Invited review

Hande Kizilocak¹, MD, M. Fatih Okcu², MD, MPH.

¹Istanbul University, Cerrahpaşa Faculty of Medicine, Department of Pediatric Hematology-Oncology, Istanbul, Turkey
²Department of Pediatrics, Section of Hematology-Oncology, Baylor College of Medicine, Texas Children’s Hematology and Oncology Centers, Houston, TX, USA

*Correspondence to: Hande Kizilocak, Istanbul University, Cerrahpaşa Faculty of Medicine, Department of Pediatric Hematology-Oncology, Istanbul, Turkey, phone: 323-361-5798, email: handekizilocak2@yahoo.com

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<table>
<thead>
<tr>
<th>Abbreviations</th>
<th>Description</th>
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<tbody>
<tr>
<td>HSCT</td>
<td>Hematopoietic stem cell transplantation</td>
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<tr>
<td>CNS</td>
<td>Central nervous system</td>
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<td>ALL</td>
<td>Acute lymphoblastic leukemia</td>
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<td>EFS</td>
<td>Event-free survival</td>
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<td>OS</td>
<td>Overall survival</td>
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<td>CRT</td>
<td>Cranial radiotherapy</td>
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<td>CCSS</td>
<td>The Childhood Cancer Survivor Study</td>
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<td>SN</td>
<td>Secondary neoplasm</td>
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<td>AML</td>
<td>Acute myeloid leukemia</td>
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<td>QOL</td>
<td>Quality of life</td>
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<td>IT</td>
<td>Intrathecal</td>
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<td>RT</td>
<td>Radiotherapy</td>
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<td>CHF</td>
<td>Congestive heart failure</td>
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<td>BMI</td>
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<td>GH</td>
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<td>TBI</td>
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<td>BMD</td>
<td>Bone mineral density</td>
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<td>ON</td>
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Late Effects of Therapy in Childhood Acute Lymphoblastic Leukemia Survivors

Abstract

Survival rates for children with acute lymphoblastic leukemia (ALL) have increased with remarkable success over the past 50 years. The optimal use of antileukemic agents in cooperative group protocols, central nervous system directed treatment, improvements in supportive care, and recognition of clinical, biological, and treatment response characteristics that identify patients at lower or higher risk of treatment failure have improved 5-year event-free survival rates to more than 85% and 5-year overall survival rates to more than 90%. Consequently characterizing the occurrence of long-term late effects has become increasingly important. Successful treatment of ALL is associated with increased risk of adverse outcomes such as late mortality, second malignancies, neurological, cardiac, endocrine and social/psychological disorders. In recent decades, cooperative groups in the United States and Europe have provided essential insights into the long-term effects of ALL therapy providing direction for screening recommendations and new approaches for reducing late morbidity and mortality. Current frontline protocols continue to examine ways to decrease amount and intensity of therapy to reduce late effects whereas survivorship studies attempt to predict such adverse effects precisely and develop targeted prevention and treatment strategies.

Introduction

Over the past 50 years remarkable success in treatment of childhood acute lymphoblastic leukemia (ALL) has been achieved through modifications of chemotherapy and radiotherapy within cooperative group trials and improved supportive care (1). As a result it became soon clear that long-term survivors of childhood ALL have been placed at increased risk for severe and life-threatening therapy-related late effects (Summarized in Table 1). In recent decades, cooperative groups in the United States and Europe have prioritized development of treatment regimens aiming to reduce the risk for late effects without adversely impacting the cure rates. While traditional and molecular epidemiology studies are pursued to describe the growing spectrum of late effects seen in survivors, development of interventions to prevent and treat late effects associated with significant morbidity and mortality has become an active area of research. In this manuscript we present a comprehensive review of the epidemiology and burden of common late effects observed in childhood ALL survivors including second malignancies, neurological, cardiac, endocrine and social/psychological disorders.

Evolution of ALL therapy

The optimal use of antileukemic agents in cooperative group protocols, central nervous system (CNS) directed treatment, improvements in supportive care, and recognition of clinical, biological, and treatment response characteristics that identify patients at lower or higher risk of treatment failure have improved 5-year event-free survival (EFS) rates to more than 85% and 5-year overall survival (OS) rates to more
than 90% (2), when few children survived fifty years ago (3).

After the initial single agent (aminopterin) and two drug combinations (mercaptopurine and methotrexate) produced breakthrough “temporary remissions” in the 1940’s and 1950’s (4,5) Pinkel and colleagues developed a multi-phase ALL treatment protocol in 1962 (6). This included remission induction, CNS-directed therapy [cranial irradiation and intrathecal (IT) methotrexate], intensification (consolidation), and continuation treatment using combination of 6-mercaptopurine and methotrexate. This success stimulated the development of similar clinical trials worldwide, with two pivotal studies in the 1970s (7,8). First the Berlin-Frankfurt-Munster group introduced “Protocol II”, treatment which specified a reinduction phase (essentially repetition of the initial remission induction therapy, currently termed delayed intensification). Secondly Dana-Farber Cancer Center incorporated weekly high-dose asparaginase into their multiagent protocol.

Simultaneously in the 1970s the use of prophylactic craniospinal radiation was the next major step in the evolution of treatment of ALL (9). While only 2% of children with ALL have overt leukemia in the spinal fluid at diagnosis approximately half will experience a CNS relapse if given systemic therapy alone. Craniospinal radiation led to several detrimental late effects including cognitive impairment, growth arrest and panhypopituitarism in most of the patients (10,11). To reduce these adverse outcomes first spine radiation was eliminated followed by reductions in the cranial radiation dose from 24 Gy to 18 Gy and then eventually to 12 Gy. Thus in the 1980s cranial radiotherapy (CRT) became a standard part of the effective multimodality therapy to treat and prevent CNS leukemia (12). But many children were still left with neurocognitive impairment that manifested as impaired processing speed, global intellectual function and executive function. Ultimately a number of randomized studies have shown that IT chemoprophylaxis with methotrexate or “triple” therapy with cytarabine, hydrocortisone and methotrexate could replace CRT with no impact on long-term outcome for most patients (13). Only those patients with overt CNS disease at diagnosis and certain ALL subtypes [T-cell ALL with hyperleukocytosis or the presence of overt CNS leukemia (CNS3 status)] with high risk for CNS failure are today treated with CRT.

Hematopoietic stem cell transplantation (HSCT) has been used with curative intent for high risk or relapsed ALL beginning in the late 1970’s. HSCT recipients are exposed to chemotherapy and/or radiation before HSCT (for management of primary cancer), at HSCT, and after HSCT (for graft versus host disease and/or relapse of primary cancer) leading to early or late morbidity. Severe or life-threatening chronic health conditions were reported in 40% of the transplant patients associated with premature mortality (14).

Ongoing recent investigational targeted therapy approaches include treatment with monoclonal antibodies such as blinatumomab and chimeric antigen receptor (CAR) T cells. This area of research may ultimately guide the development of effective therapies with a lower risk of normal tissue injury. Yet long-term outcomes of children treated with these novel agents are unknown because of the shorter follow-up time.

As summarized above, evolution of childhood ALL therapy has been a long and exciting process in time. While it represents one of the major successes of cancer
history with steady increases in survival over decades a long list of associated late effects has been realized and will be described herein.

**Late mortality**

For childhood ALL patients 5-year OS estimates, including patients who are salvaged after relapse are today >90% (3). The Childhood Cancer Survivor Study (CCSS) cohort is a multi-center North American study examining the outcomes in childhood cancer patients diagnosed between 1970 and 1999 who survived at least five years. Several reports from this cohort indicated that at 25 years from diagnosis, childhood ALL survivors are at an increased risk of early mortality beyond the 5-year mark (15,16,17) with a 13% cumulative incidence of death rate from any cause. Majority of the deaths were due to leukemia recurrence (66%) yet compared to sibling controls they were 15 times more likely to die of a subsequent cancer, 7 times more likely to die from cardiac-related events, and 2.6 times more likely to die from other medical causes (15,16). The mortality rate from recurrence among the ALL survivors markedly decline with extended follow-up. Therefore, ALL patients who survive 10 or more years from initial diagnosis have a low risk of recurrence and with the rare exception, are cured. There is a difference in OS between survivors treated with CRT (OS 87.3%) and survivors who did not (OS 96.1%) (18). In a recent study which evaluated temporal trends in late mortality among 34,033 patients in the CCSS cohort reduced rate of death from treatment-related late effects were reported in the patients treated in the 1990s compared to earlier decades (19). Reducing treatment intensity, increased use and accuracy of screening methods were associated with reduction in late mortality in patients with ALL.

**Second malignancies**

Secondary neoplasms (SNs) are one of the most serious late effects of acute leukemia therapy. Irradiation has been associated with increased risk of SN (20). The chemotherapy agents most commonly associated with development of SN include alkylating agents, anthracyclines, and etoposide (21). ALL survivors have an increased risk for acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), breast cancer, melanoma, CNS tumors, non-Hodgkin’s lymphomas and carcinomas of the parotid and thyroid glands (22,23).

The overall cumulative incidence of SNs for childhood ALL survivors ranges from 1% to 11%, depending on the treatment regimen and length of follow-up (22,24). Secondary neoplasms are predominantly in the skin (43%) and CNS (31%) (18). The majority of secondary skin cancers are basal cell carcinomas, whereas 70% of the CNS neoplasms are meningiomas (15,18). In a retrospective study of 2169 childhood ALL patients treated between 1962 and 1998 (median follow-up, 18.7 years), the overall cumulative incidence of SNs was 4% at 15 years and 11% at 30 years (24). Many of the late-developing SNs were “benign” neoplasms (basal cell carcinoma, n=14, 11.4 % and meningioma n=16, 13 %); when these diagnoses were excluded, the cumulative incidence of SNs at 30 years was 6%. Most common malignant SNs were 46 myeloid malignancies (AML, MDS), 3 lymphomas, 16
carcinomas excluding basal cell carcinoma, 6 sarcomas and 22 brain tumors. Essig S. et al described the spectrum of late effects in 556 ALL survivors (median follow up, 18.4 years) from the CCSS cohort who were 1–9.9 years old at the time of diagnosis and received therapy similar with contemporary standard-risk ALL protocols (25). Only six (1%) of them developed a subsequent malignancy (two melanomas, one astrocytoma, one large cell lymphoma, one leukemia, and one hepatocellular carcinoma).

Cranial and craniospinal radiation increase the risk of developing secondary solid tumors. Nathan et al. reported that the risk of SNs caused by radiation increases with time, and the neoplasms typically appear at least 10 to 15 years after treatment (26). In a cohort of 8831 children diagnosed with ALL and enrolled on Children's Cancer Group therapeutic protocols between 1983 and 1995, patients who received 18 Gy cranial radiation were at lower risk for SNs than those who had received 24 Gy radiation (RR 1.5; 95% CI, 0.9-2.6; and 3.9; 95% CI, 1.4-11.2, respectively) (22). The relative risk of secondary brain tumors after 12 Gy cranial radiation, the dose most commonly used in current protocols has not yet been evaluated.

As mentioned above secondary AML may also develop in ALL survivors, with significantly higher rates observed in those who were treated with higher or more frequent doses of epipodophyllotoxins and alkylating agents (27). Therefore, current regimens include relatively lower cumulative doses of cyclophosphamide and other alkylators. A recent study has suggested that secondary leukemia risk is increased in patients who receive higher starting doses of mercaptopurine during the maintenance phase (75 mg/m2/d instead of 50 mg/m2/d) (28). Whether patients with homozygous or heterozygous deficiencies in thiopurine methyltransferase are more at risk for SNs remains controversial, but the risk may depend in part on mercaptopurine dose intensity and/or duration (29).

Neurological outcomes:

Cranial radiotherapy:

Childhood ALL survivors are at risk for neurocognitive late effects, including difficulties with attention, visual-motor function, processing speed, and working memory which may affect their education achievement and quality of life (QOL) (30,31). CNS-directed therapy, including CRT and/or IT chemotherapy are established risk factors for impaired cognitive function, especially for the younger patients (18). Within the first 5 to 10 years after CRT survivors of childhood ALL are at increased risk for deficits in neurocognitive skills (2,32) as they get older global brain injury from early CRT may reduce cognitive reserve, placing them at risk for early onset dementia or memory impairment (3,33).

A study from CCSS in 556 CRT-naive long-term ALL survivors who were treated in the 1980s and 1990s reported that ALL survivors had poorer overall functional status even though their neurocognitive deficits and mental health status did not differ from matched sibling donors (34). Recent studies examining patients treated on contemporary chemotherapy-only protocols uniformly display lower performance on direct measures of attention and processing speed in 20-40% of the survivors by the end of therapy (35,36,37).
Methotrexate:

Methotrexate (MTX) is the main agent associated with neurocognitive dysfunction in ALL survivors. Majority of the published studies show that survivors who received high-dose intravenous methotrexate (> 1g/m2) had more neurocognitive problems than those given low-dose methotrexate (38,39,40). In another study cumulative doses of intravenous methotrexate increased the risk for impaired processing speed by 3% for each 1 g/m2/dose (40). IT MTX, even without CRT, may be linked to white matter changes, calcifications, leukoencephalopathy, cortical atrophy, and seizures (41). IT cytosine arabinoside may exacerbate the neurotoxicity of IT MTX (42). Childhood ALL survivors are also at increased risk for fatigue and sleep disturbance (43,44), which are associated with increased neurocognitive impairment (45). This might be not only related to side effects of drugs, but also due to longer hospitalization time. Folate pathway polymorphisms in the MTHFR 1298A>C and MS 2756A>G genes were associated with worse attention and processing speed in ALL survivors treated with contemporary protocols suggesting a role for genetic predisposition (46,47).

Corticosteroids:

Corticosteroids remain an essential component of modern ALL therapy and are most commonly given as either dexamethasone or prednisone. While studies in asthma patients suggest that corticosteroids contribute to cognitive difficulties (48), previous studies have shown that the type of steroid regimen used for ALL treatment does not differentially impact long-term neurocognitive functioning (49). However choice of corticosteroid may affect long-term QOL. Acute and long-term toxicities have been reported for prednisone and dexamethasone while evidence suggests superior penetration of dexamethasone into the CNS, which could potentially impact QOL differentially, during and after treatment.

Vincristine:

Vincristine, another essential component of childhood ALL therapy, is associated with dose-dependent peripheral neuropathy. In a study with 101 survivors, 16 (15.8%) had combined clinical and electrophysiological neuropathy (50). Those who were treated on the intermediate or high-risk chemotherapy arms with cumulative vincristine doses of 36 mg/m2 or higher, had a nine-fold increased risk of developing peripheral neuropathy compared with those treated on the standard-risk arms who received 33 mg/m2 or lower. Peripheral neuropathy was related to lower QOL as well, but no association with poorer fine or gross motor function was observed.

Quality of life (QOL):

QOL is a multidimensional construct measuring subjective well-being. In a study which evaluated the contribution of neurocognitive dysfunction to quality of life (51), 25% of ALL survivors fell below the established threshold for poor
Psychosocial QOL and 14% reported poor Physical QOL. Those with poor Psychosocial QOL were significantly more likely to be male and three times more likely to have deficits in verbal cognitive abilities and visual-motor integration skills. As in the general population, socio-economic characteristics of the family play a role in QOL in childhood ALL patients. Specifically, lower household income was associated with poor Physical QOL, as well as poor Social and Emotional QOL. This suggests that survivors from socioeconomically disadvantaged families are particularly vulnerable to poor QOL after treatment. Further attention should be paid to the assessment of socioeconomic risk factors to help at-risk families overcome barriers and access resources needed to optimize their child’s physical and psychosocial functioning.

**Cardiotoxicity**

Survivors of childhood ALL are at risk of developing late cardiotoxic effects of treatment, especially after anthracycline therapy, such as congestive heart failure (CHF), heart attacks, heart valve abnormalities and inflammation of the heart epithelium (52,53). Anthracyclines produce oxygen-free radicals that damage cardiac myocytes with resultant loss of myofibrillary content and vacuolar degeneration that lead to myocardial necrosis and fibrosis. Over time the left ventricular wall thins, thereby increasing wall stress and decreasing myocardial contractility. Progressive cardiomyopathy may occur early, within the first year of treatment, or can be delayed, being diagnosed many years following completion of therapy (54,55).

The risk of disease is dose-dependent, with incidences of CHF reported at 10% or less among patients exposed to cumulative doses of anthracyclines less than 500 mg/m² and at 36% for doses exceeding 600 mg/m² (56,57). In addition, risk of therapy-related CHF is modified by clinical variables such as young age at exposure (<5 years of age), female gender, pre-existing heart disease and concomitant mediastinal irradiation (57-60). In the CCSS cohort 30-year cumulative incidences for CHF [4.1% (95% CI: 3.2–5.0%)], myocardial infarction [1.3% (95% CI: 1.0–1.7%)], valvular abnormalities [4.0% (95% CI: 3.1–4.9%)] and pericardial disease [3.0% (95% CI: 2.1–3.9%)] were increased in the 10,367 young adult childhood cancer survivors compared to sibling controls (61). Since the risk of anthracycline cardiotoxicity is dose dependent, cumulative doses have been reduced for low-risk patients during the last decade to reduce late cardiac dysfunction (52). With cumulative doses >300 mg/m², the 20 year risk for clinical heart failure has been estimated at nearly 10%, but with doses <300mg/m² the estimated risk is 0.5% (62). Deterioration of cardiac function in longitudinal follow-up has also been noticed after doses below 300 mg/m². In a cross-sectional study in 138 adult survivors of childhood ALL, with a median follow up time of 23.4 years after diagnosis, impaired LV function was observed in the 12% of the patients treated with low cumulative anthracycline doses (40–120 mg/m²) (52), showing that there appears to be no definite safe dose of anthracyclines (63,64). Therefore, lifelong monitoring of late cardiac effects is recommended in childhood ALL survivors exposed to anthracyclines with the goal of preventing the progression from asymptomatic cardiac dysfunction to clinical CHF.

Lastly there is some evidence that hypertension may be another cardiac late effect in ALL survivors. In a study with 68 survivors treated for childhood ALL
between 1973 and 2000 evaluated for an increased risk of developing high blood pressure and increased (body mass index) BMI, diastolic and systolic blood pressure values were significantly increased compared to general population (systolic blood pressure; mean SDS 0.736, $P < 0.001$, diastolic blood pressure; mean SDS 0.409, $P = 0.041$, BMI; mean SDS 1.355, $P < 0.001$). Female survivors especially those who were treated with CRT, have a greater risk of being overweight and obese, increasing the risk of cardiovascular morbidity later in life (65).

**Endocrine and Metabolic Outcomes**

**Hormone Deficiencies:**

GH deficiency is the most common endocrinopathy detected after radiation therapy in ALL survivors due to direct injury to the hypothalamus (66,67). It is dose-dependent and mostly seen with doses of 24 Gy but has also been observed with doses as low as 18 Gy, or 10 Gy given as a single dose as part of total body irradiation (TBI) (67,68). Craniospinal radiation not only damages the hypothalamus, but also directly effects the skeletal growth resulting in growth retardation (69,70). In addition to higher CRT dose, risk factors for GH deficiency include younger age at diagnosis and female gender (67-69). Other central endocrinopathies, such as central adrenal insufficiency, hyperprolactinemia, gonadotropin insufficiency, or central (secondary) hypothyroidism, are associated with doses of 40 Gy (71), which is rarely administered in the treatment of childhood ALL. Primary hypothyroidism may occur after cranial, craniospinal radiation and TBI due to direct exposure of the thyroid gland to radiation even at relatively low doses of 10 Gy (72). Precocious puberty is a late effect of CRT in doses of 18 to 24 Gy and is more common in girls (73-75). In two large cohort studies, the CCSS and the National Cancer Institute Children’s Cancer Group Leukemia Follow-up Study, 92% of female ALL survivors reported a normal age of menarche compared with 97% and 96% of controls, respectively (76,77).

Chemotherapy agents are not associated with endocrine late effects associated with hypothalamic pituitary axis injury (67). In a report from the CCSS, young adult survivors of ALL were more than three times as likely as sibling controls to have a chronic endocrine condition. However, the risk in the nonrelapsed and nonirradiated survivors was similar to that seen in the sibling control group (15).

**Obesity:**

There are conflicting reports whether obesity is a true late effect in ALL survivors (78-81). Most indicate that adolescent and adult survivors have higher BMIs than healthy comparisons, while others report no significant differences. Also, less attention has been paid to the loss of skeletal muscle mass, which leads to sarcopenia in patients with cancer and is related to the use of high-dose glucocorticosteroid therapy. In a cross-sectional study of body composition in 75 long-term survivors of ALL, sarcopenic obesity was present in 32 subjects (43%) (82). Statistically significant and clinically important differences in overall health related QOL between subjects with and without sarcopenic obesity were stated. A recent meta-analysis showed that obesity is common among survivors who are still in childhood or early adolescence compared to reference populations (81). Survivors had a significantly higher BMI regardless of treatment type, sex, or the length of time from the
completion of treatment to the time of assessment. In another meta-analysis evaluating BMI among adult and adolescent survivors of pediatric ALL, patients were 12% to 28% more likely to be overweight/obese compared to the general population ($p<0.001$) (83). Pediatric cancer patients are rarely advised on balanced nutrition during and after treatment. Survivors of pediatric ALL require additional weight management resources such as counseling for physical activity and dietician support both early in treatment especially when on steroids and after the end of their therapy. In a study, evaluating chronic fatigue, 290 long-term survivors of childhood lymphomas ($n = 139$) and ALL ($n = 151$) were assessed by a Fatigue Questionnaire (84). A subgroup of long-term ALL survivors with persistent chronic fatigue had features characterized by higher severity level of depressive symptoms, anxiety, pain and less physical activity, which may lead to obesity.

Infertility:

Long-term male survivors of childhood ALL are at an increased risk for infertility, poor semen quality, and gonadal dysfunction because of gonadotoxic treatments, such as testicular irradiation and alkylating agents (85-89). The relationship is dose dependent for both exposures, patients treated with higher doses of gonadal radiation and higher cumulative doses of alkylating agents leading to higher risks (85). CRT doses of 24 Gy or less does not lead to azospermia in males (90).

In females, CCSS reported that the relative risk (RR) for survivors of ever being pregnant was 0.81 (95% CI, 0.73 to 0.90; $P < 0.001$) compared with female siblings. In multivariable models among survivors only, those who received a hypothalamic/pituitary radiation dose $> 30$ Gy (RR, 0.61; 95% CI, 0.44 to 0.83) or an ovarian/uterine radiation dose greater than 5 Gy were less likely to have ever been pregnant (RR, 0.56 for 5 to 10 Gy; 95% CI, 0.37 to 0.85; RR, 0.18 for $> 10$ Gy; 95% CI, 0.13 to 0.26) (91). In female cancer survivors, the accelerated loss of primordial follicles as a result of gonadal damage may lead to premature ovarian failure, which can lead to gonadal failure, reduced ovarian reserve with lower anti-mullerian hormone and higher gonadotrophins level and permanent infertility (92,93); making follow-up crucial. Additionally CCSS reported that acute ovarian failure (AOF) occurred in 6.3% of survivors (94). Exposure of the ovaries to high-dose radiation (especially over 10 Gy), alkylating agents and procarbazine, at older ages, were significant risk factors for AOF. In a retrospective cohort study, in which fertility (defined as ever pregnant) was evaluated by self-report among 182 females and 170 controls drawn from among the survivors’ female siblings, fertility deficits were noted in female survivors treated with CRT at any dose especially around the time of menarche (95).

In a recent cohort (1987–2006) of French women who are survivors of childhood ALL, TBI ($P = 0.013$) and alkylating agents ($P = 0.01$) were found to be negatively correlated with fertility, but not with the age at diagnosis or the anthracyclines doses (96). In multivariable analyses there was still a negative correlation between TBI ($P = 0.035$), as well as alkylating agents ($P = 0.028$), and fertility. Fertility was negatively correlated with cumulative cyclophosphamide equivalent dose ($P = 0.001$), with fertility decreased for doses $\geq$1g/m$^2$.

Bone toxicities:
Changes in bone metabolism are considered as important adverse late effects, through pain, fractures, decrease of bone mineral density (BMD) and chronic impairment of bone function (97,98). Treatment with high-dose methotrexate, mercaptopurine, glucocorticoids for 2-3 years and CRT with low calcium intake, decreased physical activity, and obesity are some of the factors that lead to low BMD (99,100). In addition, impaired bone metabolism and diminished bone mass in newly diagnosed ALL patients suggest a direct disease effect on BMD from leukemic infiltration of bone marrow (101). Survivors can recover lost bone mass during the post-treatment period yet some will not reach their maximum BMD acquisition potential, presenting significant bone mass deficiency (102). The first two years after the end of ALL treatment is the most critical period for bone loss, with recovery taking place after that time (103).

In a single institution study in 845 childhood ALL survivors (median age 31 years), 5.7% had osteoporosis (BMD Z-score ≤ -2) (104). No correlation was found between cumulative doses of glucocorticoid and methotrexate and low BMD but higher prednisone exposure was associated with lower BMD among female participants. The strongest risk factor for a persistently low BMD (Z-score ≤ -1) during young adulthood was high dose (≥24 Gy) cranial or craniospinal radiation, associated with an approximate 2-fold increased risk compared to no cranial radiation exposure.

In another single-center study with 101 patients (105), patients with Z-score values between -1.1 and -1.9 who were younger than 20 years had increased cumulative risk for fractures (2%) and osteonecrosis (ON) (2%). They observed that lean mass was positively correlated with whole body and lumbar spine BMD values in patients under 20 years of age, confirming its importance for healthy development of bone mass.

The overall incidence of symptomatic ON varies with percentages ranging from 1% to 38% in the literature (106). The association between ON and corticosteroids is described with at least two mechanisms: The first is represented by direct vascular damage, characterized by an inflammatory process, while the second is gaseous microembolization following hepatotoxicity from corticosteroids (107). Vascular damage could justify a higher incidence of osteonecrosis of the femoral head and load of the humeral head (108). The high frequency of necrosis at the femur head could be related to the terminal type of vascularization at this level, where any alteration to the blood supply is not compensated by collateral circulation. A similar situation has been reported for the humeral head which presents morphology and vascularization similar to that of the femur, but with a percentage of ON significantly lower than that of the femur head. In a retrospective analysis of 328 patients with ALL revealed only four (1.2%) cases with ON (109). Median time between the diagnosis of ALL and ON was 12.5 months (range, 12 to 36 months). In all cases the femoral head was involved and was associated with the scapula-humeral joint in one case. Osteonecrosis is more often associated with dexamethasone in patients older than 10 years compared to prednisone (110).

**Social/ psychological outcomes:**
Childhood ALL survivors have lower levels of education and are less often employed, married, and have children than their siblings (15,111). Cranial irradiation is the strongest predictor of these long-term effects (15,23). Young age at diagnosis and female gender have been identified as risk factors for worse future socioeconomic status (112). In a registry based study from Sweden involving 213 long term childhood ALL survivors female survivors had a greater risk of reaching a lower level of education than male survivors and population controls (113). Young age at diagnosis was associated with a lower probability of marriage, having children, and a lower level of education with lower income after adjustment for the level of education of the parents. As expected, treatment with cranial irradiation was the main culprit for these associations, while steroids and IV/IT methotrexate were also statistically significant risk factors.

**Conclusion**

More than 90% of childhood ALL survivors survive beyond 5 years after diagnosis while many experience a long list of late effects from therapy, associated with late mortality, worse social and academic achievement and QOL. Therapeutic exposures, such as CRT, HSCT, and certain chemotherapy agents place significant number of ALL survivors at risk for multiple late effects including neurocognitive and neurologic dysfunction, endocrine and metabolic abnormalities, bone toxicity, SNs, cardiac damage and social/psychological adverse effects. Current trials need to be focused not only on maintaining high cure rates, but also on further development of ALL treatments that minimize long-term adverse effects. Children’s Oncology Group has developed evidence based guidelines available to any oncologist (http://www.survivorshipguidelines.org/) for detection of late effects that may lead to remediation and improvement of overall health, QOL and prevent late mortality. Thus, life-long ideal medical care in pediatric ALL survivors should include education for late effects and advising adherence to periodic follow-up at a pediatric oncology center with an experienced survivorship team.

**References**


60. Pein F, Sakiroglu O, Dahan M, Lebidois J, Merlet P, Shamsaldin A, Villain E, de Vathaire F, Sidi D, Hartmann O. Cardiac abnormalities 15 years after adriamycin


<table>
<thead>
<tr>
<th>Table 1. Summary of Late effects in Childhood ALL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Late effects</strong></td>
</tr>
<tr>
<td>Late Mortality</td>
</tr>
<tr>
<td>Second Malignancy</td>
</tr>
<tr>
<td>Neurological/ Neurocognitive Disorders</td>
</tr>
<tr>
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<tr>
<td><strong>Cardiotoxicity</strong></td>
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<tr>
<td><strong>Endocrine Disorders (Growth Hormone Deficiency, Precocious Puberty, Obesity)</strong></td>
</tr>
<tr>
<td><strong>Bone Disorders (Osteoporosis, Osteonecrosis)</strong></td>
</tr>
<tr>
<td><strong>Social/ Psychological Disorders</strong></td>
</tr>
</tbody>
</table>

- ROS Review of Systems