CLINICAL REVIEW

Lifetime Follow-up Care After Childhood Cancer

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Cancers that occur during childhood and adolescence (ages 0 to 19 years) are very responsive to treatment, with a current overall cure rate of better than 80%. However, approximately 75% of childhood cancer survivors develop late effects, including problems with growth and development, vital organ function, reproduction, and psychological health, as well as serious complications of secondary neoplasms and recurrence. The primary physician should continue some level of involvement during all phases of patient care and pay special attention to possible late effects during the follow-up phase. (J Am Board Fam Med 2010;23:647–654.)

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Large numbers of children and adolescents are now being cured of cancer, but the therapy they have received places them at risk for future adverse consequences. Primary care physicians should remain involved with their patients during diagnosis, treatment, follow-up, and, when treatment fails, palliative care. Although specific treatment of the malignant diseases of children and adolescents is best provided by specialists trained in pediatrics and pediatric hematology/oncology, involvement of the primary care physician is especially important when specific cancer treatment is completed and the patients move on to further schooling and work. Lifelong surveillance and intervention are essential.

Scope of the Problem

According to the Centers for Disease Control and Prevention, the incidence of cancer among children (0–14 years old) and adolescents (15–19 years old) is increasing.[1] At the same time, the death rate from childhood cancer is decreasing.[1]

Incidence rates for all childhood cancers increased by 0.6% per year during 1975 to 2002.[2] The incidence of cancer for children and adolescents 0 to 19 years old—for all sites and all races—increased from 15.1 per 100,000 per year in 2002 to 16.6 per 100,000 per year in 2006 (Table 1). Cancer is the fourth most common cause of death among individuals 1 to 19 years old in the United States, after unintentional injury, homicide, and suicide.[3,4]

Death rates from all causes decreased significantly during 1990 to 2004 among both sexes, both age groups, Hispanics, non-Hispanics, all races (except American Indians and Alaska Natives), and all US census regions.[1] The death rate from cancer for children and adolescents 0 to 19 years old for all sites and all races decreased from 5.1 per 100,000 in 1975 to 2.5 per 100,000 in 2006 (Table 2).

The trend in decreasing cancer mortality (Table 3) can be attributed to improved cancer treatment. The reasons for the increased incidence of cancer are not so easy to determine because the causes of childhood cancer are largely unknown and differ from the causes of adult cancer.[5] Genetic predisposition is a known factor.[6] Increased exposure to radiation from radiology tests,[7–9] including plain radiography and computerized tomography,[10–12] and from communication systems[13] can contribute to the problem. Chemicals in food could have adverse effects. It has also been suggested that better diagnostic methods or changes in reporting might

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Table 1. Surveillance Epidemiology and End Results Age-Adjusted Childhood Cancer Incidence* among the US Population for All Races and Sexes, 2002 to 2006 by Primary Cancer Site[3]

	Incidence by Age	
	0–14 Years	0–19 Years
All sites, all races	15.1	16.6
Leukemia	5.0	4.5
Acute lymphoblastic leukemia	4.0	3.4
Brain and nervous system	3.2	2.9
Hodgkin lymphoma	0.6	1.2
Soft tissue	1.0	1.1
Non-Hodgkin lymphoma	0.9	1.1
Bone and joint	0.7	0.9
Kidney and renal pelvis	0.8	0.6

*Rates are per 100,000 and are age-adjusted to the 2000 US population.

help to explain the increased incidence of childhood cancer.[5]

Classification of Childhood Cancers

Although most adult solid cancers are carcinomas and traditionally have been classified according to primary site, childhood cancers are histologically more diverse. According to the International Classification of Diseases, childhood cancers are subdivided into 10 groups and listed according to morphology rather than frequency,[14] including nonmalignant intracranial and intraspinal tumors (Table 4).

Treatment

The primary modes of therapy for childhood and adolescent cancer are surgery, radiation, chemotherapy, and transplantation. Surgery has a role in biopsy (pathologic diagnosis); staging; and, when possible, removal of the tumor or affected organ. Because of possible microscopic residual disease or distant micrometastases, adjuvant radiation and chemotherapy are usually added to the treatment regimen.

Surgical removal of the affected kidney (nephrectomy) remains the primary treatment for Wilms tumor (nephroblastoma), the second most successfully managed malignancy of childhood, with a cure rate of 91.2% (Table 3). Studies by the National Wilms Tumor Study Group have shown radiation to be unnecessary if the tumor can be completely resected.[15] Bone tumors are treated with amputation or limb-sparing surgery; the limb-salvaging procedure results in somewhat better function than amputation.[16,17] Splenectomy, which carries a lifetime risk for sepsis, is no longer a routine staging procedure for Hodgkin lymphoma. Diagnostic imaging studies provide more accurate information about the abdominal organs and lymph nodes. Patients who are asplenic, however, must be protected against bacterial infections with immunizations and chemoprophylaxis, along with early evaluation and treatment for febrile illnesses.

Radiotherapy is an important treatment modality for a number of childhood cancers, but children and adolescents are especially sensitive and susceptible to side effects because their tissues are still growing and developing. Radiation, along with additional chemotherapy, is highly effective against Hodgkin lymphoma, which has the highest cure rate among childhood cancers at 95.5% (Table 3). Unfortunately, radiation to the mantle area or chest can place the patient at risk for thyroid disorders, pulmonary complications, and lung and breast cancers.[18,19] Radiotherapy is standard treatment for some brain tumors, as well as for some rhabdomyosarcomas and other soft tissue sarcomas of the head and neck. Radiation of the brain introduces a number of further serious neurocognitive late effects. Melanoma and other skin cancers can develop in the involved field after radiation to any area of the body.[20]

Table 2. Surveillance Epidemiology and End Results Age-Adjusted Childhood Cancer Death Rates* among the US Population for All Races and Sexes, 1975 and 2006 by Primary Cancer Site

	Death Rates by Age			
	0–14 Years		0–19 Years	
	1975	2006	1975	2006
All sites, all races	4.9	2.2	5.1	2.5
Brain and nervous system	1.0	0.6	0.9	0.7
Leukemia	2.1	0.7	2.0	0.7
Acute lymphoblastic leukemia	1.2	0.3	1.0	0.3
Soft tissue	0.1	0.1	0.2	0.2
Kidney and renal pelvis	0.2	0.1	0.1	0.1
Non-Hodgkin lymphoma	0.4	0.1	0.4	0.1
Hodgkin lymphoma	0.0	—	0.1	0.0

*Rates are per 100,000 and are age-adjusted to the 2000 US population.

Table 3. Surveillance Epidemiology and End Results 5-Year Survival Rates* among the US Population, 1975 to 1977 and 1999 to 2005, by Selected Primary Cancer Site

	Survival Rates by Age (%)			
	0–14 Years		0–19 Years	
	1975–1977	1999–2005	1975–1977	1999–2005
All sites, all races	58.1	81.3	61.6	81.0
Hodgkin lymphoma	80.5	95.4	86.0	95.5
Wilms tumor	73.1	91.2	72.6	91.2
Acute lymphoblastic leukemia	57.6	89.0	54.1	85.1
Non-Hodgkin lymphoma	43.5	86.3	44.6	84.4
Leukemia	50.4	83.6	45.5	78.7
Soft tissue	61.0	81.0	65.2	75.6
Brain and central nervous system	56.9	73.8	58.8	74.2
Neuroblastoma	52.4	74.2	52.7	73.9
Bone and joint	49.9	71.8	50.4	68.5
Acute myeloid leukemia	18.8	60.2	18.7	55.0

*Rates are based on follow-up of patients into 2006.

Chemotherapy is included in the treatment of most forms of childhood cancer to deal with residual disease and distant micrometastases, but chemotherapy alone is usually adequate for control of leukemias. Chemotherapy for acute lymphoblastic leukemia (ALL) has undergone improvement and refinement so that the 5-year survival rate is now 81.3% for children ages 0 to 14 and 85.1% for children and adolescents ages 0 to 19 years (Table 3). The first chemotherapeutic agent to achieve a temporary remission of ALL in 1948 was aminopterin, a relative of methotrexate, followed by 6-mercaptopurine in 1953, l-asparaginase in 1961, vincristine in 1962, and subsequently by corticosteroids and other agents,[21] including epipodophyllotoxins and heavy metals. More recently, monoclonal antibodies have become used as anticancer therapy.[22,23] Further refinements of the administration of chemotherapy included continuous combination therapy and intrathecal chemotherapy against leukemic cell sanctuaries in the central nervous system and meninges. The establishment of large, national, multi-institutional, cooperative study groups funded by the National Institutes of Health for the study of childhood malignancies helped to assess the effectiveness and toxicities of treatment regimens, even for cancers that were uncommon or rare.[21] The cooperative study groups in the United States have combined to become the present Children's Oncology Group.

Table 4. Childhood Cancers in Diagnostic Groups According to the International Classification of Childhood Cancer[14]

Classification	Type(s) of Cancer
I	Leukemias, myeloproliferative, and myelodysplastic diseases
II	Lymphomas and reticuloendothelial neoplasms
III	Central nervous system and other intracranial and intraspinal neoplasms
IV	Neuroblastoma and other peripheral nervous cell tumors
V	Retinoblastoma
VI	Renal tumors
VII	Hepatic tumors
VIII	Malignant bone tumors
IX	Soft tissue and other extraosseous sarcomas
X	Germ cell tumors, trophoblastic tumors, and neoplasms of gonads

Bone marrow transplantation and peripheral blood stem cell transplantation is accomplished by destruction of the cells of the marrow and replacement with the donor's own stem cells (autologous transplant), stem cells from an identical twin (syngeneic transplant), or stem cells from a matched donor, usually a close relative (allogeneic transplant). Umbilical cords are another source of stem cells. Patients with acute myeloid leukemia are the most frequent candidates for myeloblative stem cell transplant.[24] Major transplant toxicities include graft rejection, graft-versus-host disease, and the problems that go along with the necessary pro-

longed immunosuppression, such as septicemia and other infections.

Many useful current publications concerning childhood cancer survivors are from a large epidemiologic study, the Childhood Cancer Survivors Study, based at the University of Minnesota Cancer Center. Information from the Childhood Cancer Survivors Study can be accessed through the National Institutes of Health website[25] or by calling 1–800-4-CANCER. Another useful resource is the "Quick Reference for Pediatric Oncology Clinicians: The Psychiatric and Psychological Dimensions of Pediatric Cancer Symptom Management" published through the American Psychosocial Oncology Society.[26]

Late Effects

At present, treatment results in a cure rate of ≥80% for childhood cancer[27]; however, a high rate of adverse events can be expected among survivors. Reports in the literature indicate that approximately 75% of survivors have one or more late effects[28–30]; the complications of therapy may be categorized as shown in Table 5. The majority of late effects result from treatment-related toxicity or from complications of the original cancer.[27,31] Additional problems include comorbidities that might be worse than otherwise expected and health problems that occur with aging.[32]

The most common late effects are those of growth and development, including linear growth velocity, intellectual development, and sexual maturation (Table 5). Damage to the hypothalamus from cranial radiation[33,34] or from chemotherapy alone[35] can cause decreased production of growth hormones and growth failure. Learning problems and hyperactivity can also be attributed to cranial radiation.[36,37] Delayed sexual maturation can be

Table 5. Assessment of Late Effects*

Complication	Surveillance	Treatment Modality
Growth failure	History/examination	Chemotherapy
		Cranial radiation
Intellectual function	Psychiatric test	Cranial radiation
Neurological toxicity	Neurologic examination	Cranial radiation
		Vincristine
Dental	Examination	Chemotherapy
	Cleaning	Cranial radiation
Male infertility	LH, FSH	Abdominal/pelvic radiation
	Testosterone	Cyclophosphamide
	Sperm count	Doxorubicin/daunomycin
Female infertility	LH, FSH	Abdominal/pelvic radiation
	Estradial	Cyclophosphamide
		Doxorubicin/daunomycin
Cardiac	ECG, echocardiogram	Doxorubicin/daunomycin
Bladder	Urinalysis	Cyclophosphamide
		Ifosphamide
Lung	Chest radiograph	Buslfan
Liver	LFTs	Methotrexate
Bone	DEXA scan	Prednisone/dexamethasone
		Methotrexate
Eye (cataracts)	Visual acuity	Prednisone/dexamethasone
Ear (hearing)	Audiogram	Cisplatinum/carboplatinum
Second neoplasms	Examination	Radiation
	Blood count	Cyclophosphamide
	Urinalysis	Doxorubicin/daunomycin
Recurrence	History/examination	

*As recommended in "Long-Term Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers," published by the Children's Oncology Group in 2008 (www.survivorshipguidelines.org).
LH, luteinizing hormone; FSH, follicle-stimulating hormone; ECG, electrocardiogram; LFT, liver function test; DEXA, dual energy x-ray absorptiometry.

caused by cranial radiation, abdominal and pelvic radiation, and alkylating agents. Although prophylactic cranial radiation has largely been supplanted by intrathecal chemotherapy, it is still given to patients with T-cell ALL and those with a central nervous system relapse of pre–B-cell leukemia.

Obesity, which is increasing in general among children and adolescents in the United States,[38] is increasing among childhood cancer survivors as well and can be related to cranial radiation, especially in women who were treated at an early age.[39,40] There is evidence that a genetic variation in the leptin receptor gene can influence obesity among survivors,[41] and it has been suggested that adipose dysfunction could play a role in cancer pathogenesis and progression.[42] It is also important to note that a significant proportion of childhood cancer survivors are underweight as adults.[40,43]

Failure to reach peak bone mass, with 2 important resulting problems (osteoporosis/osteopenia and osteonecrosis), is not uncommon among survivors and is now beginning to receive appropriate attention.[44,45] Possible complications of bone mineral density deficits include fractures, kyphosis, lordosis, scoliosis, abnormal gait, and bone or muscle pain.[46,47]

Cardiovascular problems, the most common of the complications that affect vital organs (Table 5), can occur early or late and are seen especially among individuals who have received anthracyclines.[48–51] Even survivors who were treated with low doses should receive, in addition to routine cardiac screening, periodic echocardiography and measurement of natriuretic peptides.[48,50] Hypertension, which is not uncommon among survivors, requires attention and early intervention as a risk factor for atherosclerotic cardiovascular disease.[52] Other effects on vital organs that require attention include respiratory symptoms, changes in liver function test values, hyperglycemia, hypothyroidism, and altered renal function.

Women who have survived childhood or adolescent cancer are less likely to become pregnant than their siblings.[53,54] Hypothalamic or pituitary radiation and ovarian or uterine radiation significantly reduce the likelihood of female survivors to become pregnant, as does chemotherapy with alkylating agents, because of altered frequency of ovulation.[53,54] Infants born to female survivors do not have an increased risk of malformations but often have early delivery and low birth weight.[55] The female partners of male cancer survivors are not likely to have complicated pregnancies except for the possibility of preeclampsia and low birth weight.[56] Before the start of therapy, pediatric and adolescent cancer victims should be informed of the possible effects of treatment on fertility and of options for fertility preservation, such as ovarian transposition before pelvic radiation, sperm and embryo cryopreservation, and egg freezing.[57,58] However, delaying the start of treatment for these procedures must be given serious consideration, especially in the case of advanced cancers.

The most serious late effects to watch for are recurrences[59] and second cancers[60]; second malignancies are the leading cause of death among long-term (≥15 years) survivors.[61] Second cancers can be classified into 2 groups: (1) myelodysplasia and AML related to chemotherapy and (2) solid second malignancies related to radiation.[62] Several large, recent studies have shown that the excess risk for survivors continues for at least 3 decades.[63–65] It is important to note that some second cancers can be treated with good results,[66] but others, especially those of the brain, are not curable.

Although the majority of childhood cancer survivors do not exhibit adverse symptoms concerning their psychological health and well-being, they are significantly more likely to report depression and symptoms of somatic distress than their siblings.[36] A substantial subset of survivors has reported symptoms of posttraumatic stress disorder compared with the general population.[67] Furthermore, adult survivors of childhood cancer, especially those with physical health problems, are at increased risk for suicide ideation.[68] Regarding employment, young adult survivors report higher rates of unemployment, underemployment, and job discrimination than their siblings.[69] They are less likely to marry than their sibling controls, but their divorce pattern is similar to that of their peers[70]; not being married is likely to be associated with short stature, poor physical findings, and cognitive problems.[70]

Role of the Primary Physician

Although specific cancer treatment is best provided by specialists trained in pediatric hematology/oncology, it is essential that primary physicians remain involved in the care of children and adolescents who have malignant diseases.[71] The important phases of care include helping to make

the original diagnosis (ie, being alert for adverse symptoms that might call attention to diagnosis of childhood cancer or the onset of late effects); serving as a guide for referrals for cancer diagnosis and treatment as well as diagnosis and treatment of late effects; providing supportive emotional care to the patient and family through often stressful treatment; remaining alert to possible late effects during careful lifetime follow-up and continuing routine day-to-day medical care as needed; and, finally, assisting with end-of-life decisions and palliative care if treatment is unsuccessful.

The diagnosis is made during phase one. The early signs and symptoms of cancer are often not specific and can include fever, lethargy, weight loss, general malaise, and pain, which can be attributed to a benign cause. These complaints must be taken seriously, and they should be carefully evaluated if they persist to avoid a delayed diagnosis. The primary physician usually sends the patient for specific testing and, with either a presumptive or a definitive diagnosis, refers the family for specialty care.

The primary physician should remain involved and informed during the second phase, during which definitive treatment is conducted, to offer emotional support to the patient and family. This should include ensuring that proper attention is given to health concerns and routine medical care for siblings and other family members. If travel to a tertiary care center is difficult, the community care provider could administer and monitor certain treatments. At some point the parents need to make an important decision about which treatment plan to accept or whether or not to continue treatment. As a friend and confidant, the primary physician would be in a position to discuss alternatives and to support whatever decision is made.

The third phase follows after treatment is completed. Most specialists offer continuing care in follow-up clinics or late effects clinics, and follow-up should be lifelong. Because the primary care physician continues to be involved with day-to-day problems such as minor illnesses, playground or sports injuries, school physical examinations, and routine immunizations, he or she is likely to be the first observer of any untoward symptoms or signs. Knowing that late effects are frequent and can be expected in $\geq$70% of survivors[27] will allow the primary physician to recognize and deal promptly with problems when they occur.

A fourth and final phase occurs if treatment fails and death is inevitable. Whether the patient and his or her family choose to receive end-of-life care in the hospital, hospice, or at home, the primary physician should remain available to the patient and family.

Conclusion

It is important for primary care physicians, including family practitioners, pediatricians, and internists, to continue their involvement with child and adolescent cancer patients and their families throughout all phases of management. They should be especially alert to the possibility of late effects that may occur during the follow-up period.

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