

THE MONITORING OF POTENTIAL LONG-TERM COMPLICATIONS IN TREATED ADULT CANCER PATIENTS

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A wide variety of long-term complications may be noted following conventional cancer treatment. These include overwhelming postsplenectomy sepsis syndrome, central and peripheral nervous system toxicity, cardiovascular complications, chronic liver damage, and secondary malignancy. Follow-up monitoring usually incorporates both physical examination and the result of radiological and laboratory investigations. Primary care physicians will often be responsible for the majority of the follow-up monitoring involving cured cancer patients and need to be aware of possible long-term therapy-related problems, especially those that present years after successful treatment of the original malignancy. *Ann Saudi Med 1997;17(6):622-628.*

As an increasing number of patients are treated with curative chemotherapy, there are more long-term survivors in the general population. In North America, it has been estimated that by the year 2000, one in 900 young adults will be a long-term survivor of cancer. This figure is considerably higher when the long-term survivors of adult solid tumors are included in the statistics.¹ While specialists in oncology are sensitive to possible late sequelae of cancer treatment, many primary care physicians may be unaware of what constitutes appropriate long-term follow-up. Follow-up of cancer patients is done with several intended endpoints which tend to vary. Broadly, they include detection of recurrence with the intention of offering early salvage therapy, recognition and management of treatment-induced complications, the somewhat more difficult to measure psychological benefits of continued medical involvement from the patient's perspective, and academic/epidemiologic data gathering on survival.

Given the variable biologic behavior of different malignancies, the characteristic morbidity profiles of various therapeutic modalities, together with individual patient variables such as age, sex, performance status and lifestyle, it is clear that cancer follow-up recommendations cannot be uniformly applied across the board.

This review briefly touches upon issues pertaining to cancer recurrence during follow-up, but the main focus is to provide an overview of the nature of potential long-term complications that may follow cancer therapy, and to

outline a practical strategy for their management.

Disease Recurrence

For the majority of neoplasms, recurrence is within the first three to five years. While this is especially true of lymphomas and leukemias (85% within three years, 95% within five years), the same is true for most common solid tumors such as breast, bowel and gastrointestinal malignancy.² Notable exceptions may occur, however, in the case of some malignancies such as melanoma, where recurrences may present years after primary therapy.³ While no follow-up schedule can be advocated that will encompass all tumors, monitoring should be more frequent during the first three years after completion of initial treatment.^{1,2} Follow-up monitoring will incorporate both physical examination and the results of radiological and laboratory investigations. In the case of breast cancer, for instance, besides careful physical examination, follow-up might include periodic determinants of CA 15-3, CEA (carcinoembryonic) liver function studies, annual chest x-ray, and mammogram of the contralateral breast. Isolated abnormalities of an individual laboratory parameter (i.e., elevation of CA 15-3) should never be taken as sole proof of disease recurrence but should prompt further evaluation.² Typical clinic schedules might include visits every three months for the first year, every four months for the second and third year, every six months in the fourth year and annually thereafter. Data on the influence of an early diagnosis of recurrence on the overall prognosis of relapsing cancer is available for some tumors such as breast cancer.⁴ The important overall concept is that patients should not be lost to follow-up once treatment is completed but monitored on a regular basis, especially during the period of highest risk for disease recurrence.

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TABLE 1. Potential problems in long-term follow-up of treated cancer patients.

Potential problems	Recommendations	
	Investigation	Possible therapy
Recurrence	Close monitoring by periodic physical examination, laboratory and radiological methods, especially during the first three years	Salvage therapy if recurrence detected
Hypothalamic-pituitary dysfunction	Growth hormone; prolactin levels	Growth hormone therapy; bromocryptine or dopamine antagonists
Thyroid dysfunction	T ₄ , TSH	Thyroid replacement therapy
Gonadal dysfunction	Males: FSH, LH, testosterone, semen analysis Females: FSH, LH, estrogen	Androgen therapy; cyclic hormonal therapy for premature menopause
Cardiovascular dysfunction	Chest x-ray, ECG, radionuclide, ventriculography, echocardiography, endomyocardial biopsy; 24-hour ambulatory EKG for suspected arrhythmia; Doppler flow of digital arteries for Raynaud's phenomenon; risk profile for coronary artery disease	Pericardiectomy for constrictive pericarditis; standard measures for congestive heart failure; calcium channel blockers for Raynaud's phenomenon; modifications of other risk factors for vascular disease
Pulmonary dysfunction	Chest x-ray, pulmonary function studies including DCO	Possible steroid therapy; counselling regarding smoking cessation
Liver dysfunction	Liver function tests; consider CAT scan, MRI, hepatitis A, B and C testing	Appropriate to abnormality; avoidance of alcohol and other hepatotoxic substances
Renal dysfunction	Blood pressure, BUN, creatinine, urinalysis; depending on presentation, consider IVP, ultrasound, cystoscopy, urine cytology	Appropriate to abnormality; avoidance of aminoglycoside therapy and other nephrotoxic agents
Neurological dysfunction	Depending on presentation, consider nerve conduction studies, CAT scan, MRI, neuropsychological testing	Appropriate to abnormality; no known therapy for peripheral neuropathy or VIII nerve toxicity; avoidance of other neurotoxic drugs; counselling and behavioral therapy for neuropsychological problems
Infectious complications	Appropriate microbiological investigation at the first sign of systemic symptoms in asplenic or functionally hyposplenic individuals	Periodic antipneumococcal vaccination; consider hemophilus and meningococcal vaccines; consider Medi-Alert bracelet; supply of prophylactic antibiotics
Second malignancy	Appropriate to therapy received: post-alkylating agent therapy, yearly complete blood counts; post-thoracic irradiation: regular breast self-examination and mammography starting age 35; post-thyroid irradiation: annual thyroid examination	Appropriate to abnormality detected; pancytopenia or isolated cytopenia: bone marrow with cytogenetics; if secondary leukemia detected: hematology consultation; supportive care if elderly, consideration for marrow transplantation if younger

The early detection of recurrence should offer maximum potential for cure via salvage therapy.^{1,2,4}

Endocrine Complications

Hypothalamic Pituitary Dysfunction

While hypothalamic pituitary dysfunction is relatively common following cranial irradiation, panhypopituitarism is relatively rare.^{5,6} Growth hormone (GH) deficiency is the commonest abnormality detected and can be seen following doses of greater than 20 Grey (Gy).⁶ The role of GH replacement in adults with proven GH deficiency is under investigation.⁷ Deficiencies of other anterior pituitary hormones are less common, and usually associated with higher doses of irradiation (>35 Gy).⁸ Hyperprolactinemia associated with amenorrhoea and infertility has been noted in women treated with doses greater than 45 Gy.⁹ Hyperprolactinemia may be treated with bromocriptine or other dopamine antagonists.

Thyroid Dysfunction

Patients with Hodgkin's disease or other tumors who receive irradiation to the neck are at high risk for subsequent hypothyroidism.¹⁰⁻¹² This includes patients who receive total body irradiation as a single fraction for bone marrow transplant.¹⁰ The risk of developing hypothyroidism increases directly with the dose of irradiation and the time post-treatment.¹¹ Over a ten-year period, symptomatic hypothyroidism may develop in over 10% of patients, and elevated levels of thyroid-stimulating hormone (TSH) may be present in 50% of cases. In addition, the risk for thyroid disease seems to persist for up to 25 years post-treatment.¹² Since the combination of thyroid irradiation and prolonged TSH stimulation may lead to thyroid cancer, TSH should be checked early and the thyroid palpated at each follow-up visit. Lifelong thyroid replacement therapy should probably be commenced once an elevated TSH has been noted. Rare cases of hyperthyroidism and hyperparathyroidism have

also been reported post-radiotherapy.¹³

Testicular Dysfunction

It is important to realize that in certain malignancies, such as Hodgkin's disease, endocrine and testicular cancers, infertility may precede the diagnosis of cancer.¹⁴ Both germinal epithelium and Leydig cells appear sensitive to irradiation. In most men, proper shielding during irradiation will allow recovery of spermatogenesis.² However, chemotherapy, especially with alkylating agents, usually results in oligospermic infertility.^{14,15} Patients present with decreased testicular volume and elevated plasmal levels of follicle-stimulating hormones (FSH).¹⁵ The type of chemotherapy that was utilized is important. For instance, ABVD therapy, as opposed to MOPP chemotherapy for Hodgkin's disease, appears to have a significantly lesser effect on spermatogenesis.¹⁶ Recovery of spermatogenesis beyond five years after chemotherapy is extremely rare. In contrast to germ cells, Leydig cells appear relatively resistant to most forms of chemotherapy.¹⁴ When clinically significant Leydig cell dysfunction is suggested by changes in libido and the finding of decreased testosterone levels with elevated plasma luteinizing hormone (LH) levels, replacement therapy is indicated.

Ovarian Dysfunction

Female fertility appears to fare better with cancer therapy than in the case of males.¹⁷⁻¹⁹ The ovary at birth contains a fixed number of follicles that decrease steadily with advancing age. Thus ovarian damage is age-dependent.¹⁷ Standard chemotherapy tends not to cause permanent disruption of ovarian function for those under 25 years of age.¹⁸ There may be transient amenorrhea with elevated plasma FSH and LH levels, but menstruation will ultimately return to normal in up to 70% of women under 25 years. This figure is only 10% or less for those aged 35 or older. Once ovarian failure has been documented, recovery of normal ovarian function is rare. The dose of irradiation capable of inducing irreversible ovarian failure in women in their twenties and thirties may be as low as 1.5-3 Gy.¹⁹

Since women who become prematurely menopausal are at increased risk for osteoporosis, fractures and coronary artery disease, cyclic estrogen/progesterone therapy is warranted. In addition, such therapy may prevent menopausal vasomotor symptoms and vaginal atrophy. A commonly used monthly program consists of conjugated estrogen (Premarin) 0.625 mg daily for the first 21 days with medroxy progesterone (Provera) 5 mg daily from day 7 to 21. Fortunately, children born to cancer survivors of either sex who have not been rendered infertile have uniformly shown no increased incidence of either congenital cancer or hereditary defects.^{21,22}

Cardiovascular Complications

Radiation damage to the pericardium is common, but fortunately seldom symptomatic. Constrictive pericarditis is rare but may require pericardiectomy.²³ Direct myocardial damage post-radiotherapy is infrequent, but there are reports of coronary artery disease secondary to coronary artery fibrosis or accelerated atherosclerosis.²⁴ Mediastinal irradiation has an additive effect with anthracycline chemotherapy.²⁵ Factors thought to enhance the risk for chronic anthracycline-induced cardiac toxicity are listed in Table 2.²⁵ As cohorts of patients are followed for increasing intervals of time, concern has arisen that even conventional doses of anthracycline chemotherapy may decrease cardiac reserve and lead to delayed onset of ventricular dysfunction years after treatment. Unfortunately, patients may present with symptoms of congestive heart failure as late as 10-15 years post-chemotherapy.²⁶ Late onset of ventricular arrhythmias and sudden death have been reported up to 15 years post-anthracycline therapy.²⁵

Depending on presentation, patients developing cardiac symptoms after anthracycline chemotherapy should be investigated with radionuclide angiography, ultrasound studies and possible endomyocardial biopsy.^{25,27} In patients with suspected cardiac arrhythmia, 24-hour ambulatory EKG monitoring is advisable. A left ventricular ejection fraction of less than 35%, or a 15% decrease from base line results, is strongly suggestive of high risk or cardiac decompensation.²⁵ Other studies have indicated that determination of the left ventricular posterior wall thickness index may be a good marker for potential long-term toxicity.²⁷ Congestive failure secondary to chronic measures such as diuretics, ACE inhibition and digoxin therapy. However, the ultimate prognosis remains guarded.

A particularly disabling vascular symptom has been Raynaud's phenomenon, noted in up to one-third of long-term survivors of testicular cancer treated with combinations of bleomycin, platinum, vinblastine or etoposide.²⁸ This complication appears more frequent in those with pre-existing hypertension. The diagnosis may be confirmed with Doppler flow of digital arteries, and therapy with calcium channel blockers may provide symptomatic relief.²⁸ Because of possible long-term additive effects, the reduction of other potential risk factors for cardiovascular disease (abnormal lipid profile, smoking, alcohol abuse, hypertension) should be aggressively pursued in patients who have received chemotherapy with potential cardiovascular toxicity.

Pulmonary Complications

A number of chemotherapy agents have been associated with acute and chronic pulmonary toxicity, including the nitrosoureas, busulphan, bleomycin, cyclophosphamide and methotrexate.²⁹ Late onset of pulmonary fibrosis up to

10 years post-therapy has been described with BCNU, cyclophosphamide, bleomycin and busulfan therapy.^{30,31} A number of risk factors for bleomycin toxicity have been identified (Table 3). Bleomycin toxicity appears more severe in children and the aged than in adults. The accurate early detection of bleomycin pulmonary toxicity is limited.³¹ Symptoms may include dyspnea, nonproductive cough and fatigue. Physical examination of early cases may be nonspecific or demonstrate fine basilar rales.²⁹ A reduction in diffusion capacity for carbon monoxide (DCO) can represent a nonspecific relatively sensitive indicator of early pulmonary damage. Other pulmonary function studies may indicate a restrictive pattern with decreased vital capacity and total lung volume.³¹ Chest x-ray may be initially normal or nonspecific, but ultimately will indicate extensive or irreversible pulmonary fibrosis. Treatment with steroids is often utilized, but the ultimate value of this therapy has not been convincingly established.

Pulmonary complications following mantle irradiation have decreased as a result of smaller volumes of irradiation and superior blocking techniques. When optimum combined mediastinal irradiation and chemotherapy are given for Hodgkin's disease, a slight reduction in vital capacity persists, but DCO is frequently normal three years post-therapy.³² Patients who have received combined therapy or chemotherapy with potential pulmonary toxicity should have a careful auscultation of the chest on each return visit and be counseled regarding smoking cessation.

Gastrointestinal Complications

Fortunately, long-term gastrointestinal toxicity is rare following either radiotherapy or chemotherapy.³³⁻³⁵ Chronic liver damage has most frequently been associated with the use of methotrexate or 6-MP (mercaptopurine) therapy.³³ Patients who have received low-dose daily therapy over prolonged periods appear most prone to asymptomatic fibrosis. Unfortunately, especially in the case of methotrexate, liver function studies may remain relatively normal until cirrhosis has supervened.³⁴ Patients who present with hepatic symptomatology after chemotherapy should be investigated with liver function studies, as well as CT and/or MRI to rule out cirrhosis. Since viral hepatitis may produce an added hepatotoxic effect, serology for hepatitis A, B and C should be obtained whenever abnormal liver function is found.³⁵ Patients with chemotherapy-induced hepatic toxicity should be cautioned regarding alcohol consumption, or the future use of other potential hepatotoxic agents.

Renal Complications

While acute nephrotoxicity is a major side effect of many chemotherapeutic drugs, chronic nephrotoxicity appears to be a relatively rare complication except in

TABLE 2. Risk factors for cardiac toxicity induced by anthracycline chemotherapy.

Risk factors	Description
Age	Young children and older adults at greater risk
Sex	Female sex appears at greater risk for any given dosage
Pre-existing cardiac disease	Mechanisms not clearly understood; hypertension a risk factor; prior history of congestive heart failure a major concern
Cumulative dose	Risk <10% for doses <350 mg/m ² , linear increase with doses ≥550 mg/m ² ; documented late onset toxicity after doses as low as 200 mg/m ²
Schedule	Peak plasma levels appear to be an important factor; less toxicity with lower bolus dosing, frequent schedule of administration and continuous infusions
Concurrent mediastinal irradiation	Linear increase in risk with increasing radiation dosage
Concurrent chemotherapy	Limited data but cyclophosphamide, melphalan, dactinomycin, mitomycin, bleomycin, dacarbazine, etoposide and vincristine suspected

TABLE 3. Risk factors for pulmonary toxicity induced by bleomycin chemotherapy.

Risk factors	Description
Age	Young children and >70 years are at increased risk
Pre-existing disease	Patients with non-Hodgkin's lymphoma or decreased renal function have an increased risk
Cumulative dose	Risk increase with doses >450 U
Schedule	Bolus administration appears more toxic than continuous infusion
Concurrent mediastinal irradiation	Radiotherapy to the chest increases toxicity
Concurrent oxygen therapy	F ₁ O ₂ greater than 30%
Concurrent chemotherapy	Multi-agent chemotherapy appears to potentiate toxicity, including cisplatin and cyclophosphamide

patients with pre-existing renal disease. Long-term follow-up of patients post-cisplatin therapy has demonstrated up to a 30% persistent decrease in glomerular filtration rate but little evidence of long-term renal tubular dysfunction.³⁶ However, chronic tubular dysfunction with acquired Fanconi's syndrome has been noted as a late complication of ifosfamide administration.³⁷ Both ifosfamide and cyclophosphamide have been associated with late onset fibrosis and transitional cell carcinoma of the bladder.^{36,38} Radiation can result in long-term damage to the kidneys at a dosage of 12-15 Gy. Hypertension associated with a decreased creatinine clearance has been noted after cisplatin therapy, especially in Wilm's

tumor patients treated with combined chemotherapy and irradiation.³⁹ Blood pressure should be checked at each return visit in patients who have received potentially nephrotoxic chemotherapy. In patients with renal symptoms, urinalysis, creatinine and blood urea nitrogen should be checked, together with blood pressure. Appropriate secondary investigations of the genitourinary system, such as contrast studies, ultrasound and cystography, should be ordered when screening tests are found to be abnormal.¹

Neurological Complications

There is a wide range of acute central and peripheral nervous system toxicities associated with chemotherapy. Long-term toxicity is fortunately rare, but both vinca alkaloid- and cisplatin-induced peripheral neuropathy have been reported to persist in 30%-70% of patients several years post-treatment.⁴⁰ Taxol is a tubulin polymerization enhancer that has been increasingly used with platinum-based chemotherapy for ovary, breast, head and neck, as well as lung tumors. Unfortunately, taxol produces an additive cumulative neurotoxicity in this situation that may result in severe peripheral sensory-motor neuropathy.⁴¹ Nerve conduction studies will usually demonstrate low amplitude potentials and slowing of nerve conduction velocities. Persistent high-frequency hearing loss has been an unfortunate long-term complication of platinum-based chemotherapy. While attention has focused on cisplatin, carboplatin may also exhibit significant ototoxicity.⁴² Fortunately, the frequencies affected are usually outside the range of conversational speech. However, audiological assessment is indicated if patients become symptomatic. The late onset of neurocognitive defects has been detected in a significant number of patients who have received intensive chemotherapy and/or radiation therapy directed at the central nervous system.⁴³ Such deficits have been associated with later problems involving marriage, employment and subsequent insurability.^{44,45} Neurological follow-up should be appropriate to any abnormality detected. For example, detection of peripheral neuropathy on physical examination would be followed by nerve conduction studies, while central nervous system abnormalities would be investigated by CT scan or MRI. Counselling and behavioral therapy may be indicated in cases involving neurocognitive defects.

Infectious Complications

Patients who are functionally hyposplenic as a result of high-dose splenic irradiation or intense chemotherapy are at risk for the overwhelming post-splenectomy sepsis syndrome. This syndrome consists of fulminant septicemia, usually due to an encapsulated organism such as *Streptococcus pneumoniae* (Pneumococcus) or

Haemophilus influenzae.⁴⁶ There may be associated disseminated intravascular coagulation, hypotension and

TABLE 4. Common features of the overwhelming post-splenectomy sepsis syndrome.

Occurs in the asplenic or functionally hyposplenic
Cryptic infection (no obvious focus)
Short, nonspecific prodrome
Massive bacteremia with encapsulated organism
Less commonly, gram-negative organism
Septic shock with disseminated intravascular coagulation
Marked virulence: 50% to 70% mortality
Death may ensue in 24 to 48 hours
Appropriate vaccinations may offer partial protection

adrenal failure. Administration of various vaccines (pneumococcal, hemophilus, meningococcal) may reduce but not eliminate the risk. Pneumococcal vaccine should initially be given to all hyposplenic or asplenic patients and probably repeated at three to five yearly intervals.⁴⁷ If at all possible, patients should receive vaccination prior to splenectomy or cancer therapy. All post-splenectomy patients should be aware of their status and cautioned to seek early medical advice at the first onset of symptoms compatible with systemic infection. A Medi-Alert bracelet or wallet card may be of benefit.⁴⁶ Some doctors also issue a supply of prophylactic antibiotics with the proviso that a physician must also be contacted in the event of infectious symptoms.

Secondary Malignancy

Therapy-induced secondary malignancies remain an unfortunate long-term complication of both chemotherapy and irradiation treatment.⁴⁸⁻⁵⁰ Within the spectrum of chemotherapeutic agents, the alkylating agents and topoisomerase inhibitors have been especially implicated. For acute leukemia, there appears to be a synergistic effect of radiotherapy with chemotherapy.^{48,49} Treated adult patients with Hodgkin's disease have the highest reported risk of secondary cancers. The cumulative probability of a secondary malignancy in this patient group at 15 years is 17% (13% solid tumors, 2% leukemias, 2% lymphomas).⁵⁰ The mean time of onset is 4.5 years for secondary leukemia, five years for non-Hodgkin's lymphoma and 12 years for solid tumors. There is a plateau effect, in that adults surviving more than 10 years post-therapy do not appear to be at an increased risk for leukemia, however, the risk for solid tumors keeps increasing with time. MOPP appears to produce more secondary leukemia than ABVD chemotherapy.⁴⁹

The majority of solid tumors (lung cancer, thyroid cancer, breast cancer, bone and connective tissue tumors)

occur within the field of previous irradiation, so any such areas should be carefully examined on successive follow-up visits.⁵⁰ Women who have received mantle irradiation before the age of 30 should be taught breast self-examination and probably have baseline mammography by age 35. Unfortunately, leukemias that arise post-therapy are often cytogenetically complex (abnormalities of chromosome 7, 8) and associated with a poor prognosis. Unlike de novo leukemia, there is frequently a myelodysplastic phase lasting several months.⁴⁹ For this reason, pancytopenia, or any isolated cytopenia that represents a new finding in a treated cancer patient, should be investigated by bone marrow examination, preferably with accompanying cytogenetics. Once acute leukemia ensues, the leukemic process tends to be refractory to standard antileukemic therapy, and typical survival is in the range of two to eight months. Allogenic bone marrow transplantation is the only option with curative potential and should be considered for those under the age of 50.

Conclusion

A wide variety of long-term complications may be noted following conventional cancer therapy. The primary care physician will probably be responsible for the majority of follow-up involving cured cancer patients, and needs to be aware of possible long-term therapy-related problems. This is especially true for those complications that present years after successful treatment of the original malignancy. An awareness of those complications which are potentially treatable may help the cured cancer patient ultimately achieve a productive and healthy life.

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