Long-Term Toxicities of Cancer Therapy in Children and Adolescents

ABSTRACT: More and more cancer patients are becoming cancer survivors. With the increase in cure rates as a result of more extensive and intensive treatment modalities, survivors of cancer treatments often find themselves victims of their own therapies. Long-term toxicities are becoming the norm rather than the exception, particularly as cancer patients are living longer. These secondary toxicities not only are a reminder of the cancer patient's disease, but they serve as a challenge to health care professionals responsible for their long-term follow-up and care. Familiarity with potential toxicities and their corresponding monitoring and treatment is essential for today's health care practitioner.

Following the completion of treatment for cancer, survivors may experience an array of sequelae as a result of chemotherapy, radiation, or surgery. Often these medical problems do not become apparent to the patient or the health care provider until months or years after therapy. As more cancer patients become cancer survivors, it is important for clinicians to be familiar with potential long-term toxicities in this selected patient population. With this knowledge, the clinician can better address the health care concerns of cancer survivors and ultimately enhance their quality of life. There is a great deal of information on monitoring survivors of childhood cancers after completion of therapy.[1-6]

Susannah Koontz, PharmD, BCOP
Clinical Practice Specialist
Pediatric Hematology/Oncology
University of Texas M.D. Anderson Cancer Center
Houston, Texas

Cardiac Toxicities

One of the most extensively studied long-term complications of cancer treatments is cardiac toxicity. Agents known to cause damage to cardiac myocytes, and thus produce congestive cardiomyopathy, are the anthracyclines (e.g., doxorubicin and daunorubicin) and high doses of cyclophosphamide such as those used in preparative regimens for stem cell transplantations. Radiation therapy to the chest region, especially directed at the mediastinum, is also known to produce long-term damage to the heart. Other cardiac complications seen in cancer survivors following treatment with previously mentioned therapies include arrhythmias, coronary artery disease, valvular stenosis, and pericarditis.[6-9]

Risk factors for the development of long-term cardiac toxicities are age (younger than 5 years) at the time of treatment, female gender, and chemotherapy dose. Generally accepted lifetime doxorubicin-dosing thresholds for the development of cardiac toxicity are 550 and 300 mg/m^2 for adults and children, respectively.[10,11] The addition of radiation to treatment protocols for all patients increases the risk of developing cardiac sequelae. Patients may develop toxicities acutely during treatment; however, significant problems may take several years to manifest, and the risk for these increases as time elapses after therapy completion. Frequent signs and symptoms suggestive of toxicities are exercise intolerance, fatigue, chest pain, dizziness, dyspnea, cough, peripheral edema, changes in blood pressure, and arrhythmias.[6-11]

Lifelong monitoring for cardiac abnormalities is required in patients who have undergone cancer treatment with chest radiotherapy and/or cardiotoxic chemotherapy. Routine assessment of cardiac function is performed at regular intervals. Such tests can include electrocardiography, echocardiography, or multiple-gated acquisition (MUGA) scanning. Although guidelines regarding testing intervals can vary, survivors of childhood cancer often receive follow-up for at least 10 years after finishing therapy. Echocardiography or MUGA scanning is ordered at a minimum of every five years for patients at lowest risk and annually for those patients at highest risk. Any patient

experiencing a decline in the results of serial function exams is monitored yearly. A lipid panel is routinely evaluated at regular doctor visits to monitor for cardiovascular diseases.[6-11]

Lifestyle modifications are also essential to ensure a healthy heart. Abstinence from smoking is encouraged, and current smokers should be referred to smoking cessation programs. Maintaining a healthy weight and following a diet low in fat and salt are advocated to prevent obesity and sodium retention, which only exacerbate cardiovascular complications. Regular exercise should also be a part of a patient's routine; however, isometric exercises (e.g., weight lifting) should be discussed with a physician prior to initiation, as these activities can be detrimental to compromised cardiovascular systems.[6]

When symptoms require treatment, patients will receive therapies similar to those recommended for congestive heart failure. Diuretics can assist with mobilizing fluid and decreasing edema. Medications to help lower blood pressure and improve cardiac output, such as calcium channel blockers, beta-blockers, angiotensin-converting enzyme inhibitors, and digoxin, are frequently prescribed to alleviate patients' symptoms. Most recently, carvedilol—a nonselective beta-blocker with alpha-1-blocking and antioxidant properties—has begun to show utility in treating patients with chemotherapy-induced cardiomyopathy.[7,12] Dexrazoxane has been used to prevent cardiotoxic effects of anthracyclines; however, its use, particularly in children, should be reserved for patients enrolled in a clinical trial.[13]

Table 1
Signs and Symptoms Associated with Hypothyroidism

Fatigue
Weakness
Sore muscles or joints
Inability to tolerate exercise
Weight gain
Constipation
Decreased concentration
Changes in mood
Feelings of depression or sadness
Feeling cold all of the time
Swelling in the face (particularly around the eyes) and hands
Dry skin
Brittle or thin hair
Slow heart rate
Low blood pressure
High cholesterol level

Source: References 4-6, 27, 28.

Pulmonary Toxicities

Acute and chronic lung injury has been associated with systemic chemotherapy and radiation to the lungs. Bleomycin is the most widely recognized chemotherapeutic that is known to cause pulmonary toxicity. Pulmonary complications following its use include pulmonary fibrosis and interstitial pneumonitis; acute respiratory distress syndrome is rare. Chemotherapy agents with the propensity to cause pulmonary fibrosis are busulfan, carmustine, and lomustine. Methotrexate is more commonly associated with interstitial pneumonitis.[6,14-16]

Pulmonary toxicities can occur months to years after treatment with the previously mentioned agents. Several risk factors associated with the development of lung injury have been identified. Host factors include young age at the time of treatment, asthma, and smoking history. Treatment factors also predispose patients to lung injury, the most substantial being higher cumulative doses. For bleomycin, the risk of pulmonary fibrosis significantly increases when cumulative lifetime doses approach 400 U, although lung injury has been seen in children with cumulative doses as low as 60 to 100 U. The highest risk of pulmonary toxicity for carmustine occurs when lifetime doses reach 600 mg/m^2. Risk for lung damage is increased when agents with known pulmonary toxicity are combined with one another or with radiation to the chest region.[6,14-16]

Prior to starting therapy with these agents, a baseline pulmonary evaluation should be performed. Pulmonary function tests, such as spirometry, lung volume, and diffusion capacity, should be ordered, and a chest radiograph should be obtained. During therapy and throughout their lifetime, patients should be monitored for symptoms indicative of lung injury, e.g., cough, tachypnea, dyspnea on exertion, and orthopnea. If patients remain asymptomatic, annual monitoring is necessary, consisting of a physical exam, which may include a chest radiograph, along with pulmonary function tests performed every three to five years. During episodes of associated symptoms or pulmonary infections, a thorough medical evaluation is warranted.[6,14-16]

Methods to reduce pulmonary problems are aimed at preventive measures. All patients should avoid smoking and secondhand smoke. Current smokers should be referred to smoking cessation programs. Patients should receive the pneumococcal vaccine at a specific time upon completion of therapy and a yearly influenza vaccine, as well. Finally, patients should engage in regular physical exercise to maintain and strengthen lung function.[6]

Renal Toxicities

Cancer treatments can cause damage to the kidneys and bladder. Renal toxicities can occur within days of treat-

Table 2
Miscellaneous Long-Term Toxicities

Organ	Complications	Causative Agents	Monitoring	Comments
Eyes	Cataracts	Busulfan Corticosteroids Radiation to head	Visual acuity exam and examination for cataracts during yearly physical	If problems are detected, patients should be referred to an ophthalmologist Cataract evaluation requires funduscopic examination Wear sunglasses with UV protection when outdoors
Ears	Hearing loss	Cisplatin Carboplatin Radiation to the head		When problems are detected, audiogram can be conducted annually by an audiologist Avoid loud noises (e.g., vacuum cleaners, lawn mowers) Wear hearing protection when loud noises are unavoidable
Skin	Fibrosis Telangiectasias	Radiation	Evaluation of skin at yearly physical Monthly self-exams of skin at home due to increased risk of skin cancer in areas of radiation	Wear sunscreen and protective clothing when outdoors Avoid tanning booths
Bones	Avascular necrosis	Corticosteroids	Baseline x-rays or bone scans, then as clinically indicated when problems are detected	Avoid excessive stress on joints

Source: References 4-6, 31-35.

ment administration and continue for years after cessation of therapy. Complications attributable to chemotherapy are hemorrhagic cystitis, bladder fibrosis, dysfunctional voiding, and glomerular and tubular toxicity, which can lead to renal insufficiency. Radiotherapy can cause many of the same problems when the abdominal and pelvic regions receive high doses of radiation, or when radiation is combined with chemotherapeutics known to produce renal complications.[4,6,17] Bladder carcinoma has been known to occur following the use of cyclophosphamide.[18]

Hemorrhagic cystitis is mostly associated with the administration of ifosfamide and higher doses of cyclophosphamide, such as those used in stem cell transplantations, but it has been seen at lower doses of cyclophosphamide. This condition occurs when acrolein—a metabolite of ifosfamide and cyclophosphamide—binds to the bladder wall to produce irritation. The most common symptoms associated with hemorrhagic cystitis are microscopic or macroscopic hematuria, dysuria, frequent and/or incomplete voiding, and nonspecific lower abdominal pain. The incidence of hemorrhagic cystitis is significantly decreased via the coadministration of mesna, a uroprotectant that binds acrolein and prevents it from adhering to the bladder wall, in combination with diuretics and hyperhydration. For patients who develop this toxicity during therapy, there is concern that symptoms may return at some point in the future. Chronic cystitis is also linked with radiation to the pelvic region.[6,17]

Patients may experience glomerular and tubular toxicity with the use of cisplatin, carboplatin, or ifosfamide; methotrexate is less frequently associated with the same sequelae. A decrease in patients' glomerular filtration rate (GFR) may occur over time, thus indicating a decline in their renal function.[6,17] Fanconi's syndrome, a condition characterized by renal tubular acidosis that is accompanied by wasting of electrolytes, glucose, and protein, has been well described with the use of ifosfamide. Risk factors related to its onset include cumulative ifosfamide doses of 60 g/m^2 or higher, treatment before the age of 5 years, and unilateral nephrectomy. Patients will often excrete an excessive amount of substances normally reabsorbed by the kidney. This excretion can result in electrolyte abnormalities (hypokalemia, hypophosphatemia, and hypomagnesemia), decreased bone mineralization (rickets), abnormal bone mineralization (osteomalacia), or growth retardation. Patients

with Fanconi's syndrome are supported with electrolyte, vitamin, and mineral supplementation.[4,6,19]

Renal and urinary function evaluations should be performed in cancer survivors at annual doctor visits. Voiding history should be obtained during patient interviews, and blood pressure readings should be included in routine assessment of vital signs. Serum creatinine, blood urea nitrogen, electrolytes, and urinalysis should be ordered at the time of examination. Assessment of renal function by the measurement of creatinine clearance or a GFR scan should be conducted periodically or when clinically indicated. Urine cytology and cystoscopy are performed in patients when bladder carcinoma is suspected. Patient education should stress the importance of adequate fluid intake and the judicious use of nephrotoxic agents, such as nonsteroidal anti-inflammatory drugs. It is also important for patients to know the signs and symptoms of such problems as hematuria and dysuria and when to report their concerns to their health care providers.[4,6]

Gastrointestinal and Liver Toxicities

Although cancer treatments often produce an array of acute gastrointestinal toxicities, the persistence of these side effects, or their delay in development, is not common. The most frequently reported long-term adverse effects from cancer treatment are intestinal fibrosis and enteritis, which are usually secondary to radiation. The development of these conditions can occur as soon as five years following therapy or can be delayed for 20 years or longer. Symptoms include nausea, vomiting, diarrhea, constipation, intermittent abdominal pain, dysphagia, intestinal obstruction, weight loss, and rectal pain with or without bleeding.[4,6]

Long-term toxicity to the liver can occur following systemic chemotherapy, most notably methotrexate, mercaptopurine, thioguanine, and dactinomycin. The administration of radiotherapy to the abdominal region can also cause long-term damage. Patients at highest risk for complications are those who have received hepatotoxic chemotherapy in protracted low doses rather than intermittent high doses. The development of liver damage often follows an insidious course, and patients are often asymptomatic when mild elevations are evident on liver function tests. Signs and symptoms of liver damage can include jaundice, severe itching, the passing of clay-colored stools, and easy bruising or bleeding. In advanced stages, when patients develop fibrosis and cirrhosis, hepatomegaly and significant elevations found on liver function tests are the hallmark signs of damage.[4-6]

Screening for gastrointestinal and liver problems occurs during yearly follow-up examinations. A thorough patient history can assist in the elucidation of signs and symptoms of secondary toxicities. Routine laboratory work should involve liver function tests and a hepatitis serology if exposure to hepatitis is suspected. Imaging of the liver is performed to aid the detection of cirrhosis. Treatment of intestinal fibrosis and enteritis, such as surgery to remove damaged areas of the gastrointestinal tract, is aimed to alleviate symptoms. For cancer patients with liver dysfunction, treatment plans to ameliorate side effects resemble those for patients with other forms of cirrhosis. When clinically indicated, vaccinations against specific strains of hepatitis are administered. Additionally, to preserve liver function, patients are counseled to limit alcohol consumption, maintain a well-balanced diet, and to use hepatotoxic medications (e.g., acetaminophen) in moderation, when necessary.[4,6]

Table 3
Symptoms Associated with Secondary Malignancies

Easy bruising or bleeding
Persistent or increased fatigue
Paleness in skin color
Sores that do not heal
Appearance of lumps
Bone pain
Changes in the appearance of moles
Changes in bladder or bowel habits
Blood in urine or stool
Difficulty in swallowing
Persistent cough or hoarseness
Shortness of breath
Blood in sputum
Changes in vision

Source: References 4-6, 36-39.

Central and Peripheral Nervous System Toxicities

Delayed central nervous system toxicity has been well documented in patients who have taken methotrexate (either systemically or intrathecally) or systemic cytarabine at high doses, and in recipients of whole-brain or craniospinal radiation. Deficits in cognition, problem-solving skills, motor function, attention, memory, and hand-eye coordination are the most frequently reported problems. Seizures and leukoencephalopathy are also signs of cerebral damage. Before receiving these specific treatment modalities, many patients will have baseline examinations performed to ascertain pretreatment cognition and brain function. Cognition can be elucidated through neuropsychology testing to measure IQ and problem-solving skills. Imaging the brain (CT or MRI) is useful for characterizing its architecture. Serial testing at designated intervals, or when problems are suspected, can be performed to monitor a patient's progress and detect neurocognitive changes at their onset.[4,6,20,21]

The most common peripheral nervous system toxicity in cancer patients following chemotherapy treatments is neuropathy. Chemotherapy agents associated with the development of this toxicity are platinum compounds (e.g., cisplatin), vinca alkaloids (e.g., vincristine), and taxanes (e.g., paclitaxel). The effects are often cumulative and occur after the administration of several doses. Although neuropathies can subside after cessation of cancer treatment, some patients continue to experience the effects for years after therapy. Related symptoms include burning or numbness in the hands and feet, sensitivity in the extremities to pain or extremes of temperature, loss of deep-tendon reflexes, muscle weakness, difficulty in walking, and poor balance. Patients should be educated on these symptoms and encouraged to report problems to their physicians upon their development. Patients with this medical condition should not wear tight-fitting items (socks, shoes, hose, and gloves). The use of gabapentin can be helpful in alleviating pain associated with peripheral neuropathies.[6,22,23]

Endocrine Toxicities

Endocrine abnormalities can be numerous, with significant consequences in cancer survivors. Problems can range from transient abnormal gland function to permanent infertility. Hypothyroidism, adrenal insufficiency, and infertility are all examples of endocrine complications that may occur following cancer treatment.[4-6,24-26]

Hypothyroidism is typically seen when radiotherapy is administered to the head or neck region. A majority of patients will be asymptomatic at the time they develop hypothyroidism, which can occur in as little as six months to over seven years after therapy, with a median time of 12 months. Symptoms linked to this endocrine abnormality are listed in **TABLE 1**. During annual physicals, manual evaluation of the thyroid should be performed, and thyroid function tests should be included in laboratory tests. Treatment with thyroid hormone is warranted when clinical symptoms are present.[4,6,27,28]

Following radiation to the head or surgical removal of the pituitary gland, central adrenal insufficiency is a concern. This endocrine abnormality develops when levels of adrenocorticotropic hormone are insufficient or absent to stimulate the production of cortisol—a hormone responsible for maintaining adequate blood glucose levels and aiding the body in handling physical stress. Patients with this condition may suffer from fatigue, weakness, dizziness, poor appetite, vomiting, diarrhea, dehydration, or hypoglycemia. Annual examination of cortisol levels by laboratory evaluation helps the clinician to detect problems. Supplementation with oral hydrocortisone can alleviate symptoms when clinically indicated.[4,6,27,28]

Infertility, whether temporary or permanent, can occur in both men and women following multimodal cancer treatments. Alkylating agents are the most common agents known to induce infertility; their effect is dose-dependent. Radiation to the brain (pituitary gland), abdominal region, or gonads can also cause infertility. Younger patients, particularly prepubescent children, are less likely to experience long-term effects than are their older counterparts. Cancer survivors should have their hormone levels regularly measured for insufficiencies. When deficiencies are noted, supplementation with testosterone or estrogen should begin. Prior to initiating cancer treatments, postpubescent males should be offered sperm banking as a method to protect fertility. Currently, research into the preservation and storage of ova continues. If fertility cannot be restored when it is desirable, patients should be referred to infertility specialists for evaluation and assistance.[4,6,27,29,30]

Miscellaneous Toxicities

Since cancer treatments can include local therapies, such as surgery and radiotherapy, as well as systemic chemotherapy, any organ system can be affected. Miscellaneous toxicities are summarized in **TABLE 2**.[4-6,31-35]

Secondary Malignancies

An unfortunate consequence of cancer treatment is the development of a secondary malignancy. Although rare, secondary cancers can be quite devastating, as many of these cancers can be difficult to treat and respond poorly to standard therapies. It is estimated that 3% to 12% of patients treated for cancer during childhood will develop a second cancer within 20 years following their initial diagnosis.[2] Secondary hematological malignancies are most likely to occur during the first five years following therapy, the most common types being acute myelogenous leukemia and myelodysplastic syndrome following systemic chemotherapy. Solid tumors tend to occur later, usually five to 15 years after therapy, and are associated more with radiation therapy.[4-6,36-39]

Chemotherapy agents most commonly associated with a secondary malignancy are alkylating agents (particularly mechlorethamine, melphalan, cyclophosphamide, and procarbazine), nitrosoureas (carmustine and lomustine), anthracyclines (doxorubicin and daunorubicin), and epipodophyllotoxins (etoposide and teniposide). As tumors have a propensity to develop in previously radiated tissues, the areas that are in the field of radiation are at highest risk for damage and the development of a malignancy, especially when radiation is administered to younger patients. The most common solid tumors resulting from radiotherapy are breast, thyroid, brain, and skin carcinomas and bone and soft tissue sarcomas.[4-6,36,38]

All patients should be monitored routinely after

the completion of their cancer therapy throughout their period of risk for a secondary malignancy. Yearly physical examinations and routine laboratory analysis (particularly a complete blood count) should be conducted. Patients should be encouraged to perform routine self-examinations at home (e.g., breast and testicular self-exams) and to promptly alert their health care professional of any changes or concerns. Most symptoms related to a secondary malignancy (see **TABLE 3**) are analogous to those associated with primary malignancies.[4,6]

Although the risk of secondary cancer cannot be eliminated completely, patients can decrease their cancer risk by engaging in healthy behaviors. Patients should be encouraged to use sunscreens regularly and wear protective clothing when outdoors. Patients should avoid smoking and chewing tobacco, and alcohol consumption should be in moderation only. Dietary modifications are recommended to limit fat consumption and increase intake of fiber and foods rich in vitamin C and vitamin A (antioxidants). As with the general population, regular exercise should be part of a patient's daily routine to promote wellness.[4,6]

Summary

With judicious monitoring for medical complications from cancer treatments and the identification of therapies to alleviate symptoms, cancer survivors can expect an increase in their quality of life following the conclusion of their cancer treatment. Since any organ system of the body can be affected, thorough physical examinations, laboratory monitoring, and the performance of special medical tests (all at routine intervals) are essential for all cancer survivors. When toxicities are identified, patients should be prescribed specific therapy aimed at reversing or alleviating associated symptoms. As more cancer patients, particularly children and adolescents, achieve cures after their treatment, the health care needs of survivors will remain a concern and an area of continued research. ■

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