerve conduction abnormalities (mixed motor and sensory) in 15–68% [82, 83, 85–89], and both clinical and electrophysiological findings in 16% [88]. There seems to be poor correlation between self-reported symptoms and objective findings. Except for the association between higher cumulative doses of VCR and risk of long-term CIPN

[88], other potential risk factors for CIPN, such as age, gender, and presence of CNS leukemia, are not reported consistently. Impact of CIPN on motor performance and QoL is present in some studies [85, 86], while absent in others [88, 89], emphasizing that larger prospective follow-up studies are warranted.

Cardiovascular Late Effects

Increased risk of long-term cardiac disease, characterized mainly by dilated or restrictive cardiomyopathy, increased afterload, and arrhythmia, has primarily been associated with anthracycline exposure with cumulative doses ≥300 mg/m^2 [90], although no lower safe dose has been established [91]. Cardiomyocytes have limited capacity to regenerate and are thus vulnerable to the cytotoxic effect of anthracyclines, which can lead to apoptosis and ventricular wall thinning. Heart failure is reported in 1–16% of survivors treated with high-dose anthracyclines, although even with the low doses currently used, evaluation of true risk will require long-term follow-up [92]. The Swiss Childhood Cancer Survivor Study (CCSS) assessed self-reported cardiovascular disease among 511 5-year survivors diagnosed between 1976 and 2005 and found an overall odds ratio for cardiovascular disease of 1.9 (CI 1.3–2.8) and for heart failure of 13.9 (CI 1.8–107.4), when compared to siblings [93]. In contrast, a recent St. Jude study of 911 30-year survivors found cardiomyopathy in only 3%, which was comparable to the rate among community controls [7], likely reflecting the lower dose of anthracycline exposure in that study (mean 105 mg/m^2). Importantly, cardiac abnormalities may progress with time, not least after higher cumulative doses of anthracycline but also after low dose exposure [94, 95]. Additional risk factors for cardiotoxicity include TBI (as low as 5 Gy cardiac irradiation), young age at diagnosis, female gender, and presence of hypertension, obesity, and endocrinopathies [90]. Potential cardioprotective strategies include continuous anthracycline infusion (versus bolus), but long-term validation of the benefit hereof is lacking. Co-administration of the iron-chelating agent dexrazoxane, which prevents formation of free radicals, has been associated with fewer and less severe cardiac abnormalities on echocardiography 5 years post therapy without compromising EFS and may represent a useful future strategy to reduce long-term cardiac morbidity in the subset of children with ALL for whom anthracyclines are needed to ensure cure [90]. The antileukemic effect of anthracyclines as a single drug is well-established; however it is unclear whether and to which extent use of anthracyclines in contemporary multi-drug ALL protocols improves outcome. A 2014 Cochrane review found no evidence from randomized controlled trials (RCTs) to favor the use of anthracyclines in ALL therapy; however, as pointed out by the authors, this could be due to low power and short follow-up in the review, and results from ongoing and unpublished RCTs are awaited [96].

Pulmonary Late Effects

Symptomatic pulmonary late effects, including obstructive and restrictive ventilatory defects and impaired diffusion capacity, are rare except following TBI and high-dose alkylating agents in the setting of hSCT [97–99]. Patients exposed to chemotherapy only have been shown to have slight, subclinical, restrictive ventilatory insufficiency, being associated with younger age at treatment and more intensive protocols that include higher cumulative doses of anthracyclines, cytarabine, and cyclophosphamide [100]. However, for these survivors, lung function is generally within normal range [98].

Immune Reconstitution

Chemotherapy-induced dysfunction of humoral and cellular immune function (including leuko-, neutro-, and lymphopenia, hypogammaglobinemia, and abnormal levels of lymphocyte subsets and natural killer cells) is generally thought to resolve within 6–12 months from therapy cessation. Some studies have found immune deficits several years later; however no larger studies with long follow-up exist. Normalization of cell counts occurs before serum immunoglobulin levels, reflecting a longer recovery phase for B-cell function [101]. Several studies have reported a correlation between younger age at diagnosis and degree of immune deficiency during follow-up. A significant proportion of survivors lose pre-existing immunity (e.g., against measles, mumps, rubella, VZV) [102]. Revaccination does not restore immunity in all; however even subtherapeutic levels of antibodies have been shown to offer some protection. There is consensus to revaccinate transplanted survivors; however, no international guidelines exist regarding revaccination of non-hSCT survivors. An association between chemotherapy-induced microbial dysbiosis and immune dysregulation has been reported in recent, smaller studies, indicating a role of the microbiome in both impaired immune function and increased inflammation [103]. The prevalence of long-term immune deficiencies, not least B-cell dysfunction, may increase second to the intensified chemotherapy and wider use of immunotherapy [104]. Research assessing long-term outcome will be key to the understanding of this field.

Cellular Aging

In addition to the well-characterized organ-specific late effects, survivors are at risk for less uniformly defined conditions including moderate cognitive dysfunction, reduced muscle strength, and poor exercise tolerance, resulting in frailty – a state of reduced physiological reserve and a predecessor of chronic disease and early death [105]. The overall pattern of morbidity in childhood ALL survivors mimics the

aging phenotype, however appearing decades before expected among survivors [106]. The highly complex aging process at a cellular level is still poorly understood; however nine tentative hallmarks of aging include genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication [107]. Chemotherapy has been found to accelerate aging, through epigenetic alterations, DNA damage, reduced telomere length, and cellular senescence [108–110]. Few studies have investigated these hallmarks in childhood cancer survivors; however, both shortened telomere length, senescence, and chronic inflammation (which can both induce and result from cellular senescence) have been reported among childhood leukemia survivors, who were found to have a cellular phenotype similar to that observed in controls who were two to three decades older [111–113]. There is no gold standard when estimating age at the cellular level, since this field is still exploratory. However, emerging research may uncover shared underlying cellular mechanisms leading to frailty and age-related disease across several organs and risk profiles. Such findings could facilitate development and testing of interventions (senolytics), aiming to reduce the overall treatment-related burden among survivors.

Leukemia Predisposition

Recent research has identified several germline mutations in genes that play a critical role in hematopoiesis and lymphoid development, many of which are also frequently somatically mutated in ALL, such as *RAS*, *TP53*, *PAX5* [114, 115], *ETV6* [116, 117], *RUNX11* [118], *IKZF1* [119] and *DDX41* [120], which align with the findings of high subtype concordance in familial cases of ALL [121]. Combined, these syndromes may account for 5% of ALL cases, and more are expected to emerge in parallel with the growing number of patients being germline DNA sequenced and with an increasing understanding of the continuum between germline and acquired mutations.

Several of these syndromes are dominated by their non-malignant phenotype, including Down syndrome, ataxia telangiectasia and Nijmegen breakage syndrome, Recklinghausen neurofibromatosis, Noonan syndrome, constitutional biallelic mismatch repair syndrome, and Fanconi anemia, although not all have been diagnosed at the time ALL emerges. The most common ALL prone syndrome is Down syndrome, accounting for 2–3% of all childhood ALL cases [122]. It has been associated with excessive risk of acute toxicity [123], including treatment-related mortality, but long-term follow-up studies to map their late effects are lacking.

In general, the impact of ALL predisposing germline DNA variants on acute and late effects is poorly explored, but a few (*TP53*, *ETV6*, and *RUNX1*) seem associated with an increased risk of SMN [124, 125]. Thus, any patient with unusual, severe acute toxicities and/or SMN should be explored for an underlying leukemia-prone syndrome [126].

Common Germline DNA Variants

Multiple variants in germline DNA have been associated with the pharmacology of antileukemic agents, including the risk of toxicities [9, 14, 127], but their individual hazard ratios are generally low (<2.0), the variants are rare, or they lack replication in independent patient cohorts. Thus, except for *TPMT* and *NUDT15* homozygous low-activity variants, treatment adaptation according to host DNA polymorphisms has so far not been implemented in childhood ALL therapy. As the *CEP72* TT genotype has been associated with an increased risk of peripheral neuropathy, the St. Jude Children's Research Hospital is currently exploring if reduced VCR dosing in patients with *CEP72* TT will reduce their risk of acute and long-term neuropathy without increasing their risk of relapse (www.clinicaltrials.gov ID: NCT03117751).

Furthermore, the international Ponte di Legno Toxicity Working Group is now collecting deep phenotypes of several acute toxicities (e.g. osteonecrosis, thromboembolism, and neurotoxicity with many hundreds of cases of each) to associate phenotypes with germline DNA variants [14] for which polygenic risk scores may identify DNA profiles that define patients for whom future antileukemic therapy should be individualized to avoid unacceptable short- and long-term toxicities.

Patient and Society

Danish population- and register-based studies have shown that compared with the background population, survivors of childhood leukemia leave their parental home at the same age range as their peers and have similar educational choices and partner at the same rate [128–130].

The work situation of parents during and immediately following cancer treatment of their child and the work situation of the childhood cancer survivors are significantly affected. Parental socioeconomic status is anticipated to influence education and labor market affiliation among childhood cancer survivors the same way as in their peers, but no study has thoroughly explored the issue. Bearing this in mind, a systematic review of 35 eligible papers revealed that hematological childhood cancers had a substantial impact on parent socioeconomic situation including disruptions in parental employment, particularly among mothers [131].

Whereas some countries provide full coverage of childhood cancer survivors through taxation-based health-care systems (e.g., most European countries and Canada), others primarily have a private insurance system (e.g., the USA), which may limit access to insurance and health care for adult survivors of childhood cancer [132, 133].

Although the social welfare and health insurance system of the surrounding society may affect the socioeconomic profiles of childhood ALL survivors, many studies across different countries have shown significant impact of childhood leukemia treatment on long-term socioeconomic outcomes.

A recent Canadian study, including more than 3900 childhood cancer survivors, showed significantly lower earnings compared to the background population [134]. In another cohort of 2844 adult survivors or childhood hSCT from the USA, South America, Europe, Asia, and Australia/New Zealand, unemployment rates persisted to be high at all attained ages [135]. Finally, a nationwide questionnaire study from the British Childhood Cancer Survivor Group (~10,000 childhood cancer survivors) showed that survivors were less likely to work than a control cohort with an odds ratio of 0.89 (95% CI, 0.81–0.98) [136].

Quality of Life (QoL)

Consensus measures of QoL for survivors of life-threatening disease are difficult to establish and furthermore prone to individual perceptions of the imagined future as well as the surrounding society's view on these individuals, which can influence both perceptions of and actual relationships, work, income, and daily life. Thus, QoL is a construct dwelling on other concepts that has no absolute beginning and no end in time or impact. Accordingly, one should observe the QoL critically and be cautious not to make too strong conclusions based on the available data. That being said, QoL survey studies generally indicate that ALL survivors have worse or equivalent health-related QoL compared with the background population [137]. The overall quality of life is typically influenced by treatment protocol and a number of phenotypic characteristics in parents and the patient [138].

However, risk factors for poor health-related QoL among childhood ALL survivors, including severity of late effects, disfigurement due to treatment, educational problems, and insecurity in establishing intimate relationships, are reported with wide variability.

Conclusion and Future Research

The currently obtained cure rates of 90% or more for childhood ALL are one of the most impressive successes of modern medicine, naturally leading to an increased focus on late effects. Exploration and prevention of significant treatment-related morbidity have become more relevant than ever before. Of equal importance is the implementation of a standardized reporting of consensus-defined severe toxicities that will allow an objective comparison of the burden of late effects across treatment protocols, thereby supplementing the traditional objective outcome measures.

Although EFS and OS are quite similar across the ALL study groups, there may be wide differences in the distribution of unacceptable acute, persisting, and late occurring morbidity. ALL trials generally register acute toxicities to assess the acute treatment burden, but with diverse focus on specific toxicities, which may influence the reported frequencies. The recent PTWG consensus definitions of relevant

toxicities have simplified and even encouraged a unified capture strategy, allowing both powerful association studies, comparisons across treatment strategies, and long-term outcome of acute toxicities [13, 14, 139]. These efforts can ultimately result in novel treatment strategies with reduced toxicities. However, late effects are in general not captured in a consensus-based fashion, if captured at all. Thus, we are missing systematic and reliable registration of the long-term sequelae and the true chronic burden of treatment when assessing therapy outcome. The first steps toward solving this are to create and implement a consensus strategy for outcome analyses that integrate persistent, serious toxicities with the traditional cure rate measures. Subsequent international consensus on reporting these outcomes will allow reliable comparison of diverse treatment strategies, focusing not only on the traditional five events and OS but in addition the frequencies of unacceptable toxicities that are associated with significant costs for both the individual and society. As a starting point, the Ponte di Legno Toxicity Working Group has developed the measure of STFS which can facilitate reliable comparison of the frequency of unacceptable toxicities (e.g., osteonecrosis requiring joint replacement or renal failure requiring dialysis or kidney transplant) across treatment protocols [21]. The STFS measure is now beeing quantified in several large (>1000 patients) cohorts.

Although most long-term survivors can obtain an education, manage a job, and establish a family, including having children, many will be burdened by significant late effects requiring life-long medical attention. In addition, survivors could be at risk of premature aging (e.g., dementia or atherosclerosis), but little is known, since almost none was cured just a few decades ago. Thus, there is a need for systematic follow-up of the survivors, including identification of risk factors for adverse outcomes that can be integrated into future individualized therapy.

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