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EDITORIAL COMMENT

# Cardiovascular Toxicity With Cisplatin in Patients With Testicular Cancer

## Looking for Something Heavier Than Heavy Metal*

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It is said that two-thirds of anticancer drugs have their origin in serendipity, and this is most certainly true for cisplatin (1). Fifty-five years ago, Barnett Rosenberg inquired about the influence of an electrical field on cell division and found that the division of *Escherichia coli* showed an on-off effect depending on the power state (2). Two years later came the realization that the antiproliferative phenomenon had nothing to do with electricity but rather the release of a heavy metal, platinum, from the electrodes. Translating this knowledge to cancer cells was seemingly more straightforward and rewarding, and clinical trials commenced in 1972, leading to the approval of cisplatin for testicular cancer in 1978. Since then platinum drugs have been a game changer in the treatment of testicular cancer in particular, with a decrease in death rates by two thirds. In combination with other drugs, most commonly etoposide or bleomycin and etoposide (BEP), and orchidectomy and radiation therapy, cure rates for testicular cancer have exceeded 90%.

One of the most prominent toxicities noted in the original experimental studies was renal failure, and this concern has persisted. Other side effects noted relatively early in clinical practice included vascular events. These were primarily of two kinds: vasospasm, especially Raynauds, and venous and arterial thrombosis (3). Of interest, atherosclerotic plaques do not seem to be a prerequisite for acute coronary events in patients undergoing platinum-based therapies (4,5). This may suggest that induction of endothelial apoptosis with an erosion-type acute coronary syndrome might be the underlying mechanism (or thromboembolism from an alternate source) (6–8). Of further interest, even after the active treatment period, patients with testicular cancer may remain at higher risk for vascular disease and related events (9). Defining the excess cardiovascular risk, however, has not been easy, especially treatment-related cardiovascular mortality (9). In addition to the debate on the magnitude and duration of excess cardiovascular risk, there is the debate of whether cisplatin, alone or in combination with other therapies, even plays a causal role. Metabolic changes and the adverse cardiovascular effects of hypogonadism are well described in testicular cancer survivors (9).

The study by Cameron et al. (10) in this issue of *JACC: CardioOncology* aimed to address the nebulous landscape of cisplatin vascular toxicity in an elegant investigation of two cohorts of patients with testicular cancer. The first group included those with active disease for the assessment of early effects. Patients were stratified based on disease severity and related treatment strategy (active surveillance; 1 to 2 cycles of BEP; and 3 to 4 cycles of BEP). The second group included testicular cancer survivors 1 to 7 years from diagnosis, stratified by their management approach at the time: active surveillance or 3 to 4 cycles of BEP therapy. The key observations were as follows: in the early effects cohort, a decrease in flow-mediated dilation (FMD) of the brachial artery was recognized in the first 24 h of treatment in both BEP therapy

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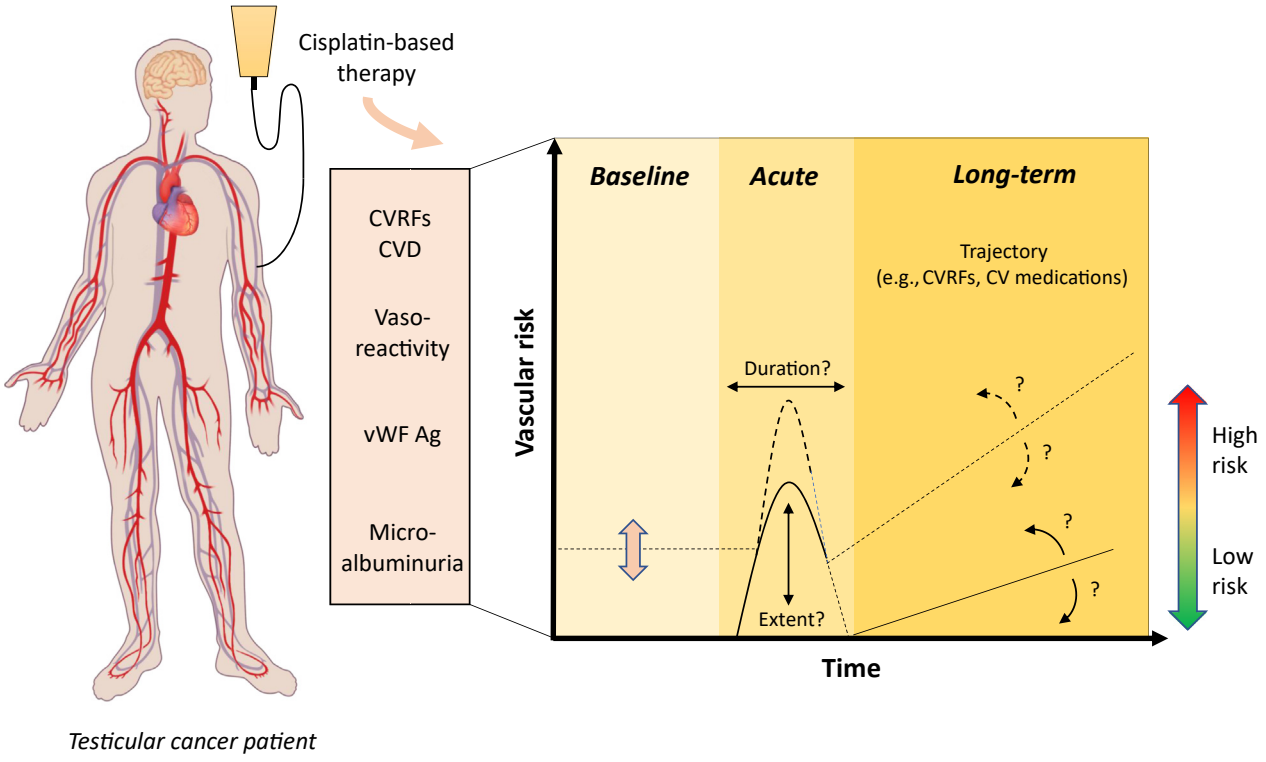
**FIGURE 1** Risk of Vascular Disease and Events in Patient With Testicular Cancer




Patients with testicular cancer are at risk of vascular disease and events. Those with higher-dose cisplatin therapy face a higher acute and potentially long-term risk. Cardiovascular risk factors (CVRFs) and cardiovascular diseases (CVD) set a baseline risk level, and the acute risk with cancer therapy remains variable in extent and duration. Conceivably some patients show complete reversibility to baseline levels but others do not. The long-term risk is illustrated as a linear risk model, but may differ in reality and is influenced by various factors in the individual patient. Vasoreactivity testing in particular seems to be well suited to follow patients across this continuum of care and possibly to gauge the need and benefit of therapeutic interventions. CV = cardiovascular; vWF Ag = von Willebrand factor antigen.

groups, but the effect was more profound and statistically significant in those receiving 3 to 4 cycles. Of note, the absolute value of FMD was not different between the 1 to 2 and 3 to 4 cycle groups, rather the latter group started with a higher baseline value. The duration of the effect was said not to differ between the two groups, but a recurrent decrease was noted at 9 months in the 3 to 4 cycle group. Von Willebrand factor (vWF) antigen levels increased significantly from baseline to 6 weeks in the 3 to 4 cycles of BEP group but not otherwise. High-sensitive troponin-I, intercellular adhesion molecule-1, and high-sensitivity C-reactive protein remained unchanged in all groups at all time points. The albumin-creatinine ratio increased in both treatment groups within 24 h and this increase persisted for 6 weeks in the 3 to 4 cycle group. An increase in urine interleukin-18 was seen in both treatment groups at 24 h, whereas an increase in Cystatin C was seen only in the 3 to 4 cycle group, with a lower level. In the survivor cohort, based on forearm blood flow response to bradykinin, acetylcholine and sodium nitroprusside (by venous occlusion plethysmography) showed no differences between those on surveillance and those who had received BEP. Likewise, bradykinin induced a dose-dependent net tissue plasminogen activator (but not plasminogen activator inhibitor-1) antigen release in both survivor groups. In human aortic endothelial cells, tissue plasminogen activator and plasminogen activator inhibitor-1 messenger RNA expression decreased significantly and nonsignificantly in cells exposed to cisplatin. An increase in protein kinase B and extracellular signal-regulated kinase 1/2 phosphorylation was seen seemingly with a defined optimum for dose and time constellation (maximal at an intermediate cisplatin dose and 15-min stimulation).

The results, as reported, echo prior studies in the field and thereby consolidate the evidence. For instance, in women with ovarian and endometrial

cancer an acute decrease in FMD was seen as early as with the first cycle of carboplatin and paclitaxel chemotherapy (11). In conjunction with the current findings, one would conclude that the common denominator is platinum drugs and that there is no gender-related difference. Furthermore, one would conclude that platinum drugs seemingly induce relatively acute changes in endothelial cells that translate into a reduction in flow-mediated vasodilation and alterations in nitric oxide bioavailability. Indeed, a reduction of inducible nitric oxide production was shown in human umbilical vein cells along with a reduction in inducible protein kinase B and endothelial nitric oxide synthase phosphorylation (11). It is of interest that FMD decreased again in the 3 to 4 BEP cycle group at 9 months, although reportedly not to a significant degree. Nevertheless, it would be of interest to see if this recurrent decrease relates to any clinical events, and, in general, if long-term serial assessment of vascular reactivity, possibly even with other devices such as the EndoPAT (Itamar Medical, Caesarea, Hefa, Israel), can inform and guide management.

A high-risk vascular fingerprint for patients with testicular cancer undergoing cisplatin therapy was recently proposed, consisting of ≥3 of the following: body mass index >25 kg/m$^2$, current smoking, blood pressure >140/90 mm Hg (or treated), hyperlipidemia (or treated), and elevated fasting plasma glucose (12). vWF levels increased much more during therapy in the high-risk fingerprint group, which included 3 of 4 patients with arterial ischemic events. The dynamics of vWF levels were recapitulated in the current study by Cameron et al. (10), and it will remain important to confirm if such increases identify those at risk of (arterial) thrombotic events. Whether high-risk patients should be started on antiplatelet therapy is unknown at present and suitable for testing in a clinical trial.

Interestingly, a prior study in testicular cancer survivors showed that those patients who were exposed to cisplatin-based chemotherapy nearly 3 to more than 20 years ago had a more severe reduction in FMD and higher levels of circulating endothelial cells than those not exposed (13). The fact that cisplatin levels are detectable even nearly 30 years from therapy supports the theory of long-term exposure and endothelial injury (14). A difference in vascular reactivity between cisplatin-exposed and cisplatin-nonexposed was not seen in the current study by Cameron et al. (10). It is important, however, to realize that the vascular response was blunted in both groups, even in comparison with patients with metabolic syndrome (considered to account for the vascular outcomes in testicular cancer survivors as mentioned) (15). Such results can also not be unequivocally attributed to hypogonadism (16,17). Accordingly, more studies are needed to define the nature of the reduced vasoreactivity in patients with testicular cancer as well as the therapeutic and prognostic implications.

In summary, the authors are to be congratulated for their efforts and their contributions to the field. Their work raises awareness for the development of renal and endothelial dysfunction in patients with testicular cancer, which can progress to acute and chronic renal failure and acute and chronic vascular events. The risk of the individual patient, however, is still hard to predict. Of the various parameters, vascular reactivity testing is well suited to serve as a parameter of cardiovascular health and its modification by therapies and lifestyle interventions (**Figure 1**). All in all, patients with testicular cancer are a prime example of individuals who benefit from being followed in a cardio-oncology approach. Optimal management of cardiovascular risk factors and cardiovascular disease entities (as well as any renal disease) is as important as their most optimal oncology treatment approach. After all, cardiovascular toxicity with cisplatin use in patients with testicular cancer is a reality with the potential for something heavier than heavy metal serendipity.

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## REFERENCES

**1.** Hargrave-Thomas E, Yu B, Reynisson J. Serendipity in anticancer drug discovery. World J Clin Oncol 2012;3:1–6.

**2.** Monneret C. Platinum anticancer drugs. From serendipity to rational design. Ann Pharm Fr 2011;69:286–95.

**3.** Doll DC, List AF, Greco FA, Hainsworth JD, Hande KR, Johnson DH. Acute vascular ischemic events after cisplatin-based combination chemotherapy for germ-cell tumors of the testis. Ann Intern Med 1986;105:48–51.

**4.** Dieckmann KP, Gerl A, Witt J, Hartmann JT. Myocardial infarction and other major vascular events during chemotherapy for testicular cancer. Ann Oncol 2010;21:1607–11.

**5.** Ito D, Shiraishi J, Nakamura T, et al. Primary percutaneous coronary intervention and

intravascular ultrasound imaging for coronary thrombosis after cisplatin-based chemotherapy. Heart Vessels 2012;27:634–8.

**6.** Dursun B, He Z, Somerset H, Oh DJ, Faubel S, Edelstein CL. Caspases and calpain are independent mediators of cisplatin-induced endothelial cell necrosis. Am J Physiol Renal Physiol 2006; 291:F578–87.

**7.** Oren O, Herrmann J. Arterial events in cancer patients-the case of acute coronary thrombosis. J Thorac Dis 2018;10:S4367–85.

**8.** Herrmann J. Vascular toxic effects of cancer therapies. Nat Rev Cardiol 2020;17:503–22.

**9.** Gugic J, Zaletel LZ, Oblak I. Treatment-related cardiovascular toxicity in long-term survivors of testicular cancer. Radiol Oncol 2017;51:221–7.

**10.** Cameron AC, McMahon K, Hall M, et al. Comprehensive characterisation of the vascular effects of cisplatin-based chemotherapy in patients with testicular cancer. J Am Coll Cardiol CardioOnc 2020;2:443–55.

**11.** Sekijima T, Tanabe A, Maruoka R, et al. Impact of platinum-based chemotherapy on the progression of atherosclerosis. Climacteric 2011;14:31–40.

**12.** Lubberts S, Boer H, Altena R, et al. Vascular fingerprint and vascular damage markers associated with vascular events in testicular cancer patients during and after chemotherapy. Eur J Cancer 2016;63:180–8.

**13.** Vaughn DJ, Palmer SC, Carver JR, Jacobs LA, Mohler ER. Cardiovascular risk in long-term survivors of testicular cancer. Cancer 2008;112: 1949–53.

**14.** Hjelle LV, Gundersen PO, Oldenburg J, et al. Long-term platinum retention after platinum-based chemotherapy in testicular cancer survivors: a 20-year follow-up study. Anticancer Res 2015;35:1619–25.

**15.** Schinzari F, Iantorno M, Campia U, et al. Vasodilator responses and endothelin-dependent vasoconstriction in metabolically healthy obesity and the metabolic syndrome. Am J Physiol Endocrinol Metab 2015;309: E787–92.

**16.** Deniz F, Ermis N, Kepez A, et al. Evaluation of vascular reactivity of young male hypogonadotrophic hypogonadism patients. Int J Cardiovasc Imaging 2010;26:35–40.

**17.** Sader MA, Griffiths KA, Skilton MR, Wishart SM, Handelsman DJ, Celermajer DS. Physiological testosterone replacement and arterial endothelial function in men. Clin Endocrinol (Oxf) 2003;59:62–7.

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