At what price do we treat patients with testicular cancer?

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In 2013 testicular cancer (TC) represents the most curable solid tumour. The high cure rate is associated with a significant long-term morbidity. Long-term effects after TC treatment can be divided into life-threatening (e.g. secondary tumours and cardiovascular disease) or effects on single organs (e.g. nephro-, neuro- and pulmonary toxicity, hypogonadism or decreased fertility). Psychosocial effects are also a major issue, with fatigue, influence on sexuality, work, cognitive function, quality of life, lifestyle factors, etc. Some of these side effects are discussed below, with a focus on future studies. Testicular cancer survivors are at significantly increased risk of solid tumours for at least 35 years after treatment, with a higher incidence in patients who have had a seminoma compared to non-seminoma [1,2]. However, published studies lack detailed information concerning treatment or refer to formerly used treatments.

Several studies have demonstrated increased risk of cardiovascular disease [3–7]. A Norwegian study found a 5.7-fold higher risk for coronary artery disease after bleomycin, etoposide and cisplatin (BEP) treatment, with a median observation time of 19 years [3]. Hypogonadism, hyperlipidaemia [4] and metabolic syndrome [4,7] have been mentioned as risk factors. Metabolic syndrome in particular could be linked to subclinical testosterone deficiency.

It is necessary to increase our knowledge concerning the impact of cisplatin-based chemotherapy, lifestyle factors (diet, tobacco, physical activity), hypogonadism, family history concerning cardiovascular disease (CVD), alcohol, abnormal blood samples and gene changes on the development of cardiovascular disease in TC patients. Given the increased incidence of CVD in TC patients it would be relevant to look at genetic markers which in the general population have been found to predispose to these diseases. To develop risk models that include the above-mentioned factors, international cooperation is needed. This could make it possible to stratify TC patients into risk groups and develop evidence-based intervention according to the risk factors.

Testicular cancer patients should be tested for subclinical hypogonadism. We know that after treatment, the serum testosterone concentration is in the lower part of the normal range [8] and that 12–16% of long-term survivors have developed hypogonadism. Most younger TC patients exhibit some dysfunction of the Leydig cells, which is compensated by an increase in luteinising hormone (LH) levels. Whether this compensation is adequate in elderly TC patients is not known. The clinical significance of low testosterone levels is under discussion, but most people believe that a sustained reduction in testosterone is a contributing factor in the development of metabolic syndrome, type-2 diabetes, osteoporosis, decreased quality of life and premature ageing [9]. Hypogonadism could be a significant and independent predictor for the development of CVD, and if this is the case, testosterone replacement should be examined.

All TC patients treated with cisplatin will experience a decline in glomerular filtration rate (GFR). This reduction will in some patients be reversible, whereas in others GFR shows a permanent decrease of up to 30% or more [10,11]. There is no long-term monitoring of renal function in TC patients treated with cisplatin. Experimental and clinical data suggest that hypomagnesaemia is important for the development of nephrotoxicity [12]. There are several unanswered questions related to nephrotoxicity in this group of patients. It is unknown whether the natural age loss in GFR is accelerated in TC patients treated with platinum or whether the nephrotoxicity is exacerbated in older platinum-treated TC patients. Another important issue to clarify is the influence of a decline in GFR on the development of cardiovascular disease and death from all causes.

The high survival rate and young age of patients with TC entails that the treatment effect on reproductive function, fertility and offspring health is a very significant factor. Affected Sertoli-cell function and impaired Leydig-cell function in a subset of TC patients result from testicular dysgenesis syndrome [13] which may explain the increased incidence of oligo-and azospermi in TC patients both before and after orchiectomy, but before further treatment.

Most long-term survivors after treatment for TC can become biological fathers without medical assistance [14]. Yet

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the 10-year paternity rate is reduced by 30% compared with the normal population. All studies concerning gonadal function in TC patients is based on data from a single department, with a limited number of patients and few details about the treatment.

With the development of modern assisting reproductive techniques, even men with significant gonadal dysfunction will be able to have children. Cryopreservation of semen, optimally performed before orchiectomy, is offered in most places in order to increase the likelihood of subsequent fatherhood. In view of the increased opportunity and use of frozen semen for later artificial insemination, it is important to clarify whether pregnancies obtained with frozen semen of low quality are subject to more abortions, stillbirths or deformed children. These data will be essential in order to advise the TC patients. Larger-scale data concerning fertility in patients with TC treated with either surveillance or chemotherapy (three or four cycles of BEP) are needed.

Data regarding the factors leading to long-term side effects of treatment remain scarce. Molecular testing methods might help in identifying patients at high risk for therapy-related complications and guide risk-adapted screening and intervention strategies. In recent years, screening for variations in polymorphisms has proved to be a valuable tool to investigate the genetic predisposition for late effects. There is a relatively high incidence of single-nucleotide polymorphisms (SNPs) in genes which affect the cellular response in relation to the cytotoxic treatment for TC [15].

In order to gain further knowledge on the development of late effects in TC patients we need to have detailed information about treatment, to include genetic research methods, and to study side effects over time. The hope is that increased knowledge can lead to interventional studies with reduction or prevention of late effects.

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