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Original Research

Vascular fingerprint and vascular damage markers associated with vascular events in testicular cancer patients during and after chemotherapy

S. Lubberts [a], H. Boer [a], R. Altena [a], C. Meijer [a], A.M. van Roon [b], N. Zwart [a], S.F. Oosting [a], P.W. Kamphuisen [b], J. Nuver [a], A.J. Smit [b], A.B. Mulder [c], J.D. Lefrandt [b], J.A. Gietema [a,*]

[a] *Department of Medical Oncology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands*
[b] *Department of Vascular Medicine, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands*
[c] *Department of Laboratory Medicine, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands*

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Abstract ***Background:*** Metastatic testicular cancer (TC) can be cured with bleomycin, etoposide and cisplatin (BEP) chemotherapy. This comes at the price of an increased cardiovascular disease risk, not only years afterwards, but also during and shortly after chemotherapy. To prevent cardiovascular events, high-risk patients should be identified. The aim of this study was to assess BEP-chemotherapy induced vascular damage and to find risk factors for early vascular events.

Patients and methods: A prospective cohort study was performed in (B)EP treated TC patients. Development of venous and arterial vascular events was assessed. Vascular damage markers (von Willebrand factor [vWF], coagulation factor VIII [FVIII], intima media thickness [IMT]) and cardiovascular risk factors were assessed before and until 1 year after chemotherapy. Before start of chemotherapy a vascular fingerprint was estimated. Presence of $\geq$3 risk factors was defined as high-risk vascular fingerprint: body mass index >25 kg/m^2, current smoking, blood pressure >140/90 mm Hg, total cholesterol >5.1 and/or low-density lipoprotein >2.5 mmol/L or glucose $\geq$7 mmol/L.

Results: Seventy-three patients were included. Eight (11%) developed vascular events (four arterial events, four pulmonary embolisms). vWF and FVIII increased during chemotherapy, especially in patients with vascular events. Sixteen patients (22%) had a high-risk vascular

* *Corresponding author*: Department of Medical Oncology, University Medical Center Groningen, P.O. Box 30.001, 9700 RB Groningen, The Netherlands. Tel.: +31 50 3612821.
E-mail address: j.a.gietema@umcg.nl (J.A. Gietema).

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fingerprint before start of chemotherapy. These patients had arterial events more often (3/16 [19%] versus 1/57 [2%]; p = 0.031) and higher vWF levels and IMT.
Conclusions: Endothelial activation and upregulation of procoagulant activity seem important mechanisms involved in early (B)EP-chemotherapy-induced vascular events. Before chemotherapy, a quarter already had cardiovascular risk factors. A vascular fingerprint could identify patients at risk for arterial events. This vascular fingerprint, when validated, can be used as a tool to select patients who may benefit from preventive strategies.

1. Introduction

Since the introduction of platinum-based chemotherapy in 1977, the prognosis of metastatic testicular cancer (TC) improved remarkably, with survival rates of 80–90% [1]. Treatment consists of orchidectomy followed by bleomycin, etoposide and cisplatin (BEP) combination chemotherapy [2]. However, cure rates are compromised by the increased risk of cardiovascular disease (CVD) both during or shortly after treatment (acute onset) [3,4] as well as years after treatment (late onset) [5,6]. The pathophysiology is not fully understood, and probably differs between acute and late CVD onset. One of the contributing factors for both types appears to be occurrence of endothelial dysfunction [7], which can occur either as a direct chemotherapy effect or can be mediated by development of cardiovascular risk factors; TC survivorship is generally associated with an unfavourable cardiovascular risk profile [8,9].

That early onset CVD is a source of serious treatment-induced morbidity and mortality was recently confirmed by Fung *et al.* [10]. If high-risk patients could be identified before start of chemotherapy, preventive strategies for this group can be explored to prevent early cardiovascular events.

Therefore, the aim of this study was to assess BEP-chemotherapy-induced (subclinical) vascular damage and to find clues to identify patients at risk for early vascular events. To assess vascular damage we prospectively measured different markers for subclinical vascular damage and cardiovascular risk factors. We looked into the relationship of these markers and risk factors with development of both arterial and venous vascular events.

2. Methods

2.1. Patients

We performed a prospective cohort study in metastatic TC patients, aged 18–50 years, treated with first-line (B)EP chemotherapy in the University Medical Center of Groningen, the Netherlands. Exclusion criteria were previous chemo-/radiotherapy, previous vascular events, erythropoietin use or glomerular filtration rate <60 ml/min. The ethics committee approved this study. All participants gave written informed consent. Patients received three or four (B)EP courses (etoposide 100 mg/m^2, days 1–5, cisplatin 20 mg/m^2, days 1–5, with/without bleomycin 30 USP, days 2, 8, 15) every 3 weeks and were during the first 6 d of every course hydrated with 4 l saline per 24 h. They received dexamethasone and ondansetron as antiemetics. Vascular events of both arterial and venous origin (WHO ICD-10 I1-I99) were included as possible events. Symptomatic as well as asymptomatic vascular events (discovered on staging computed tomography [CT] scans) which developed after start of chemotherapy until 2 years afterwards were taken into account.

The Khorana score, risk prediction model for venous thrombosis [11], was assessed for every patient before start of chemotherapy.

2.2. Plasma biomarkers

Von Willebrand factor (vWF) was measured in citrated plasma as described earlier [4]. Coagulation factor VIII (FVIII) was measured in stored citrated plasma (−80 °C) using an automatic haemostasis testing system (ACL TOP 500, IL, the Netherlands), measuring Activated Partial Thromboplastin Time (APTT) and using FVIII deficient plasma (SynthASil kit, IL, the Netherlands). Plasminogen activator inhibitor-1 (PAI-1) and tissue plasminogen activator (t-PA) were measured in citrated plasma as described previously [4]. Growth differentiation factor 15 (GDF-15; Human GDF-15 Quantikine ELISA kit [R&D Systems, United States of America {USA}]) and high sensitive C-reactive protein (hs-CRP; BNII Nephelometer [Siemens Healthcare Diagnostics BV, the Netherlands]) were measured in stored EDTA plasma (−20 °C).

2.3. Intima media thickness (IMT)

Posterior wall IMT of the right common carotid artery was measured using an ultrasound device, as described earlier [4]. The highest value from three measurements was recorded; maximal IMT best reflects atherosclerotic