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Anticancer treatment and fertility: Effect of therapeutic modalities on reproductive system and functions

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ABSTRACT

The significant improvement of cancer treatments entailed a longer life in cancer survivors and raised expectations for higher quality of life with minimized long-term toxicity. Infertility and gonadal dysfunction are adverse effects of anticancer therapy or may be related to specific tumors. In female cancer survivors, premature ovarian failure is common after antineoplastic treatments resulting in infertility and other morbidities related to oestrogen deficiency such as osteoporosis. In male cancer survivors, infertility and persistent a zoospermia is a more common long-term adverse effect than hypogonadism because germ cells are more sensitive to chemotherapy and radiotherapy than leydig cells. Gonadal toxicity and compromise of reproductive functions will be more efficiently prevented and treated if addressed before treatment initiation.

This review focuses on these issues in young cancer survivors of childbearing age, where methods of protecting or restoring endocrine function and fertility need to be considered.

1. Introduction

Survival from cancer has markedly been improved over the past few decades following major advances in available diagnostic tools, treatments and therapeutic modalities. As a result of early detection and successful adjuvant treatments, the number of young long term survivors is increasing and subsequently the strategy of management has changed from cure with any cost to

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one in which quality of life has become increasingly important. Anti-cancer treatment necessitates a multi-disciplinary approach combining surgery, chemotherapy and radiotherapy with cytotoxic chemotherapy being the cornerstone in the adjuvant setting. In general, cytotoxic therapy targets rapidly dividing cells and is therefore not surprising that spermatogenesis and oogenesis can be damaged after anticancer treatment. The exact mechanism is uncertain but appears to involve depletion of the proliferating germ cell pool, by killing cells not only at the stage of differentiating spermatogonia (Meistrich et al., 1982) but also stem cells (Bucci et al., 1986) with additional failure of surviving cells to differentiate further (Kangasniemi et al., 1996). There is also a reduction in the number of ovarian follicles with possible amenorrhea. Depletion of non-dividing primordial germ cells additionally contributes to gonadotoxicity caused by radiotherapy and systemic antineoplastic therapy (Meirow and Nugent, 2001). Hormonal changes that are observed after anticancer treatment (e.g., cranial radiotherapy), as well as physical and emotional alterations caused by cancer and its treatment can frequently affect sexual function and secondarily the ability to bring a child into the world. Although data from large clinical trials are lacking, the American Society for Reproductive medicine (ASRM) (Ethics Comittee of American Society for Reproductive Medicine, 2013) and more recently the European Society of Medical Oncology (ESMO) reported guidelines for the management of cancer patients diagnosed during pregnancy as well as for fertility preservation in cancer survivors (Peccatori et al., 2013).

2. Toxicity in spermatogenesis and male infertility

Nitrogen mustard was the first anticancer drug linked to azoospermia (Spitz, 1948). Since then, a number of anticancer agents have been related to long-lasting or permanent gonadal dysfunction including alkylating agents such as cyclophosphamide, chlorambucil (Schrader et al., 2002), antimetabolites such as cytarabine, and others as procarbazine and cisplatin (Das et al., 2002). Most of these drugs are given as part of multi-agent regimens, and therefore it is difficult to evaluate the contribution of each one separately.

Gonadal dysfunction is due to direct toxic effects of chemotherapy and radiation therapy on spermatogonia (stem cells). Later stage germ cells are generally more resistant. Administration of alkylating agents as anticancer therapy in post-pubertal males can cause basal membrane thickening, interstitial fibrosis and germinal epithelium aplasia with reduction of the tubular fertility index. In the meantime, spermatogenesis is inhibited resulting in azoospermia and a feedback rise in FSH. Consequently, FSH levels appear to correlate with fertility status after treatment (Sieniawski et al., 2008). It has also been suggested that the germinal epithelium of the adult testis is more susceptible to anticancer treatment than that of the prepubertal testis (Rowley et al., 1974). Although the prepubertal testis does not complete spermatogenesis and does not produce mature spermatozoa, in fact the testis in this age group is sensitive to cytotoxic drugs and therefore chemotherapy given to prepubertal boys may impair their future fertility (Whitehead et al., 1982a; Relander et al., 2000; Chemes, 2001). Finally, spermatogenesis has been shown to be impaired in patients with a variety of malignant diseases before treatment (Hallak et al., 2000).

The germinal epithelium is more sensitive than the Leydig cells as a result of its high mitotic rate (Brydoy et al., 2007; Donohue et al., 1993; Peckham et al., 1982). Consequently, patients who have received chemotherapy, may be rendered oligospermic or azoospermic but still can have normally developed their secondary sexual characteristics as testosterone production by the Leydig cells is usually not affected (Thomson et al., 2002; Kreuser et al., 1987). However, it is possible that Leydig cell dysfunction becomes apparent, following higher, cumulative doses of gonadotoxic chemotherapy (Gerl et al., 2001).

Testicular impairment is drug specific and dose related (Pryzant et al., 1993; Meistrich et al., 1989; da Cunha et al., 1984; Watson et al., 1985). The impact of cytotoxic chemotherapy on testicular function has been extensively studied in patients treated for Hodgkin's lymphoma. According to an analysis conducted by the UK's population-based Haematological Malignancy Research Network within a population of nearly 4 million lymphoma data from an established patient cohort, Hodgkin and Burkitt lymphomas dominate at the paediatric population of patients less than 15 years old, the mean age of patients with Hodgkin lymphoma is 41.3 years (range 26.8–63.5) and the survival of patients with nodular lymphocyte predominant Hodgkin lymphoma approaches that of the general population (Smith et al., 2015). Since the prognosis of patients with Hodgkin's lymphoma has improved substantially over the last decades (Rosenberg, 1996; Diehl et al., 2003; Bonadonna et al., 2004) and most patients are young long-term side effects of treatment, especially infertility, are becoming increasingly important. Chemotherapy regiments, which include alkylating agents such as cyclophosphamide and procarbazine, were particularly associated with permanent azoospermia and infertility (Kreuser et al., 1987; Kulkarni et al., 1997; Behringer et al., 2005). Several studies considering children who received chemotherapy for Hodgkin's disease demonstrated a severe damage to the seminiferous epithelium up to ten years following therapy (Mackie et al., 1996; Whitehead et al., 1982b). In view of these studies, treatment for Hodgkin's disease has been modified in an attempt to reduce the gonadotoxicity, whilst maintaining long-term survival (Thomson et al., 2002). Gonadal damage may be lesser for both genders by removing alkylating agents and procarbazine altogether, such as with the 'ABVD' regimen (adriamycin, bleomycin, vinblastine, dacarbazine). This protocol is significantly less gonadotoxic than 'MOPP' (Viviani et al., 1985).

Radiotherapy also can cause gonadal toxicity leading to permanent azoospermia at the level of 20 Gy in fractionated doses for testicular cancer (Albers et al., 2005; Petersen et al., 2002). Although Leydig cells are relatively radioresistant, such radiotherapy might be followed by reduction in testosterone production (Hermann et al., 2005). When different types of abdomino-pelvic radiotherapy are compared, the highest scattered doses reaching the testis are seen in patients treated for rectal cancer. This exposure puts patients at a high risk of developing permanent infertility due to reduction of testosterone levels (Hermann et al., 2005). Spermatogenesis seems to be only minimally inhibited after brachytherapy of prostate cancer (Mydlo and Lebed, 2004).

High-dose radiotherapy of the pelvis can cause endothelial dysfunction and subendothelial thickening of the intima in the pelvic arteries (Basavaraju and Easterly, 2002) and microvessels responsible for penile blood flow. This might cause a luminal stenosis and hypovascularization of the corpora cavernosa, and result in a long term erectile dysfunction, such as in patients who underwent radiotherapy for prostate cancer (Potosky et al., 2004).

Hormone therapy used for advanced prostate cancer is another factor offending male fertility. Androgen ablation with gonadotrophin releasing hormone (GnRH) analogues can impair all phases of sexual function by reducing testosterone and can lead to sexual dysfunction, loss of libido, difficulty in erection and, gynecomastia (Thompson et al., 2003). Aditionally, androgen deprivation therapy and subsequent hypogonadism reduce intavesicular testosterone production which leads to infertility by impairing spermatogenesis and reducing sperm count. Therefore, androgen ablation-induced hypogonadism and low serum testosterone, can be associated with oligospermia and azoospermia leading to infertility (Mulhall and Hsiao, 2014).