e13 Late Consequences of Cancer and Its Treatment

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Over 9 million Americans alive today have had cancer. Virtually all of these survivors will bear some mark of their diagnosis and its therapy, and many will experience long-term complications, including medical problems, psychosocial disturbances, sexual dysfunction, and inability to find employment or insurance.

Problems may be related to the cancer itself (e.g., patients with primary cancers of the head and neck are at increased risk for subsequent lung cancer) or to the normal aging process (surviving one cancer does not necessarily alter the risk of other common tumors that increase in frequency with age). However, many of the problems affecting cured patients are related to the treatments. Individuals carefully followed for periods up to 30 years have taught us the spectrum of problems that can be encountered. Because of heterogeneity in treatment details and incompleteness of follow-up, some treatment-related problems went undetected for many years. However, studies of long-term survivors of childhood cancers, acute leukemia, Hodgkin's disease, lymphomas, testicular cancer, and localized solid tumors have identified the features of cancer treatment that are associated with later morbidity and mortality. We have been somewhat slow to act in changing those aspects of primary treatment that contribute to these late problems. This reticence is due to the uncertainty associated with changing a treatment that is known to work before having a replacement that works as well.

Survivorship issues have been addressed by the Institute of Medicine and the National Research Council, who have published a monograph on this subject—*From Cancer Patient to Cancer Survivor: Lost in Transition*. Their "Survivorship Care Plan," if uniformly carried out, would inform clinicians who assume the care of cancer survivors of their previous treatments; signs and symptoms of late effects; and, where established, guidelines for intervention. An "End-of-Treatment Consultation Note" would include the date, physician's name, date of tissue diagnosis, diagnosis, stage, pathologic findings, initial treatment plan, and treatment received. In addition, unusual or unexpected toxicities would be noted and the expected short- and long-term effects of treatment detailed. Suggestions for monitoring for late toxicity should be given as well, including recommendations for surveillance for recurrence and second malignancies, the physician(s) responsible for monitoring, and any identified psychosocial issues or concerns.

The first task in a newly diagnosed patient is always to eradicate the diagnosed malignancy. Late problems occurring in cured patients reflect the success of such treatment. These problems never develop in those who do not survive the cancer. Morbidity and mortality from iatrogenic disease should be avoided, if possible; however, the risk of late complications should not lead to the failure to apply potentially curative treatment. The challenge is to preserve or augment the cure rate while decreasing the risk of serious treatment-related illness.

The mechanisms of damage vary. Surgical procedures can create abnormal physiology (such as blind loops leading to malabsorption) or interfere with normal organ function (splenectomy leading to impaired immune response). Radiation therapy can damage organ function directly (salivary gland toxicity leading to dry mouth and dental caries), act as a carcinogen (second solid tumors in radiation ports), or promote accelerated aging-associated changes (atherosclerosis). Cancer chemotherapy can produce damage to the bone marrow and immune system and induce a spectrum of organ dysfunctions. Therapy may produce subclinical damage that may only become recognized in the presence of a second inciting factor (such as the increased incidence of melanoma in patients with dysplastic nevus syndrome treated for Hodgkin's disease with radiation therapy). Finally, cancer and its treatment are associated with psychosocial problems that can impair the survivor's ability to adapt to life after cancer.

Late effects by treatment modality are shown in Table e13-1. Drug toxicities and radiation therapy toxicities are discussed in Chap. 81.

CONSEQUENCES BY ORGAN SYSTEM

CARDIOVASCULAR DYSFUNCTION

Most anthracyclines damage the heart muscle. A dose-dependent dropout of myocardial cells is seen on endomyocardial biopsy, and eventually ventricular failure ensues. About 5% of patients who receive >550 mg/m^2 of doxorubicin will develop congestive heart failure (CHF). Coexisting cardiac disease, hypertension, advanced age, and concomitant therapy with thoracic radiation therapy may hasten the onset of CHF. Anthracycline-induced CHF is not readily reversible;

TABLE e13-1 LATE EFFECTS OF CANCER THERAPY

Surgical Procedure		Effect
Amputation		Functional loss
Lymph node dissection		Risk of lymphedema
Ostomy		Psychosocial impact
Splenectomy		Risk of sepsis
Adhesions		Risk of obstruction
Bowel anastomoses		Malabsorption syndromes
Radiation Therapy		**Effect**
Organ		
Bone		Premature termination of growth, osteonecrosis
Soft tissues		Atrophy, fibrosis
Brain		Neuropsychiatric deficits, cognitive dysfunction
Thyroid		Hypothyroidism, Graves' disease, cancer
Salivary glands		Dry mouth, caries, dysgeusia
Eyes		Cataracts
Heart		Pericarditis, myocarditis, coronary artery disease
Lung		Pulmonary fibrosis
Kidney		Decreased function, hypertension
Liver		Decreased function
Intestine		Malabsorption, stricture
Gonads		Infertility, premature menopause
Any		Secondary neoplasia
Chemotherapy		**Effect**
Organ	Drug	
Bone	Glucocorticoids	Osteoporosis, avascular necrosis
Brain	Methotrexate, ara-C, others	Neuropsychiatric deficits, cognitive decline?
Peripheral nerves	Vincristine, platinum, taxanes	Neuropathy, hearing loss
Eyes	Glucocorticoids	Cataracts
Heart	Anthracyclines, trastuzumab	Cardiomyopathy
Lung	Bleomycin	Pulmonary fibrosis
	Methotrexate	Pulmonary hypersensitivity
Kidney	Platinum, others	Decreased function, hypomagnesemia
Liver	Various	Altered function
Gonads	Alkylating agents, others	Infertility, premature menopause
Bone marrow	Various	Aplasia, myelodysplasia, secondary leukemia

mortality is as high as 50%, thus, prevention is the best approach. Mitoxantrone is a related drug that has less cardiac toxicity. Administration of doxorubicin by continuous intravenous infusion or encapsulated in liposomes appears to decrease the risk of heart damage. Dexrazoxane, an intracellular iron chelator, may protect the heart against anthracycline toxicity by preventing iron-dependent free-radical generation. Concern about antagonism of antitumor effects has restricted its use.

Mediastinal radiation therapy that includes the heart can induce acute pericarditis, chronic constrictive pericarditis, myocardial fibrosis, valvular abnormalities, or accelerated premature coronary atherosclerosis. The incidence of acute pericarditis is 5–13%; patients may be asymptomatic or have dyspnea on exertion, fever, and chest pain. The onset is insidious, with a peak about 9 months after treatment. Pericardial effusion may be present. Chronic constrictive pericarditis can develop 5–10 years after treatment and usually presents with dyspnea on exertion. Myocardial fibrosis may present as unexplained CHF with diagnostic evaluation showing restrictive cardiomyopathy. Patients may have aortic insufficiency from valvular thickening or mitral regurgitation from papillary muscle dysfunction. Patients who receive mantle field radiation therapy have a threefold increased risk of *fatal* myocardial infarction. Similarly, radiation of the carotids is associated with premature atherosclerosis of the carotids and can produce central nervous system (CNS) embolic disease. At very high doses, such as those used before hematopoietic stem cell transplantation, cyclophosphamide can produce a hemorrhagic myocarditis. Trastuzumab (herceptin) has been associated with heart failure, particularly in patients also receiving anthracyclines. Compromised ejection fraction is noted in about 10% of patients; it is usually reversible with the cessation of therapy.

PULMONARY DYSFUNCTION

Pulmonary fibrosis from bleomycin is dose-related, with potential exacerbation by age, preexisting lung disease, thoracic radiation, high concentrations of inhaled oxygen, and the concomitant use of other chemotherapeutic agents. Several other chemotherapy agents and radiation therapy can cause pulmonary fibrosis, and several can cause pulmonary venoocclusive disease, especially following high-dose therapy such as that involved in hematopoietic stem cell transplantation.

LIVER DYSFUNCTION

Clinically significant long-term damage to the liver from standard-dose chemotherapy is relatively infrequent and mostly confined to patients who have received chronic methotrexate for maintenance therapy of acute lymphoblastic leukemia. Radiation doses to the liver >1500 cGy can produce liver dysfunction. Although rarely seen with standard-dose chemotherapy, hepatic venoocclusive disease is more common with high-dose therapy, such as that given to prepare patients for autologous or allogeneic stem cell transplantation. Endothelial damage is probably the inciting event.

RENAL/BLADDER DYSFUNCTION

Reduced renal function may be produced by cisplatin; it is usually asymptomatic but may render the patient more susceptible to other renal insults. Cyclophosphamide cystitis may eventually lead to the development of bladder cancer. Ifosfamide produces cystitis and a proximal tubular defect, a Fanconi-like syndrome that is usually, but not always, reversible.

ENDOCRINE DYSFUNCTION

Long-term survivors of childhood cancer who received cranial irradiation are shorter, more likely to be obese, and have reductions in strength, exercise tolerance, and bone mineral density. The obesity may be related to alterations in leptin biology. Growth hormone deficiency is the most common hormone deficiency.

Thyroid disease is common in patients who have received radiation therapy to the neck, such as patients with Hodgkin's disease, with an incidence of up to 62% at 26 years post-therapy. Hypothyroidism is the most common abnormality, followed by Graves' disease, thyroiditis, and cancer. Such patients should have frequent measurement of thyroid-stimulating hormone (TSH) levels to detect hypothyroidism early and suppress the TSH drive, which may contribute to thyroid cancer.

NERVOUS SYSTEM DYSFUNCTION

Although many patients experience peripheral neuropathy during chemotherapy, only a few have chronic problems, perhaps because they have other coexisting diseases such as diabetes mellitus. High doses of cisplatin can produce severe sensorimotor neuropathy. Vincristine may produce permanent numbness and tingling in the fingers and toes.

Neurocognitive sequelae from intrathecal chemotherapy, with or without radiation therapy, are recognized complications of the successful therapy of childhood acute lymphoblastic leukemia. Cognitive decline has been attributed to CNS radiation in the treatment of a variety of tumor types. In addition, cognitive decline ("chemo brain") can follow the use of adjuvant chemotherapy in women being treated for breast cancer. Because the agents are given at modest doses and are not thought to cross the blood-brain barrier, the mechanism of the cognitive decline is not defined. The phenomenon has not yet been documented in adequately designed studies that take into account the normal age-associated decline in cognition.

Many patients suffer intrusive thoughts about cancer recurrence for many years after successful treatment. Adjustment to normal expectations can be difficult. Cancer survivors may often have more problems holding a job, staying in a stable relationship, and coping with the usual stresses of daily life. Suicidal symptoms are reported by a significant minority of adult survivors of childhood cancer and represent treatable conditions requiring follow-up care.

A dose-related hearing loss can occur with the use of cisplatin, usually with doses >400 mg/m^2. This is irreversible, and patients should be screened with audiometric examinations periodically during such therapy.

EYES

Cataracts may be caused by chronic glucocorticoid use, radiation therapy to the head, and, rarely, by tamoxifen.

SEXUAL AND REPRODUCTIVE DYSFUNCTION

Reversible azoospermia can be caused by many chemotherapy agents. The gonads may also be permanently damaged by radiation therapy or by chemotherapeutic agents, particularly the alkylating agents. The extent of the damage depends upon the patient's age and the total dose administered. As a woman nears menopause, smaller amounts of chemotherapy will produce ovarian failure. In men, chemotherapy may produce infertility, but hormone production is not usually affected. Women, however, commonly lose both fertility and hormone production. The premature induction of menopause in a young woman can have serious medical and psychological consequences. Hormone replacement therapy is controversial. Paroxetine and related drugs may be useful in controlling hot flashes.

MUSCULOSKELETAL DYSFUNCTION

Late consequences of radiation therapy on the musculoskeletal system occur mostly in children and are related to the radiation dose, volume of tissue irradiated, and the age of the child at the time of therapy. Damage to the microvasculature of the epiphyseal growth zone may result in leg length discrepancy, scoliosis, and short stature.

RAYNAUD'S PHENOMENON

Up to 40% of patients with testicular cancer treated with bleomycin may experience Raynaud's phenomenon varying in severity from mild and transient to severe. The mechanism is unknown.

ORAL COMPLICATIONS

Radiation therapy can damage the salivary glands, producing dry mouth. Without saliva, dental caries develop, and many patients have

poor dentition. In rare patients, taste can be adversely affected and appetite can be suppressed.

SECOND MALIGNANCIES

Second malignancies are a major cause of death for those cured of cancer. Second malignancies can be grouped into three categories: those associated with the primary cancer, those caused by radiation therapy, and those caused by chemotherapy.

Primary cancers increase the risk of secondary cancers in a number of settings. Patients with head and neck cancers are at increased risk of developing a lung or esophageal cancer, and vice versa, probably because of shared risk factors, especially tobacco abuse. Patients with breast cancer are at increased risk of a second breast cancer in the contralateral breast. Patients with Hodgkin's disease are at increased risk of non-Hodgkin's lymphoma. Patients with genetic syndromes, such as multiple endocrine neoplasia type 1 or Lynch syndrome, are at increased risk of second cancers of specific types. In none of these examples does it appear that treatment of the primary cancer is the cause of the secondary cancer, but a role for treatment is difficult to exclude. These predispositions should result in heightened surveillance in persons at risk. The risk of second cancer is often sufficiently high that cured cancer patients would make excellent candidates to assess chemoprevention strategies.

Patients treated with radiation therapy have an increasing and apparently lifelong risk of developing second solid tumors, usually in or adjacent to the radiation field. The risk is modest in the first decade after treatment but reaches 1–2% per year in the second decade, such that populations followed for 25 years or more have a ≥25% chance of developing a second treatment-related tumor. Some organs differ in their susceptibility to radiation carcinogenesis with age; women receiving chest radiation therapy after age 30 have a small increased risk of breast cancer, but those <30 have a 19-fold increased risk. A 25-year-old woman who received mantle-field radiation therapy for Hodgkin's disease has an absolute risk of 29% of developing breast cancer by age 55 years. The chances of curing the second malignancies hinge on early diagnosis. Patients who were treated with radiation therapy should be carefully examined on an annual basis and evaluated for any abnormalities in organs and tissues that were in the radiation field. Symptoms in a patient cured of cancer should not be dismissed as they may be an early sign of second cancers. Studies are needed to assess preventive measures in patients at high risk of second cancers.

Chemotherapy produces two clinical syndromes that can be fatal: myelodysplasia and acute myeloid leukemia. Two types of acute leukemia have been described. The first occurs in patients treated with alkylating agents, especially over a protracted period. The malignant cells frequently carry genetic deletions in chromosomes 5 or 7. The lifetime risk is about 2%; the risk is increased by the addition of radiation therapy and is about three times higher in people treated over age 40. It peaks in incidence 4–6 years after treatment; the risk returns to baseline if no disease has developed within 10 years of treatment. The second type of acute leukemia occurs after exposure to topoisomerase II inhibitors such as doxorubicin or etoposide. It is morphologically indistinguishable from the first but contains a characteristic chromosome translocation involving 10q23. The incidence is <1%, and it usually occurs 1.5–3 years after treatment. Both forms of acute leukemia are highly refractory to treatment, and no preventive strategy has been developed.

Hormonal manipulations can also cause second tumors. Tamoxifen induces endometrial cancer in about 1–2% of women taking it for 5 years or longer. Usually these tumors are found at an early stage; mortality from endometrial cancer is very low compared to the benefit from tamoxifen use as adjuvant therapy in women with breast cancer.

CONSEQUENCES BY CANCER TYPE

PEDIATRIC CANCERS

Quality of life is often excellent, although the majority have at least one late effect. About one-third of long-term survivors have moderate to severe problems. Cognitive function may be impaired. Late effects are worse for those with poor socioeconomic status. Functional impairments in the cardiovascular system due to radiation therapy and anthracyclines, and in the lungs due to radiation therapy, are rare. Scoliosis and/or delayed growth due to radiation of the skeleton are more common. Many survivors have psychosocial and sexual problems. Second malignant neoplasms are a significant cause of death.

HODGKIN'S DISEASE

The patient cured of Hodgkin's disease remains subject to long-term medical problems such as thyroid dysfunction, premature coronary artery disease, gonadal dysfunction, postsplenectomy sepsis, and second malignancies. The second malignancies encountered include myelodysplasia and acute myeloid leukemia, non-Hodgkin's lymphomas, breast cancer, lung cancer, and melanoma. The major risk factor for hematologic malignancies is treatment with alkylating agents plus radiation therapy, while solid tumors are more likely to be seen with the use of radiation therapy. Patients cured of Hodgkin's disease seem to experience greater fatigue, have more psychosocial and sexual problems, and report a poorer quality of life than patients cured of acute leukemia.

NON-HODGKIN'S LYMPHOMAS

The patient cured of a non-Hodgkin's lymphoma may be at increased risk of myelodysplasia and acute leukemia if high doses or prolonged courses of alkylating agents were used. Chronic exposure to cyclophosphamide increases the risk of bladder cancer. Patients cured of lymphoma report a very good quality of life.

ACUTE LEUKEMIA

The late effects of antileukemic therapy include second malignancies (hematologic and solid tumors), neuropsychiatric difficulties, subnormal growth, thyroid abnormalities, and infertility.

HEAD AND NECK CANCER

Patients frequently have poor dentition, dry mouth, trismus, difficulty in eating, and poor nutrition. Those with nasopharyngeal cancer report the poorest long-term quality of life, possibly related to the volume of disease that is radiated.

STEM CELL TRANSPLANTATION

Cured patients are at risk of second cancers, especially if radiation therapy was part of the treatment. They are also subject to gonadal damage and infertility. Graft-versus-host disease is the leading factor contributing to the morbidity and mortality from allogeneic bone marrow transplantation, with an immune-mediated attack against the skin, liver, and gut epithelium. About half of patients report psychosexual problems.

BREAST CANCER

Patients treated with adjuvant chemotherapy and/or hormonal therapy for breast cancer are at risk for endometrial cancer from the use of tamoxifen. The alternatives to tamoxifen, the aromatase inhibitors, do not protect against osteoporosis and may increase the risk of this complication. Those patients who have received chemotherapy may be at risk from doxorubicin- or radiation-induced cardiomyopathy and acute leukemia. Trastuzumab (Herceptin) may contribute to heart failure. The development of premature ovarian failure from chemotherapy may cause hormone-deficient symptoms (hot flashes, decreased vaginal secretions, dyspareunia) and places women at risk for osteoporosis and cardiovascular death. Patients commonly report intrusive thoughts of cancer and psychological distress.

TESTICULAR CANCER

Depending on the modalities used for therapy, patients cured of testicular cancer can anticipate Raynaud's phenomenon, renal and/or pulmonary damage from chemotherapy, and retrograde ejaculation from retroperitoneal lymph node dissection. Sexual dysfunction is reported by 15% of patients cured of testicular cancer.

COLON CANCER

To date the major threat to patients with colorectal cancer treated with chemotherapy and/or radiation therapy remains the risk of a second colorectal cancer. Quality of life is reported as high in long-term survivors.

PROSTATE CANCER

Radical surgical treatment is often accompanied by impotence, and about 10–15% develop some urine incontinence. Use of radiation therapy increases the risk of second cancers and may produce chronic prostitis or cystitis.

OUTLOOK

The challenge for the future is to integrate new chemotherapy and biologic agents and newer techniques of delivering radiation therapy in a fashion that increases cure rates and lowers the late effects of treatment. Additional populations at risk for late effects include those with cancers where therapy is becoming more effective, such as ovarian cancer, and cancers where chemotherapy and radiation therapy are used together in an organ-sparing approach, such as bladder, anal, and laryngeal cancers. Patients who have been cured of a cancer represent an important resource for cancer prevention studies. The Childhood Cancer Survivor Study reported that survivors have a high rate of illness due to chronic health conditions. This incidence increases with time and does not appear to plateau, indicating that monitoring of survivors is a critical component of their overall health care.

FURTHER READINGS

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