

review

Treatment-related cardiovascular toxicity in long-term survivors of testicular cancer

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Backgrounds. Testicular cancer is the most common malignancy in young men. Considering increasing incidence, exceptionally high cure rate, as well as long life expectancy, assessment of long term toxicity in testicular cancer survivors is of great importance. In the last decades a major effort has been made in order to reduce toxicity of treatment, while maintaining its high effectiveness.

Conclusions. Actual knowledge on treatment toxicity is based on outdated treatment modalities. Hopefully, modern treatment modalities could reduce toxicity, but, there is no firm confirmation for that at the moment, as data dealing with late sequelae of modern treatment of testicular cancer are not available yet due to the short period of observation. The life-threatening cardiovascular toxicity in testicular cancer survivors is major complication of platinum-based chemotherapy, mediastinal radiotherapy and even subdiaphragmatic radiotherapy.

Key words: testicular cancer; cardiovascular toxicity; long-term survivors

Introduction

Although rare disease, testicular cancer is the most common malignancy in young men aged 20 to 40 years. Considering increasing incidence worldwide¹⁻³, exceptionally high cure rate with 5-year survival rate exceeding 95% for all stages⁴ and life expectancy almost comparable to age-matched healthy male population⁵, evaluation of treatment-related long-term morbidity has become increasingly important. In the past decades efforts have been made in order to optimize treatment with objective to decrease toxicity, while maintaining high cure rates. The introduction of less toxic chemotherapeutic schemes⁶⁻⁸, reduction in radiation doses and volumes⁹⁻¹¹ and preferred use of active surveillance¹², have all led to reduced treatment toxicity. Irrespective of that, some treatment-related sequelae remained unavoidable. Most of the current studies represent complications of treatment modalities administered several years or even decades ago, but are still of a major concern.

With the 25-year risk of approximately 16%, cardiovascular diseases (CVD) are among the most important life-threatening long-term complications in testicular cancer survivors.¹³ Long-term testicular cancer survivors are more likely to develop unfavourable cardiovascular risk profile.¹⁴⁻²¹ In addition, an increased risk of mortality caused by CVD has also been observed.^{5,22-24}

According to the current knowledge, cardiovascular toxicity is mainly due to cisplatin based chemotherapy and mediastinal radiation therapy^{13,19,25}; although subdiaphragmatic radiotherapy is associated with an increased risk of CVD as well.^{14,26}

Treatment-related cardiovascular morbidity

The introduction of cisplatin based chemotherapeutic regimens into treatment of testicular cancer in the early 1970s represents cornerstone in

TABLE 1. Risk for coronary artery disease in testicular cancer survivors regarding to different treatment modalities

Author (year)	N	Period of treatment	Median follow up (range), in years	Age at diagnosis (range)	Age at follow-up (range)	Risk for CAD (CI 95 %)	Treatment Modalities	Note
Meinardi <i>et al.</i> ¹⁷ (2000)	87	Before 1987 ^a	14 (10 to 20)	27 (17-36)	42 (30-50)	SIR=7.1 (1.9 to 18.3)	ChT	Age adjusted results. Older than 50 years at follow-up were excluded.
Huddart <i>et al.</i> ²⁴ (2003)	992	1982-1992	10.2 (0 to 20.3)	31.7 (10-82)	44 (23-78)	RR=1.00 (reference) RR=2.59 (1.15 to 5.84) RR=2.40 (1.04 to 5.45) RR=2.78 (1.09 to 7.07)	Surveillance ChT RT ChT and RT	Age adjusted results. Only 8.3 % of RT treated patients had also med. RT.
Van der Belt-Dusebut <i>et al.</i> ¹¹ (2006)	2339	1965-1995	18.4 (5 to 38.4)	38.3 ^b (n.r.) 28.1 ^c (n.r.)	59.8 ^b (n.r.) 50.4 ^c (n.r.)	SIR=0.94 (0.61 to 1.39) SIR=1.35 (0.97 to 1.83) SIR=1.07 (0.92 to 1.23) SIR=2.48 (1.77 to 3.37) SIR=0.92 (0.77 to 1.08) SIR=2.97 (1.73 to 4.77) SIR=1.83 (1.08 to 2.90)	Surveillance ChT RT RT – med. RT – subdia. RT – med. + ChT RT – subdia. + ChT	Patients with CAD before or within 5 years from diagnosis were excluded.
Haughnes <i>et al.</i> ¹² (2010)	990	1980-1994	19 (13 to 28)	31 (15-53)	51 (31-69)	HR=1.0 (reference) HR=2.0 (0.64 to 6.1) HR=5.7 (1.9 to 17.1) HR=2.1 (0.78 to 5.4) HR=5.3 (1.5 to 18.3)	Surveillance ChT (CVB) ChT (BEP) RT ChT + RT	Age adjusted results. Patients with CAD before or within 2 years from diagnosis were excluded. Only 3 of 420 RT treated patients had also med. RT.

BEP = bleomycin, etoposid, cisplatin; CAD = coronary artery disease; ChT = chemotherapy; CVB = cisplatin, etoposid, bleomycin; HR = hazard ratio; med. = mediastinal; N = number of patients; n.r. = not reported; RT = radiotherapy; RR = relative risk; SIR = standardized incidence ratio; subdia. = subdiaphragmatic;

^a All patients treated with cisplatin based chemotherapy before 1987.

^b Age for seminoma patients.

^c Age for nonseminoma patients.

testicular cancer management. Prior to that, different chemotherapeutic regimens were used, some of them containing even anthracyclines, cytotoxic drugs with well known cardiotoxic effect. Although reports on cisplatin cardiovascular toxicity date back to the 1980s^{20,27-29}, first study systematically reporting the frequency of late cardiac morbidity by Meinardi *et al.* was published in 2000. After a median follow up of 14 years, a major cardiac event was documented in 5 of 87 patients (5.8%) treated with cisplatin based chemotherapy; myocardial infarction in 2 (2.3%) and angina pectoris in the remaining 3 (3.5%) patients. Compared with the general male population, this corresponded to approximately 7-fold increased risk (observed-to-expected ratio [O/E] = 7.1, 95% confidence interval [CI], 1.9 to 18.3-fold). In this study, additional analysis of subclinical cardiac disease was performed as well. Echocardiographic evaluation showed abnormal diastolic function of the left ventricle in 33% of the patients treated with cisplatin based chemotherapy, probably as an early sign of microvasculopathy.¹⁹

Subsequent studies with larger testicular cancer cohorts in following years revealed the magnitude of the problem (Table 1). Huddart *et al.* reported on cardiovascular morbidity in 992 testicular cancer survivors, treated between 1982 and 1992 at the Royal Marsden Health Service Trust. In particular, they reported on cardiac events, comprising

angina pectoris, long-term chest pain, myocardial infarction, surgery for coronary artery disease and others cardiac abnormalities. Approximately two thirds of the patients were treated with chemotherapy; cisplatin-based in two thirds and carboplatin-based in remaining third. After a median follow up of 10.2 years, age-adjusted relative risk (RR) for cardiac events was 2.59 (95% CI, 1.15 to 5.84) with no significant difference between patients treated with cisplatin and those treated with carboplatin. There was no difference in risk for cardiac events between patients treated with bleomycin containing regimens and those, who didn't get bleomycin, indicating that bleomycin did not significantly contribute to cardiac damage. Moreover, in this study, risk for cardiac events was increased in patients treated with radiotherapy (RR = 2.4, 95% CI, 1.04 to 5.45), although a minority of them - only 8.3%, received mediastinal radiotherapy. Patients treated with chemotherapy and radiotherapy were, as expected, at the highest risk, with age-adjusted RR = 2.78 (95% CI, 1.09 to 7.07).²⁶

After a median follow up of 18.4 years, van der Belt-Dusebut *et al.* reported on 694 cardiovascular events in 2 512 5-year testicular cancer survivors. The overall standardized incidence ratio (SIR) for coronary artery disease was significantly elevated (SIR = 1.17, 95% CI, 1.04 to 1.31). They found slightly, but not significantly increased risk for coronary artery disease in chemotherapy treated patients

compared to the general population (SIR = 1.35, 95% CI, 0.97 to 1.83). Chemotherapy with cisplatin, vinblastine, bleomycin (PVB) regimen was associated with 1.9-fold (95% CI, 1.7 to 2.0-fold), significantly increased risk for myocardial infarction, while chemotherapy with bleomycin, etoposide, cisplatin (BEP) was associated with borderline significantly increased risk for CVD (SIR = 1.5, 95% CI, 1.0 to 2.2), but not for myocardial infarction. Analysis of patients treated with radiotherapy revealed 3.7-fold (95% CI, 2.2 to 6.2-fold) increased risk for myocardial infarction after a mediastinal radiotherapy, while there was no increased risk for CVD after subdiaphragmatic radiotherapy. There was a trend towards higher risk for coronary artery disease with younger age at diagnosis and younger age at follow up as well, for the whole study group. In addition, in nonseminoma group of patients there was a significant influence of attained age of patient on the risk for myocardial infarction, with increased risk in 54 years old or younger (SIR = 1.86, 95% CI, 1.20 to 2.74), even higher risk in younger than 45 years (SIR = 2.06, 95% CI, 1.15 to 3.41) and decreased risk in 55 years or older (SIR = 0.53, 95% CI, 0.25 to 0.98).¹³

Haugnes *et al.* recently reported on cardiovascular morbidity in 990 testicular cancer survivors treated between 1980 and 1994. The incidence of two end-points were evaluated: coronary artery disease, including myocardial infarction and angina pectoris and atherosclerotic diseases, including coronary artery disease, cerebrovascular insult, transitory ischemic attack, carotid stenosis and other peripheral atherosclerotic disease. With a median follow up of 19 years, testicular cancer survivors treated with chemotherapy had increased risk for coronary artery disease (hazard ratio [HR] = 2.6, 95% CI, 0.96 to 6.9) and atherosclerotic disease (HR = 2.6, 95% CI, 1.1 to 5.9), compared to surgery only group. Treatment with BEP was associated with a 5.7-fold (95% CI, 1.9 to 17.1-fold), significantly increased risk for coronary artery disease and a 4.7-fold (95% CI, 1.8 to 12.2-fold), significantly increased risk for atherosclerotic disease, while treatment with CVB was associated with nonsignificantly increased risk for CVD, in contrary with the results of van der Belt-Dusebout study. Additional subanalyses, taking into account chemotherapy type, revealed that higher cumulative dose of etoposide was associated with increased risk for coronary artery disease, while higher cumulative doses of etoposide and cisplatin were associated with increased risk for atherosclerotic disease as well. Interestingly, risk for coronary artery disease

and atherosclerotic disease were increased even in patients treated with mostly non-mediastinal radiotherapy (only 3 of 420 irradiated patients received mediastinal radiotherapy), being 2.1-fold (95% CI, 0.78 to 5.4-fold) and 2.3-fold (95% CI, 1.03 to 5.3-fold), respectively. In accordance with results of other studies, treatment with chemotherapy and radiotherapy posed the highest risk, 5.3-fold (95% CI, 1.5 to 18.3-fold) for coronary artery disease and 4.7-fold (95% CI, 1.6 to 14.1-fold) for atherosclerotic disease, respectively.¹⁴

Treatment-related cardiovascular mortality

Hanks *et al.* reported on elevated cardiac mortality after 15-years follow up in 387 testicular cancer survivors treated with radiotherapy in 1973 and 1974. Seventy-nine percent of patients with stage II and 27% of patients with stage I had mediastinal irradiation. A significant, 3.1-fold increase in non-cancer mortality was observed compared to general male population. Further analysis of causes of death revealed a 2.3-fold increase in cardiac deaths. Eight out of ten patients, who died due to cardiac disease, received mediastinal irradiation.²²

In Zagars' study only minority of patients (71 of 477) received mediastinal irradiation. The cardiac mortality rate was significantly elevated only beyond 15 years of follow-up with standardized mortality ratio (SMR) 1.95 (95% CI, 1.24 to 2.94). Cardiac mortality rate was not significantly elevated during the first 15 years of follow up for the whole group of patients, except for the subgroup of patients treated with mediastinal irradiation (SMR = 1.63, 95% CI, 0.44 to 4.17).²³

Fossa *et al.* was the first author reporting on cardiac mortality among testicular cancer survivors treated with combination of radiotherapy and chemotherapy. They found slightly, but significantly increased risk of dying from circulatory disease (SMR = 1.20, 95% CI, 1.0 to 1.5). A comparison according to the diagnostic periods failed to show increase of mortality after the introduction of cisplatin, probably due to other treatment modifications that happened in that period: omission of mediastinal irradiation, confinement of subdiaphragmatic fields and introduction of modern radiotherapy planning and delivery facilities.²⁴

In another large international study by Fossa *et al.*, there was no significant increase in overall mortality from circulatory disease in whole study population of 38 907 patients treated for testicular cancer with only surgery, chemotherapy or ra-

diotherapy or with combination of chemotherapy and radiotherapy. However, a significantly increased mortality due to hypertensive disorder (SMR = 1.39, 95% CI, 1.01 to 1.89) was documented. Mortality caused by all circulatory diseases was significantly higher in testicular cancer survivors treated with chemotherapy (SMR = 1.44, 95% CI, 1.06 to 1.91) compared to group of patients treated with radiotherapy or surgery only. The risk was even higher in testicular cancer survivors treated with radiotherapy and chemotherapy (SMR = 2.06, 95% CI, 1.27 to 3.14). In comparison with the general population, mortality from circulatory disease was significantly increased in patients treated with radiotherapy at the age under 35 years (SMR = 1.7, 95% CI, 1.21 to 2.31), as well as in patients treated with chemotherapy (with or without radiotherapy) at the age under 35 years after 1975 (SMR = 1.58, 95% CI, 1.25 to 2.01). The latter coincides with introduction of cisplatin based chemotherapy.⁵

Pathophysiology of CVD caused by cisplatin based chemotherapy

Although mechanisms that would explain an increased risk of CVD after cisplatin based chemotherapy are not completely clarified, endothelial damage is considered to play a main role in pathogenesis. Microalbuminuria, thought to be an early sign of endothelial damage, was reported by Meinardi *et al.* in 22% of patients treated with cisplatin based chemotherapy.¹⁹ Patients with microalbuminuria had a tendency of higher blood pressure, which could be a consequence of systemic endothelial damage as well.³⁰ Moreover, microalbuminuria was shown to be a predictor of cardiac events.^{31,32} Nuver *et al.* observed microalbuminuria in 12% of patients treated with cisplatin based chemotherapy for testicular cancer after median follow up of 7 years, compared to 0% in surgery only group and 4.6% in a larger group of healthy men from general population.³³

Nuver *et al.* proposed other endothelial and inflammatory markers as potential early indicators of endothelial damage and atherosclerosis, which is essentially an inflammatory process.³³ Namely, they found significantly higher levels of von Willebrandt factor (vWF), tissue plasminogen activator (t-PA), plasminogen activator inhibitor-1 (PAI-1), fibrinogen and high sensitivity C-reactive protein (hs-CRP) in patients treated with chemotherapy compared to healthy men. Elevated levels of endothelial and inflammatory markers were shown to be associated with higher risk for

coronary artery disease.^{34,35} In addition, elevated levels of inflammatory proteins were associated with more pronounced atherosclerosis as well.³⁶ Moreover, according to the available data from the literature, hs-CRP could be a predictive marker for CVD.³⁶⁻³⁹ In the same study by Nuver *et al.* evaluation of vascular structure and function of common carotid artery was performed. Irrespective of high levels of endothelial and inflammatory markers, this evaluation failed to show any significant changes in wall structure or function of blood vessel, except a small, but statistically significant increase in carotid wall stiffness. Explanation for this could be impairment of microvasculature at the early stages, with later impairment of the macrovasculature. The same author in another study also reported on small, but statistically significant increase in carotid intima media thickness in patients treated with cisplatin based chemotherapy, which was shown to be associated with higher myocardial infarction incidence.⁴⁰

Gietema *et al.* showed a presence of circulating platinum in plasma up to 20 years after treatment with cisplatin based chemotherapy in testicular cancer survivors, which, together with the awareness of signs for endothelial damage, led to the theory that cisplatin may chronically stimulate the endothelium, eventually resulting in vasculature impairment.^{41,42} Correlation between cisplatin plasma levels and severity of neurotoxicity was recently shown, indicating that cisplatin level may serve as a putative marker for long-term toxicity, perhaps even for CVD.⁴³

Unfavourable cardiovascular risk profile, metabolic syndrome and hypogonadism in testicular cancer survivors

CVD following cisplatin based chemotherapy could, on the other hand, be caused by a gradual development of unfavourable cardiovascular risk profile. Namely, several studies reported significantly higher prevalence of hypertension in testicular cancer survivors treated with platinum based chemotherapy.^{14,16,19} Another cause of hypertension in testicular cancer survivors could be abdominal radiotherapy. Namely, some studies with patients treated with abdominal radiotherapy for malignant disease in abdomen reported on increased risk of hypertension. Possible explanation for this is development of radiation nephropathy with resulting hypertension, probably through a renovascular mechanism with activation of the renin-angiotensin-aldosterone system.⁴⁴⁻⁴⁶ Furthermore, a

few studies reported on increased risk for hypercholesterolemia, as well as increased prevalence of obesity following cisplatin based chemotherapy in testicular cancer survivors, which was, on the other hand, not confirmed by others.^{14-19,21} Haugnes *et al.* found significantly higher levels of HbA1c in all chemotherapy and radiotherapy treated testicular cancer patients compared to surgery only group, moreover, patients treated with radiotherapy were at a greater risk of being diagnosed with diabetes as well. Namely, the prevalence of diabetes for the whole study group was 7.3%, while it was 10.2% and 15.6% for radiotherapy and radiotherapy/chemotherapy group, respectively. The most likely explanation for this is radiation damage of pancreatic gland tissue, as the large part of the gland is included in subdiaphragmatic radiation field. Insulin resistance in testicular cancer patients treated with chemotherapy could be a consequence of persistent hypomagnesemia, caused by cisplatin-induced damage of proximal renal tubules. In Haugnes' study it was found that the prevalence of other unfavourable risk factors for CVD was the highest in radiotherapy/chemotherapy group as well, suggesting a possibility of synergistic effect.¹⁴

Hypertension, dyslipidaemia, obesity and insulin resistance are all components of the metabolic syndrome. Considering that testicular cancer survivors are at greater risk to have one or more of these components, the metabolic syndrome could be a possible causal link between cytotoxic treatment and CVD.^{47,48} The prevalence rates of metabolic syndrome in testicular cancer survivors range from 8% to 40%, depending on applied criteria for diagnosis of this syndrome. Patients treated with chemotherapy are at higher risk for development of metabolic syndrome, compared to controls and to radiotherapy or surgery only group. This is especially true for patients receiving higher cumulative dose of cisplatin – 850 mg or more. Beside association with cumulative dose of cisplatin, a positive correlation was demonstrated between prevalence of metabolic syndrome and cumulative doses of bleomycin and etoposide as well.⁴⁸ The aetiology of the metabolic syndrome is not entirely clear. Gietema *et al.* were the first authors reporting on the possible association of metabolic syndrome with low serum testosterone levels in patients who received chemotherapy.⁴⁹ Nuver *et al.* proposed that low serum testosterone level and metabolic syndrome could be associated through increased body mass index.⁴⁸

It's well known that hypogonadism increases risk for CVD and correlates with the severity of ath-

erosclerosis, even in a healthy male population. In addition, it was shown that gonadal dysfunction is associated with obesity, dyslipidaemia and insulin resistance, as well as with higher levels of markers of endothelial damage. A middle aged men from general population with free testosterone levels in the lower third of normal range were at a 2.7-fold (95% CI, 2.0 to 3.7-fold) increased risk for metabolic syndrome in age-adjusted analyses. After further adjusting for body mass index, low free testosterone level was associated with 1.7-fold (95% CI, 1.2 to 2.4-fold) increased risk for metabolic syndrome. This correlation was even more pronounced for total testosterone levels and sex-hormone binding globulin levels.⁵⁰ In testicular cancer survivors, gonadal dysfunction may be result of prior treatment with chemotherapy, subdiaphragmatic radiotherapy and with surgery as well.⁵¹

However, it is still ongoing debate, whether metabolic syndrome is a consequence of hypogonadism or intrinsic feature of testicular cancer survivors, as a part of testicular dysgenesis syndrome. If the first assumption is true, the testosterone substitution therapy could have a favourable impact on metabolic syndrome and development of CVD in testicular cancer survivors. To date, there is no evidence for that. According to the literature, substitution therapy with testosterone might be useful in men with significantly reduced testosterone levels, while its benefit is questionable in a case of modest hypogonadism.⁴⁸

Pathophysiology of CVD caused by irradiation

Increased risk for CVD after mediastinal radiotherapy in patients treated for testicular cancer is a consequence of a direct exposure of the heart to irradiation.⁵²⁻⁵⁴ Data from the literature indicate that irradiation of the heart leads to the tissue damage through microvasculopathy and eventually macrovasculopathy. Endothelial damage of small blood vessels is due to radiation induced generation of reactive oxygen species. Typically, irregularities of the endothelial cell membranes, cytoplasmic swelling, thrombosis and rupture of the walls are present in early phase. This eventually results in reduced ratio of capillaries to myocytes by approximately 50%, leading to ischaemia and fibrosis in late phase.⁵⁵

Less is known about pathologic association between subdiaphragmatic radiotherapy and CVD. According to the physical model, in series of Huddart *et al.*, the expected mean dose to the

heart in a case of “dog leg” radiation field, extending upwards to the bottom of tenth thoracic vertebra, was approximately 2.5% of the total dose, which is unlikely to cause any serious damage.²⁶ Possible mechanism of CVD in patients treated with abdominal radiotherapy could be radiation nephropathy, as well as hypogonadism, as mentioned above. A direct endothelial damage, eventually resulting in atherosclerosis, is another possible mechanism, supported by increased levels of hs-CRP in patients treated with radiotherapy.⁵⁶

Up to 1980's, total dose of subdiaphragmatic radiotherapy was 36 to 40 Gy and even more. After that, radiation dose was gradually reduced, being 20 Gy for stage I seminoma, 30 Gy for stage II A and 36 Gy for stage II B. In case of prophylactic mediastinal irradiation, testicular cancer survivors usually received 30 Gy. Fractionation, mainly used in subdiaphragmatic, as well as in mediastinal irradiation, is 2 Gy daily fractions 5 days per week.

Implication for future

Current knowledge about long-term treatment-related toxicity in testicular cancer survivors is based on treatment modalities administered years to decades ago. Optimization of treatment, including omission of mediastinal irradiation, confinement of subdiaphragmatic fields, use of modern radiotherapy planning and delivery techniques, lowering the cumulative doses of cytotoxic drugs and preferential use of active surveillance will probably all reduce risk for cardiac toxicity.⁷⁻¹² However, as data from newer studies are not yet available, we do not have confirmation for this and further research is essential.⁵⁷

Following successful treatment, most of the testicular cancer survivors are under the medical surveillance of their oncologists for subsequent 5 to 10 years. Obviously, these patients need a longer, probably life-long follow-up with special attention to modifiable CVD risk factors. Patients should be treated for hypertension, diabetes, hyperlipidaemia and dyslipidaemia and advised about healthy lifestyle. A smoking cessation is highly recommended, along with regular physical activity and maintaining of optimal body weight. At the moment, no guidelines concerning CVD risk in testicular cancer survivors are available and several study groups proposed their development.²⁵

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