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Long-term toxicity of the treatment for germ cell-cancer. A review

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ABSTRACT

Testicular germ-cell cancer (GCC) is a curable disease. Stage I patients are mostly cured by surgery alone. For those with good prognosis advanced disease, radiotherapy in some patients with stage II Seminoma and chemotherapy for all other patients, are responsible for 95% of long-term survivors. Unfortunately, despite this high level of curability, overall survival has been reported lower for those patients receiving either radiotherapy or chemotherapy versus patients treated by surgery alone. Long-term survivors face a higher incidence of second neoplasms, and a higher risk of cardiovascular disease and metabolic syndrome than expected. Other non-life-threatening toxicities such as ototoxicity, neurotoxicity and fertility problems are common. This paper reviews the potential causes of the higher mortality among long-term survivors of testicular tumors, the incidence of them and some recommendations for the diagnoses and prevention of long-term sequelae in patients with GCC.

1. Introduction

Nowadays GCC is the most curable solid tumour, with a 10-year survival rate of more than 95% (Verdecchia et al., 2007). As GCC affects young men with a future life span of 40 or 50 years, long-term sequelae of therapy has become a real concern for the worldwide oncological community. Mortality rates for long-term survivors of GCC for cancer is higher than that of a population with age-matched controls (Demark-Wahnefried et al., 2005); unfortunately, these differences persist even after the incorporation of modern chemotherapy or reduced fields' radiotherapy (Fossa et al., 2007). In fact, for the highly curable seminoma, a report has shown that the excess non-tumour related mortality after one year exceeded that due to tumour by a factor of approximately three (Zagars et al., 2004). In addition to radiotherapy, chemotherapy has also played a significant role in this excess of mortality. For example, persistence of platinum-DNA adducts can be detected in numerous tissues, as well as in serum (Gietema et al., 2000), up to several years after treatment (Tothill et al., 1992). In an attempt to diminish toxicity, GCC chemotherapy has increasingly moved to the minimum in terms of both the number of cycles and the number of patients receiving treatment, avoiding unnecessary adjuvant therapies for patients with a high probability of having been previously cured by surgery. For those patients where chemotherapy was unavoidable, recommendations by an International panel on prevention of long-term toxicity recommended the following: implementation of lifelong follow-up, development of comprehensive risk prediction models, shedding light on the effects of decades-long exposure to platinum, and finally, the eventual formulation of evidence-based long-term follow-up guidelines (Travis et al., 2006).

In this review, for educational purposes, long-term toxicity has been grouped as life-threatening (second cancers and cardiovascular disorders), and non-life-threatening (fertility, ototoxicity, peripheral neuropathy, fatigue and Raynaud́s syndrome) (Stephenson et al., 1995; Vaughn et al., 2002).

2. Life-threatening toxicity

2.1. Second cancers

According to the available data, the relative risk of a second solid non-germ-cell tumour is approximately doubled after radiotherapy or chemotherapy. Solid second tumours are usually diagnosed more than 10 years after treatment as opposed to chemotherapy-related leukaemia, which commonly emerge within one decade after treatment. Two factors increase the relative risk of second tumours: age (the younger the patient the higher the risk) and the amount of chemo received by the patient. Additionally, high-dose chemotherapy has also been associated with an excess of both solid and haematological (Necchi et al., 2017) second tumours. Following high-dose chemotherapy, haematological tumours were diagnosed within the first two years of follow-up, and solid tumours at a median of five years after therapy.

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2.2. Radiation-induced malignancies

The risk of developing second tumours in patients with germ-cell cancer is also higher if radiotherapy was part of the therapy. Most radiation-induced malignancies are located within, or close to, initial abdominal radiation fields (bladder, stomach and colon cancer). In a series of 40,576 testicular cancer survivors, the overall post-testicular cancer observed/expected ratio for developing a solid second cancer was 1.55 (95% CI, 1.48-1.62) in 10-year survivors (Travis et al., 2005). In the series of Hemminki et al. (Hemminki et al., 2009), second neoplasms were more frequent in patients with seminoma (2.1%) than after a non-seminomatous tumour (1.3%). It is worth paying attention to the fact that in this series the highest increase in cancer risk in patients cured of a seminomatous tumour was kidney (relative risk: 3.65, range 1.82-6.53) and oesophagus cancer (relative risk: range 4.95, 1.82-10.78).

2.3. Chemotherapy-Induced malignancies

In the series of Hemminki et al., for patients cured of a non-seminomatous tumours, the highest relative risk for cancer was for kidney cancer and leukaemia (4.19, 1.36–9.79 and 4.08, 1.5–8.89, respectively); furthermore, there was an increase in bladder cancer especially in younger patients, most likely related to carcinogens eliminated through the urine. Travis et al. (Travis et al., 1997) analysed the risk of second neoplasms in a series of 29.000 long-term survivors of TGT from different registries in North America and Europe. 1406 s tumours were identified, representing a RR of 1.43, with the highest risk for haematological malignancies, although pancreatic tumours, gastric cancer, colorectal carcinomas, kidney and bladder cancer, melanoma and sarcoma also increased. Even though the excess risk initially described could be related to the use of “old” chemotherapy, an increased risk of cancer has also been unfortunately observed in patients receiving modern chemotherapy (Fung et al., 2013). Cisplatin is a carcinogen in animal models (World Health Organization, 2017), accumulation of platinum in specific organs may, in part, provide a pathophysiological explanation (Wanderas et al., 1997) as well as direct toxicity through urinary elimination. As previously described, an excess of bladder and kidney cancer has been reported in patients after cisplatin-based chemotherapy between 15–20 years after therapy.

Leukaemia increases by 2.6 in long-term survivors of testicular cancer. Although Cisplatin is leukemogen, etoposide possibly is the main risk factor for developing a secondary acute myeloblastic leukaemia. Risk of therapy-related leukaemia is dose-dependent (0.5% and 2% after cumulative etoposide doses of $< 2\ g/m^2$ and $> 2\ g/m^2$, respectively) (Travis et al., 2010). There is an observed association through chromosome-12 between leukaemia and germ-cell mediastinal tumours; however, features of the latter are different from therapy-related leukaemia (Nichols et al., 1993; Boshoff et al., 1995).

Finally, it is well known that teratoma may undergo malignant transformation to any histologic subtype, with soft tissue sarcoma being the most frequent (63%) (Motzer et al., 1998). Early-onset sarcomas may represent transformation of teratoma after chemotherapy, whereas late-onset sarcomas may reflect to some extent the late effects of alkylating agents (Jenkinson et al., 2007).

3. Cardiovascular disease

3.1. Metabolic syndrome

It has been reported that patients with testicular cancer treated with chemotherapy experience vascular complications, including pulmonary emboli, myocardial infarction (MI), venous thrombosis, and Raynaúds phenomenon. Patients under chemotherapy may experience an acute cardiovascular toxicity (deep venous thrombosis, pulmonary emboli) (González-Vilallabeitia et al., 2017), and a late chronic vascular toxicity that increases with time (De Haas et al., 2013).

A decline in cardiac function has been described in long-term survivors of GCC receiving cisplatin-based chemotherapy, especially regarding diastolic function, faster than would be expected by the aging process alone. The decline in diastolic function is faster if the patient presents obesity and/or hypertension (Altena et al., 2011). The incidence of major cardiovascular events (angina with proven myocardial ischemia or myocardial infarction) among 87 GCC survivors who were given cisplatin-based therapy was estimated in a study to be as high as 6%, which represents 7.1 more than expected (95% CI = 1.9–18.3) (Meinardi et al., 2003). Analyses of 2707 survivors that have received either radiotherapy, chemotherapy or both showed the highest risk of developing vascular disease for those receiving both radiotherapy and chemotherapy; nonetheless, those patients receiving only chemotherapy had 4.1 higher incidence (not mortality) of cardiac disease than those treated only by surgery (Van den Belt et al., 2007).

Mechanisms of cardiovascular disease damage in GCC survivors are still unclear but may include direct vascular injury from chemotherapy or radiation. Raynaúds phenomenon can be detected in 37% of the patients receiving bleomycin (Vogelzang et al., 1981a) and it might represent an early biomarker for cardiovascular toxicity (Glendenning et al., 2010). Microalbuminuria (an early marker of endothelial damage) can be detected in up to 11% of patients after chemotherapy (Nuver et al., 2004). The picture is even more complex. It has been observed that more than half of the survivors of testicular cancer maintain a sedentary life-style. Smoking habit persists in up to 39% of survivors. Not only that, diagnoses of metabolic syndrome (defined as the presence of at least 3 of troncular obesity, triglycerides above $>$ 1.7 mmol/L, low HDL-cholesterol $<$ 1 mmol/L, glycaemia $>$ 6.1 mmol/L, high blood pressure ($>$ 130/85) (George et al., 2005), is increased in long-term GCC survivors, affecting as much as 16% of patients (Bokemeyer et al., 1996; Nuver et al., 2005a). Incidence increases when total platinum dose is over 850 mg, with higher levels of blood pressure and body weight compared to survivors that had received lower doses or surgery alone (Sagstuen et al., 2005). Recently, a report analysing adverse health outcome results in long-term survivors of germ-cell cancer has been published (Fung et al., 2017). Long-term complications such as ototoxicity, high blood pressure, elevated BMI, hypercholesterolemia or second malignancies were seen. For patients with obesity, low daily physical exercise or smokers, the number of adverse health events was significantly higher, supporting a lifestyle change for long-term survivors of testicular cancer.

3.2. Physiopathology of the metabolic syndrome in survivors of GCC

It appears that single orchiectomy does not affect serum testosterone levels, at least for the first decades after surgery, although a low decline might be observed over time. If an additional treatment is administered, serum testosterone levels may be further affected, and be typically at the lower spectrum of the normal range (Huddart et al., 2005; Brennemann et al., 1997). After therapy with cisplatin, a higher level of FSH and LH can be detected (Efstathiou and Logothetis, 2006), as a result of secondary hypogondism through damage to Sertoli and Leydig cells. Maintained lower levels of testosterone could be related to the development of the metabolic syndrome (Laadsonen et al., 2003). As a result, low testosterone levels in long-term survivors of germ-cell cancer may contribute to a higher risk of metabolic syndrome as well as a general poorer aging process, increasing morbidity and mortality (Issam et al., 2017). This phenomenon is observed in patients with diabetes, where low testosterone levels are associated with a higher risk of the development of metabolic syndrome (Yeap, 2009).

Other potential pathophysiological mechanisms of chemotherapy-related cardiovascular toxicity occurring during treatment could be mediated by increases in von Willebrand factor levels (Dieckman et al., 2011) and increases in carotid intima-media thickness (Nuver et al., 2005b). Moreover, Cisplatin-based chemotherapy induces