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Adverse effects of treatment in childhood acute lymphoblastic leukemia: general overview and implications for long-term cardiac health

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Abstract

Survival of childhood acute lymphoblastic leukemia (ALL) is one of the greatest medical success stories of the last four decades. Unfortunately, childhood ALL survivors experience medical late effects that increase their risk of morbidity and premature death, often due to heart and vascular disease. Research has helped elucidate the mechanisms and trajectory of direct damage to the heart from treatment exposure, particularly to anthracyclines, and has also contributed knowledge on the influences of related chronic conditions, such as obesity and insulin resistance on heart health in these survivors. This article summarizes the key issues associated with early morbidity and mortality from cardiac-related disease in childhood ALL survivors and suggests directions for interventions to improve long-term outcomes.

Keywords

acute lymphoblastic leukemia; cardiac; epidemiology; healthy lifestyle; insulin resistance; late effects; obesity; pediatric; survivorship

Childhood acute lymphoblastic leukemia incidence, survival & related chronic disease

Acute lymphoblastic leukemia (ALL) is the most common cancer among children, comprising 25–30% of the annually registered cases of cancer among children aged 0–14 years in the UK [201] and the USA [1], with an annual incidence rate of approximately 3.9 per 100,000 children. Multimodal therapy and enhanced supportive care have resulted in 5 year survival rates that approach 90% for those diagnosed at 14 years of age and younger [2]. Thus, there has recently been a steady increase in the number of adult survivors of

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childhood ALL [3]. For example, it is estimated that 1 in 715 young adults in the UK are survivors of a childhood malignancy [4] and 15% of survivors between the ages of 20 and 39 years were treated for childhood ALL [5]. Unfortunately, there are consequences to cure; childhood ALL survivors are at an increased risk of chronic morbidity and early mortality, often from adverse cardiovascular events that are related to both treatment exposures and associated behavioral causes [6,7]. This article represents a focused qualitative review, rather than a systematic review or comparative analysis of studies, of the literature on factors related to cardiac disease risk and associated outcomes in those treated for ALL as children.

Treatment for childhood ALL

Acute lymphoblastic leukemia reflects a heterogeneous group of diseases that are characterized by variability in immunophenotype, cytogenetics and clinical features [8]. Specific approaches to therapy for childhood ALL have changed over time; however, the treatment phases continue to involve 2.5 to 3 years of induction, early CNS prophylaxis, intensification and maintenance. Three or four chemotherapeutic agents are used initially: a glucocorticoid, vincristine, L-asparaginase and/or an anthracycline. Children who fail therapy are often candidates for allogeneic stem cell transplantation [9]. CNS prophylaxis or treatment for apparent CNS disease previously required cranial or craniospinal radiation. However, to reduce neurotoxic sequelae, modern therapeutic modalities usually use early intensive intrathecal therapy with methotrexate, hydrocortisone and cytarabine rather than cranial radiation [2]. Today, CNS-directed radiation is reserved for children who do not respond to triple intrathecal therapy, although many adult survivors of childhood ALL received cranial radiation as part of their routine treatment. Intensification (consolidation) is designed to eliminate residual leukemia and includes a readministration of the initial therapy 24 weeks to 3 months following remission. To enhance continuation of remission, children with ALL receive maintenance chemotherapy for 2–2.5 years following consolidation. Weekly doses of methotrexate and daily mercaptopurine are standard, with intermittent pulses of vincristine and a glucocorticoid administered in most settings [9].

The consequences of cure

Although usually effective in children, ALL therapy is toxic and has the potential to damage or interfere with function in many organ systems. Children who survive ALL and its treatment experience have significantly elevated risk for second malignancies [10,11] and early mortality [12] from a variety of causes, particularly cardiac events [13,14]. Cardiac complications in long-term survivors may result from treatment-related damage to the myocardium and vascular structures [15,16], and/or from damage to other organ systems. Suboptimal organ system function may contribute to long-term cardiac disease risk, or interfere with abilities to maintain a lifestyle consistent with optimal cardiac health.

Recent reports from the Childhood Cancer Survivor Study (CCSS), a large follow-up epidemiologic study in the USA and Canada, indicate that, in addition to increased risk of death from heart disease [14], leukemia survivors have elevated risk of myocardial infarction (hazard ratio [HR]: 3.3; 95% CI: 1.2–8.6), congestive heart failure (HR: 4.2; 95% CI: 2.3–7.4), and pericardial disease (HR: 2.6; 95% CI: 1.2–5.5), relative to a sibling comparison group [17]. ALL survivors also have increased risk of obesity [18], endocrine and metabolic disorders [19–22], muscle weakness [23–25], neurosensory impairments [26] and neurocognitive deficits [27]. These chronic conditions, alone or in combination, have the potential to contribute to poor cardiac health outcomes.

It should be noted that there are limitations in the literature on long-term adverse effects of treatment in children who have survived ALL. Although strong methodological studies based on registry data are available to describe hard outcomes such as mortality [28] and

second cancers [29], only smaller, usually single institution clinical studies are available for many chronic disease outcomes. These studies may overestimate the prevalence of chronic disease as a result of a selection bias [30], and rarely include very-long-term ALL survivors because these children often lose contact with their original pediatric hospital once they reach adulthood [31]. The more robust sources of data describing medical outcomes among childhood ALL survivors are those derived from large cohort studies in the USA [32,33] and the UK [34]. However, these epidemiologic studies rely heavily on self-report and may not capture conditions with symptoms not severe enough to prompt a visit to a clinician [35]. Nevertheless, the results from these epidemiologic studies are consistent enough to allow confidence in the profile of late effects described in this report.

Early mortality

The increased risk of early death among survivors of childhood cancer has been clearly documented. In the British Childhood Cancer Survivor Study (BCCSS), which included 17,981 5-year or longer survivors of childhood cancer diagnosed between 1940 and 1991, the number of deaths were ascertained by linking survivors with the National Health Service Central Registration. With 370,025 person years of follow-up from 5-year survival, there were 3049 deaths. The standardized mortality ratios (SMR) – the number of observed deaths divided by the number of expected deaths in a given population – were 3.9 (95% CI: 3.7–4.1) from all causes excluding recurrence, 7.3 (95% CI: 6.7–8.0) from second cancers and 3.5 (95% CI: 2.9–4.2) from cardiac-related disease [36]. Similarly, in the CCSS cohort, 20,483 5-year or longer survivors of childhood cancer diagnosed between 1970 and 1986 were evaluated by death certificates and the USA National Death Index. With 337,334 person-years of follow-up, the cumulative mortality of the cohort was 18% at 30 years from diagnosis. For childhood ALL, the SMR from all causes was 9.5 (95% CI: 8.8–10.2), with most excess deaths attributable to second malignant neoplasms (SMR: 14.7; 95% CI: 11.8–18.1), cardiac events (SMR: 4.2; 95% CI: 2.3–6.9) or pulmonary disease (SMR: 4.2; 95% CI: 1.7–8.6) [13,14]. A population-based Nordic study of 13,711 persons diagnosed with cancer before 20 years of age between 1960 and 1989, and surviving at least 5 years, also reported an elevated SMR from cardiac-related death of 5.8 (95% CI: 4.2–7.6) [13]. Model-based estimates of excess mortality in survivors of ALL indicate an absolute annual excess mortality rate of 1 per 10,000 due to cardiac causes, and a nonrecurrence-related reduction in life expectancy of 3.3 years when compared with the general population [37].

Cardiac outcomes

Survivors of childhood leukemia are at excess risk of developing problems such as heart failure, heart attacks, heart valve abnormalities and inflammation of the heart epithelium long after receiving their cancer therapy [38]. Mulrooney *et al.* reported 30-year cumulative incidences of 4.1% (95% CI: 3.2–5.0%) for congestive heart failure, 1.3% (95% CI: 1.0–1.7%) for myocardial infarctions, 4.0% (95% CI: 3.1–4.9%) for valvular abnormalities and 3.0% (95% CI: 2.1–3.9%) for pericardial disease in 10,367 young adult childhood cancer survivors in the US CCSS cohort [17]. Age-adjusted incidence rates per 10,000 person-years were 9.5 (95% CI: 9.4–10.1) for congestive heart failure, 2.8 (95% CI: 2.4–3.3) for myocardial infarction, 6.4 (95% CI: 5.9–7.1) for valvular abnormalities and 5.8 (95% CI: 5.6–6.4) for pericardial disease. In this same cohort of CCSS survivors, 8.8% were taking medication for hypertension, 5.2% for dyslipidemia and 2.3% for diabetes, compared with rates of 5.7% for hypertension, 4.0% for dyslipidemia and 1.7% for diabetes in a sibling comparison group [39]. In addition, improved long-term survival has increased the demand for heart transplantation in this population. In the UK, 43 out of 52,313 children with cancer diagnosed between 1970 and 2005 were referred for a heart transplant following treatment

for cancer. A total of 35 individuals received a single heart transplant and one had a second transplant [40].

Anthracycline damage to the myocardium

Anthracyclines are a primary culprit in adverse cardiac-related outcomes among childhood ALL survivors. The anthracyclines, particularly doxorubicin and daunomyocin, are used widely to treat pediatric malignancies. These well known cardiotoxic agents are part of the treatment for up to 60% of childhood cancer cases and for nearly all children with ALL [41]. Anthracyclines produce oxygen-free radicals that damage cardiac myocytes [42]; it is believed that resultant loss of myofibrillar content and vacuolar degeneration leads to myocardial necrosis and fibrosis [43]. Over time, the left ventricular wall thins, thereby increasing wall stress and decreasing myocardial contractility [42]. Progressive cardiomyopathy may occur early, within the first year of treatment, or can be delayed, being diagnosed many years following completion of therapy. The risk of disease is dose-dependent [42,44,45], with incidences of congestive heart failure (CHF) reported at 10% or less among patients exposed to cumulative doses of anthracycline less than 500 mg/m² and at 36% for doses exceeding 600 mg/m² [46,47]. In addition, risk of therapy-related CHF is modified by clinical variables such as young age at exposure (younger than 5 years of age), female gender, pre-existing heart disease and concomitant mediastinal irradiation [47–50]. Unfortunately, outcomes following diagnosis of clinical CHF are poor, with reported 5-year overall survival rates of less than 50% [51].

As a result of the established cardiotoxicity, current ALL protocols for children use substantially lower doses of anthracyclines than in previous decades. However, even lower doses may result in unfavorable cardiac outcomes that are not overt CHF, but are still potentially dangerous for survivors as they go through adulthood. In a systematic review, Kremer *et al.* reported a prevalence range for subclinical cardiotoxicity of 0–57.4% among long-term survivors [47]. Frequencies were greater in individuals whose anthracycline dose was higher than 300 mg/m². Several other studies have reported apparent deficiencies at lower doses, particularly when imaging and exercise tests were combined to detect problems. Smibert *et al.* reported an increase in fractional shortening among children 1 year after anthracycline administration [52]. Deficits were related to anthracycline dose in increments greater than 100 mg/m² and were detected with echocardiography, following completion of a submaximal exercise protocol. A study by Hudson *et al.* found that the highest risk for increased afterload and fractional shortening occurred among survivors whose anthracycline doses exceeded 270 mg/m² [53]. Only those who received less than 100 mg/m² did not appear to be at risk for deficits. A recent evaluation of 80 patients who were treated with less than 300 mg/m² demonstrated a decline in ejection fraction over time; however, clinical symptoms were not associated with a decline in measured function [54].

As the well-recognized clinical and therapeutic risk factors do not fully explain the wide interindividual variability in susceptibility to therapy-related cardiac dysfunction, particularly among ALL survivors with low-dose exposure, there are probably some genetic risk factors for the development of therapy-related CHF. Using a candidate gene approach, studies have identified genetic polymorphisms involved in the metabolism of anthracyclines, the myocardial response to the drug, as well as other factors thought to play a role in susceptibility to *de novo* disease, which could place survivors at an increased risk for therapy-related CHF [55,56]. A recent report from the Children's Oncology Group identified a potential association between a polymorphism in carbonyl reductase 3, *CBR3 V244M*, and risk of CHF (odds ratio [OR]: 1.49; *p* = 0.08 for GG vs AA or GA) [57]. The risk was greatest for CHF among survivors exposed to low dose anthracyclines (≤ 250 mg/m²: OR: 6.38; *p* = 0.006), suggesting that functional *CBR3 V244M* polymorphism may impact the

risk of anthracycline-related CHF by modulating intracardiac formation of cardiotoxic anthracycline metabolites.

With longer follow-up of childhood cancer survivors, it has become apparent that even lower cumulative doses of anthracyclines place children at risk for cardiac compromise, suggesting that there may be no safe dose [45]. Recent advances in noninvasive cardiac imaging indicate that there is a growing population of survivors with asymptomatic left ventricular dysfunction who are at risk of late CHF. Newer technologies (three dimensional echocardiography and cardiac MRI) [58,59] provide mechanisms to screen for early disease and set the stage for the development of potential early interventions with the goal of preventing the progression from asymptomatic cardiac dysfunction to clinical CHF [53,60].

Obesity

There is a good amount of robust literature that describes excess weight gain and obesity during and after treatment for childhood ALL [18]. One of the first studies was published by Zee and Chen in 1986 on 414 patients seen at St. Jude Children's Research Hospital (Memphis, TN, USA) [61]. The distribution of BMI in patients, compared with age- and sex-specific population norms, was skewed toward leanness at diagnosis, reached normal levels by the end of treatment, and was higher than normal by 1 year post-treatment. At that time, 35% of patients in the series had BMI values over the 80th percentile. Similarly, Reilly *et al.* followed 98 childhood ALL patients for 3 years post-diagnosis, finding that only 2% of patients had a BMI z-score of 2 or greater at diagnosis compared with 16% at 3 years post-diagnosis [62]. An analysis of 1765 adult survivors of childhood ALL in the CCSS cohort, median age of 23 years (range 18–42), confirms the elevated risk of obesity for many years following ALL, particularly in females and for those treated with cranial radiation [63]. The age- and race-adjusted OR for being obese (BMI >30) in survivors relative to a sibling comparison group (median age: 28 years) was 2.6 for adult females and 1.9 for adult males who were treated with 20 Gy or higher doses of cranial radiation. Withycombe *et al.* recently evaluated 1638 children enrolled in a children's cancer group ALL treatment protocol from 1996–2002 and found that 23% were obese (BMI ≥95th percentile) by the end of treatment (median age: 11.7 years) compared with 14% at diagnosis [64]. Notably, the increased risk of obesity in this study was independent of cranial irradiation. Rogers *et al.* reviewed the prevalence of obese or overweight individuals from 12 studies of childhood ALL survivors published between 1994 and 2001 [65]. The prevalence of obese or overweight individuals ranged from 11–56%; all but two studies observed a prevalence of 24% or higher. Given the current 'epidemic' of obesity in children, obesity rates from these older studies might not seem excessive; however, the high susceptibility to cardiovascular disease among ALL survivors greatly heightens the concern about long-term health and clearly calls for interventions that target modifiable risk factors to improve health profiles.

There are several hypothesized contributing factors to deleterious weight gain in ALL survivors. Treatment factors include steroid-induced energy imbalance, physical inactivity related to chemotherapy-induced neuromuscular impairments [66], parental concerns and behaviors related to their child's nutritional needs during chemotherapy [67] and cranial irradiation [66]. Corticosteroids are believed to be an important contributor to excess weight gain in ALL, perhaps through disruption of normal energy intake and energy expenditure [66]. For example, using a double-labeled water method, Reilly *et al.* documented significantly reduced total energy expenditure in childhood ALL patients relative to matched controls in 20 study pairs [68]. Jansen *et al.* compared energy intake and physical activity among 16 children with ALL and found a significant increase in energy intake and a decrease in physical activity during periods when they were receiving dexamethasone compared with periods when they were not receiving dexamethasone [69]. Additionally, the

mean increase in BMI z-score was 1.1 from diagnosis to the completion of the study (median time: 1.7 years) in the leukemia patients compared with an increase of only 0.2 ($p < 0.05$) in 17 healthy controls.

Endocrine & metabolic disorders

Growth hormone deficiency

In addition to, or in conjunction with, obesity, survivors of childhood ALL, particularly those who were treated with cranial radiation, are at risk of growth hormone deficiency (GHD) and associated metabolic disorders. Prevalence of GHD in cohorts of ALL survivors treated with cranial radiation have been estimated at 53–73% [70,71]. GHD and metabolic disturbances increase cardiovascular disease risk and alter body composition.

Hyperlipidemia, increased carotid intima media thickness, elevated C-reactive protein, elevated homocysteine, reduced lean body mass, increased fat mass and abnormal bone mineral density have all been reported among GHD adults who were treated with cranial radiation for childhood ALL.

It has been consistently documented that the risk for cardiovascular disease and obesity appears to start early in ALL survivors. Taskinen *et al.* evaluated a cohort of 31 adolescent survivors previously transplanted for leukemia ($n = 26$) or nonmalignant hematologic diseases ($n = 5$) [72]. They reported that 12 patients (39%) had metabolic syndrome; a constellation of problems characterized by hyperinsulinemia, dyslipidemia, hypertension and obesity. Nine out of 12 patients with metabolic syndrome (75%) had insufficient growth hormone (GH) response after provocative testing, as opposed to six out of 19 (31%) without metabolic syndrome. In a slightly older group of ALL survivors, Gurney *et al.* reported similar findings [73]. Among the ALL survivors with prevalent untreated GHD, 41% had two or more components of the metabolic syndrome, compared with 23% of those without GHD. Link *et al.* evaluated the association between GHD and cardiovascular disease risk factors in 44 adult survivors of childhood ALL and found significant negative correlations between peak GH response to provocative stimulation and plasma insulin, leptin, total body fat mass and waist circumference to hip circumference ratio (W/H ratio) [74].

Additional evidence documenting adverse cardiovascular health among ALL survivors with GHD has been reported in at least three other studies [75–77]. Talvensaari *et al.* reported a combination of obesity, glucose intolerance, hyperinsulinemia and an abnormal lipid profile among 16% of 50 childhood cancer survivors who were treated with cranial radiation, with no evidence of a similar prevalence among normal controls [77]. This constellation of problems was associated with reduced spontaneous GH secretion, as well as additional features of the metabolic syndrome, such as higher systolic blood pressure, plasma glucose and serum triglyceride levels. Brennan *et al.* evaluated 32 survivors of childhood ALL who were treated with cranial radiation and reported that 21 patients were either GH-insufficient or had overt GHD [75]. Absolute lean mass, measured with dual x-ray absorptiometry, was significantly reduced and leptin concentrations were significantly increased among ALL survivors when compared with a group of healthy controls. BMI, fat mass and leptin concentrations were highest among survivors with GHD. Jarfelt *et al.* reported an increase in body fat and a tendency towards an abnormal lipid profile in 47 adult survivors of childhood ALL [76]. In their cohort, peak GH secretion was positively correlated with fat-free mass and high-density lipoprotein (HDL) cholesterol, and inversely correlated with body fat, leptin levels and low-density lipoprotein cholesterol.

Insulin resistance

Metabolic disorders are not limited to ALL survivors who develop GH insufficiency or to those who were treated with cranial radiation. Large waist circumference is also a strong risk

factor for insulin resistance [78–80], and obesity and metabolic syndrome are associated with elevated risk for cardiovascular disease and diabetes [81,82]. Elevated BMI was strongly correlated with insulin resistance in a study of childhood ALL patients off treatment for 9 months or longer [83], and among long-term survivors. In an evaluation of 75 adult survivors of childhood ALL with a mean age of 30 years and a mean time off treatment of 25 years [73], 60% of subjects treated with cranial irradiation had two or more components of the metabolic syndrome, as did 20% of those who were not exposed to cranial radiation. These findings are consistent with another study that compared 50 long-term childhood cancer survivors, including 28 with ALL, with 50 sex- and age-matched healthy controls [84]. Relative to controls, survivors had significantly higher weight and body fat, higher fasting glucose and insulin levels, and significantly decreased HDL-cholesterol. A combination of obesity, hyperinsulinemia and low HDL-cholesterol was seen in eight (16%) of the survivors (four received cranial radiation and four did not), but in none of the controls [84].

Oeffinger *et al.* evaluated insulin resistance and other cardiovascular disease risk factors in 118 young adult survivors of childhood ALL (median age: 23 years) and found that both men and women had significantly higher insulin resistance as measured by the homeostatic model assessment of insulin resistance index, whether or not they were treated with cranial radiation, relative to controls [85]. Insulin resistance is emerging as a concern for long-term ALL survivors, as is diabetes. Diabetes, hypertension and cardiovascular events were evaluated in 1089 participants of the Bone Marrow Transplant Survivor Study (mean age: 39 years), with acute leukemia being the most common diagnosis (33%) [86,87]. After adjusting for age, sex, race and BMI, the OR for diabetes among survivors of allogeneic transplantation relative to a sibling comparison group was 3.65 (95% CI: 1.82–7.32). A recent report from the CCSS found that adult childhood cancer survivors (n = 8599) were more likely than siblings to take medication for diabetes (OR: 1.7; 95% CI: 1.2–2.3), dyslipidemia (OR: 1.6; 95% CI: 1.3–2.0) and hypertension (OR: 1.9; 95% CI: 1.6–2.2) [39].

Muscle weakness & neurosensory impairments

Muscle weakness

Obesity, GHDs and insulin resistance are accompanied by corresponding muscle strength deficits in children with ALL, and among survivors of childhood ALL [23,88]. Evidence from several cross-sectional studies suggests that muscle strength deficits occur in children during treatment for ALL and that these deficits may persist long after the end of treatment. Gocha Marchese *et al.* reported decreased knee extension and ankle dorsiflexion strength among a group of 5–14 year old children during treatment for ALL when compared with age- and gender-matched controls [89]. Another study reported both hand grip and overall strength deficits in children who were at least 1 year post-treatment for ALL [90]. In female adolescent and young adult survivors of childhood ALL, Hovi *et al.* reported lower extremity strength deficits [23], and Talvensaari *et al.* reported decreased trunk muscle torque and overall work capacity [84]. In a study that included 75 adult survivors of childhood ALL, Ness *et al.* found significant deficits in knee extension strength when survivors were compared with population-based normative values [88]. Among the studies mentioned earlier, those that evaluated body composition also documented a correlation between muscle strength deficits, muscle mass and/or muscle cross-sectional area [23,88].

The associations between less muscle mass, strength deficits and previous treatment with radiation are fairly conclusive [88]; however, those that have attempted to identify a particular chemotherapy agent or dose to explain the deficits offer fewer answers. Most studies have been small or at a single institution, where participants were treated with homogeneous chemotherapy regimens, making it difficult to detect an association between a

specific chemotherapeutic agent and/or dose and muscle mass or strength deficits. A few studies suggest that dexamethasone may cause greater risk for poor muscle outcome when compared with prednisone [91,92]. Mitchell *et al.* reported a greater number of steroid-related toxicities, including myopathy and weight gain, among children who received dexamethasone than among those who received prednisolone [91]. Dexamethasone has also been implicated in studies of cognitive sequelae where motor function was a required part of the cognitive task. Waber *et al.* reported decreased performance among children treated with dexamethasone when compared with those who received prednisone on the structural accuracy portion of the Rey–Osterrieth Complex Figure Test [92]. This copying task requires both motor control and adequate hand strength. Deficits were not associated with methotrexate dose or cranial radiation. The authors concluded that dexamethasone may be responsible for the poor outcomes because of its effect on the CNS; however, structural brain abnormalities, peripheral sensation and hand grip strength were not evaluated. It is possible that the poor motor outcomes on this neuropsychological test were associated with deficits in muscle strength rather than deficits in actual neurological output.

Peripheral neuropathy

Acute axonal peripheral neuropathy has been documented in children during treatment for ALL [93]. This distal polyneuropathy is initially painful, affecting both sensory and motor functions. Bed rest and immobility during painful neuropathy contributes to muscle wasting and can be accompanied by a loss in ankle and wrist dorsiflexion range of motion. Reinders-Messelink *et al.* reported mild deficits in vibration perception, reduced amplitude action potentials in median, ulnar and fibular sensory nerves and mild muscle weakness in 11 children as they progressed through eight treatments of 1.5 mg/m² of vincristine for induction and intensification therapy [94]. Delayed recovery after initial injury is expected; however, there are some reports of persistent problems [95]. Harila-Saari *et al.* evaluated motor evoked potentials in 32 children following treatment for ALL and found prolonged latencies in both upper and lower extremity axons when responses were compared with an age-, gender- and height-matched control group [96]. Wright *et al.* reported 10° differences in ankle dorsiflexion range of motion when they compared ALL survivors at least 1 year after therapy to age- and gender-matched normal controls [97]. Previous reports have dismissed this acute effect of chemotherapy as transient; however, recent findings indicate that, although not readily apparent, long-term neuropathy may be present in some survivors [98]. Ramchandren *et al.* evaluated 37 survivors of childhood ALL 8–18 years of age and reported motor nerve conduction study abnormalities in 29.7% [98]. In another study by Harila-Saari *et al.*, the authors evaluated somatosensory evoked potentials to detect signs of nerve lesions in the peripheral nerves of 31 childhood ALL survivors at least 2 years after therapy [99]. When compared with age- and gender-matched controls, ALL survivors had prolonged somatosensory evoked potential latencies from the median nerve at the brachial plexus and spinal cord, and from the tibial nerve at the knee, spinal cord and cortex. Deep tendon reflexes and motor skills were impaired in a third of the children examined.

Peripheral neuropathy, sensory loss and range of motion limitations during treatment for ALL are associated with vincristine and possibly with intrathecal methotrexate. Vincristine, a vinca alkaloid, binds with tubulin and blocks polymerization into microtubules; the objective being to arrest mitosis in metaphase. This mechanism also affects axonal transport [100]. Structural changes in the cytoskeleton of large myelinated axons and accumulation of neuro-filaments in dorsal sensory ganglion neurons have been documented in animal studies [101]. Reports also indicate that vincristine can unmask underlying hereditary neuropathies [102], and that a drug interaction between vincristine and an antifungal azole may exacerbate a mild neuropathy [103–105]. Animal and human studies indicate that the rate of vincristine clearance is associated with age, perhaps accounting for higher rates of

vincristine neurotoxicity among adolescents and young adults [106,107]. Harila-Saari *et al.* suspect that symptoms of spinal demyelination may be due to intrathecal methotrexate administration [99]. In addition, Waber *et al.* reported dexamethasone-related motor output problems in children treated for ALL [92].

Balance

Perhaps compounding the effects of muscle weakness on physical activity and related cardiovascular health, children diagnosed with ALL demonstrate problems with balance immediately after diagnosis and during and after treatment. Reinders-Messelink *et al.* reported an increased prevalence of balance deficits among 17 children with ALL soon after diagnosis, during treatment, and 46 weeks from diagnosis when compared with population norms and to an age- and gender-matched comparison group [108]. Galea *et al.* [109], Wright *et al.* [90,110] and Hartman *et al.* [111] reported deficits in performance on functional evaluations of both static [109] and dynamic [90,110,111] balance among children who were at least 1 year post-treatment for ALL when compared with age- and gender-matched controls. Quantitative balance deficits among adult survivors of childhood ALL have not been reported in the literature; however, 39% of leukemia survivors in the CCSS indicate that they have been told by a physician that they have long-term neurological impairments, with 7.3% reporting a specific problem with balance [7].

Fitness

Direct cardiac damage, obesity, endocrine dysfunction, metabolic abnormalities, reduced muscle strength, poor sensation and impaired balance all potentially contribute to poor cardiac fitness among ALL survivors. Even among ALL survivors who do not have overt clinical evidence of cardiovascular disease, mild problems with myocardial contractility, large body size, muscle weakness and poor sensation, and impaired balance may make it difficult to move efficiently [90,97,110]. GHD is associated with fatigue [112] and insulin resistance with altered energy requirements [113] in other populations. These factors also probably contribute to the high rates of poor cardiac fitness observed among ALL survivors. For example, Warner *et al.* reported a 10.8 ml/kg/min difference in maximum oxygen uptake values per volume over time (VO₂ maximum) between female survivors of childhood leukemia and a 7.7 ml/kg/min difference in VO₂ maximum between male survivors of childhood leukemia (age range: 7–19 years at the time of evaluation), when compared with siblings [114]. De Caro *et al.* evaluated exercise capacity among another group of childhood cancer survivors (n = 84; age range: 7–19 years) exposed to anthracyclines, chest irradiation, or both, and compared their exercise response to healthy controls [115]. The male cancer survivors in this study, asymptomatic at the time of exercise testing, had lower peak oxygen uptake than their same-age counterparts. In a recent meta-analysis that evaluated peak oxygen consumption during graded exercise testing among 102 childhood leukemia survivors 7–19-years of age, the authors found that peak VO₂ values in survivors were almost 6 ml/kg/min lower than 99 healthy controls during graded exercise testing [116]. Fitness studies among childhood ALL survivors mostly been limited to participants still in childhood or adolescence; however, it appears that fitness deficits persist for survivors into their adult years as well. Among 75 adult survivors of childhood ALL, self-reported cardiopulmonary fitness levels were significantly lower than expected [88]. Mean estimates of peak oxygen uptake were 8.60 mg/kg/min (p < 0.001) lower than expected among males and 4.62 mg/kg/min lower than expected among females [117].

Neurocognitive impairment

Treatment for childhood ALL can damage the CNS with resultant declines in cognitive function. Neurocognitive impairment in survivors is associated with important life outcomes

into adulthood, such as lower educational achievement, unemployment, lower likelihood of marrying and lack of independent living [118]. Although this phenomenon was originally described for children who were exposed to cranial radiation, subsequent studies have demonstrated that children treated only with chemotherapy are also at risk for neurocognitive deficits [119–123].

Histological changes associated with cranial radiation therapy include subacute leukoencephalopathy, mineralizing microangiopathy and cortical atrophy, most often becoming apparent several months to years after treatment [124–126]. White matter is especially vulnerable to radiation exposure, and white matter damage correlates with severity of functional impairment [127]. Neurobehavioral impairment after cranial radiation therapy is observed in the domains of working memory, distractibility, fine motor coordination, visual–spatial ability and somatosensory functioning [128–133]. These cognitive impairments are associated with significantly reduced intelligence quotient and academic difficulties [130]. Deficits can first emerge several years after diagnosis [121] and are most severe in those treated at an age younger than 6 years [129] and among females [134].

Both intrathecal methotrexate and intrathecal cytarabine are associated with acute neurotoxicity. Stroke-like syndromes, myelopathy, encephalopathy and seizures have been reported in childhood ALL survivors [135,136]. These agents also have long-term effects. Systemic administration of methotrexate appears to intensify both acute and late toxicities of other CNS-directed therapies. Among children with ALL treated on a nonradiation-containing protocol, acute neurotoxic events occurred significantly more often among those children who received intravenous methotrexate in addition to intrathecal methotrexate during consolidation therapy [137]. Genetic polymorphisms of 5,10-methylenetetrahydroreductase, important in methotrexate metabolism, may explain individual variation in function [138]; other inherited factors are also being examined [139].

The independent effect of glucocorticoids on the CNS among ALL survivors is difficult to study owing to confounding by other concurrent neurotoxic therapies. Studies in noncancer populations suggest that exposure to corticosteroids contributes to cognitive difficulties. For example, children with asthma demonstrate diminished verbal memory during short-term prednisone therapy [140]; neonates randomized to dexamethasone instead of placebo for lung disease of prematurity have lower intelligence quotients and worse visual motor integration [141]; and healthy male volunteers administered 10 days of hydrocortisone treatment display impairments in visual–spatial memory [142]. Murine studies indicate that higher dexamethasone doses are associated with worse neurotoxicity [143]. Dexamethasone does not seem to confer greater risk of impairment than prednisone [144–146].

Mild neurocognitive deficits may influence health knowledge and understanding among ALL survivors. For example, 70 young adult survivors of childhood ALL, frequency matched by age, sex and BMI to 210 population-based healthy controls, were evaluated for their knowledge of the symptoms of heart attack and stroke using questions from the 2002 Behavior Risk Factor Surveillance Study [147]. A remarkable deficit in basic knowledge of symptoms was found in the ALL survivors and their knowledge was considerably worse than that of the population comparison group. For example, 24% of survivors, compared with 6% of controls, incorrectly answered a question about pain and discomfort in the arms and shoulders as a symptom of heart attack (OR: 5.2; 95% CI: 2.3–11.6). For stroke, 34% of survivors, compared with 8% of controls, incorrectly answered a question identifying sudden trouble walking, dizziness or loss of balance as a symptom (OR: 6.6; 95% CI: 3.1–13.7). In addition, a high proportion of adult survivors of childhood cancer have significant knowledge deficits about their past diagnosis and cancer treatment, including exposure to

cardiotoxic therapy [148]. There appears to be an important gap in health knowledge and a need for health education related to cardiovascular disease risks among childhood ALL survivors.

Potential modification of poor cardiac outcomes

Many late effects of cancer treatment may not be modifiable. However, protection of the myocardium from anthracycline damage may be possible and appropriate screening and early intervention may allow for early treatment designed to limit progression of existing myocardial damage. In addition, the difficulties associated with adopting a healthy lifestyle experienced by ALL survivors owing to their therapy-induced chronic conditions can probably be addressed with tailored interventions designed to modify many of the risk factors for cardiovascular disease.

Certain analogs of doxorubicin and daunomyocin and liposomal anthracyclines that appear to have decreased cardiotoxicity with equivalent anti-tumor activity, have been explored in clinical trials in an attempt to reduce initial toxicities [41]. Dexrazoxane, a chelator of intracellular iron, has been shown to be the most promising cardioprotectant for use in conjunction with anthracyclines [149]. In a randomized trial of children diagnosed with ALL, those who received dexrazoxane prior to doxorubicin were less likely to have cardiac injury during treatment, as measured by cardiac troponin levels [150]. Several trials have since demonstrated that it is possible to use dexrazoxane for prevention of cardiomyopathy without compromising disease-related outcomes [149]. The role of pharmacologic intervention for prevention of CHF in asymptomatic survivors with left ventricular function is being explored [151]. A randomized placebo-controlled study using angiotensin-converting enzyme (ACE) inhibitors demonstrated that while ACE inhibitors did not prevent decline in ventricular function, they were able to provide some respite in the form of afterload reduction [152].

Patients who received anthracyclines require ongoing monitoring for late-onset cardiomyopathy using serial noninvasive testing (i.e., echocardiogram, electrocardiogram) and physical examination [60]. The frequency of echocardiograms can range from annually to every 5 years, depending on the level of risk. Pregnant women previously treated with anthracyclines should be closely monitored, as changes in volume during the third trimester could add significant stress to a potentially compromised myocardium [86]. ALL survivors should be monitored for obesity, endocrine and metabolic disorders and be considered for appropriate medical interventions. Those exposed to CNS toxins (essentially all childhood ALL survivors) should undergo neuropsychological testing during childhood and the data should be used to identify appropriate educational accommodation and remediation. Additional specific recommendations for surveillance, based on age and therapeutic exposure, are delineated within the Children's Oncology Group long-term follow-up guidelines available on the survivorship guidelines website [202].

Heart-healthy lifestyles should be actively encouraged for all survivors, including implementation of a regular exercise program and an appropriate diet. Physical activity levels among ALL survivors are not optimal [153–156], and two recent small randomized trials of traditional exercise and physical activity interventions during treatment did not result in significant improvements [157,158], primarily owing to poor compliance with the prescribed program [157]. The dietary modification included in one intervention during maintenance chemotherapy for children with ALL was unsuccessful [158], and evidence suggests that young adult survivors of childhood ALL adhere poorly to published dietary guidelines [159].

Expert commentary

Survivors of childhood ALL possess unique physiologic, behavioral and psychological characteristics that require tailored behavioral interventions to meet their needs. Innovation is necessary with an approach that accommodates phenotypic late effects in both the content and structure of the intervention. For example, the content of an exercise intervention must address issues such as neuromuscular deficits, which may inhibit confidence and the ability to be physically active. The content of a dietary intervention should take into account poor dietary habits that may have originated during the long treatment course.

Interventions should be conducted early and might be best accomplished during adolescence when independent patterns of health behaviors are beginning to emerge. Intervention content will have to account for important developmental issues. These young people are in a transition to more independent management of their health, and still interacting with parents who, from clinical experience, can (for logical reasons) be somewhat overprotective. In addition, given the documented subtle deficits in attention and executive function in survivors of childhood ALL, interventions should include contacts that are brief, but frequent and focused.

Structurally, any interventions for this population must address their geographic dispersion. As treatment and follow-up services for childhood cancer are almost always provided at tertiary care specialty centers, families usually travel large distances for their care. The use of web-based interventions that incorporate telephone modalities and perhaps social media outlets may offer an opportunity for more survivors to participate.

Five-year view

In the next 5–10 years, new technologies and biomarkers to identify early markers of cardiac disease in children undergoing treatment for ALL will probably be identified or better developed. Trials of new or existing agents to prevent and remediate myocardial damage will begin to mature, providing information for clinicians as they design a new generation of clinical trials to cure disease and minimize toxicity. These technologies will also be applied to identify subclinical disease in survivors of ALL and allow early intervention with new and known cardio-protective medications. Both pharmaceutical and tailored web-based behavioral interventions to remediate contributing chronic conditions among ALL survivors are currently being developed, and early results should be available to inform guidelines for providers of long-term ALL survivor care.

Key issues

- Following a diagnosis of childhood acute lymphoblastic leukemia (ALL), 5-year survival is approaching 90%; as such, the survivor population throughout the developed nations is growing substantially.
- Evaluation of long-term survivors indicates that anthracycline-induced cardiotoxicity effects persist many years after treatment.
- Multiple other chronic conditions associated with treatment for childhood ALL may contribute to poor cardiac health.
- Studies to identify the best technologies for uncovering subclinical cardiac disease and allow for early medical interventions are ongoing.
- Interventions to prevent and to remediate cardiac disease and to optimize behaviors that promote a heart-healthy lifestyle are needed.

- Behavioral health interventions need to take into account the unique medical, physical, cognitive and geographic needs of ALL survivors.

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- of considerable interest

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