ELSEVIER

Urologic Oncology: Seminars and Original Investigations ▮ (2016) ▮▮▮–▮▮▮

UROLOGIC ONCOLOGY

Original article

Associations between long-term serum platinum and neurotoxicity and ototoxicity, endocrine gonadal function, and cardiovascular disease in testicular cancer survivors

Line V. Hjelle[a,b,*], Roy M. Bremnes[a,b], Per O.M. Gundersen[c], Mette Sprauten[d], Marianne Brydøy[e], Torgrim Tandstad[f], Tom Wilsgaard[g], Sophie D. Fossåd[,h,i], Jan Oldenburg[d,h], Hege S. Haugnes[a,b]

[a] *Depatement of Clinical Medicine, Arctic University of Tromsø, Tromsø, Norway*
[b] *Department of Oncology, University Hospital of North Norway, Tromsø, Norway*
[c] *Department of Clinical Pharmacology, St. Olavs University Hospital, Trondheim, Norway*
[d] *Department of Oncology, Oslo University Hospital, Oslo, Norway*
[e] *Department of Oncology and Medical Physics, Haukeland University Hospital, Bergen, Norway*
[f] *The cancer Clinic, St. Olavs University Hospital, Trondheim, Norway*
[g] *Institute of Community Medicine, Arctic University of Tromsø, Tromsø, Norway*
[h] *Medical faculty, University of Oslo, Oslo, Norway*
[i] *Cancer Registry of Norway, Oslo, Norway*

Received 26 February 2016; received in revised form 13 June 2016; accepted 16 June 2016

Abstract

Objective: To evaluate the associations between long-term serum levels of platinum (se-Pt) and neurotoxicity and ototoxicity (NTX), endocrine gonadal function (endocrine-GF), and cardiovascular disease (CVD) in testicular cancer survivors.

Material and methods: A total of 292 cisplatin-treated testicular cancer survivors (1980–1994) participated in a national follow-up study (2007–2008). Se-Pt was quantified by inductively coupled plasma mass spectrometry, and categorized in quartiles. Symptoms of NTX were assessed with scale for chemotherapy-induced neurotoxicity (SCIN), with each symptom in 4 categories and total SCIN score categorized in quartiles. Endocrine-GF was categorized according to cutoff values for the 25, 50, and 75 percentiles of luteinizing hormone (LH) and testosterone within each decadal age group established from a control group. CVD was defined as ischemic heart disease, stroke, or artery occlusion. Associations between se-Pt levels and NTX, endocrine-GF, or risk for CVD, were analyzed with ordinal logistic regression and Cox regression, respectively.

Results: Median follow-up was 19 years (range: 13–28). In ordinal regression analyses, increasing quartiles of se-Pt were significantly associated with increasing quartiles of SCIN (P for trend $=$ 0.05), increased tinnitus ($P<0.001$), and increased hearing impairment ($P = 0.04$). The association remained significant for tinnitus when adjusting for cisplatin dose. Increasing LH quartiles was associated with increasing se-Pt quartiles ($P = 0.04$). No association between se-Pt in quartiles and CVD was established.

Conclusion: Median 19 years after treatment, increasing quartiles of se-Pt are associated with increasing SCIN score, tinnitus, hearing impairment, and increasing LH levels. However, these associations remained significant only for tinnitus and LH when adjusting for administered cisplatin dose.

Keywords: Testicular cancer; Long-term follow-up; Cisplatin retention

1. Introduction

Cisplatin remains the cornerstone in the treatment of advanced testicular cancer (TC) [1], and life expectancy of TC survivors (TCS) is presumed to be near normal.

This work was funded by the Norwegian Cancer Society, Norway (salary H.S.H., grant no. 2010/176-144/404).

* Corresponding author. Tel.: +47-77-53-6927.
E-mail address: line.v.hjelle@uit.no (L.V. Hjelle).

http://dx.doi.org/10.1016/j.urolonc.2016.06.012
1078-1439/

Well-documented cisplatin-related late effects include increased risk of hypertension, obesity, metabolic syndrome [2–4], and disturbed endocrine gonadal function (endocrine-GF) with impaired testosterone production and compensatory increased luteinizing hormone (LH) levels [5], and neurotoxicity and ototoxicity (NTX) including peripheral paresthesias/neuropathy, Raynaud phenomenon, hearing impairment, and tinnitus [6]. Nevertheless, the mechanisms behind these effects partly remain unclear.

Increasing cumulative cisplatin doses are positively associated with serum platinum (se-Pt) levels median 20 years later [7–9]. Further research to clarify associations between long-term se-Pt and late effects in TCS has been recommended [10]. An association between increasing se-Pt levels median 12 years after treatment and increasing severity of NTX was described for the first time by our research group. The assumption that reactive se-Pt several years after chemotherapy exposition may contribute to vascular and organ damage was then hypothesized [11].

The aim of the present study was to evaluate the association between long-term se-Pt median 19 years after treatment and NTX, endocrine-GF, and cardiovascular disease (CVD) risk factors and events, in TCS treated with platinum-based chemotherapy. Additionally, we wanted to address the possible effect of smoking on these late effects.

2. Patients and methods

2.1. Study population and design

All Norwegian long-term survivors of unilateral TC aged 18 to 75 years, treated in the period 1980 to 1994, were invited to participate in a national multicenter follow-up survey performed at 5 university hospitals. Of 1,814 eligible men, 1,463 (81%) participated in Survey I (SI) (1998–2002) [6]. During 2007 to 2008, a second Survey (SII) was conducted with 1,093 (80% of eligible men, Fig. 1) of the same TCS participants. SII included a physical examination and blood samples at the general practitioner, as well as a questionnaire.

The present study is restricted to 292 TCS previously treated with cisplatin- or carboplatin-based chemotherapy for which se-Pt measurements were available (Fig. 1). All men receiving testosterone substitution ($N = 17$) were excluded for analyses of se-Pt and hormone levels, leaving 275 men assessable for hormone analyses. The Committee for Medical Research Ethics, the Southern Health Region of Norway, approved both surveys.

2.2. Standards of treatment, 1980 to 1994

All patients with TC initially underwent unilateral orchiectomy and staging according to the Royal Marsden Hospital System [12]. Principles for the cytotoxic treatment of TC in Norway between 1980 and 1994 have been described previously [13]. Cisplatin-based chemotherapy was combined with bleomycin and either etoposide (BEP) or vinblastine (CVB) in most patients.

All patients receiving carboplatin had corresponding cisplatin doses calculated, by dividing carboplatin doses by 4, giving equivalent clinical doses [14].

2.3. Assessments and definitions

The questionnaire in SII included a validated 6-item scale for chemotherapy-induced neurotoxicity (SCIN) addressing neuropathy, Raynaud-like phenomena in hands and feet, tinnitus, and impaired hearing. The item scores ranged from not at all (0) to very much (3), and summation of the 6 items yielded a total SCIN score ranging from 0 to 18 [6]. Additionally, the questionnaire addressed comorbidities, medication use, and smoking habits. All self-reported CVD events were validated.

Resting blood pressure was measured with an automatic device or manually. Fasting blood samples were drawn by venipuncture before 11 AM at the TCS general practitioner office to assess levels of blood lipids, glucose, LH, testosterone, and se-Pt. All routine blood samples were analyzed at Oslo University Hospital. Total testosterone and LH were determined using a commercial immunoassay [15]. Se-Pt was quantified at St. Olavs University Hospital by inductively coupled plasma mass spectrometry, with limit of quantification 15 ng/l [7]. Se-Pt concentrations measured below limit of quantification had values set to zero.

Levels of testosterone and LH from 599 controls were categorized from 1 to 4 according to cutoff values for the 25, 50, and 75 percentiles within each decadal age group to establish reference intervals [15,16]. Testosterone and LH levels in the 275 TCS were assigned to one of these 4 categories, based on the percentiles derived from the controls. Levels between 2.5 and 97.5 percentiles in healthy controls determined the reference range.

CVD was defined as ischemic heart disease (angina and myocardial infarction), stroke, or artery occlusion based on data from the questionnaire. Hypertension, obesity, and metabolic syndrome were defined by National Cholesterol Education Program Criteria [17]. Diabetes was defined as previously diagnosed diabetes based on information in the questionnaire or serum glucose ≥ 11 mmol/l. Information regarding smoking, current antihypertensive, and lipid-lowering treatment and diabetes was retrieved from the questionnaire, and missing data were categorized as being a never smoker, without such treatment, or nondiabetic, respectively. Smoking was categorized as current, former, and never smoking.

2.4. Statistical methods

Pearson correlation was used to assess univariate associations among continuous variables. Spearman correlation