

## Highlights

- Treatments for childhood leukemia and lymphoma have led to increased survival rates. However, some treatments may cause significant long-term or late effects.
- Follow-up medical care to monitor survivors for possible long-term or late effects is important.
- Parents should discuss possible long-term and late effects of treatment with their child's healthcare providers for the purposes of planning, evaluation and follow-up.
- Factors that determine a child's risk for long-term or late effects include type and duration of treatment, age at time of treatment, gender and overall health.
- Parents may need to educate family members and friends about the challenges posed by the long-term and late effects of treatment. Parents need to advocate with school personnel on their child's behalf.
- Improvements in treatment have resulted in minimizing certain adverse effects of cancer therapies but more research in this area is needed.
- Long-term and late effects of treatment are important, ongoing areas of study. Researchers are working to improve the understanding of long-term and late effects and to create guidelines on follow-up care.
- Survivorship care plans are an important part of a child's long-term health plan. There is value in creating and using these plans for lifelong benefits.

## Introduction

New drugs and new uses for existing drugs, as well as improvements in radiation therapy and stem cell transplantation techniques, have greatly improved cure rates and remission periods for children with leukemia or lymphoma. Research to improve outcomes for greater numbers of children is ongoing. There is an emphasis on tailoring therapies to decrease side effects as well as long-term and late effects.

Most survivors of childhood leukemia or lymphoma do not develop significant long-term or late effects of treatment. Effects can range from mild to severe. However, it is important for parents to discuss possible long-term and late effects with their child's treatment team so that the proper planning, evaluation and follow-up can take place.

Factors that influence a child's risk for developing long-term or late effects include

- Type and duration of treatment
- Gender and age at time of treatment
- Overall health.

This publication can help you understand long-term and late effects and it provides guidance and resources for dealing with these treatment effects.

## Long-Term and Late Effects

“Long-term effects” of cancer therapy are medical problems that persist for months or years after treatment ends. Examples of long-term effects are infertility, growth problems and treatment-related fatigue.

“Late effects” are medical problems that do not develop or become apparent until years after treatment ends. Examples of late effects include the development of a treatment-related cancer or heart disease.

The long-term and late effects for survivors of childhood leukemia or lymphoma that may occur include effects on

- Learning, called “cognitive effects”
- Physical development
- Psychological development.

Specific effects depend upon a child's age, gender, type of treatment and additional factors. The range and severity of potential long-term and late effects vary. Some children will have no significant long-term or late effects or very mild effects, and others may have serious complications. Some long-term and late effects become evident with maturation (puberty), growth and the normal aging process. It is important for all children to be evaluated. Early intervention and healthy lifestyle practices (not smoking, good nutrition and exercise, regular screening and follow-up) may have a positive effect on the occurrence and/or severity of effects.

### Learning (Cognitive) Effects

Learning disabilities can begin during treatment or become evident months or years after treatment. Mathematics, spatial relationships, problem solving, attention span, reading and spelling, processing of information, planning and organizing, and concentration skills are all areas of learning that may be affected. Problems with fine motor coordination, which might cause poor handwriting, can also develop.

### Physical Effects

Children treated for leukemia or lymphoma may be at risk for fatigue, growth delays, thyroid dysfunction, hearing loss and the development of a secondary cancer. Children may also become infertile. The risk of infertility is related to the areas of the body involved with cancer and the type, dose and combination of therapy. Age at treatment, sex and genetic factors influence this risk.

### Psychological Effects

Most childhood survivors of cancer are psychologically healthy. However, some studies indicate that a small number of childhood leukemia or lymphoma survivors were more likely than healthy peers to report changes in mood, feelings or behavior, including depression or posttraumatic stress disorder.

### Managing Long-Term and Late Effects

Treatment for childhood leukemia or lymphoma consists of chemotherapy and other drug therapies and may include radiation therapy or allogeneic stem cell transplantation. There are risks for long-term and late effects common to all of these treatments, which may include learning problems, fatigue, bone or joint pain and an increased risk for developing a secondary cancer. Please see *Examples of Long-Term and Late Effects of Treatment* on page 3.

Parents may need to educate other family members, friends, school personnel and healthcare providers about long-term and late effects.

Here are some ideas for steps parents can take:

- Talk to your child's doctors and discuss the potential for long-term and late effects, as well as an ongoing plan to evaluate possible effects of treatment.
- Keep a record of physical and emotional symptoms that your child experiences and discuss them with your child's treatment team.
- Make sure that your child's oncology team, primary care providers and specialists—for example, cardiologists, allergists and endocrinologists—communicate with each other.
- Keep all medical records, including dates and locations of treatment, specific drug and supportive therapies (for example, blood transfusions) and dosages, and specific sites and amounts of radiation therapy, if applicable. Keep copies of blood, marrow and imaging test (MRI, CT scan, x-ray) results.
- Ask your child's doctor for a written summary of the cancer treatment that your child received, including names of all drugs used, whether or not radiation was used, what type of surgical procedures were performed and whether your child experienced any unusual or especially severe acute complications of cancer therapy. This summary is called a "survivorship care plan." You can read more about this on page 3.
- Help your child to develop and maintain a healthy lifestyle after treatment ends, including appropriate exercise, sun protection, good nutrition and not smoking. Enlist the help of health professionals as needed.
- Keep medical follow-up appointments with the oncology team even if your child is feeling well.

### Returning to School

School personnel may not be aware of the potential for long-term and late effects of treatment. Parents and medical professionals need to inform educators about the child's education needs before the child returns to school. Parents, educators and medical professionals can work together to develop a program tailored to the child's specific needs. The program may include

- Baseline testing—Children may benefit from baseline testing before treatment, if possible, and continued comparative testing during and after treatment to

determine whether neurocognitive problems or associated learning disabilities have developed.

- Special accommodations—Steps can be taken to assist a child's return to school, such as allowing him or her more time to complete class work or take exams. Children adversely affected by cancer treatment may qualify for aid under three different federal laws: the Americans with Disabilities Act, the Individuals with Disabilities Education Act and the Rehabilitation Act.
- Long-term planning—Plans can be developed to help a child through certain situations such as transitioning from middle school to high school or going on from high school to secondary education and adult life.

More information is available about the transition back to school in the free LLS publication *Learning & Living With Cancer: Advocating for your child's educational needs*.

### Follow-up Care

Childhood cancer survivors should have physical examinations yearly or more often, as needed. Regular medical follow-up for childhood cancer survivors enables doctors to assess the effects of therapy, identify recurrence of the disease and detect long-term or late effects.

A child who has been treated for cancer should see his or her primary care doctor for general health examinations and an oncologist for follow-up care related to cancer. Some treatment centers have follow-up clinics, which provide a comprehensive, multidisciplinary approach to monitoring and supporting cancer survivors. The Pediatric Oncology (Ped-Onc) Resource Center maintains a list of follow-up clinics at <http://ped-onc.acor.org/treatment/surclinics.html>.

Your child's oncologist should help create a survivorship care plan or follow-up plan to monitor for late effects. This can help the primary care doctor who might not be familiar with possible problems. These plans are individualized and long-term. It is helpful for a child to be seen yearly at a long-term follow-up clinic along with regular visits to a pediatrician.

You can find information about survivorship plans and guidelines for survivors of childhood, adolescent and young adult cancers by visiting the *Resources* section on page 7.

Children treated with

- Radiation therapy should have yearly physical examinations, including growth, thyroid, bone and hormone monitoring. Girls treated with mediastinal radiation therapy should be taught breast self-examination; begin baseline mammograms at age

25-30 years or 10 years after radiation therapy; have annual clinical breast examinations and repeat mammograms every 2-3 years, depending on breast tissue.

- Cranial radiation therapy should undergo neurocognitive testing at baseline, then whenever the clinical need arises.
- Anthracycline, high-dose cyclophosphamide, or mediastinal or spinal radiation therapy should have baseline testing for heart function, then every 3-5 years after treatment or as needed if abnormalities are present. Cholesterol and triglyceride levels should be tracked as they may affect development of coronary artery heart disease.
- Chest or mediastinal radiation, bleomycin, or carmustine or lomustine therapy should have baseline lung function testing, then every 3-5 years as needed. Educate these (and all) children on the importance of not smoking.
- Cisplatin or carboplatin should have creatinine clearance measured at baseline and then every 3-5 years as needed.
- Ifosfamide should be monitored yearly for evidence of Fanconi syndrome, a type of kidney problem.
- 6-mercaptopurine, methotrexate, actinomycin-D, or abdominal radiation therapy should have liver function tests every 1-3 years.
- Etoposide or alkylating agents should get complete blood counts (CBCs) yearly for evidence of myelodysplastic syndromes or a secondary leukemia.
- Allogeneic stem cell transplantation and children who have experienced chronic graft-versus-host disease should be monitored for secondary cancers in the gastrointestinal tract and skin, an ability to fight off common infections, bone health (osteoporosis) and chronic lung disease.

Data has not been collected for a long enough time period for the long-term and late effects of newer drugs to be identified. Talk to your doctor for more information.

### Examples of Long-Term and Late Effects of Treatment

The following is a general list of examples of potential risks for long-term or late effects. Keep in mind that risk depends on many factors, including treatment, treatment combinations, dosages and other individual risk factors. The following information is provided as a basis for discussion between parents and doctors. Talk to your child's treatment team about the actual risks of your child's treatment.

## Drug Therapy

A number of chemotherapies and other drugs are used to treat children with leukemia or lymphoma. Some of the types of drugs used and their potential long-term and late effects are listed below.

**Alkylating drugs** have been associated with heart and lung problems, risk for secondary cancers, low testosterone levels and sperm counts in boys and premature ovarian failure (POF) or premature menopause in girls. The combination of alkylating drugs and radiation therapy increases the risk for fertility problems. Examples of alkylating drugs are

- Cyclophosphamide, which can increase risk for chronic heart failure, myelodysplastic syndromes and acute myeloid leukemia (AML).
- Procarbazine, nitrogen mustard, and ifosfamide, which can increase risk for myelodysplastic syndromes and acute myeloid leukemia.
- Carmustine and busulfan, which can increase risk for scarring and inflammation of the lungs.
- Carboplatin and cisplatin, which can increase risk for hearing loss and peripheral neuropathy or contribute to heart damage.

**Anthracyclines** have been associated with heart damage (e.g., heart muscle injury, chronic heart failure). Heart muscle damage is usually related to the cumulative dose of anthracyclines, which may be used to treat children with acute myeloid leukemia, acute lymphoblastic leukemia (ALL) and Hodgkin or non-Hodgkin lymphoma. Anthracyclines include doxorubicin, idarubicin and daunorubicin. Children appear to have less tolerance to doses of multiple chemotherapeutic agents than adults do, and when chest radiation is combined with these chemotherapeutic agents, the risk for heart failure is possible at lower dosages of the drugs. Scientists are also studying whether exposure to anthracyclines affects later development of coronary artery disease.

Anthracycline drugs may also increase the risk for developing a secondary cancer, such as acute myeloid leukemia or myelodysplastic syndrome.

**Bleomycin** is an antitumor antibiotic drug therapy commonly used to treat germ cell tumors and lymphoma that, when used in high dosages, can potentially result in acute respiratory distress syndrome and lung failure.

**Corticosteroids** have been associated with osteoporosis and cataracts. Corticosteroids have been used to treat children with leukemia and lymphoma. High dosages of

corticosteroids (sometimes used to treat children with acute lymphoblastic leukemia) may be associated with avascular necrosis of the hip, a condition that may require hip joint replacement. Common drugs in this class include prednisone and dexamethasone.

**DNA repair enzyme inhibitors**, which are derived from toxins found in certain plants, can cause acute myeloid leukemia. Etoposide and teniposide are examples of this class of drugs.

**Drugs that prevent the cells from dividing by blocking mitosis**, such as vincristine and vinblastine, have been associated with peripheral neuropathy.

**Methotrexate** is used to treat leukemia and lymphoma and has been associated with osteoporosis and lung damage. Intrathecal and intravenous methotrexate can cause cognitive impairment.

Research is ongoing to understand the potential long-term and late effects for newer therapies, including imatinib mesylate (Gleevec®) and dasatinib (Sprycel®) for Philadelphia chromosome-positive acute lymphoblastic leukemia (ALL). In children and adolescents taking imatinib who have been diagnosed with chronic myeloid leukemia (CML), a long-term effect being studied is failure to gain appropriate height when imatinib was started before puberty. Studies are ongoing to determine other long-term and late effects for CML patients.

## Radiation Therapy

Radiation therapy is the use of ionizing radiation to kill cancer cells. For some children, radiation therapy to the head and neck may lead to

- Learning disabilities (cognitive impairment)
- Growth hormone deficiency
- Hypothyroidism or hyperthyroidism
- Hearing loss
- Vision problems such as cataracts or glaucoma
- Dental abnormalities
- Brain or thyroid cancer
- Osteoporosis.

Some children who receive radiation to the brain may not reach puberty at the appropriate age. A small percentage experience premature puberty, while in other children puberty is significantly delayed.



Radiation therapy to the chest can cause

- Lung damage (scarring, inflammation, breathing difficulties)
- Heart damage (scarring, inflammation, coronary heart disease)
- Osteosarcoma
- Breast or thyroid cancer
- Hypothyroidism or hyperthyroidism.

In boys, radiation therapy to the testes (as is sometimes done in patients with acute lymphoblastic leukemia) or stomach radiation (as is sometimes done for advanced Hodgkin lymphoma) may cause fertility problems. In girls, stomach radiation may cause fertility problems including premature ovarian failure or premature menopause. The effect of radiation on the ovaries and testes depends upon age, dosage and location.

Total body irradiation for individuals undergoing hematopoietic stem cell transplantation can potentially cause gonadal failure and fertility issues.

High-dose radiation to the spleen can increase the risk of repeated bacterial infections.

### Treatments Under Investigation

Research to learn more about long-term and late effects continues to increase. Patients may have the opportunity to take part in clinical trials. These trials, conducted under rigorous guidelines, help clinicians and researchers to determine the beneficial and adverse effects of potential new treatments. Studies are also conducted to evaluate new indications for therapies that are already approved for other diseases.

In addition, research to better understand and treat long-term and late effects associated with certain cancer therapies is ongoing. Researchers are studying ways to lessen or minimize the negative impact of existing therapies. Researchers are also identifying biomarkers—high levels of certain substances in the body, such as antibodies or hormones, or genetic factors that might increase susceptibility to certain effects. These biomarkers may indicate a higher-than-normal risk for developing a specific long-term or late effect. Knowing the identity of these biomarkers allows researchers to develop tests that detect their presence in an individual. Test results can predict a patient at risk for the specific effects associated with a particular biomarker and thus allow doctors to plan treatment accordingly. Current research seeks to understand

how factors such as aging and socioeconomic status influence long-term and late effects.

LLS is funding research in identifying risk factors for osteonecrosis (bone death) to avoid later complications, to see if vitamin D deficiency and change in body fat has a role in bone loss, to document the risk for graft-versus-host disease (GVHD) after transplants using peripheral-blood stem cells instead of bone marrow and its effect on survival and to examine the role of genetic variation on the development of treatment-related obesity. For more information about clinical trials, see the free LLS publication *Understanding Clinical Trials for Blood Cancers* at [www.LLS.org/resourcecenter](http://www.LLS.org/resourcecenter) or call our Information Specialists.

### Glossary

You may see or hear some of the following terms. However, not all terms will apply to your child's treatment or treatment effects.

#### Avascular Necrosis

A condition in which the blood vessels that nourish the bones die, causing parts of the bone to weaken or collapse.

#### Cognitive Impairment

See Learning Disabilities

#### Dental Abnormalities

The most common dental problems are failure of the teeth to develop (dental or tooth agenesis), arrested root development, microdontia (unusually small teeth), underdevelopment of the jaw and enamel abnormalities.

#### Fatigue

An unusual tiredness that interferes with daily life and cannot be overcome by resting or a good night's sleep. It affects many patients (of all ages) treated for leukemia, Hodgkin and non-Hodgkin lymphoma. For some patients, fatigue following treatment can last for months or years, causing physical issues such as difficulty performing daily tasks and cognitive issues such as concentration problems.

#### Fertility

The ability to become pregnant or father a child. Some cancer treatments affect fertility in males and females. Survivors of leukemia or lymphoma who have been treated with modern conventional therapy have relatively low risk for infertility or delayed or impaired puberty. Most go on to have normal fertility and healthy offspring. However, a small

number are unable to have children. Certain drug therapies can be harmful to sperm production; however, production may resume months to years after chemotherapy ends.

Both males and females may experience some sexual effects during and after treatment. Males may have difficulty sustaining an erection, may have low sperm counts and may become sterile. Females may fail to ovulate and/or conceive, have irregular menses, experience painful intercourse and develop early menopausal signs such as hot flashes, insomnia and increased irritability.

### Hyperthyroidism

Too much activity of the thyroid gland. The highly variable symptoms include nervousness, sudden weight loss, rapid heartbeat, fatigue and increased sensitivity to heat.

### Hypothyroidism

Too little activity of the thyroid gland. The highly variable symptoms include increased sensitivity to cold, weight gain, painful joints, muscle aches and pale, dry skin. Hypothyroidism is more common than hyperthyroidism.

### Learning Disabilities (Cognitive Impairment)

Problems that affect thinking or memory, including organization, reading, processing speed, visual memory, understanding math concepts or remembering math facts. The degree of impairment depends on whether or not cranial radiation is part of treatment, the dosage of radiation or drugs and/or a child's age and gender. Children treated during infancy or early childhood are at the highest risk. Girls are more susceptible to such effects than boys.

### Osteoporosis

A condition in which decreased bone density results in abnormally thin bones that are prone to fracture.

### Peripheral Neuropathy

Numbness, tingling or pain in the hands and feet may persist for months or years following treatment with certain drugs that are toxic to the nerves. The peripheral nerves are the nerves found outside of the central nervous system (brain and spinal cord).

### Premature Ovarian Failure

Premature ovarian failure, or POF, is also called "premature menopause." With POF, a female may still have follicles that can become eggs. However, she may have fewer of these than a female without POF. With menopause, a female has no follicles left at all. For this reason, she no longer gets a

period. A girl with POF can still get a period, but it is not likely to be a regular period. Unlike menopause, it is possible for POF to be temporary.

### Secondary Cancers

Cancer survivors treated with chemotherapy or radiation therapy are at some increased risk for developing a second malignant neoplasm (SMN) compared to the general population. The risk is greater in younger patients and increases with total dosage of radiation. Survivors of childhood Hodgkin lymphoma have the greatest risk for developing a secondary cancer.

- Acute Myeloid Leukemia and Myelodysplastic Syndromes—Treatment-related acute myeloid leukemia/myelodysplastic syndromes may occur in some people who received treatment with alkylating drugs or DNA repair enzyme inhibitors.
- Brain Tumors—The incidence of secondary solid tumors is very low following diagnosis of childhood acute lymphoblastic leukemia (ALL). Central nervous system tumors are the most common secondary malignancy seen in childhood ALL survivors and are mainly associated with exposure to cranial radiation.
- Breast Cancer—Treatment with mantle radiation therapy for Hodgkin lymphoma increases the risk for breast cancer. Females treated before the age of 21 years have a significantly greater risk than adult women. Younger women should receive annual mammograms and biannual breast exams, starting a decade after their treatment.
- Osteosarcoma—Patients who have received mantle radiation therapy for Hodgkin lymphoma have an increased risk for developing osteosarcoma, the most common type of bone cancer. The risk for developing osteosarcoma depends upon the dosage of radiation and whether individuals were also concurrently treated with alkylating drugs.

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## We're Here to Help

LLS is the world's largest voluntary health organization dedicated to funding blood cancer research, education and patient services. LLS has chapters throughout the country and in Canada. To find the chapter nearest you, enter your ZIP code into "Find your Chapter" at [www.LLS.org](http://www.LLS.org) or contact

### The Leukemia & Lymphoma Society

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Callers may speak directly with an Information Specialist Monday through Friday, from 9 a.m. to 6 p.m. ET. You may also contact an Information Specialist between 10 a.m. and 5 p.m. ET by clicking on "Live Chat" at [www.LLS.org](http://www.LLS.org) or by sending an email. Information Specialists can answer general questions about diagnosis and treatment options, offer guidance and support and assist with clinical-trial searches for leukemia, lymphoma, myeloma, myelodysplastic syndromes and myeloproliferative neoplasms. The LLS website has information about how to find a clinical trial, including a link to TrialCheck®, a clinical-trial search service.

LLS also provides free publications that can be ordered via the 800 number or through the "Free Education Materials" option at [www.LLS.org/resourcecenter](http://www.LLS.org/resourcecenter).

## Resources

### Centers for Disease Control and Prevention (CDC). Cancer Prevention and Control, Cancer Survivorship.

[www.cdc.gov/cancer/survivorship](http://www.cdc.gov/cancer/survivorship)

CDC works with public, nonprofit, and private partners to create and implement strategies to help the millions of people in the United States who live with, through, and beyond cancer.

### Children's Oncology Group

[www.childrensoncologygroup.org/](http://www.childrensoncologygroup.org/)

The Children's Oncology Group offers a Family Handbook which provides families with reliable information about

treatment, support, and follow-up care for children and young people with cancer. To reach their *Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent and Young Adult Cancers* visit <http://www.survivorshipguidelines.org/>

### LIVESTRONG

[www.livestrongcareplan.org](http://www.livestrongcareplan.org)

LIVESTRONG provides the LIVESTRONG Care Plan, a "survivorship care plan" that is individualized based on the answers provided in a brief questionnaire.

### National Cancer Institute (NCI). Office of Cancer Survivorship.

<http://dccps.nci.nih.gov/ocs>

The mission of the Office of Cancer Survivorship (OCS) is to enhance the quality and length of survival of all persons diagnosed with cancer and to minimize or stabilize adverse effects experienced during cancer survivorship. OCS conducts and supports research that both examines and addresses the long- and short-term physical, psychological, social, and economic effects of cancer and its treatment among pediatric and adult survivors of cancer and their families.

### The Pediatric Oncology (Ped-Onc) Resource Center

<http://ped-onc.org/survivors/index.html>

This website offers information on cancer survivorship including a list of follow-up clinics.

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