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Gonadal function recovery in very long-term male survivors of childhood cancer ☆

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Abstract ***Background:*** Although gonadal toxicity has been reported, no data are available on recovery of gonadal function in very long-term survivors of childhood cancer. Inhibin B is a *novel* reliable serum marker which has been shown to be of value in childhood cancer survivor studies to identify risk groups for impaired gonadal function, but consecutive long-term follow-up studies using serum inhibin B as a marker are not available.
Objective: To evaluate possible recovery of gonadal dysfunction over time in adult male survivors of childhood cancer.
Methods: In this retrospective study, adult male long-term childhood cancer survivors ($n = 201$) who visited our outpatient late effects clinic were included and we used inhibin B as a surrogate marker for gonadal function.
Results: Median age at diagnosis was 5.9 years (range 0.0–17.5) and discontinuation of treatment was reached at a median age of 8.2 years (range 0.0–20.8). Inhibin B levels were first

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measured after a median follow-up time of 15.7 years (range 3.0–37.0). Median interval between the first (T1) and second measurement (T2) was 3.3 years (range 0.7–11.3). Median inhibin B level was 127 ng/L (range 5–366) at T1 and 155 ng/L (range 10–507) at T2. The prediction model suggests that inhibin B levels do not normalise in survivors with a very low Inhibin B level at T1.

Conclusions: Our results suggest that recovery of gonadal function is possible even long after discontinuation of treatment. However, this recovery does not seem to occur in survivors who already reached critically low inhibin B levels after discontinuation of treatment.

1. Introduction

Due to improved survival rates,[1] long-term side-effects of cancer treatment, such as gonadal dysfunction, became increasingly important. Gonadal dysfunction can be caused by chemotherapy and radiotherapy.[2–6] Specific chemotherapeutics such as alkylating agents and cytosine arabinoside,[7,8] total body irradiation (TBI) and local irradiation including the testis[9–11] were found to be highly gonadotoxic.

To assess gonadal function, performing semen analysis is the most direct way to establish a men's fertility potential. However, in adolescents as well as in young adults providing a semen sample for analysis might be difficult. Hence, the use of an alternative first screening method would be of value. Serum inhibin B levels are currently used to assess gonadal function as a first screening.[12–16] Inhibin B is directly produced by Sertoli cells in the seminiferous tubules.[17] Inhibin B levels are strongly associated with sperm quantity and thereby constituting a marker which might identify childhood cancer survivors (CCS) at risk of infertility.[18–20]

In survivors of adult Hodgkin lymphoma, interestingly, after well-documented damage of spermatogenesis in some CCS, sperm quality can improve over time after long-term follow-up. Recovery of spermatogenesis has even been described at more than 10 years after treatment.[2] Even after high doses of cyclophosphamide, a slow recovery of spermatogenesis was described.[3] Recovery after low doses of alkylating agents in adulthood has been reported as well.[4,5,21] In survivors of childhood cancer however, only two small studies evaluated the follow-up of gonadal function. In 2 out of 12 survivors of Hodgkin lymphoma, recovery has been observed at 12–15 years following treatment, whereas a second study could not confirm this recovery in 19 survivors at 10 years after treatment.[22,23] To our knowledge, follow-up studies in other subsets of adult and childhood cancer have not been performed.

We performed this study to evaluate recovery of spermatogenesis over time in a large single centre cohort of male long-term CCS using inhibin B as a surrogate marker and using paired analyses.

2. Materials and methods

2.1. Subjects

A cross-sectional retrospective single-centre study was performed in our adult late-effects outpatient clinic for long-term CCS. Survivors were in continuous complete remission and older than 18 years. Male survivors, diagnosed between 1964 and 2005, who visited our late-effects outpatient clinic twice or more were included between 2004 and 2010. Written informed consent was obtained from all participants.

Information on the type of disease, patient characteristics, treatment regimes and follow-up data were retrieved from the medical records. Recently, the alkylating agent dose (AAD) score was introduced to determine the effect of high-risk chemotherapy. We calculated this score by determining the drug dose tertile distribution in our entire cohort of survivors and adding the tertile scores (1–2–3) for each of the alkylating agents given to a particular patient as previously used in childhood cancer survivors by Green et al.[8,24] An AAD score of zero was assigned to patients not exposed to alkylating agents. Radiotherapy at high risk for gonadal dysfunction was defined by TBI and testis irradiation.

2.2. Hormones

We obtained peripheral blood samples, which were stored at –20 °C until analysis. Inhibin B levels were measured using kits purchased from Serotec Ltd (Oxford, United Kingdom [UK]). Within-assay and between-assay coefficients of variation (CV) were <9%, and <15%, respectively. Serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH) were determined with the Immulite assay (Diagnostic Products Corporation (DPC), Los Angeles, CA, United States of America [USA]). Within-assay and between-assay CV were <6% and <9%, and <5% and 11% for FSH and LH, respectively. Serum testosterone levels were determined using coated tube radioimmunoassays (DPD). Intra-assay and inter-assay variation coefficients were 3% and 4.5%. The reference values of LH, FSH and testosterone for male adults in our institute are