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HOW TO

How to Manage Cisplatin-Based Chemotherapy–Related Cardiovascular Disease in Patients With Testicular Cancer

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CLINICAL CASE

A 49-year-old man with a limited medical history presented with lower abdominal pain, intermittent low-grade fevers, and night sweats. Computed tomography of the abdomen and pelvis showed multiple enlarged retroperitoneal lymph nodes. Testicular ultrasound showed bilateral testicular lesions with microlithiasis. His tumor markers showed normal α-fetoprotein but elevated β-human chorionic gonadotropin and lactate dehydrogenase. He underwent computed tomography-guided biopsy of a retroperitoneal lymph node. Pathology showed seminoma, a type of testicular cancer (TC).

MANAGEMENT OF METASTATIC TC

TC is the most common solid tumor malignancy in young adult men, with incidence increasing over the past 2 decades.[1] The 5-year overall relative survival of patients with TC (all stages) is >95%. Standard chemotherapy for International Germ Cell Cancer Collaborative Group good-risk metastatic TC consists of 3 cycles of bleomycin, etoposide, and cisplatin (BEP) or 4 cycles of etoposide and cisplatin. For intermediate- or poor-risk metastatic TC, 4 cycles of BEP or etoposide, ifosfamide, and cisplatin is the standard treatment. Given the high cure rate, long-term treatment-related adverse events are important to identify and manage in survivorship, including cardiovascular side effects related to cisplatin-based chemotherapy (CBCT).[2,3]

CLINICAL CASE CONTINUED

The patient was diagnosed with stage IIC extragonadal retroperitoneal seminoma. He was initiated on 3 cycles of BEP. After the second cycle of chemotherapy, he developed acute arterial thromboembolism (ATE) in the distal portions of the right peroneal, anterior tibial, posterior tibial, and dorsalis pedis arteries. He received heparin infusion and underwent thromboembolectomy with a 4-part compartment fasciotomy of the right calf. He also received dual antiplatelet therapy with aspirin and clopidogrel. After recovery, the patient completed the remaining cycles of CBCT in the postsurgical setting.

MANAGEMENT OF ACUTE THROMBOEMBOLISM

Patients with TC treated with CBCT are at increased risk for vascular toxicity within the first year, which is associated with high morbidity and mortality. These events manifest as vascular thromboembolism, ATE, cerebrovascular accident (CVA), myocardial infarction (MI), and increased cardiovascular mortality within the first year.[2-5]

Approximately 9% to 19% of patients with TC treated with CBCT developed VTE, occurring shortly before or during the first 90 days of chemotherapy initiation.[4,5] Factors associated with an increased risk for VTE include International Germ Cell Cancer Collaborative Group intermediate- and poor-risk groups, large retroperitoneal lymph node

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metastases, central venous catheter presence, and elevated C-reactive protein. The data on thromboprophylaxis for patients with TC remain mixed, and 2 recent studies have offered conflicting recommendations on empirical thromboprophylaxis during CBCT,[4,5] and we do not routinely do so in our practice.

ATE occurs in 0.3% to 1.2% of patients, with older age, obesity, and tobacco use as risk factors.[4] A recent study showed that a majority of ATEs occurred during the first year and during CBCT.[4] ATE, though less common than vascular thromboembolism, confers significant morbidity and mortality.[2,3] Patients who present with vascular thrombosis, as our patient did, or with CVA and MI are treated according to the standard of care. Multidisciplinary management discussions are critical, as we consider antiplatelet therapy because of bleeding risk in the setting of thrombocytopenia during CBCT.

CLINICAL CASE CONTINUED

The patient had a complete disease response to CBCT and had no evidence of TC at 8-year follow-up. In the first year after completion of CBCT, he developed hypertension, hyperlipidemia, and obesity, with his body mass index increasing from 27.1 to 30.8 kg/m^2. He was started on metoprolol and rosuvastatin. TC survivors (TCS) are followed by the oncology team for at least 5 to 10 years on the basis of risk for TC recurrence and preference of patients and their oncologists. Subsequently, survivorship care is typically transitioned to the patient's primary care physician.

MANAGEMENT OF LONG-TERM CARDIOVASCULAR DISEASE RISKS IN TCS

The development of cardiovascular disease (CVD) risk factors can occur within the first year or may manifest years after exposure to CBCT (**Figure 1**). Treatment with CBCT increases the prevalence of CVD risk factors such as hypertension, hyperlipidemia, diabetes, obesity, and CVD among TCS.[2,3,6] It is postulated that circulating cisplatin, detected up to 20 years after CBCT, results in these changes.[7]

INCREASED INCIDENCE OF CARDIOVASCULAR RISK FACTORS AND METABOLIC SYNDROME IN TCS

Several large national registry studies demonstrate increased rates of hypertension and hyperlipidemia in TCS.[2,3,6] In a large Danish registry study, Lauritsen et al[2] evaluated the prevalence of CVD risk factors and CVD after treatment for TC (N = 5,185; median follow-up 15.8 years).[2] Hypertension (HR: 1.4; 95% CI: 1.2-1.6) and hyperlipidemia (HR: 1.3; 95% CI: 1.1-1.5) were increased in TCS compared with the general population, manifesting in years 1 to 10 after exposure and persisting >10 years. A similar Norwegian longitudinal cohort study noted that TCS treated with CBCT 30 years previously reported increased use of antihypertensive medications (55% vs 24%; $P \leq 0.001$) and lipid-lowering medications (44% vs 18%; $P \leq 0.001$) compared with age-matched male control subjects in the general population.[6] These data suggest that the manifestation of hypertension and hyperlipidemia begins after the first year and is persistent at higher rates compared with patients who did not receive CBCT (**Figure 1**). There are limited data to support that CBCT in itself confers additive risk for diabetes mellitus in TCS.[2,3]

MetS, comprising hypertension, dyslipidemia, insulin resistance, and abdominal obesity, is highly prevalent in 13% to 39% of TCS and is hypothesized to be driven mainly by CBCT and hypogonadism as primary causes rather than sedentary lifestyle and excess caloric intake.[8,9] Zaid et al[8] compared TCS (N = 486, mean age 38 years) with NHANES (National Health and Nutrition Examination Survey) control subjects, with a median time from treatment to study enrollment of 4.7 years (range: 0.4-23.9 years). TCS were significantly more likely to have hypertension (43.2% vs 30.7%; $P < 0.001$), elevated low-density lipoprotein (17.7% vs 9.3%; $P < 0.001$), total cholesterol (26.3% vs 11.1%; $P < 0.001$), and body mass index ≥25 kg/m^2 (75.1% vs 69.1%; $P = 0.04$). Compared with NHANES control subjects, increased age, hypogonadism with testosterone level ≤3.0 ng/mL, and elevated serum soluble cell adhesion molecule-1 level

HIGHLIGHTS

- Patients with advanced testicular cancer receive cisplatin-based chemotherapy with a high rate of cure.
- Cisplatin-based chemotherapy increases risks of acute vascular complications among testicular cancer survivors.
- Cisplatin-based chemotherapy increases cardiovascular disease risk factors and cardiovascular disease among testicular cancer survivors.
- Long-term management of cardiovascular risk factors and cardiovascular disease in testicular cancer survivors is recommended.

FIGURE 1 Risk for Cardiovascular Disease After Platinum Chemotherapy in Testicular Cancer Survivors

	Time from Exposure to Cisplatin-based Chemotherapy		
	<1 year	Years 1-10	>10 years
Cardiovascular Risk Factors			
Hypertension	Increased Risk [2]	Increased Risk [2]	Increased Risk [2, 6]
Hypercholesterolemia		Increased Risk [2]	Increased Risk [2, 6]
Diabetes or Insulin Resistance		Unclear Risk [2]	Unclear Risk [2, 6]
MetS		Increased Risk [8]	Increased Risk[8]
Cardiovascular Disease Outcomes			
CAD/MI	Highest risk [2-4]		Increased Risk [2]
CVA/Stroke/TIA	Highest risk [2-4]		
ATE	Highest risk [2-4]		
VTE	Highest risk [2-5]	Highest Risk[2]	
Cardiovascular deaths (secondary to CAD/MI/CVA)	Highest risk [2-4]		

Risk defined by HR in large registry studies: highest risk, HR >2.0; increased risk, HR >1.3; unclear risk, HR not significant. ATE = arterial thromboembolism; CAD = coronary artery disease; CVA = cerebrovascular accident; MetS = metabolic syndrome; MI = myocardial infarction; TIA = transient ischemic attack; VTE = venous thromboembolism.

were associated with the development of MetS. Importantly, TCS were less likely to be current smokers and were at least twice as likely than NHANES control subjects to engage in moderate- or vigorous-intensity physical activity. It is hypothesized that hypogonadism likely also plays a role in developing MetS and CVD risk factors, contributing to this paradox of increased CVD risk factors despite engaging in physical activity and not smoking. The exact contribution of hypogonadism vs CBCT in causing MetS in TCS remains unknown.

There are mixed data on the role of cumulative cisplatin dose in the development of MetS and other CVD risk factors. For example, Haugnes et al[9] previously found that patients who received a cumulative dose of cisplatin of >850 mg had 2.8-fold increased odds of MetS. In contrast, Zaid et al[8] found no difference in the prevalence of MetS and chemotherapy regimen (BEP vs etoposide and cisplatin) or cumulative dose of cisplatin or bleomycin.

INCREASED CVD RISK AND CVD-ASSOCIATED MORTALITY

Lauritsen et al[2] also noted that CVD risk was highest within the first year after treatment with BEP, including an increased risk for MI (HR: 6.3; 95% CI: 2.9-13.9) and CVA (HR: 6.0; 95% CI: 2.6-14.1), and was higher in younger patients than older patients. These findings were similar to the North American retrospective study by Fung et al,[3] which demonstrated that increased CVD mortality after chemotherapy was restricted to the first year after TC diagnosis (HR: 4.86; 95% CI: 1.25-32.08), with distant disease ($P < 0.05$) and older age at diagnosis ($P < 0.01$) as independent risk factors. In contrast, in the study by Lauritsen et al, risk for CVD in patients with TC between 1 and 10 years after treatment with CBCT was similar to the general population. However, late events, defined as >10 years after CBCT, demonstrated an increase in MI (HR: 1.4; 95% CI: 1.0-2.0) and cardiovascular death (HR: 1.6; 95% CI: 1.0-2.5). It is important to note that the findings reported by Fung et al and Lauritsen et al were based on relatively few incident cases of MI (ie, 7 among 1,360 patients in the Lauritsen et al). Yet despite the low rate of CVD-associated mortality in studies of TCS, we highlight the importance of screening for and treating CVD risk factors, particularly in long-term survivorship (**Figure 1**).

PRACTICAL CONSIDERATIONS IN THE MANAGEMENT OF CVD IN TCS

For the first year after CBCT, most TCS are seen in close follow-up by their medical oncologists. We recommend screening and treating hypertension, hyperlipidemia, and MetS in the first year. In the long-term setting, given the young age of patients diagnosed with TC, it is imperative to identify TCS at high risk for CVD and manage risk factors, particularly in years 1 to 10 after CBCT. In our practice, we are working to

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identify those cisplatin-treated patients, especially those who had advanced-stage TC and those treated with more than 1 line of CBCT and/or high-dose chemotherapy followed by autologous bone marrow transplantation. We are working with our adult medical oncology and adolescent and young adult survivorship clinics to facilitate systematic screening for CVD risk factors. Anecdotally, we note that many young patients with TC are lost to follow-up medical care, particularly during this vulnerable time when they may manifest cardiovascular risk factors and their TC treatment history is not typically revisited in subsequent routine care. As such, we also seek to disseminate the need for earlier, more aggressive cardiovascular screening with local primary care physicians, especially as they transition from our respective academic referral oncology centers.

When TCS are referred to cardio-oncology clinics, we obtain comprehensive treatment histories and screening for cardiovascular risk factors at the time of consultation. Although the data on cisplatin-dose toxicity is unclear, we routinely record the types and number of CBCT episodes, including cumulative cisplatin dose, in our cardio-oncology consultations. Although not specific for TCS, for those <40 years of age at the time of the cardio-oncology clinic visit, we use the CCSS (Childhood Cancer Survivor Study) Cardiovascular Risk Calculator, a validated risk assessment tool for predicting the risk for heart failure, ischemic heart disease, and stroke by 50 years of age among childhood cancer survivors.[10] Typically, we recommend screening echocardiography, particularly to screen for diastolic dysfunction,[6] especially those who have already manifested hypertension or other components of MetS. We use these aggregate measures to have shared decision-making discussions with patients regarding lifestyle modification, including following a heart-healthy diet, engaging in routine exercise, and potentially starting antihypertensive or lipid-lowering medications.

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