

CONTINUING EDUCATION

Cardiovascular Risk in Testicular Cancer Survivors Treated With Chemotherapy: Incidence, Significance, and Practice Implications

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Purpose/Objectives: To explore what is known regarding cardiovascular late effects of treatment, such as Raynaud phenomenon, hypertension, hyperlipidemia, and coronary artery disease as well as the risk for cardiovascular events experienced by patients with testicular cancer treated with chemotherapy.

Data Sources: Literature review of treatment options and cardiovascular risk in patients with testicular cancer from PubMed, MEDLINE®, oncology nursing literature, and the Internet.

Data Synthesis: Evidence exists that chemotherapy used to treat testicular cancer may increase risk of cardiovascular disease. More research is needed to clarify the risks further. Patients and their healthcare providers must be aware of the potential toxicities.

Conclusions: A limited but growing body of research is focused on defining cardiovascular risks in this population.

Implications for Nursing: Nurses have an important role in exploring and identifying cardiovascular risk factors in patients, furthering research to clarify the risks, and using the knowledge to improve patient care and education.

Key Points . . .

- Testicular cancer is the most common cancer affecting young men.
- Cisplatin-based, combination chemotherapy is largely responsible for long-term survival; however, it also may be responsible for significant cardiovascular morbidity and mortality.
- The vast majority of testicular cancer survivors live for many years, and understanding potential long-term toxicity related to treatment is critically important for such men.

Goal for CE Enrollees:

To enhance the nurse's knowledge regarding the cardiovascular risks associated with testicular cancer.

Objectives for CE Enrollees:

1. Describe the long-term cardiovascular risks associated with testicular cancer.
2. Identify treatment protocols that may put patients at greater risk for the development of long-term cardiovascular health risks.
3. Identify signs and symptoms that are associated with cardiovascular late effects that may be expected in the testicular cancer population.

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Testicular cancer is the most common cancer in young men, generally affecting those aged 15–35 years. The greatest incidence is found in Europe and North America. For reasons that remain unclear, the incidence has been increasing since the 1960s (Chaudhary & Haldas, 2003; Dodd & Kelly, 2001). In 2005, about 8,010 men in the United States will be diagnosed with the disease, but only 390 are expected to die from cancer (Jemal et al., 2005).

Testicular cancer, a germ cell tumor, has been identified as one of the most curable malignancies. It has been described as a “model for a curable neoplasm” (Einhorn, 1981, p. 3275). Even in patients with metastatic disease, as many as 80% can be expected to achieve durable complete remission. Patients with testicular cancer are relatively young at diagnosis, and treatment is highly effective. Consequently, patients can expect to live many more years as cancer survivors; therefore, late effects of treatment become an increasingly important issue (Bokemeyer, Berger, Kuczyk, & Schmoll, 1996; Vaughn, Gignac, & Meadows, 2002).

Late effects of treatment are a new area of clinical focus and research for this population. Long-term toxicities of chemotherapy for testicular cancer survivors include secondary cancers, infertility, nephrotoxicity, neurotoxicity, pulmonary

toxicity, and cardiovascular toxicity (Chaudhary & Haldas, 2003; Vaughn et al., 2002).

The degree of long-term health risks related to cancer treatment with this population still is not clear and appears to have been underestimated in the past. Cardiovascular toxicities are among the more consequential effects that have been identified for testicular cancer survivors and can result in significant morbidity and mortality. The effects include Raynaud phenomenon, hypertension, coronary artery disease, and thrombotic events such as stroke, pulmonary emboli, and acute myocardial infarction (Berger, Bokemeyer, Schneider, Kuczyk, & Schmoll, 1995; Chaudhary & Haldas, 2003). Vascular side effects first were reported in 1977; since then, a small body of research has emerged attempting to evaluate the incidence and significance of cardiovascular toxicities in long-term survivors of testicular cancer (Berger et al.).

Risk Categories and Treatment

Radical unilateral orchiectomy is the standard approach for diagnosis and treatment in all cases of gonadal germ cell tumors. After orchiectomy, patients with stage I seminoma receive local radiation or surveillance. For patients with non-seminoma tumor types, surveillance or retroperitoneal lymph node dissection (RPLND) is employed. After RPLND, patients who have significant retroperitoneal metastases on pathology receive two cycles of adjuvant chemotherapy. The treatment decision is based on a number of patient-specific issues. Patients with stage IIa and IIb seminoma receive standard radiation therapy following orchiectomy; chemotherapy is used for patients with stage IIc disease. Stage II nonseminoma with low tumor burden usually is treated with RPLND or chemotherapy, depending on the extent and size of the tumor and on lymph node involvement. Metastatic disease is divided further into risk classifications: good risk, intermediate risk, and poor risk. This is based on whether the primary tumor is testicular or mediastinal, whether the metastasis is pulmonary or visceral, and the extent to which tumor markers are elevated. In advanced disease, good-risk patients receive three cycles of bleomycin, etoposide, and cisplatin (BEP) or four cycles of etoposide and cisplatin. Four cycles of BEP are used for poor-risk patients (Chaudhary & Haldas, 2003; Dodd & Kelly, 2001; National Comprehensive Cancer Network, 2004), as shown in Table 1. In summary, patients with testicular cancer and their oncologists must weigh the risks and benefits of treatment that includes chemotherapy. In some patients, chemotherapy is essential for cure.

An understanding of the regimens used in the past and at present is relevant when evaluating possible long-term toxicities related to treatment. In the 1970s, chemotherapy initially consisted of bleomycin and vinblastine. Regimens later added cisplatin, which greatly improved the cure rate (Gerl, 1994). The use of cisplatin, vinblastine, and bleomycin (PVB) then became standard first-line therapy. Cyclophosphamide and dactinomycin also were included in some regimens in the 1980s, and etoposide replaced vinblastine in the late 1980s. In the early 1990s, the standard treatment for metastatic disease became BEP (Gerl), and it remains the standard today.

Much of the comparative research on late toxicities in patients with testicular cancer treated with cisplatin-based chemotherapy compares treated patients to patients with early-stage disease who do not require chemotherapy. This

Table 1. Diagnoses and Treatments That Put Patients at Cardiovascular Risk

Diagnosis	Treatment
Stage I seminoma	Radiation therapy or surveillance
stage IIa or IIb seminoma	Radiation therapy
Stage IIc or III seminoma	Chemotherapy
Stage I nonseminoma	Retroperitoneal lymph node dissection or surveillance
Stage II nonseminoma	Depending on the extent of lymph node involvement
• Low tumor burden	Retroperitoneal lymph node dissection with or without adjuvant chemotherapy in select patients
• High tumor burden	Chemotherapy
Stage III nonseminoma	Chemotherapy
• Good risk	Three cycles of bleomycin, etoposide, and cisplatin or four cycles of etoposide and cisplatin
• Poor risk	Four cycles of bleomycin, etoposide, and cisplatin

Note. After chemotherapy, surgery may be indicated in select patients.

helps to decrease the chance of different underlying predispositions for risk factors in age-matched patients who do not have testicular cancer.

Cardiovascular Toxicities

Raynaud Phenomenon

Raynaud phenomenon, or Raynaud-like symptoms, is the most common vascular toxicity in patients with germ cell tumors after chemotherapy. It is characterized by transient episodes of vasoconstriction of the digital arteries precipitated by cold or stress, manifested by changes in the color of the affected digits, beginning with pallor followed by cyanosis, redness, and pain. Although Raynaud phenomenon certainly is not the most serious of the toxicities, it is responsible for discomfort and adversely affects quality of life. Its importance also lies in its possible association with other, more significant risk factors. A correlation between the appearance of Raynaud phenomenon and hypertension suggests a similar pathologic mechanism (Hennessy, O'Connor, & Carney, 2002). Erectile dysfunction also is believed to be associated with Raynaud phenomenon because angiopathy of the penile arteries also may be involved (Hennessy et al.; Meinardi, Gietema, van Veldhuisen, et al., 2000). The incidence of Raynaud phenomenon in various studies ranges from 21%–57%. The onset of symptoms may occur anytime during treatment and as long as 36 months after completing treatment. Some patients have gradual resolution of symptoms. However, 20%–25% of patients have been found to have chronic symptoms lasting more than 10 years after completion of treatment (Berger et al., 1995; Chaudhary & Haldas, 2003; Gerl, 1994).

The variations in the incidence of Raynaud phenomenon may be attributed to several factors, including inconsistency in methodologies used to measure the condition (Strumberg et al., 2002). A review by Berger et al. (1995) found that the incidence of Raynaud phenomenon was evaluated by numerous methods in different trials. Some investigators used specific measurements such as vasospastic responses to cold

provocation using photoelectric plethysmyography to record volume pulses of fingers, whereas others relied on clinical examinations and observations or chart reviews and mailed questionnaires.

Other discrepancies among studies can be explained by differences in chemotherapy regimens employed, particularly for patients treated prior to the 1990s (Chaudhary & Haldas, 2003). Statistical differences also may be the result of individual patient risk factors as well as the addition of supportive medications during treatment. Berger et al. (1995) found a slight protective effect in patients who received high-dose steroids, but the difference was not significant. In addition, because cold is a common provoking factor, climate could affect incidence, severity, and time to resolution (Meinardi, Gietema, van Veldhuisen, et al., 2000).

Bleomycin is thought to be the most significant drug directly implicated in Raynaud phenomenon. The addition of cisplatin or vinblastine may be additive or synergistic (Chaudhary & Haldas, 2003; Meinardi, Gietema, van Veldhuisen, et al., 2000). Cigarette smoking also can increase the chance of developing Raynaud phenomenon because the mechanism is thought to be arteriolar vasospasms, which can be exacerbated by smoking (Hennessy et al., 2002). Endothelia that already have been injured by tobacco may be more vulnerable to chemotherapy; however, some studies failed to document a significant correlation (Meinardi, Gietema, van Veldhuisen, et al.).

Cardiovascular Risk Factors

Chemotherapy can have chronic, damaging effects on the cardiovascular system and contribute to the development of long-term cardiovascular morbidity that may include elevated serum cholesterol, hypertension, and increased body mass index (BMI), as shown in Figure 1. The impact of cardiovascular risk factors may be aggravated by chemotherapy-associated vascular abnormalities, such as those that cause Raynaud phenomenon and obesity, a known factor in the development of cardiovascular disease. One study reported that BMI for patients with testicular cancer who received chemotherapy was 3% above expected levels four to six years after chemotherapy but returned to normal three to four years later. Whether the eventual resolution was related to lifestyle changes is unclear (Meinardi, Gietema, van der Graaf, et al., 2000). A 2003 study concluded that patients treated before 30 years of age, especially those who received chemotherapy, were at higher risk of abnormal BMI increases. About 14 years after treatment, testicular cancer survivors were found to have abnormal increases in BMI. This was believed to be associated with the young age of the patients at diagnosis. Chemotherapy was an additional independent parameter (Nord, Fossa, & Egeland, 2003).

Raynaud phenomenon
Hypertension
Elevated lipid profile
Elevated body mass index
Premature development of atherosclerosis
Hypercoagulable state
Angina or chest pain
Myocardial infarction

Figure 1. Chemotherapy-Induced Cardiovascular Toxicities

One of the more significant risk factors noted by Boyer et al. (1990) was that hypercholesterolemia was common in testicular cancer survivors. The finding was corroborated by Raghan, Cox, Childs, Grygiel, and Sullivan (1992), who confirmed a high prevalence of hypercholesterolemia in testicular cancer survivors treated with cisplatin-based chemotherapy. In two separate trials, they demonstrated a significant elevation of total cholesterol in 41% and 66% of patients studied. The difference in the rates may be related to the fact that in the former study, the subjects had a shorter follow-up and that the lipid values from the latter study were from older patients.

In a more recent study, Strumberg et al. (2002) also found elevated total cholesterol levels in patients with gonadal germ cell tumors who were treated with cisplatin-based therapy. Hypercholesterolemia (i.e., levels higher than 200 mg/dl) was observed in 81% of patients who had normal serum cholesterol levels prior to treatment. This was higher than expected in comparison to age-matched controls. Furthermore, 44% of the patients had elevated triglycerides. Similar results were found by Meinardi, Gietema, van der Graaf, et al. (2000), who discovered that total fasting cholesterol and triglycerides were elevated after chemotherapy compared to matched patients with testicular cancer who had only surveillance. In contrast, another study demonstrated no such treatment effect. Elevated cholesterol levels and the number of patients taking cholesterol-lowering medication were the same between patients with testicular cancer treated with cisplatin-based chemotherapy and patients who did not receive cisplatin-based therapy, although the data were based on random cholesterol measurements (Huddart et al., 2003).

The cause of hypercholesterolemia in testicular cancer survivors after chemotherapy still is uncertain and needs to be explored. Some thought has been given to additional indirect effects. For example, metabolic changes associated with chemotherapy-induced alterations in gonadal function have been known to affect lipid levels. A large percentage of treated and untreated patients were found to have elevated levels of luteinizing hormone, indicating Leydig cell dysfunction. Leydig cells are responsible for the production of testosterone, and testosterone levels were found to be lower in patients who were treated with chemotherapy than those who were not (Meinardi, Gietema, van der Graaf, et al., 2000). Bokemeyer et al. (1996) studied 90 chemotherapy survivors, with a median age of 28, for as long as 159 months. In the study, 30 patients were treated with PVB, 26 with BEP, 22 with BEP and vinblastine, and the remaining 12 with other cisplatin-based regimens. Alterations in follicle stimulating hormone and luteinizing hormone were found in as many as 68% of patients and Leydig cell insufficiency in 33%. Of note, elevated levels of gonadotropins were found to be associated with higher drug doses. This indicates that chemotherapy could contribute to additional damage to gonadal function. Patients who received cisplatin-based chemotherapy demonstrated a negative correlation between insulin resistance and testosterone. Investigators postulated that this could be a metabolic consequence of long-term gonadal toxicity resulting in excess weight, hypertension, insulin resistance, and elevated lipids such as that found with metabolic syndrome-X (Meinardi, Gietema, van der Graaf, et al., 2000).

Hypertension, another significant risk factor for cardiovascular disease, also has been linked to the chemotherapy used to treat germ cell tumors. In one study, 39% of 62 patients

postchemotherapy had hypertension (i.e., systolic blood pressure greater than 150 mmHg or diastolic greater than 95 mmHg). All had normal blood pressures prior to chemotherapy, and the mean systolic and diastolic blood pressures in the treated group were significantly higher than those of their untreated cohorts. The median time from treatment to the diagnosis of hypertension was 7.5 years. The hypertensive post-treatment patients with testicular cancer also were found to have greater left ventricular wall thickness than the normotensive patients (Meinardi, Gietema, van der Graaf, et al., 2000). Huddart et al. (2003) found no evidence of higher systolic or diastolic blood pressures, although more patients reported taking antihypertensive medications; however, when compared to the surveillance cohort, the difference was not significant.

Cisplatin-induced renal tubular injury has been known to cause hypomagnesemia and may induce renin secretion. In several studies, hypomagnesemia was implicated in the development of hypertension. Increased plasma renin activity has been associated with elevated levels of angiotensin II, which may accelerate vascular damage and also is associated with Raynaud phenomenon. Cisplatin-induced hypomagnesemia can lead to vasospasm of the coronary arteries (Chaudhary & Haldas, 2003). Several studies have identified that patients with essential hypertension and reduced plasma renin activity are more prone to cerebrovascular accidents and cardiac events (Bosl et al., 1986; Vogelzang, Torkelson, & Kennedy, 1985). Damage to the endothelium may be caused by cisplatin-induced hypomagnesemia, altering intracellular calcium concentrations (Vogelzang et al.).

Cardiac Events

Cisplatin-based chemotherapy appears to initiate thrombus formation through damage to the endothelium, resulting in a hypercoagulable state. Whether single-agent cisplatin is solely responsible is not clear because acute events also have been reported with etoposide alone, vinblastine plus cisplatin, PVB, and BEP combinations. The most concerning vascular toxicity is damage to the coronary arteries that can lead to life-threatening acute myocardial infarction (MI). This first was reported in 1979, after two young men treated with PVB were found to have severe atherosclerosis despite a lack of risk factors (Meinardi, Gietema, van Veldhuisen, et al., 2000). However, the findings were disputed in a review by Chaudhary and Haldas (2003), who determined the incidence of acute MI to be rare during and after chemotherapy.

A comprehensive study by Huddart et al. (2003) examined the data on cardiovascular events from 992 patients in the United Kingdom treated from 1982–1992. Cardiac events were defined as (a) death from MI or cardiac-related episode, (b) reported angina or MI, or (c) cardiac surgery for coronary artery disease. The study concluded that after a median follow-up of 10 years, the risk of a cardiac event for postchemotherapy patients, when compared to untreated cohorts, represented a statistically significant 2.4- to 2.8-fold increased risk. The investigators concluded that this was not likely a result of increased cardiac risk factors but rather was suggestive of direct or indirect effects of the chemotherapy. Investigators appeared to agree that cisplatin was the agent most likely responsible for cardiac events.

A smaller study evaluated 87 patients aged 30–50 who were 10–20 years postchemotherapy. Of the patients, 6%

experienced major cardiac events, including MI, angina, and myocardial ischemia 9–16 years after chemotherapy. This resulted in an increased observed-to-expected ratio of 7.1 when compared to the general male Dutch population (Meinardi, Gietema, van der Graaf, et al., 2000).

Conclusions and Implications for Nursing

Evidence exists that chemotherapy used in the treatment of testicular cancer increases the risk of cardiovascular disease and that the development of cardiovascular disease may be a greater risk to patients than cancer recurrence is (Huddart et al., 2003; Strumberg et al., 2002). Despite the increased risk of cardiovascular complications, researchers agree, based on the likelihood of cure in this population, that the benefit of treatment far outweighs the potential risks. Researchers concurred that a continuing effort should be made to explore new and modified treatments and to customize or minimize chemotherapy exposure to specific agents when possible, without compromising cure.

A paucity of nursing literature exists on issues related to treatment for testicular cancer and specific recommendations for follow-up care. Most of the information on late effects of cancer treatment relates to psychosocial issues and not issues of late physiologic effects. Nurses, particularly advanced practice nurses in oncology, should take an active role in researching, disseminating, and using information about long-term, treatment-related cardiovascular effects experienced by patients with testicular cancer.

Research is needed to examine the late effects of treatment with cisplatin-based chemotherapy, and care should be taken when designing protocols to use specific definitions for effects studied. For example, specific parameters should be used to define hypertension and elevated lipids. Patients should be followed long term, and controls should be matched closely.

Patients with testicular cancer who require chemotherapy should be informed about known risk factors for cardiovascular disease and counseled regarding tobacco cessation, diet modifications, and weight control (Vaughn et al., 2002). Patients treated with bleomycin should be monitored for toxicity symptoms, including Raynaud phenomenon. Patients should be made aware that Raynaud symptoms can be lessened by avoiding exposure to cold. Calcium channel blockers also have been used with some success and can be prescribed, if appropriate, for this problem (Chaudhary & Haldas, 2003).

Patients should be made aware of the possible long-term cardiovascular effects when determining treatment options based on pathology and staging. Family history, personal history, and lifestyle should be considered when planning treatment and outlining possible risks for side effects of treatment. Patients with testicular cancer and their healthcare providers should have in-depth discussions regarding the risks and benefits of each treatment to make informed treatment decisions. Nurses should know the treatment options available and ensure that patients receive information prior to making treatment decisions. In addition, survivors of testicular cancer must be made aware of the importance of long-term follow-up for surveillance for early detection of disease recurrence as well as for late effects of treatment. Special attention should be given to cardiovascular risk factors, including high blood pressure and hyperlipidemia (Vaughn et al., 2002).

The needs of adult cancer survivors are not yet clear, and standards of care have not been developed. Much remains to be done to provide testicular cancer survivors with accurate information concerning the potentially serious vascular and cardiovascular effects of their curative treatments. In summary, oncology nurses, in collaboration with medical oncology colleagues, should play a critical role in the assessment, management, and follow-up care of patients with testicular cancer. Collaborative activities should include (a) development of clinical research protocols to further identify the scope and incidence of cardiovascular effects after chemotherapy, (b) careful clinical assessment and documentation of signs and symptoms of possible toxicities, (c) pretreatment education

and counseling based on data from the literature, (d) education of patients about surveillance, risk factors, and the importance of continued follow-up, (e) recommendation and prescription of lifestyle changes and therapies to decrease cardiovascular alterations and risk factors, and (f) education of and collaboration with primary care providers. Only through research and knowledge of the disease and treatment options, as well as late effects of treatment, can nurses provide evidence-based comprehensive care to testicular cancer survivors.

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