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Testis Cancer

Paternity and Testicular Function Among Testicular Cancer Survivors Treated With Two to Four Cycles of Cisplatin-Based Chemotherapy

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Abstract

Background: Preserved fertility is an important issue for testicular cancer (TC) survivors.
Objective: Our aim was to examine any difference regarding paternity and testicular function following two, three, or four cycles of cisplatin-based chemotherapy for TC.
Design, setting, and participants: A national multicentre follow-up survey assessing morbidity among survivors of unilateral TC diagnosed from 1980 to 1994 was conducted during the period 1998 to 2002. Of the 1814 men invited, 1462 (80.6%) participated by responding to a mailed questionnaire and/or undergoing a clinical examination including laboratory assessments. The present study includes the 316 participants up to 65 yr of age treated with two to four cycles of standard cisplatin-based chemotherapy without additional treatment beyond surgery.
Measurements: Self-reported paternity following treatment for TC according to number of cycles was assessed among men who reported antegrade ejaculation and attempts at posttreatment conception ($n = 106$). Kaplan-Meier analysis, log-rank test, and Cox regression were applied. Gonadal hormones ($n = 305–314$) and sperm counts ($n = 71$) by number of cycles were assessed by linear by linear association or Mann-Whitney tests.
Results and limitations: At median 12-yr follow-up, 80% (85 of 106) had succeeded in their attempts of achieving posttreatment paternity (two cycles: 100%; three: 83%; four: 76%; $p = 0.022$). For all patients the 15-yr actuarial paternity rate was 85%. The association between posttreatment paternity and number of cycles remained significant in the multivariate analysis ($p = 0.032$). High serum follicle-stimulating hormone values were more common with increasing number of cycles ($p = 0.037$), but there were no differences in serum luteinising hormone, serum testosterone, or sperm counts. Few men treated with two cycles and a limited number of sperm samples are the main limitations of this study.
Conclusions: The prospects of future paternity after two to four cycles of cisplatin-based chemotherapy are good, and our data suggest that the prospects improve with decreasing number of cycles.

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1. Introduction

Testicular cancer (TC) typically occurs at the peak of reproductive age, and the ability to father children in the future is an important issue. However, impaired fertility and TC may share aetiological factors, and reduced spermatogenesis is often evident when TC is diagnosed [1]. Although cancer treatment commonly further impairs fertility, spermatogenesis often improves with time, depending on the extent of treatment [2–4].

Conception rates of about 71–85% (actual and cumulative, respectively) have been reported in two large studies among TC survivors who had attempted conception following chemotherapy [5,6]. We have previously reported 15-yr actuarial posttreatment paternity rates of 92% following orchiectomy only, compared with 63% and 48% following chemotherapy with cumulative cisplatin doses ≤850 mg and >850 mg, respectively (including combinations with retroperitoneal lymph node dissection [RPLND] and/or radiotherapy) [7].

During the last two decades, risk-adapted toxicity-sparing treatment strategies have increasingly been followed [8,9], and paternity rates were improved following fertility-sparing treatment modifications in the late 1980 s [7]. Whether the paternity chances are different following two, three, or four cycles of cisplatin-based combination chemotherapy remains an open question [10]. The aim of this study was to address this issue. We also report on gonadal hormones and sperm counts.

2. Materials and methods

2.1. Population and study design

From 1998 to 2002, a Norwegian national multicentre follow-up survey was conducted to assess long-term morbidity in TC survivors who were diagnosed with unilateral germ cell TC in 1980–1994 (the Norwegian Urologic Cancer Group [NUCG] III study). Exclusion criteria were bilateral orchiectomy for any reason, extragonadal germ cell cancer, other malignancies except skin cancer, and mental retardation. The Committee for Medical Research Ethics of the Southern Health Region of Norway approved the study. A total of 1814 men were invited, and after giving their written consent, 1462 (80.6%) participated by answering a 219-item questionnaire and/or undergoing an outpatient examination including laboratory assessments (Fig. 1) [7]. The questionnaire included 14 items assessing pre- and posttreatment fertility. Data including primary and relapse treatment were retrieved from the medical records. Initially, total cumulative cisplatin doses were collected [7]; details regarding type of combination regimen and number of cycles subsequently were retrieved for the present study.

The current report includes the 316 of the 1462 participants who fulfilled the following selection criteria (Fig. 1): Men up to 65 yr of age at the time of the survey who had been treated with two to four cycles of standard cisplatin-based chemotherapy, with cisplatin administered at 20 mg/m^2 per day for 5 consecutive days (BEP [cisplatin, etoposide, and bleomycin], n = 183; EP [cisplatin and etoposide], n = 4; or CVB [cisplatin, vinblastine, and bleomycin], n = 116), without additional treatment beyond surgery (orchiectomy with or without RPLND). Thirteen men received both CVB and BEP/EP. The total number of cycles were two (n = 20), three (n = 79), and four (n = 217) (Table 1). Men receiving androgen substitution therapy (n = 11) were categorised as having low

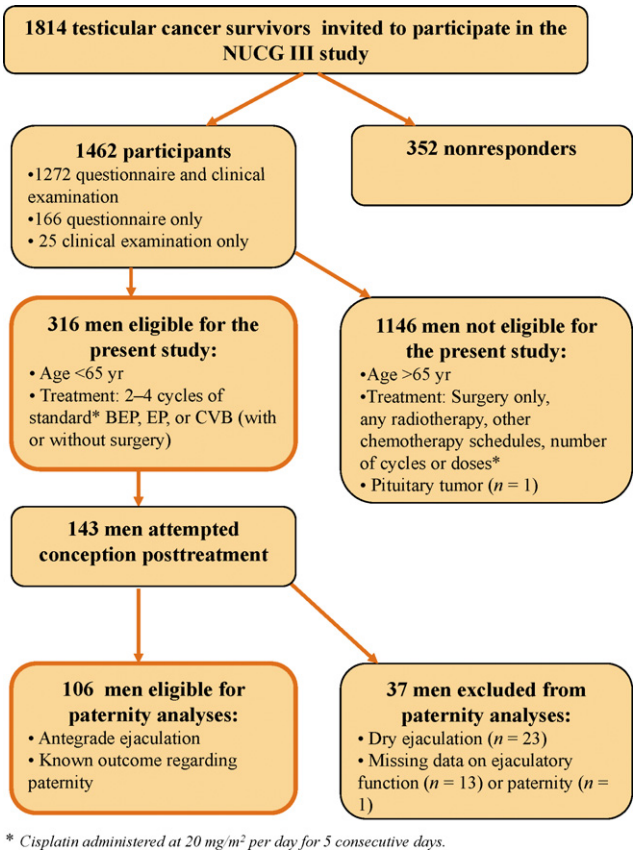

Fig. 1 – An overview of the selection criteria and number of men in the study samples presented (outline in orange), in relation to the whole Norwegian Urology Cancer Group (NUCG) III cohort.

testosterone, and they were excluded from the analyses of sperm counts, serum follicle-stimulating hormone (s-FSH), and serum luteinising hormone (s-LH).

The paternity analyses were confined to men who reported antegrade ejaculation, attempts at posttreatment conception, and whether or not they had fathered a child. Of 143 men reporting attempts at posttreatment conception, 106 were eligible for the paternity analyses (Fig. 1). For comparison, the actuarial paternity rate of 46 men with orchiectomy only who otherwise fulfilled the same selection criteria were included in Fig. 2 only.

2.2. Laboratory assessments

All 316 participants were eligible for hormone analyses. The blood samples were drawn by venipuncture, usually between 8 AM and 12 AM. Hormone assessments were based on commercial immunoassay technology at each of the five collaborating laboratories, with similar methods and reference ranges. The cut-off limits considered normal in this study were s-LH < 12 IU/l, s-FSH < 12 IU/l, and serum total testosterone (s-testosterone) ≥10 nmol/l. Optional semen specimens were collected from those participating at two of the collaborating hospitals, and sperm counts (million per millilitre) were assessed in accordance with the World Health Organisation guidelines [11].

2.3. Statistical analysis

The Kruskal-Wallis test (exact using Monte Carlo method) was used for group comparisons of continuous data, and the exact chi-square, linear