

# Long-Term and Late Effects of Treatment for Childhood Leukemia or Lymphoma

*No. 15 in a series providing the latest information on blood cancers for patients, caregivers and healthcare professionals*

## 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. 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.

## 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 fact sheet 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.

### *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, and these may include problems with learning, 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 6.

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 potential 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—are in communication.
- 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.
- 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 including The Leukemia & Lymphoma Society (LLS) free booklet, *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 physician 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://www.acor.org/ped-onc/treatment/surclinics.html>.

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.

- *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 myelodysplasia or a secondary leukemia.

## Research

### *Predictive tests*

Research is under way to identify biomarkers that may indicate a higher-than-normal risk for developing a specific long-term or late effect. Biomarkers could be high levels of certain substances in the body, such as antibodies or hormones, or genetic factors that might increase susceptibility to certain effects. Identifying these biomarkers will allow researchers to develop tests that can predict what effects an individual is at risk for developing, thereby allowing doctors to plan treatment accordingly.

### *Clinical Trials*

Clinical trials explore new drugs, new treatment combinations or new uses for approved drugs for blood cancers and other diseases. New drugs and new combinations of therapies are needed to further improve outcomes and find cures for individuals with leukemia, lymphoma and myelodysplastic syndromes. In addition, research to better understand and treat long-term and late effects associated with certain cancer therapies is ongoing. Researchers are also studying ways to lessen or minimize the negative impact of existing therapies. Current research is also seeking to understand how factors such as aging and socioeconomic status influence long-term and late effects.

### *Guidelines*

Several organizations are working on evidence-based guidelines for patients and physicians that will standardize and enhance follow-up care and increase awareness about long-term and late effects. For more information, see the **Resources** section on page 10.

Current information about specific clinical trials can be obtained by calling the Information Resource Center of LLS at (800) 955-4572.

### 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 physicians. 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

**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 myelogenous leukemia (AML).

*Procarbazine*, *nitrogen mustard*, and *ifosfamide*, which can increase risk for myelodysplastic syndromes and acute myelogenous 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 myelogenous leukemia, acute lymphocytic 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.

Anthracycline drugs may also increase the risk for developing a secondary cancer, such as acute myelogenous 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. High dosages of corticosteroids (sometimes used to treat children with acute lymphocytic leukemia) may be associated with avascular necrosis of the hip, a condition that may require hip joint replacement. Corticosteroids have been used to treat children with leukemia and lymphoma. 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 myelogenous 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* and *dasatinib* for pH-positive acute lymphocytic leukemia.

#### *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 lymphocytic 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 a hematopoietic stem cell transplant can potentially cause gonadal failure and fertility issues.

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

### **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 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 second cancer.

- *Acute Myelogenous Leukemia and Myelodysplastic Syndromes* — Treatment-related acute myelogenous 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 lymphocytic leukemia. 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.

## **Resources**

### **The Leukemia & Lymphoma Society (LLS)**

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, visit our Web site at [www.LLS.org](http://www.LLS.org) or contact:

The Leukemia & Lymphoma Society  
1311 Mamaroneck Ave  
White Plains, NY 10605  
(800) 955-4572

**Through the Information Resource Center at LLS, callers may speak directly with an Information Specialist, Monday-Friday, 9 AM-6 PM, ET at (800) 955-4572. To contact an Information Specialist, click on Live Help (10 AM-5 PM) on our Web site at [www.lls.org](http://www.lls.org), or email us at [infocenter@LLS.org](mailto:infocenter@LLS.org).**

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 diseases. The LLS Web site has information about how to find a clinical trial, including a link to TrialCheck®, a clinical trials search service provided by LLS.

LLS provides fact sheets and booklets that can be ordered via the 800 number or through the “Free Materials” section at [www.lls.org](http://www.lls.org).

### **Cancer Survivorship Home of the Centers for Disease Control and Prevention (CDC)**

<http://www.cdc.gov/cancer/survivorship>

### **Children's Oncology Group Long-Term Follow-up Guidelines, 2006**

is available on the Web site:

[www.childrensoncologygroup.org](http://www.childrensoncologygroup.org). Then click on “Long-Term Follow-up Guidelines.”

## Resources (continued)

### The Lance Armstrong Foundation offers

- The Livestrong SurvivorCare Program, which provides assistance to all cancer survivors.  
[www.livestrong.org/survivorcare](http://www.livestrong.org/survivorcare)
- A list of NCI-designated Comprehensive Cancer Centers which are members of the Livestrong Survivorship Center of Excellence Network.  
[www.livestrong.org/site/c.khLXK1PxHmF/b.2662091/](http://www.livestrong.org/site/c.khLXK1PxHmF/b.2662091/)

### Office of Cancer Survivorship of the National Cancer Institute

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

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

- An informative Web site on cancer survivorship  
[www.acor.org/ped-onc/survivors/index.html](http://www.acor.org/ped-onc/survivors/index.html)
- A list of follow-up clinics  
[www.acor.org/ped-onc/treatment/surclinics.html](http://www.acor.org/ped-onc/treatment/surclinics.html)

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