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REVIEW

Long-term toxicity of cisplatin in germ-cell tumor survivors

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Context: Testicular germ-cell tumors (GCT) are highly curable. A multidisciplinary approach, including cisplatin-based chemotherapy has resulted in cure in the majority of patients with GCT. Thus, the life expectancy of survivors will extend to many decades post-diagnosis. Late treatment toxicities associated with cisplatin-based chemotherapy may impact their future health.

Objective: To systematically evaluate evidence regarding the long-term toxicity of cisplatin in GCT survivors.

Evidence acquisition: We carried out a critical review of PubMed/Medline in February 2017 according to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement. Identified reports were reviewed according to the Consolidated Standards of Reporting Trials (CONSORT) criteria. Eighty-three publications were selected for inclusion in this analysis.

Evidence synthesis: Included reports evaluated long-term toxicities of cisplatin-based chemotherapy in GCT survivors. Studies reporting neuro- and ototoxicity, secondary malignancies, cardiovascular, renal and pulmonary toxicities, hypogonadism and infertility were found. Seven studies (8%) reported genetic underpinnings of long-term toxicities and 3 (4%) and 14 (19%) studies correlated long-term toxicities with circulating platinum levels and cumulative dose of cisplatin, respectively. Significant risks for long-term toxicities associated with cisplatin and platinum-based regimens were reported. The cumulative dose of cisplatin and circulating platinum were reported as risk factors. Several single-nucleotide polymorphisms identified patients susceptible to cisplatin compared with wild-type individuals.

Conclusions: GCT survivors cured with cisplatin-based chemotherapy are at risk for long-term side-effects. Detection of single-nucleotide polymorphisms could be a valuable tool for predicting long-term toxicities.

Patient summary: Herein, this article summarizes the available evidence of long-term toxicity of cisplatin-based chemotherapy in GCT survivors and provide insights from Indiana University.

Key words: germ-cell tumor, treatment, cisplatin, late toxicity, survivor, quality of life

Introduction

The cure of metastatic testicular germ-cell tumors (GCT) is an example of life saving achievements in clinical oncology. Before the advent of effective chemotherapy, metastatic disease was nearly 100% fatal. Advances in multi-disciplinary care, including the incorporation of surgery and multi-agent chemotherapy, have resulted in the dramatic improvement in the cure rate for this once fatal disease. The curative treatment of metastatic GCT consists of cisplatin combination chemotherapy. The most widely used first-line regimens include: BEP (bleomycin, etoposide, and cisplatin), EP (etoposide, cisplatin) and VIP (cisplatin, etoposide, ifosfamide) [1]. The majority of patients with metastatic GCT will be cured with 3–4 cycles of chemotherapy, which includes a cumulative dose of 300–400 mg/m^2 of cisplatin. Consequently, these patients are susceptible to the late toxic side-effects of treatment [2, 3].

The National Coalition for Cancer Survivorship defines a GCT survivor as any person living with, through and beyond a GCT diagnosis. The most common age at diagnosis of patient with GCT is 15–35 [4]. Survivors living decades later may experience

secondary malignancies, cardiovascular, neuro-, renal and pulmonary toxicity, hypogonadism, infertility and a decline in quality of life (QoL) [5, 6]. Traceable levels of cisplatin that can be detected in the plasma and urine decades after treatment causes a concern [3]. Platinum serum levels are 100- to 1000-fold higher compared with GCT patients never receiving platinum therapy, up to 20 years after treatment [7, 8]. Herein, we summarize the most common late toxicities of cisplatin treatment in a population of long-term survivors of testicular GCT.

Review criteria

We conducted a search from PubMed database for articles with the terms 'testicular cancer', 'germ-cell tumors', 'late toxicity', 'long-term toxicity', 'cisplatin', 'survivor', 'neurotoxicity', 'neuropathy', 'ototoxicity', 'cardiovascular toxicity', 'renal toxicity', 'nephrotoxicity', 'pulmonary toxicity', 'hypogonadism', and 'infertility'. Original full-text articles published in English were reviewed. Based on this search, 1594 potentially relevant articles were found and 1511 were excluded on basis of title, abstract or the content. Reference lists of identified articles were searched for further relevant papers. No limits were set on the years of publication. To limit the number of references throughout this paper, we have cited reviews rather than original articles when dealing with matters that are well established or of general nature.

Cisplatin-induced toxicity

Cisplatin-induced peripheral neuropathy

Cisplatin-induced peripheral neuropathy (CIPN) is one of the most common dose-limiting problems of treatment closely associated with increasing cumulative dose of cisplatin [9, 10].

The onset of CIPN is typically delayed until a cumulative dose $>300 \, mg/m^2$ has been received. CIPN will gradually lessen after treatment discontinuation; however, it can remain durable to some degree in 20%–40% of patients [11–14]. In one study, the long-term exposure to circulating cisplatin was associated with an increased risk for permanent paresthesia in 33 of 99 patients from the Netherlands. The mean terminal half-life for serum platinum decay was 3.7 years (range 2.5–5.2). Patients with paresthesias had higher platinum area under the curve (AUC) between 1 and 3 years after treatment (30.9 versus 27.0 μg/l month) compared with those without paresthesias ($P = 0.021$) [15]. A persistent long-term increase in serum platinum was associated with CIPN in 292 Norwegian survivors ($P = 0.05$) at 19-year median follow-up [16]. In another study, a 2- to 4-fold increase in the risk for persistent paresthesias in survivors was reported in the highest residual serum cisplatin quartile compared with the lowest (OR 4.69; 95% CI 1.82–12.08) in 169 GCT survivors at 20 years of follow-up (Table 1) [12].

Genomic researchers are attempting to identify the underlying mechanisms and pathways of CIPN (Table 1). Single-nucleotide polymorphisms (SNP) in DNA repair pathways may play a key role in the induction of CIPN [17]. Oldenburg et al. observed functional SNPs in *glutathione-s-transferase P1 (GSTP1)* and *M1 (GSTM1)* leading to an increase in self-reported neurotoxicity in Norwegian GCT survivors. Patients with *GSTP1-GG* reported significantly less paresthesias in fingers and toes compared with patients with *GSTP1 AA/AG* and/or *GSTM1* [$P = 0.0038$, OR = 0.46 (0.22–0.96)]. The protective role of *GSTP1-GG* seemed to be over-ridden by an increasing dose of cisplatin [18]. El Charif et al reported a large genome-wide association study (GWAS) of 847 survivors, 57% of whom experienced CIPN symptoms after a median dose of $400 \, mg/m^2$ of cisplatin. The study identified several SNPs from 677 survivors that passed quality control for inclusion into the GWAS, demonstrating a greater risk of sensory neuropathy. Two SNPs which are

Table 1. Neurotoxicity in association with serum levels of cisplatin and genomic changes

Study	No of survivors	Variable		P value/OR	Neurotoxicity	SNPs
Boer 2015	99	Serum Pt levels between 1 and 3 years (μg/l month) Paresthesia 30.9 No paresthesia 27.0		$P=0.021$	Paresthesias	N/A
Sprauten 2012	169	Residual serum Pt quartile 2- to 4-fold increase in highest quartile compared with the lowest		OR 4.69; 95% CI 1.82–12.08	Paresthesias	N/A
Oldenburg 2007	238	*GSTP1-GG* *GSTP1 AA/AG and/or GSTM1*	Less paresthesias More paresthesias	$P=0.0038$, OR 0.46 (95% CI 0.22–0.96)	Paresthesias	*GSTP1 GSTM1*
El Charif 2016	677	*LYPD3 (rs12797447), SNX8* and *GCTT1 (rs4757366)* Greater risk for sensory neuropathy		OR=1.9 (95% CI 1.5–2.4) and 1.9 (95% CI 1.5–2.5)	Sensory neuropathy	*LYPD3 (rs12797447), SNX8* and *GCTT1 (rs4757366)*
Dolan 2017	680	Age, smoking, excess drinking, hypertension		all OR > 1, all $P>0.05$	Peripheral neuropathy	*RPRD1B*

expression quantitative trait loci for *LYPD3 (rs12797447), SNX8* and *GCTT1 (rs4757366)* in lymphoblastoid cell lines were also associated with a greater risk of sensory neuropathy with OR = 1.9 (95% CI 1.5–2.4) and 1.9 (95% CI 1.5–2.5) [19]. Additionally, lower expression of *RPRD1B* (regulation of nuclear pre-mRNA domain containing 1B, participates in dephosphory-lation of C-terminal domain) was associated with higher risk for CIPN in 680 GCT survivors [20].

Cisplatin-induced ototoxicity

Cisplatin is one of the most ototoxic agents used in clinical practice. Estimates of patients experiencing serious, permanent, bilateral sensorineural hearing loss range from 20% to 75% of patients, including 20%–40% who experience permanent tinnitus [9]. The prevalence of permanent symptoms increases to over 60% in patients with cumulative doses of cisplatin >600 mg/m^2 [21, 22].

Fossa et al. collected QoL data via the QLQ-C30 from 666 patients before administering treatment, as well as at 3, 6, 12, and 24 months after being treated with 3–4 cycles of BEP administered for 3 or 5 days. Out of the 286 patients eligible for evaluation at the end of the study, 21%–26% of patients suffered from tinnitus, or reduced hearing at 2-year follow-up. The factor that was found to reduce the risk of ototoxicity was a peak concentration of cisplatin if given at 100 mg/m^2 over 5 versus 3 days [23]. Cisplatin administered at the dose of 100 mg/m^2 or higher over 2 versus 5 days was also responsible for significantly more severity in all ototoxicity measures in 1409 Norwegian GCT survivors [11].

Frisina et al. have reported the most comprehensive audiometric evaluation of audiological measures to date in 488 North American GCT survivors. Every 100 mg/m^2 increase in cumulative dose of cisplatin resulted in 3.2 dB impairment in age-adjusted overall hearing threshold (4–12 kHz, $P < 0.001$) resulting in 18% of patients experiencing severe to profound hearing loss, 40% with tinnitus and 80% with some form of ototoxicity. A cumulative dose of >300 mg/m^2 seems to be a boundary for an increase in American Speech-Language-Hearing Association–defined hearing loss severity, although one-third of patients with lower cumulative dose still developed moderately severe to profound hearing loss (Table 2). Patients with profound hearing loss were recommended to use hearing aids, but few used them, likely because cost/insurance/aesthetic issues [24] This study, however, has some limitation, such as absence of pretreatment assessment, ototoxicity-related QoL data, adjustment for other ototoxic drugs (e.g. aminoglycosides) or occupational hearing loss. Additional longitudinal assessment would also provide more data on age-related vulnerability. The important question of the impact of BEPx1 versus surveillance in stage I patients remains unanswered, while patients treated with EPx4 versus BEPx3 for good risk disease had significantly increased long-term hearing impairment. However, the clinical implication of these findings are not entirely clear, as additional longitudinal and QoL data would provide more robust concept for treatment recommendations and follow-up [25]. The genetic underpinnings of cisplatin-associated ototoxicity in adults remained poorly understood until recently [26, 27]. Oldenburg et al. reported that both alleles for ^{105}Val-GSTP1 offer protection against cisplatin-induced hearing impairment [28]. A multi-institutional United States genome-wide association initiative uncovered that SNP in *rs62283056*, in the first intron of Mendelian deafness gene *WFS1* (wolframin ER transmembrane glycoprotein, mutations in *WFS1* cause both autosomal dominant low-frequency sensorineural hearing loss and Wolfram syndrome, characterized as autosomal recessive hearing loss, diabetes mellitus, diabetes insipidus and optic atrophy) was significantly associated with hearing loss in 849 GCT survivors ($P = 1.4 \times 10^{-8}$). A higher cumulative dose of cisplatin was responsible for worsening hearing loss in patients with a minor allele ($P = 0.035$) [29]. Decreased expression of *WFS1* and its association to hearing loss was replicated in a BioVU cohort of 18 620 patients (Table 2) [30].

Cisplatin-induced secondary malignancies

Second malignancies have emerged as a concern among GCT survivors [31–33]. Results from pooled population registries have uncovered a higher incidence and mortality from secondary malignancies in GCT survivors with a standardized incidence ratio of 1.65 (95% CI 1.57–1.73) and a standardized mortality ratio of 2.0 (95% CI: 1.7–2.4) [31, 34]. However, these data also included radiotherapy, limiting the interpretation of the results in context of exclusive toxicity of cisplatin (Table 3). Travis et al. analyzed 40 576 patients with GCT from 14 population-based tumor registries in Europe and North America (1943–2001) and identified the most common secondary malignancies to be mesothelioma, oesophageal, lung, colon, bladder, pancreas and stomach cancer. The risk of a solid organ cancer in a group treated with platinum based chemotherapy alone was 1.8 (95% CI 1.3–2.5) compared with the general population [32]. The assessment of second solid tumors in series of 12 691 testicular cancer survivors have shown a standardized incidence ratio of 1.43 (95% CI 1.18–1.17) for patients treated with chemotherapy versus surgery only [35]. Travis et al. also addressed the risk of secondary leukemia induced by chemotherapy in GCT survivors. Cumulative doses of cisplatin are associated with an excess of leukemia risk (P for trend = 0.001). The relative risk reached 3.3 (95% CI 1.5–8.4) at cumulative doses of 650 mg, and a 6-fold increase in GCT patients receiving >1000 mg [36]. The increased risk of secondary leukemia compared with general population was also reported from Memorial-Sloan Kettering and Indiana University Cancer Centres, although only about 1 of 450 patients developed leukemia after treatment of GCT [37, 38].

Radiotherapy to retroperitoneal lymph nodes is also a major concern for the long-term risk of secondary malignancies [39]. Van den Belt-Dusebout et al. provided data that addition of radiotherapy to chemotherapy substantially increases the cumulative risk for secondary malignancies from 8.0% to 13.9% at 20 years of follow-up [40].

Cisplatin-induced cardiovascular toxicity

Cardiovascular toxicity is amongst the most prevalent long-term risks in GCT survivors, regardless of treatment selection [41]. The effects of late toxicity of cisplatin containing chemotherapy were reported as early as 2000 from an analysis carried out on a group of male Dutch GCT survivors treated before 1987 (Table 4). Out of 87 patients examined, five were discovered to have

Table 2. Ototoxicity in association with serum levels of cisplatin and genomic changes

Study	No of survivors	Variable		P value/OR	Ototoxicity	SNPs
Frisina 2016	488	Pt—every 100 mg/m^2 increase	3.2 dB impairment in hearing threshold	$P < 0.001$	Hearing loss (audiometric measures)	N/A
		Pt > 300 mg/m^2	Severe hearing loss	$P=0.006$ OR $= 1.59$		
Wheeler 2016	849	SNP in *rs62283056* (first intron of *WFS*)	Hearing loss	$P=1.4\times10^{-8}$	Hearing loss	SNP in *rs62283056* (first intron of *WFS*)
		Higher cumulative dose of Pt	Hearing loss in pts with minor allele	$P = 0.035$		
Wheeler 2016—BioVU independent cohort replication	18 620	Decreased expression of WFS1 Hearing loss		$P<0.002$	Hearing loss, sensorineural hearing loss	–

OR, odds ratio.

Table 3. Risk of secondary malignancies among GCT survivors treated with cisplatin-based chemotherapy

Study	No of survivors	Long-term toxicity in chemotherapy group	Risk	
Fung 2013	12 691	Secondary malignancies	SIR 1.43 (95% CI 1.18–1.17)	
Richiardi 2007	29 511	Secondary malignancies[a]	SIR 1.65 (95% CI 1.57–1.73)	
Fossa 2004	3378	Secondary malignancies[a]	SMR 2.0 (95% CI: 1.7–2.4)	
Travis 2005	40 576	Secondary malignancies	RR 1.8 (95% CI 1.3–2.5)	
Travis 2000	18 567	Secondary leukemias	**Cisplatin cumulative dose**	**RR**
			650 mg	3.3 (95% CI 1.5–8.4)
			>1000 mg	5.9 (95% CI 2.0–26.0)

[a]These studies included survivors treated with chemotherapy and radiotherapy.
SIR, standardized incidence ratio; SMR, standardized mortality ratio; RR, relative risk.

Table 4. A risk of cardiovascular toxicity among GCT survivors treated with cisplatin-based chemotherapy

Study	No of survivors	Cardiovascular toxicity		Risk/frequency
Meinardi 2000	62[a] (in the chemotherapy group)	Coronary artery disease		7.1 (95% CI 1.0–18.3)[b]
		Hypertension		40%
		Raynaud phenomenon		25%
Van den Belt-Dusebout 2006	2512	Cardiovascular disease	PVB	N/A
			BEP	1.5-fold (95% CI, 1.0- to 2.2-fold)
		Myocardial infarction	PVB	1.9-fold (95% CI, 1.7- to 2.0-fold)
			BEP	HR = 1.2; 95% CI, 0.7–2.1)
Haugnes 2007	1135	Metabolic syndrome		40%
Huddart 2003	992	Any cardiac event		2.6 (95% CI 1.2–5.8[c]
Haugnes 2010	990	Coronary artery disease	BEP versus surgery	5.7-fold (95% CI 1.9–17.1)
		Myocardial infarction	BEP versus age matched male controls	3.1-fold (95% CI 1.2–7.7)

[a]No of survivors in the chemotherapy group.
[b]Observed-to-expected ratio; compared with general population.
[c]Risk ratio; compared with surgery alone.
PVB, cisplatin, vinblastine, bleomycin; BEP, bleomycin, etoposide, cisplatin; HR, hazard ratio.

experienced a major cardiac event 9–16 years after treatment. A subgroup of 62 patients were additionally evaluated for cardiac damage and their cardiovascular risk profile was then compared with that of 40 patients of similar age who had undergone an orchiectomy for stage 1 testicular cancer. Among the 62 patients that had undergone cisplatin containing chemotherapy 80% had hypercholesterolemia, 40% had hypertension and 25% experienced Raynaud phenomenon. The study also revealed an increased observed-to-expected ratio of 7.1 (95% CI 1.0–18.3) for coronary artery disease when compared with the general male Dutch population [42].

The same research group analyzed a cohort of 2512 patients and reported that treatment with PVB (bleomycin, vinblastine, cisplatin) and BEP were associated with 1.9- and 1.5-fold increases in the risk of cardiovascular disease (95% CI, 1.7–2.0 and 95% CI, 1.0–2.2, respectively) compared with the general population. In addition, smoking increased myocardial infarction risk to 2.6-fold (95% CI, 1.8–3.9). Moreover, 18% of patients in this cohort developed cardiovascular disease within 20 years of cancer treatment [43]. Observations from the surveillance, epidemiology and end results program (SEER) database showed significantly increased cardiovascular mortality in the first year after chemotherapy [44]. An increase of cardiovascular morbidity was also reported from series of 390 patients from UK between 1982 and 1992. Patients who received chemotherapy had an age-adjusted risk ratio of 2.6 (95% CI 1.2–5.8) for any cardiac event compared with GCT patients treated with surgery alone [45]. GCT survivors treated with chemotherapy from five Norwegian centers had a 23% higher prevalence of antihypertensive drugs usage in comparison with age-matched controls. The odds ratio for the use of antihypertensive and lipid-lowering drugs was 3.3 ($P < 0.05$) and 2.1 ($P < 0.05$), respectively. Treatment with BEP increased the risk of coronary artery disease by 5.7-fold (95% CI 1.9–17.1) compared with surgery and increased the risk for myocardial infarction by 3.1-fold (95% CI 1.2–7.7) compared with age-matched controls (Table 4). Patients receiving chemotherapy and radiotherapy had significantly increased risk for cardiovascular disease at median of 21 years of follow-up (HR = 5.3; 95% CI 1.5–18.5) [46].

Cisplatin-induced pulmonary toxicity

Pulmonary toxicity has been historically associated with bleomycin-induced pulmonary fibrosis. However, long-term pulmonary function also seems to be affected by cumulative dose of cisplatin reciprocally to other long-term toxicities in GCT survivors. Evaluation of pulmonary function derived from a large Norwegian study of 1049 GCT survivors demonstrated decreased spirometry variables at 11-year follow-up in chemotherapy survivors compared with surgery-only treated individuals. Forced

expiratory volume (FVC) of <80% was prevalent in 8% of GCT survivors. The highest prevalence was observed in individuals treated with cumulative dose of cisplatin >850 mg and when cisplatin treatment was followed by thoracic surgery. Multivariable analysis with cumulative dose of bleomycin, etoposide and vinblastine confirmed that only cisplatin dose ($P = 0.007$) and age ($P = 0.008$) were significantly increased with prevalent restrictive lung disease. Interestingly, the effect of cumulative cisplatin dose was equal to the 2- to 4-fold effect of smoking on lung function [47]. Fossa et al. observed higher mortality from all respiratory diseases with standardized mortality ratio of 2.53 (95% CI 1.26–4.53) in 38 907 1-year survivors within 14 population-based registries [48].

Cisplatin-induced renal toxicity

Acute damage to proximal tubular epithelium in kidney has been well defined with cisplatin treatment. The long-term risk of renal impairment in 85 patients >10 years from treatment with different cisplatin-based regimens with or without surgery/radiotherapy was reported by Fossa et al. Renal function was assessed with 131 Iodine Hippuran clearance or ^{99}mDTPA (^{99}mTc-diaethyl-triamin-penta-acetic acid) glomerular filtration rate before treatment and 4 times during 14 years of follow-up. A significant difference in long-term renal function was observed in patients with retroperitoneal lymph node dissection (RPLND) compared with patients receiving chemotherapy ($P = 0.004$) (Table 5). The cumulative dose of cisplatin was associated with the degree of renal function impairment ($P = 0.02$) with the most pronounced impairment among patients receiving >850 mg ($P = 0.03$). Patients who received chemotherapy and abdominal radiotherapy had also increased renal impairment ($P = 0.0003$). A mean 14% reduction of renal function was observed among patients who received chemotherapy compared with RPLND in long-term follow-up [49]. A strong correlation between circulating cisplatin levels with the cumulative cisplatin dose and renal function before and after chemotherapy was described recently by Boer et al. A relationship of circulating platinum levels and long-term late effects such as paresthesia, hypogonadism, higher LDL-cholesterol and hypertension, suggesting renal impairment and subsequent long-term platinum exposures as one of the mechanisms responsible for late cisplatin consequences was described [15]. Astor et al. have reported that decreased glomerular filtration rate (GFR) can carry a partial attribution to the incidence of cardiovascular events among 14 586 adults with an incidence rate ratio of 1.29 (95% CI 1.06–1.55) for cardiovascular mortality [17].

An analysis of 1206 GCT patients from the Danish DaTeCa database have shown a decrease in GFR after 3, 4 or 5+ cycles of

Table 5. Renal toxicity among GCT survivors treated with cisplatin-based chemotherapy

Study	No of survivors	Renal toxicity	Variable	P value
Fossa 2002	85	Decrease in GFR	chemotherapy versus RPLND	0.004
Boer 2015	99	Increase in median serum creatinine level after chemotherapy	–	<0.001
Lauritsen 2015	1206	Decrease in GFR with subsequent rebound	–	–

BEP with a significant rebound of GFR during the follow-up. The risk for cardiovascular disease was, however, increased in all patients treated with chemotherapy irrespective of change in renal function during the treatment [50].

Cisplatin-induced hypogonadism and metabolic syndrome

The risk of hypogonadism in GCT survivors varies according to treatment intensity and is diagnosed in ~15% of all survivors [51, 52]. A decreased testosterone level may affect the ability to father children, contribute to the development of cardiovascular disease, osteoporosis, metabolic syndrome, type 2 diabetes and overall diminished QoL [53]. Lower testosterone levels have been reported in 86 GCT survivors treated with cisplatin-based chemotherapy compared with 47 healthy controls [median 18.0 nmol/l (range 5.0–37.0) and 23.0 nmol/l (range 13.0–56), respectively; $P < 0.05$] [54]. A study from Germany identified subnormal testosterone levels (<10 nmol/l) in 5%, 11% and 20% of patients who had no chemotherapy, received ≤ 400 mg/m^2 or >400 mg/m^2 of cisplatin, respectively (Table 6). A significant positive correlation was found for LH and FSH ($R = 0.78$; $P < 0.0001$) [55]. Another long-term follow-up study conducted by Huddart et al. demonstrated a decrease in testosterone (<10 nmol/l) in patients treated with both chemotherapy and radiotherapy ($P = 0.0006$), but not with chemotherapy alone ($P > 0.05$). However, patients with cisplatin-based treatment had significantly elevated LH compared with orchiectomy ($P < 0.01$) [56]. In addition, a Dutch study in 99 GCT survivors have recently shown an association of higher circulating cisplatin levels with hypogonadism (OR 1.10; 95% CI 1.02–1.18; $P = 0.016$) (Table 6) [15]. Sprauten et al. described accelerated hormonal aging in terms of declining testosterone percentiles at median of 9 and 18 years after treatment, emphasizing extended follow-up as an important outlook for premature testosterone decline [57]. In a study evaluating adverse health outcomes in GCT survivors related to hypogonadism, lower number of patients with hypogonadism versus those without hypogonadism (35% versus 49%) reported 0–1 adverse health outcomes ($P = 0.003$). Survivors with hypogonadism were more likely to have CIPN and take medication for dyslipidemia, hypertension, erectile dysfunction, diabetes or anxiety/depression (all $P < 0.05$) [58]. Therefore,

patients with symptomatic hypogonadism may benefit from testosterone replacement therapy. The long-term benefit of testosterone replacement is, however, not clear [59]. Hypogonadism was associated with osteopenia/osteoporosis in a large retrospective cohort of 1249 GCT survivors from Slovakia [60]. The loss of bone density was observed in 36 GCT survivors, however, the association with hypogonadism, vitamin D or cumulative dose of cisplatin was not seen [61]. A study by Schepisi et al. reported a vitamin D deficiency in 10 of 58 GCT survivors, however, it did not provide the data about the impact of cisplatin-based chemotherapy [62].

Hyperlipidemia and metabolic syndrome is found in up to 80% and 40% of patients, respectively [42, 63, 64]. A national follow-up of 1463 GCT survivors from Norway identified increased odds for metabolic syndrome in all subjects treated with chemotherapy. The highest risk for metabolic syndrome was exhibited in a group receiving a cumulative dose of cisplatin of >850 mg (OR = 2.8, 95% CI 1.6–4.7) [63]. Nuver et al. associated the metabolic syndrome with the higher body mass index, lower testosterone and higher cortisol metabolite excretion [54]. A SNP in the 5-α-reductase gene *(SRD5A2)* was associated with increased prevalence of metabolic syndrome in 173 GCT survivors from Netherlands. Survivors who were homozygous or heterozygous for *SRD5A2 rs523349* had higher prevalence of metabolic syndrome compared with wild-type survivors (33% versus 19%, $P = 0.032$). The highest prevalence (66.7%) was observed in patients with testosterone levels <15 nmol/l and a variant genotype [65].

Cisplatin-induced infertility

Lampe et al reported long-term infertility with oligospermia or azoospermia after cisplatin related to baseline sperm counts. The majority of patients (80%) recovered their spermatogenesis by 5 years from treatment. However, the probability to recover spermatogenesis in patients with oligospermic and normospermic levels was significantly higher in patients treated with carboplatin-based compared with cisplatin-based chemotherapy ($P < 0.0001$) (Table 6) [66]. An Italian study evaluated the impact of BEP or carboplatin chemotherapy on testicular function (seminal parameters, sperm aneuploidy, sperm DNA integrity, sex hormones, volume of the residual testis) compared with

Table 6. Hypogonadism and infertility among GCT survivors treated with cisplatin-based chemotherapy

Study	No of survivors	Toxicity		Risk/frequency/*P* value
Nuver 2005	86	Lower testosterone levels compared with controls		$P < 0.05$
Gerl 2001	244	Testosterone <10 nmol/l	No chemotherapy	5%
			Cisplatin ≤ 400 mg/m^2	11%
			Cisplatin >400 mg/m^2	20%
Huddart 2005	680	Testosterone <10 nmol/l	Chemotherapy and radiotherapy	$P = 0.0006$
			Chemotherapy only	$P > 0.05$
		Higher LH levels	Chemotherapy only versus orchiectomy	$P < 0.01$
		Lower conception success	Chemotherapy versus surveillance	$P = 0.028$
Boer 2015	99	Hypogonadism	Higher circulating cisplatin	$P = 0.016$
Lampe 1997	178	Higher probability to recover spermatogenesis	Carboplatin- versus cisplatin-based chemotherapy	$P < 0.0001$

orchiectomy alone. A significant reduction in sperm count and concentration, and increase in sperm aneuploidy and DNA alterations was observed after 12 and 24 months in BEP, but not carboplatin/surveillance groups [67]. Survivors who were attempting to conceive after cisplatin-based chemotherapy (with or without fertility treatment) had a lower success rate compared with a surveillance group (75% versus 88%; $P = 0.028$) [56]. There is no evidence of an increase in birth defects in children of testicular cancer patients who received chemotherapy.

Social, family and employment issues

Treatment of GCT is associated with emotional distress and impairment of sexuality and body image [68–70]. Anxiety and depression was seen in 6.1% and 7.9% of survivors from Germany [71]. A recent population-based study from Norway reported unsettling findings of suicide and violent deaths among childhood, adolescence and young adulthood GCT survivors (HR = 2.9; 95% CI 1.3–6.4) [72]. Increased use of marijuana was reported by Trabert et al. suggesting the link between GCT diagnosis and the mental health [73]. Employment issues may be of concern, however, reliable data is missing. GCT survivors treated with chemotherapy reported family problems in QLQ-TC26 and had a lower level of education compared with non-chemotherapy controls [74]. Moreover, paternity rates in GCT survivors were lower compared with the healthy controls, but the likelihood for marriage was unaltered [75]. Additionally, a study from Japan did not show changes in patient-reported relationships with family and friends [76].

Practical recommendations for prevention and management of late toxicities

CIPN and ototoxicity

No standard treatment is known to reduce the risk of CIPN. Further knowledge in genetic variants will provide information to identify patients at risk thus helping to determine preventive and treatment strategies. The practical recommendation to reduce the risk of ototoxicity for treating oncologist is to avoid higher concentration of cisplatin (50 mg/m^2×2 days) and use the standard cisplatin dose over 5 days (i.e. 20 mg/m^2×5 days).

Secondary malignancies

Given the increased risk for secondary malignancies, we suggest a life-long follow-up, especially for survivors cured with chemotherapy and radiotherapy. Individuals with adjacent risk factors (family history and health habits) should be considered for screening strategies. As an example, smokers may benefit from screening for lung cancer with low dose spiral chest CT scans and survivors with strong family history for cancer may benefit from a thorough routine clinical examination. Well-designed studies are needed to provide further recommendations in the absence of evidence-based data. Patients should be encouraged to be non-smokers, exercise regularly, maintain normal body weight and pursue healthy diet and life-style. Smoking and obesity represent the two major preventative causes of secondary cancers.

Cardiovascular toxicity

Exercise training may have the potential to ameliorate and/or reverse the long-term cardiovascular disease sequelae. The promotion of exercise research in this setting could aid in providing recommendations [77, 78]. Reduction of known risk factors for cardiovascular disease such as smoking and obesity or a management of dyslipidemia, high blood pressure and hypogonadism may lead to a decrease in the cardiovascular toxicity. Treatment with aspirin may be suggested as prevention of coronary artery disease with respect to each patient's risk [41].

Pulmonary toxicity

Cessation of smoking seems to be a variable with possible preventive outcome. Although no standard recommendations exist, we suggest a close communication with survivors and their families to educate them about the importance of their health habits.

Renal toxicity

Intensive saline hydration before administration of chemotherapy is recommended [79]. Clinicians should be cautious with vigorous saline hydration in elderly GCT patients or patients with cardiac disease. Other than hydration before cisplatin, clinicians should avoid drugs with potency for further renal damage.

Hypogonadism and infertility

Symptomatic hypogonadism should be treated with replacement testosterone [58]. Testosterone replacement therapy rises a concern for creating a risk for infertility, however, a high quality longitudinal studies are needed to generate the better understanding about male reproductive endocrinology [80]. To increase the odds of fathering children, patients may undergo sperm banking before the initiation of chemotherapy [2].

Aims of surveillance in GCT survivors

GCT patients who have been cured of their disease remain at risk of relapse or developing a contralateral testicular tumor. Guidelines have focused on surveillance schedules and plans to recognize these entities. However, a comprehensive surveillance strategy should also identify late treatment toxicities [81]. According to our experience as a major referral center, we employ annual visits since the completion of treatment with focus on late toxicity concurrently with the routine follow-up. We do not perform any CT imaging beyond 5th year at Indiana University and second to clinical examination and serum tumor markers, our interest is drawn towards survivors QoL, persistent, worsened or newly diagnosed adverse health outcomes that might be connected to previous cisplatin treatment. The concern for secondary malignancies should not be addressed by long-term CT scan surveillance, but rather by careful history and clinical examination. Although a risk for second cancer with the rationally provided CT imaging is low [82], we feel that further repeated CT imaging in survivors previously treated with chemotherapy, often

radiotherapy and several CT imaging studies may represent unnecessary cost and additional risk for radiation-induced second cancers. A consensus conferences including specialists treating various disorders from different countries could contribute to establishment of recommendations according to the opportunities of each country's health care system. One of the most important goals of surveillance strategy in GCT survivors is a decline of morbidity and mortality associated with late treatment consequences. Early identification of distinct types of late toxicities could enable to create intervention program, such as involvement of regular physical activity, diet adjustment, smoking cessation, early pharmacological treatment and close communication with survivors and their families.

Our understanding of underlining mechanisms of late toxicity induction is still limited and a vivid research in this field is warranted. A major multi-institutional genomic study of long-term toxicity is currently underway in USA, which will provide more insights into genetic risks for late toxicity of cisplatin. Better understanding of genetic associations with late toxicity might lead to creation of risk prediction models and possible treatment targets.

Conclusion

Cisplatin combination chemotherapy represented a landmark achievement in oncology. While majority of cured patients rate their health as excellent [83], a significant number of survivors will experience long-term toxicity to some degree. However, a deletion of cisplatin from the treatment of metastatic disease is not an option. Given the young age of GCT survivors, the risk of platinum toxicity should be a major determinant of primary care beyond the cure of these individuals. The focus should be aimed on preventive causes of late morbidity, such as insufficient exercise, obesity, lipid profile, blood pressure or smoking. Treatment of hypogonadism may prevent a metabolic syndrome and cardiovascular disease resulting from low testosterone levels. A life-long follow-up should be defined for patients with high-risk for such toxicities based on well-designed prospective studies. Risk factors, such as cumulative dose of cisplatin/etoposide, radiotherapy and lifestyle may be considered for risk stratification.

Disclosure

The authors have declared no conflicts of interest.

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