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Survivorship Issues in Testicular Cancer

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Introduction

Testicular cancer (TC) is the most prevalent tumor in young men aged 15–40 years,[1] with an annual incidence of 3–11 new cases per 100,000 males in Western countries.[2] In 2020, the International Agency for Research on Cancer reported 74,458 newly diagnosed cases of TC globally.[3] The etiology of TC is complex and includes both genetic and environmental factors. The prognosis of TC is excellent with a >90% cure rate and a >95% 5-year survival rate with appropriate treatment.[4] Treatments for TC include active surveillance, chemotherapy, radiotherapy, and retroperitoneal lymph node dissection, depending on the clinical stage and tumor subtype. It is crucial that patients receive information on the diagnosis, therapeutic management options, consequences of treatments, and surveillance protocols, which allows the patient to play an active role in the decision-making process. Fear of recurrence often affects TC survivors. Therefore, it is essential to fully involve the patient in the choice of the treatment to ensure an optimal compliance, especially when selecting the active surveillance strategy.[5] In the modern era, in light of the excellent outcomes achieved in TC management, one of the high priorities is to deliver curative treatments while minimizing long-term toxicity. This focus can have a positive impact on quality of life and life expectancy of TC survivors.

Chemotherapy Toxicities

The most common chemotherapy regimens for TC treatment are cisplatin-based and include bleomycin, etoposide, and cisplatin (BEP) or etoposide, ifosfamide, and cisplatin (VIP). In cases in which the disease persists after initial chemotherapy, several successful salvage strategies are available, including either standard or high-dose chemotherapy approaches.[6]

Lung toxicity. The most severe and life threatening adverse effect of bleomycin is lung toxicity, characterized by dry cough, dyspnea, tachypnea, cyanosis, decreased exercise tolerance, and fever.[7] Short-term respiratory complications at 3 years occur in up to 46% of patients (usually mild, self-limiting), however, a small fraction of patients may develop pulmonary fibrosis which carries a 10% mortality rate.[8] Owing to fibrotic transformation in both lungs, with reticular opacities and the typical honeycomb pattern, interstitial lung diseases are more easily diagnosed using high-resolution computed tomography scans.[9] Pre-treatment pulmonary function tests may be useful to monitor toxicity on treatment. An international study involving 38,907 patients demonstrated that the relationship between bleomycin and the development of pulmonary fibrosis had a statistically significant association with an increased risk of mortality from respiratory disorders.[10] In addition, the cumulative dose, age at diagnosis, smoking history, renal impairment, and mediastinal radiation treatment are also risk factors for bleomycin-associated pneumonia.[11]

Nephrotoxicity. It is well known that cisplatin damages the proximal and distal renal tubule epithelium and renal collecting duct system, as well as the glomeruli at higher doses.[12] Two long-term studies reported a persistent reduction in renal function in testicular cancer survivors (TCS) for many years after completion of chemotherapy compared to their baseline renal function.[13,14] Furthermore, a Norwegian study involving 85 patients showed that more than 10 years after the end of treatment renal function was reduced by 14% among TCS who received chemotherapy, and by 8% in patients receiving radiotherapy alone.[14] To limit the severity of kidney damage, healthcare professionals should administer hydration and avoid nephrotoxic drugs during cisplatin-based chemotherapy.

Peripheral neuropathy. After cisplatin-based chemotherapy, 20–40% of patients develop chronic peripheral neuropathy symptoms owing to the neurotoxic effect of cisplatin.[15,16] Chronic peripheral neuropathy tends to improve gradually within a few months after the conclusion of treatment. However, in some patients the damage becomes chronic and does not regress.

It is important to point out that the risk of cisplatin-induced peripheral neuropathy is related to its cumulative dose.[17] In the majority of patients, peripheral neuropathy resolves within 12 months, although it could persist beyond this timeframe in approximately 17% of the patients.[18]

Ototoxicity. Cisplatin is known to selectively damage the outer hair cells of the cochlea, causing tinnitus and high frequency hearing loss.[19] Severe ototoxicity has been independently associated with older age, higher cumulative cisplatin dose, history of noise exposure, hypertension, and baseline renal impairment.[20,21] There are no approved pharmacological treatments or preventative measures for cisplatin-induced ototoxicity. If possible, patients should use ear protection when exposed to loud noises. The 5-day BEP regimen is preferred to a 3-day regimen because maximal cisplatin concentrations may be directly related to the severity of ototoxicity.[22]

Ocular toxicity. Retinal damage has also been associated with cisplatin treatment.[23,24] High dose cisplatin can lead to retinal toxicity and macula pigmentary alterations.[25]

Vascular toxicity. Patients with TC are at a higher risk of experiencing Raynaud's phenomenon. The symptoms usually start within a year after the therapy and primarily affect the fingers. Digital ischemia has been documented in 37% of TC patients receiving vinblastine-and bleomycin-containing combination treatment.[26] Those who smoke daily had a significantly stronger association with Raynaud-like symptoms and paresthesias (with odds ratios ranging from 1.5–2.2) compared to those who never smoked.[27]

Chronic Cancer-Related Fatigue

Fatigue is a common and significant issue for TCS. The causes of fatigue in TCS are multifactorial and consist of physical, emotional, and psychosocial factors, including the cancer itself and the treatments used. Physical fatigue leads to decreased energy levels, muscle weakness, and difficulty in performing routine tasks. Cognitive fatigue, characterized by mental exhaustion and difficulty concentrating, can affect work performance, memory, and decision-making abilities. Chemotherapy and radiation therapy cause long-lasting fatigue owing to their impact on healthy cells and overall energy levels. A Norwegian multicenter study analyzed questionnaires from 1,431 patients concerning the evaluation of cancer-related fatigue and chronic general fatigue and reported a high prevalence of cancer-related fatigue among TCS compared to that of the general population.[28] Another study has shown that in TCS there is a notable increase in chronic fatigue, anxiety, and depression more than 10 years after treatment completion, along with lower testosterone levels. Moderate-to-high physical activity appeared to offer a protective effect.[29]

Avascular Necrosis of the Hip

Avascular necrosis (AVN) of the hip, also known as osteonecrosis of the femoral head, is a debilitating condition that affects 1–2% of long-term survivors of TC. Common signs and symptoms of AVN include persistent pain in the hip joint, limited range of motion, and radiation of pain from the hip joint to the groin or thigh area. Owing to its rarity, most of the reported cases of AVN of the hip are in the form of case reports.[30,31] In AVN, the blood supply to the femoral head is disrupted, leading to the death of bone tissue. Cisplatin-based chemotherapy, especially when it includes high dose corticosteroids used as antiemetics, have negative effects on the blood vessels supplying the hip joint. Radiotherapy directed at the pelvic region can also cause damage to the blood vessels, resulting in an increased risk of AVN.[32] The signs of AVN may be detected using MRI or CT scans. In severe cases of AVN, total hip replacement surgery may be necessary to alleviate pain and restore mobility.[33]

Changes in Serum Testosterone, Luteinizing Hormone (LH) and Follicle-Stimulating Hormone (FSH), Hypogonadism, Fertility, Sexual Dysfunction

Treatments employed in TC can have long-term effects on the endocrine system. Several studies have reported that TCS often experience reductions in serum testosterone levels[34-37] resulting from the direct destruction of Leydig cells, which are responsible for testosterone production. Disruption in the hypothalamic-pituitary-gonadal (HPG) axis can occur with consequent changes in luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels.[38,39] Low testosterone levels result in various symptoms, including fatigue, decreased

libido, erectile dysfunction, and reduced muscle mass.[40] It is important to monitor hormone levels in TCS and consider appropriate interventions, such as testosterone replacement therapy. The long-term effects of cisplatin-based chemotherapy on reproductive health and sexual function have become increasingly important. Studies have shown that up to 80% of TCS treated with more than 4 cycles of cisplatin-based chemotherapy experience hypogonadism.[41] The most common causes of hypogonadism are age, testicular dysgenesis syndrome, chemotherapy, or post-orchiectomy radiation. According to a Norwegian study, TCS treated with radiation therapy or chemotherapy had a significantly increased risk of low testosterone levels. Additionally, they showed elevated levels of LH and FSH during long-term follow up. Possible effects of hypogonadism include decreased libido, erectile dysfunction, muscular weakness, osteoporosis, fatigue, and depression.[42] Moreover, TC and its treatments can have a significant impact on fertility. It has been observed that the production of spermatozoa is often reduced or even absent at diagnosis in patients with TC.[43,44] Radiotherapy and chemotherapy treatments have the ability to induce alterations in the quality and quantity of spermatozoa in up to 30% of patients.[45,46] In particular, the greatest impact on the deficiency in the quality and quantity of spermatozoa seems to occur 3–6 months after the end of treatments, with variations related to the specific therapy, dose, and duration of administration. It is also known that the recovery time of spermatogenesis is slower (up to 24 months after the end of treatments) in cases in which more than 3 cycles of chemotherapy were delivered or after radiotherapy.[47] Therefore, it is crucial to discuss fertility preservation options with TC patients before starting treatment. Erectile dysfunction is caused by the physical and psychological effects of the disease itself, as well as the treatments involved, especially considering that radiotherapy mainly leads to erectile dysfunction, while retroperitoneal lymph node dissection is mainly responsible for ejaculatory dysfunction.[48] Overall, sexual dysfunction has been reported in 30–50% of patients.[49,50]

Finally, vitamin D deficiency has been reported in TC patients. It is unclear if the deficiency is related to the reduced gonadal activation of vitamin D or if it is a pre-existing condition. Some data also suggest a specific association of vitamin D deficiency with specific subtypes of germ cell tumors.[51]

Cardiotoxicity and Metabolic Syndrome

Chemotherapy has been associated with an increased risk of the development of heart failure, arrhythmias, and impaired cardiac function in TCS. A recent retrospective analysis performed on 44,975 U.S. men with TC that is registered in the Surveillance, Epidemiology, and End Results (SEER) database has shown that the most common noncancer cause of death, at least one year after diagnosis, was heart disease.[52] In addition, radiotherapy has been associated with a higher long-term risk of diabetes.[53] Compared to patients only receiving surgery, those treated with radiation therapy or chemotherapy were more likely to receive cardiologic drugs.[54] Several mechanisms have been proposed to explain the cardiotoxic effects of these agents. According to the direct vascular damage hypothesis, cisplatin or bleomycin cause direct damage to blood vessels as demonstrated by an increased release of Von Willebrand factor from endothelial cells.[55] Hypogonadism and testosterone deficiency can also lead to a pro-inflammatory state, endothelial dysfunction, and an increased risk of cardiovascular disease.[56,57] A study involving TCS that included a 4-year follow-up has demonstrated that patients who underwent chemotherapy were more likely to have metabolic syndrome than patients who underwent surgery alone. Furthermore, the incidence of metabolic syndrome was cisplatin dose dependent.[57] Monitoring cardiac function through echocardiography and with electrocardiograms can help detect early signs of cardiotoxicity in TCS.

Risk of Secondary Malignancies and Metachronous Contralateral TC

Over the years, numerous studies have documented an increased risk of second malignancies in TCS. The risk appears to be increased especially after radiotherapy, although chemotherapy alone and the association of radiotherapy and chemotherapy can effectively contribute to the development of secondary tumors. For instance, radiotherapy has been associated with a 1.5- to 4.4-fold increase in the risk of gastrointestinal, lung, and genitourinary cancers.[58] Moreover, the risk of leukemia has been shown to be three times higher in patients

treated with radiotherapy.[59] The risk of cancer after ionizing radiation follows a linear dose-response model.[60] Chemotherapy with cisplatin and etoposide has also been associated with significantly elevated risks of secondary leukemia and a 2-fold greater risk of developing solid tumors compared with surgery alone.[61] Moreover, there is evidence suggesting a significant correlation between the cumulative dose of cisplatin and etoposide, and the risk of leukemia.[62-66] These risks appear to be similar for seminoma and nonseminoma types of TC.[67] Patients treated with both radiotherapy and chemotherapy have the highest risk of developing secondary malignancies.[61,68]

Metachronous contralateral testicular cancer occurs in approximately 1% to 5% of TCS.[69] Younger age and seminoma histology are associated with a higher risk of contralateral involvement.[70,71] Individuals with a family history of TC, cryptorchidism, infertility, or certain genetic abnormalities also have an increased risk of developing contralateral cancer.[55,72-74]

Psychosocial Distress

TC has a profound psychological and emotional impact on TCS. The experience of the diagnosis of TC occurs in a critical period of life in which young people are preparing to become independent, establish intimate emotional relationships, along with the prospect of creating a family, explore their sexuality, and cultivate professional prospects. The desire for normality is strongly felt in these patients. It is not uncommon for survivors to experience anxiety, depression, and feelings of uncertainty about their future. The diagnosis and treatment process can be emotionally challenging, often leading to a sense of loss, body image issues, and sexual concerns. Additionally, survivors may struggle with fear of recurrence, financial burdens, and difficulties in maintaining relationships.[75-78] Furthermore, the physical changes resulting from surgery, chemotherapy, or radiation therapy have a significant impact on body image and self-esteem. The loss of a testicle can lead to an alteration in the perception of oneself and to sexual disorders that affect one's sense of masculinity, which can cause feelings of inadequacy or insecurity. Additionally, the fear of cancer recurrence and the uncertainty surrounding long-term prognosis can create significant psychological distress.[79] This psychological distress impacts their ability to engage in daily activities, maintain relationships, and pursue future goals.[80-82]

However, with proper support and psychological interventions, survivors can effectively manage and cope with psychosocial distress, improving their quality of life.

Taking care of patients with TC necessarily involves the existence of an integrated multidisciplinary team, with specific expertise in communication and the doctor-patient relationship.[5,83-85]

Long-Term Mortality

Although effective treatments and early detection have significantly improved the prognosis for TC patients, the long-term toxicities negatively impact their long-term survival.[10,86-88] High mortality seen with long term follow up has been reported in a Norwegian study that analyzed TC survival in a population-based database. The long-term relative survival (RS) among TC patients was significantly shorter than that of non testis cancer patients, especially after 30 years of follow-up. The authors observed a continuous decline in long-term RS, except for seminomas diagnosed after 1999, owing to the extensive use of adjuvant radiotherapy before that period. RS was also significantly reduced among patients >40 years of age at the time of the diagnosis. The main cause of the decline in RS was attributed to the late toxicity of chemotherapy and radiation therapy.[89]

In conclusion, understanding the long-term mortality of TCS has important implications for their long-term health and well-being. It is important for survivors to be cognizant of these potential risks and take proactive action to mitigate long-term mortality. Changes in treatment modalities, regular follow-up appointments, lifestyle modifications, and participation in supportive care programs are essential components of a comprehensive approach to long-term survivorship.

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