

CLINICAL PRACTICE

Adult Primary Care after Childhood Acute Lymphoblastic Leukemia

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This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.

A 26-year-old woman presents to an internist to establish primary care. Her medical history includes a diagnosis of acute lymphoblastic leukemia (ALL) at 3 years of age. She does not know what therapies she received, but her parents told her that she was treated for 2 years and that her leukemia never recurred. She is a high-school graduate and works as a receptionist. What are the issues to consider in the care of this long-term survivor of childhood leukemia?

THE CLINICAL PROBLEM

Because of the extraordinary advances in pediatric cancer treatment during the past five decades, more than 325,000 adults living in the United States are survivors of childhood cancer.¹ British,² North American,³ and other cohort studies⁴⁻⁶ have shown that survivors of childhood cancer face considerable health challenges in adulthood. For example, reports from the Childhood Cancer Survivor Study (CCSS), a North American cohort study of more than 17,000 survivors of childhood cancer treated between 1970 and 1986, suggest that by 25 years after treatment, 27.5% of adult survivors report at least one severe, life-threatening, or disabling condition (as compared with 5.2% of siblings who are close in age).^{7,8}

ALL is the most common childhood cancer; in the United States, approximately 2400 new cases are diagnosed annually in persons younger than 20 years.⁹ The cure rate has exceeded 70% for more than 25 years; the most recent 5-year survival estimates exceed 85% (Fig. 1). As of 2006, there were an estimated 50,000 survivors of childhood leukemia in the United States, more than half of whom were 20 years of age or older.¹

Childhood ALL can be successfully treated with multiple-agent chemotherapy, delivered over a period of 2 to 3 years. ALL treatment protocols almost always include high-dose glucocorticoids, and — depending on the treatment center and the decade — some or all of the following: vincristine, mercaptopurine, methotrexate, asparaginase, anthracyclines (typically doxorubicin), alkylating agents (usually cyclophosphamide), and topoisomerase II inhibitors (etoposide or teniposide). Early treatment trials used cranial or craniospinal radiotherapy for prophylaxis against central nervous system recurrence. In the 1970s and early 1980s, doses of 24 Gy and 18 Gy of cranial radiation were used, but, with recognition of the adverse long-term effects, doses of radiation were reduced or eliminated and replaced with higher-dose systemic therapy and intensive intrathecal chemotherapy. Central nervous system irradiation is still used in patients who have central nervous system disease at diagnosis or are at high risk for central nervous system involvement.

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KEY CLINICAL POINTS

TREATING ADULT SURVIVORS OF CHILDHOOD LEUKEMIA

Acute lymphoblastic leukemia (ALL) is the most common childhood cancer, and 5-year survival rates in the United States have exceeded 70% for over two decades.

Adult survivors of childhood leukemia have increased risks of secondary cancers, cardiovascular disease, and other chronic illnesses, largely secondary to therapies for childhood cancer.

Clinicians caring for adult survivors of childhood leukemia should

- Request a treatment summary from the treating oncologist, a pediatric oncology program, or a local “survivor clinic.”
- Be aware that adults who received cranial radiotherapy as a component of treatment have increased risks of secondary tumors, stroke, growth hormone deficiency, and neurocognitive deficits.
- Check BMI, blood pressure, and lipids, since survivors of ALL have increased risks of obesity and associated metabolic derangements.
- Consider bone-density testing, since peak bone density is often reduced after childhood exposure to high-dose glucocorticoids and other therapies.
- Screen for left ventricular dysfunction in survivors who received anthracycline therapy, particularly if there was a high cumulative dose or treatment was before the age of 5 years.

STRATEGIES AND EVIDENCE

OBTAINING A TREATMENT SUMMARY

A critical step in providing medical care for a survivor of childhood cancer is to obtain accurate information about the diagnosis and prior therapy. A history obtained from the patient will probably be incomplete, given the complexity of previous therapy, the young age at treatment, the time since treatment, and the exposure to therapies that might impair cognitive function.¹⁰ The current recommended practice for pediatric oncologists is to provide each patient with a treatment summary, but adult survivors may not have access to such information. Referral of an adult patient to a pediatric oncologist or a “survivor clinic,” where available, is recommended, to obtain information regarding the previous diagnosis, therapy, and potential late effects of therapy. (A list of North American oncology programs that provide this service is available at <http://www.ped-onc.org/treatment/surclinics.html>.) If a treatment summary cannot be obtained, the clinician should work with the available medical records, the patient, and the patient’s parents (if available) to construct a summary. A template for a summary is shown in Fig. 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org.

Once a patient’s treatment summary is obtained, a follow-up plan can be developed, based on the known risks of therapy, available guidelines,¹¹⁻¹³ and the presence of any signs or symptoms to suggest conditions potentially related to previous disease or treatment.

HEALTH RISKS AFTER CHILDHOOD LEUKEMIA*Cancer*

Adult survivors of childhood cancer are at increased risk for subsequent cancers, largely because of previous exposures to chemotherapy or radiotherapy and, in some survivors, because of an underlying increased familial risk of cancer. In the CCSS, the cumulative incidence of a secondary cancer (excluding nonmelanoma skin cancer) 30 years after treatment of ALL was 5.2% (vs. the expected cumulative incidence of <1.5%).^{14,15} ALL survivors in continuous remission for more than 20 years after diagnosis have virtually no risk of ALL recurrence, but they are at risk for myelodysplasia and therapy-associated acute myelogenous leukemia, usually within the first 15 years after treatment; the risk and latency vary depending on the primary chemotherapy received.¹⁶

Approximately 80% of solid tumors in ALL survivors occur in persons who received radiation therapy.¹⁵ The incidence of secondary solid

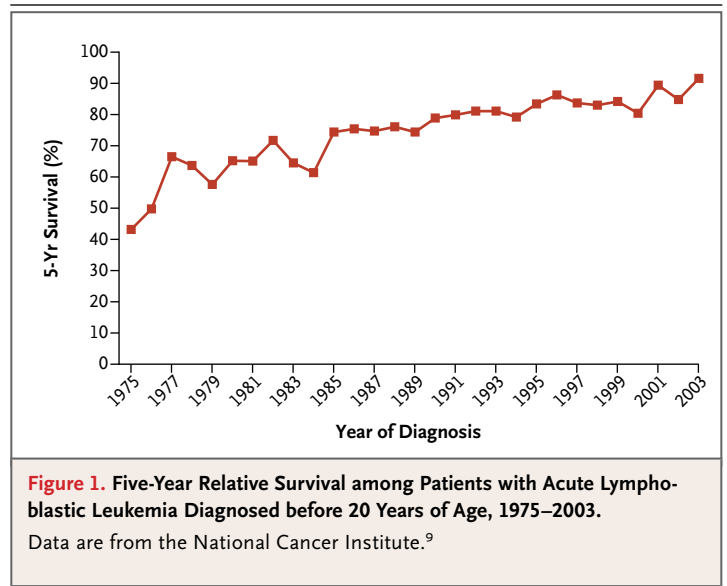
tumors does not appear to plateau over time. In a retrospective study involving 2169 ALL survivors, the cumulative incidence of a secondary solid tumor after radiation treatment was 5.4% at 20 years and 10.8% at 30 years.¹⁶ Postradiation tumors include brain tumors, parotid-gland tumors, thyroid cancers, basal-cell and squamous-cell carcinomas, and soft-tissue and bone sarcomas.¹⁵⁻²⁰

Cranial irradiation is associated with an increased risk of meningioma, with a reported cumulative incidence of 4 to 6% 30 years after the diagnosis of leukemia.^{14,18} Studies involving magnetic resonance imaging surveillance for meningioma suggest a higher cumulative incidence of occult disease (15 to 22% at 20 years) and have shown synchronous detection of multiple meningiomas in some cases.^{21,22} In the CCSS, the cumulative incidence of nonmelanoma skin cancer in ALL survivors was 10% at 30 years,¹⁴ and these skin cancers accounted for nearly 30% of the secondary cancers among ALL survivors in a British cohort.²³

Given the increased risks of a secondary cancer, guidelines for the care of ALL survivors emphasize a detailed assessment of the family history with attention to a possible cancer-predisposition syndrome; physical examination, particularly of skin and of irradiated sites; and education regarding healthy lifestyle behaviors, sun protection, and prompt reporting of signs and symptoms. Guidelines¹¹⁻¹³ do not recommend active surveillance for meningiomas in asymptomatic survivors, but there should be a low threshold for radiographic evaluation of neurologic symptoms in patients who received cranial irradiation.

Cardiovascular Toxicity

ALL survivors are at risk for therapy-induced cardiac disease. British and North American cohort studies showed that the risk of death from cardiac causes was four to six times as high among ALL survivors as the risk observed in the overall healthy population.^{2,24} Exposure to anthracyclines during childhood can cause heart failure in adulthood; the risk increases with higher cumulative doses, younger age (<5 years) at exposure, longer time since treatment, and female sex.^{25,26} Echocardiographic evaluations have shown progressive reductions in left ventricular fractional shortening and thinning of the ventricular wall, as well as increased afterload in asymptomatic long-term sur-



vivors treated with anthracyclines, with progression of observed abnormalities over time.²⁵⁻²⁷ Studies suggest that among patients exposed to doxorubicin, 5 to 10% will have clinical congestive heart failure within 20 to 30 years after exposure; doses exceeding 250 to 300 mg per square meter of body-surface area are associated with a higher risk.^{26,28} Guidelines recommend that persons treated with anthracyclines in childhood undergo baseline echocardiography at the start of long-term follow-up and at intervals of 3 to 5 years, with a shorter interval for patients who were given higher doses (e.g., doxorubicin, ≥ 250 to 300 mg per square meter), received chest radiotherapy, or had a history of acute cardiotoxic effects during treatment in childhood.^{12,13} Echocardiography is also recommended before pregnancy or in early pregnancy for women previously treated with anthracyclines, given reports of deterioration of myocardial function during pregnancy in such women.²⁹

Studies have shown that after follow-up of 25 years or more, the risks of death from cerebrovascular causes² and stroke³⁰ among childhood ALL survivors are increased by a factor of 5 to 6, as compared with the expected rates; a history of leukemia recurrence or cranial irradiation is associated with an increased risk of stroke, although risk ratios are elevated even in the absence of a history of irradiation.³⁰ Clinicians caring for ALL survivors should have a high index of suspicion for cerebrovascular disease in patients with

suggestive symptoms, even those who are relatively young adults.

Studies of ALL survivors, as compared with control populations, have also shown an increased prevalence of components of the metabolic syndrome, including a high body-mass index (BMI), truncal obesity, insulin resistance, hypertension, and dyslipidemia.³¹⁻³³ Medication use for hypertension and diabetes³⁴ is more common in childhood ALL survivors than in their siblings; a higher BMI may not fully account for this observation. Cranial irradiation, female sex, and young age at treatment are risk factors for a high BMI.³² Potential contributors to the high rate of metabolic abnormalities include cranial irradiation and the resultant blunted growth hormone responsiveness, physical inactivity (possibly because of social isolation or vincristine-associated residual weakness), and late effects of other therapies (e.g., cardiac irradiation or anthracyclines).³⁵ The extent to which the risk of coronary artery disease is increased among survivors of childhood ALL has not been established, although a recent study of self-reported myocardial infarction among ALL survivors treated between 1970 and 1986 showed a risk that was three times as high among these survivors as that among their siblings.²⁸ Current guidelines recommend screening for obesity and other cardiovascular risk factors in survivors of childhood ALL.¹¹⁻¹³

Skeletal Toxicity

Survivors of childhood leukemia have attenuated bone mineral accretion, which may result in an increased incidence of osteopenia, early-onset osteopenia, or both.³⁶ In one study, low bone mineral density (z score, -1 or less) was observed in 24% of adult survivors of childhood ALL at a mean age of 30 years.³⁷ Contributors to low bone mineral density in ALL survivors include prolonged glucocorticoid exposure, methotrexate exposure, inactivity or nutritional compromise, and treatment-related endocrinopathies such as growth hormone deficiency and hypogonadism.^{36,38} Data are lacking to indicate an increased risk of late hip or spine fractures in this population; however, the oldest survivors of childhood leukemia are not yet elderly, and longer-term follow-up is warranted. Guidelines recommend measuring bone density at entry into long-term follow-up and then as clinically indicated.^{12,13}

Osteonecrosis has long been recognized as an early complication of cancer therapy, but it may

also occur late. Risk estimates vary, depending on the age at cancer diagnosis, the method of diagnosis, and the duration of follow-up⁸; in one study, older age at diagnosis was associated with increased risk, with a cumulative incidence of 3% among survivors of adolescent-onset ALL at 20-year follow-up.³⁹ The occurrence of bone or joint pain in a survivor of childhood ALL should prompt consideration of osteonecrosis.

Other Organ Toxicity

Growth hormone deficiency is the most common neuroendocrine complication after therapy for leukemia and is associated, in a dose-dependent fashion, with exposure to cranial irradiation. Approximately 20 to 30% of adults treated with cranial irradiation for childhood leukemia have blunted growth hormone responses on provocative testing.^{40,41} Adult survivors treated with exogenous growth hormone during childhood may not have short stature, despite growth hormone deficiency. Long-term risks associated with growth hormone treatment remain uncertain, although an increased risk of osteosarcoma has been reported among ALL survivors who received growth hormone during childhood, as compared with those without this exposure.^{42,43} The use of exogenous growth hormone in adulthood to ameliorate clinical features of growth hormone deficiency (e.g., dyslipidemia, central adiposity, and decreased energy) is controversial and beyond the scope of this article.

Other pituitary hormone deficiencies (e.g., those seen in survivors of brain tumors) are rare after cranial irradiation in the dose range used for leukemia, although patients with a history of ALL relapse who received higher total doses of cranial radiation may have other hypothalamic or pituitary insufficiencies. Patients who received craniospinal radiotherapy are at risk for hypothyroidism owing to scatter radiation to the thyroid.⁴⁴

Adult ALL survivors may have other treatment-related organ-system damage. Long-term hepatic dysfunction from chemotherapy is unusual, but clinically silent viral hepatitis may have been acquired from a blood transfusion during childhood. The relatively low total dose of alkylating agents (e.g., cyclophosphamide) used in most ALL protocols rarely impair spermatogenesis or ovarian function. However, gonadal failure is observed after direct testicular irradiation (used as treatment or prophylaxis in boys in

the 1970s) and after alkylator-intensive or myeloablative therapy for relapse. ALL survivors may have impaired dental health related to poor dental hygiene during illness in childhood as well as abnormal tooth or jaw development from cranial irradiation at a young age.⁴⁵ The risk of cataracts, which is related to exposure to glucocorticoids and cranial irradiation, is also increased; in one study, the cumulative self-reported incidence of cataracts was 3.5% 20 years after diagnosis; this rate was more than five times as high as the expected rate.^{46,47}

Neurocognitive and Developmental Impairment

Children treated for cancer at young ages may not have normal development; health limitations during childhood might have prevented regular school attendance and achievement of normal developmental milestones. Brain irradiation at a young age, as well as intensive intrathecal therapy, have been associated with impaired neurocognitive development and subsequent functional impairment.^{48,49} Neuropsychological testing of ALL survivors who received 18 Gy of cranial radiation before the age of 5 years revealed scores approximately 1 SD lower than population means in measures of intelligence, attention, and processing.⁵⁰ As compared with their siblings, ALL survivors in the CCSS had about twice the prevalence of deficits in memory (14% vs. 8%), emotional regulation (26% vs. 14%), and the ability to complete tasks efficiently (16% vs. 7%).⁵¹ Survivors of childhood leukemia are less likely than their siblings to graduate from college, to be fully employed, or to obtain health insurance.¹⁵

AREAS OF UNCERTAINTY

There are no data from randomized trials assessing outcomes of recommended surveillance programs or schedules for adult survivors of childhood leukemia. Given the variation in treatments, the long interval between treatment and long-term outcomes, and the rarity of certain long-term complications, such trials are unlikely to be conducted. Optimal strategies for ensuring comprehensive care for adult survivors of childhood cancer have not been established, and the cost-effectiveness of recommended surveillance strategies is unclear. More study is needed of factors, including genetic variants, that might refine risk estimates for an individual survivor for specific outcomes. Continued follow-up of established

cohorts of survivors of childhood cancer and expansion of cohort studies to include patients treated with more current therapies are needed to better understand the effects of cancer therapy on health outcomes, especially as survivors continue to age. Once disease is diagnosed, treatment is similar to that given to patients not previously treated for childhood cancer, except in special circumstances. For example, previous exposure to radiation or anthracyclines may limit the safe use of these agents in the treatment of adult-onset cancers.

GUIDELINES

Guidelines for the care of survivors of childhood cancer that are based on expert panel review of the available literature on long-term disease risks (Table 1) have been published by the Children's Oncology Group,¹² the Scottish Intercollegiate Guidelines Network,¹¹ and the United Kingdom Children's Cancer Study Group.¹³ The recommendations provided in this article are generally consistent with these guidelines.

CONCLUSIONS AND RECOMMENDATIONS

An adult survivor of childhood cancer seeking primary care, such as the patient described in the vignette and the patient shown in Figure 2, should be encouraged to obtain a treatment summary from a pediatric oncology program or a survivor clinic. The treatment summary should guide the provider's evaluation, which should include a thorough medical history, social history, and review of systems, with assessment for evidence of potential complications of therapies. The physical examination should include examination of any irradiated area of the skin, as well as a neurologic evaluation.

Although data are lacking to fully define optimal strategies for screening and following survivors of childhood ALL, consensus guidelines support screening for several conditions for which these patients are recognized to be at increased risk. Given increased rates of obesity and associated metabolic abnormalities among survivors, they should be assessed for obesity; screened for hypertension, dyslipidemia, and glucose intolerance; and educated regarding diet, exercise, and avoidance of smoking. Hepatitis C screening should be performed in all sur-

Table 1. Major Long-Term Risks of Disease among Adult Survivors of Childhood Acute Lymphoblastic Leukemia.*

Potential Late Effect	Exposure	Guidelines for Care and Testing	Comments
Secondary cancers	Cranial or craniospinal irradiation or irradiation at other sites	Perform physical examination and obtain history; recommend sun protection; provide counseling about healthy lifestyle and smoking cessation	Perform aggressive workup for neurologic symptoms, given increased risk of meningioma; if a woman has a history of chest irradiation for mediastinal mass, perform enhanced breast-cancer screening (mammography with or without breast MRI annually starting at 25 yr of age)
Cardiomyopathy	Anthracycline exposure (higher risk with higher-dose anthracyclines, young age at diagnosis, female sex, history of cardiomyopathy, and chest irradiation)	Perform physical examination and review of systems; perform echocardiography and ECG at entry to long-term follow-up, then periodically, according to risk and findings	Pregnancy may be a risk factor for clinical progression of subclinical disease; refer patient to cardiologist in the case of abnormal findings; if patient received >30 Gy of chest radiation in addition to anthracyclines, consider cardiology referral, given increased risk of premature coronary artery disease
Obesity and the metabolic syndrome	Cranial irradiation; glucocorticoid exposure; chemotherapy-associated neuropathy and other toxic effects; lifestyle	Perform physical examination, check blood pressure, glycated hemoglobin or fasting blood glucose level, lipid profile	Consider consultation with endocrinologist
Stroke and cerebrovascular disease	Cranial irradiation; intrathecal therapy	Perform neurologic examination	Highest risks are associated with radiation dose >18 Gy
Decreased bone mineral density	Cranial irradiation; methotrexate; glucocorticoids; sedentary lifestyle	Perform bone-density evaluation at entry into long-term follow-up; repeat as clinically indicated	Ensure adequate vitamin D and calcium intake; encourage weight-bearing exercise
Growth hormone deficiency	Cranial irradiation ≥ 18 Gy	Assess for short stature or history of treatment with growth hormone during childhood	Consider referral to endocrinologist for assessment of risks and benefits of adult growth hormone-replacement therapy
Neurocognitive deficits	Cranial irradiation; intrathecal chemotherapy	Consider referral for formal neuropsychological evaluation	Treatment before 4 yr of age results in higher risk and more pronounced deficits; neurocognitive testing may be indicated in adulthood, depending on educational and work performance
Cataracts	Glucocorticoid therapy; cranial irradiation	Perform ophthalmologic evaluation	Most cataracts in survivors are posterior subcapsular cataracts and may not have clinically significant effects on vision
Transfusion-associated hepatitis	Transfusion before 1992	If diagnosis made before 1972, test for hepatitis B and C; if diagnosis made between 1972 and 1992, test for hepatitis C	Assume all childhood leukemia survivors received transfusions during therapy
Hypothyroidism	Craniospinal irradiation	Obtain history, perform physical examination; test thyrotropin level annually	
Dental disease	Cranial irradiation	Refer for dental evaluation and recommend regular dental hygiene	Highest risk of dental abnormalities occurs among patients treated before 5 yr of age and among patients who received a radiation dose ≥ 24 Gy

* Data are from clinical guidelines for long-term follow-up of survivors of childhood cancer.¹¹⁻¹³ ECG denotes electrocardiography, and MRI magnetic resonance imaging.



Figure 2. Identical Twins at 26 Years of Age.

The twin on the right was treated for childhood acute lymphoblastic leukemia at 4 years of age. She received many of the therapies that were described in the text, including 24 Gy of cranial radiation.

vivors of leukemia treated before 1992. Survivors should have regular dental and ophthalmologic evaluations. Given reduced bone accretion asso-

ciated with treatment for childhood cancer, bone-density assessment is recommended at entry into adult primary care. Optimal nutrition and exercise to promote bone mineralization should be encouraged. Survivors who were exposed to anthracycline therapy should have a baseline echocardiographic evaluation, with the follow-up frequency dependent on the findings. Patients who underwent cranial irradiation are at particularly high risk for adverse late outcomes, including secondary cancers in the radiation field, growth hormone deficiency, neurocognitive and vocational disability, and cerebrovascular events. If a patient reports difficulties in school or the workplace, neuropsychological testing may be helpful for identifying specific deficits and potential compensatory strategies. Referral to an endocrinologist should also be considered for patients who underwent cranial irradiation in childhood, given the prevalence of growth hormone deficiency.

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Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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