Effects of taxane-based chemotherapy on inhibin B and gonadotropins as biomarkers of spermatogenesis

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Objective: To assess the effects of taxane-based chemotherapy on the male reproductive axis, and, therefore, its impact on spermatogenesis and fertility.
Design: Controlled clinical study.
Setting: Patients with cancer in an academic research environment.
Patient(s): Forty male patients of reproductive age with cancer with solid tumor at diagnosis, who had been scheduled to receive taxane-based chemotherapy.
Intervention(s): The patients were given treatment with docetaxel or paclitaxel combined with gemcitabine or carboplatin. Blood sampling and testicular ultrasonography were performed before and after completion of chemotherapy.
Main Outcome Measure(s): In all patients, serum levels of inhibin B, FSH, and LH were measured, and, in half of the patients, bilateral testicular volume was also measured.
Result(s): There was a statistically significant decrease in serum inhibin B and increase in serum FSH in all patients after the completion of the taxane-based chemotherapy. The median LH levels did not exhibit a statistically significant increase after the last cycle. Bilateral testicular volume exhibited a statistically significant decrease in 19 out of 20 patients (95%) after completion of chemotherapy.
Conclusion(s): Taxane-based chemotherapy induces the reduction of inhibin B and the reciprocal elevation of FSH, which are associated with significant gonadal damage in the early stages after completion of chemotherapy. (Fertil Steril® 2010;94:558–63. ©2010 by American Society for Reproductive Medicine.)

Key Words: Chemotherapy, docetaxel, gonadotoxicity, infertility, paclitaxel, taxanes

During the last two decades, new cytostatic drugs with significant effectiveness against cancer have become available to oncologists. Among the new cytostatic drugs, the taxanes, paclitaxel and docetaxel, are effective agents against several malignancies, and their application in oncology had a favorable influence on tumor response and patients' survival. The unique chemical structure and mechanism of action of the taxanes, combined with their broad antitumor activities, has rendered them one of the most important categories of anticancer agents (1).

The most important clinical outcomes in the care of the patient with cancer are overall and disease-free survival, as well as quality of life and toxicity (2). Chemotherapy toxicity is an important end point in clinical trials, and major effort is made toward achieving the best efficacy and minimal toxicity of each regimen. There are several toxicity grading scales to assess treatment-related toxicities. The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0 is a descriptive terminology that can be used for adverse event reporting. A grading (severity) scale is provided for each adverse event. According to the NCI-CTCAE the reproductive function and the endocrine system are separate categories associated with fertility and infertility (3).

Fertility is of principal concern in patients of reproductive age who have cancer and a major aspect of their quality of life. Oncologists should be aware of the potential gonadotoxic effects of the regimens they use for the treatment of reproductive-aged patients. They are also responsible to inform the patient about the risk of treatment-induced infertility. Recent surveys of male and female cancer survivors of reproductive age show that at least half of the patients have no recollection of a discussion concerning fertility before starting chemotherapy (4–8). Patients should be aware of the possibility of sperm banking before the initiation of chemotherapy. It seems that cryopreservation is the only preemptive measure available to preserve fertility in young patients with cancer. There are, however, a number of drawbacks concerning this method. Serious concerns have been raised regarding possible negative effect of cryopreservation on a variety of sperm functions, as well as on overall sperm quality. Decrease in sperm concentration and motility owing to the freezing process is considered the main cause. Furthermore, ethical and cultural considerations may be

Received February 21, 2009; revised March 14, 2009; accepted March 16, 2009; published online September 17, 2009.
E.C. has nothing to disclose. N.M. has nothing to disclose. L.G. has nothing to disclose. E.G. has nothing to disclose. C.A. has nothing to disclose. K.S. has nothing to disclose.
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0015-0282/$36.00
doi:10.1016/j.fertnstert.2009.03.068

involved in a patient's final decision regarding sperm banking (9, 10).

The risk of infertility and the impact of cancer treatment on spermatogenesis are described in literature. The chemosensitivity variables that correlate with the spermatoxicity of chemotherapy are the category and number of antineoplastic agents used, the total dose, the duration of treatment, and the age and the individual sensitivity of each patient. Nevertheless, the gonadotoxic effects of newer chemotherapeutic agents, such as taxanes, remain unknown in human beings (4, 9, 11, 12). The only reproductive and developmental studies concerning taxanes have been performed on experimental animals (13). As far as other chemotherapeutic drugs are concerned, platinum compounds are likely to induce azoospermia, but this has been observed when they are coadministered with other high-sterilizing agents (9). Carboplatin seems to cause less sterility than cisplatin (14). The potential gonadotoxic effect of the antimetabolite gemcitabine has been observed only in experimental studies in male mice and ranges from moderate to severe (15).

The testis consists of the germinal epithelium arranged in tubules and of the endocrine components (Leydig cells). The seminiferous tubules contain the germ cells and the Sertoli cells, which support and regulate germ cell differentiation. Drugs enter the testis by the vasculature in the interstitial region and then can reach the Leydig and Sertoli cells, as well as the spermatogonia, which are at the outer rim of the tubules. Many chemotherapeutic agents can even penetrate the Sertoli cell barrier and damage late-stage germ cells. The final recovery of sperm production depends on the survival of the spermatogonial stem cells and their ability to differentiate (16). Sertoli cells primarily secrete a 32-kDa glycoprotein hormone, the inhibin, which suppresses FSH secretion by gonadotropes. The form of inhibin that is secreted by human Sertoli cells, inhibin B, selectively suppresses FSH secretion in gonadotropes by inhibiting transcription of the gene encoding the β subunit of FSH (17).

The loss of germ cells has secondary effects on the hypothalamic-pituitary-gonadal axis. Inhibin B secretion by the Sertoli cells decreases, and as inhibin B limits FSH secretion by the pituitary, serum FSH rises. Germinal aplasia results in decreased levels of inhibin B and increased levels of FSH. Although FSH measurements have been used as a surrogate for sperm count, they only show an imperfect correlation, partly because of interpatient variability in baseline levels; inhibin B would be more reliable but is not routinely measured. Germinal aplasia also reduces testis size (16). This study was conducted to assess the effects of taxane-based chemotherapy on the male reproductive axis and, therefore, its impact on fertility.

MATERIALS AND METHODS

Patients

From January 2005 to March 2007, 40 patients of reproductive age with cancer with solid tumor at diagnosis who had been scheduled to receive taxane-based chemotherapy were recruited to the study. Exclusion criteria were prior cancer treatment (either radiotherapy or chemotherapy), testicular cancer, medical history of infertility, genital abnormality or infection, and finally age younger than 20 years or older than 60 years. The patients were given docetaxel (70–80 mg/m^2) or paclitaxel (130–200 mg/m^2) combined with gemcitabine (1,000 mg/m^2) or carboplatin (400 mg/m^2). Treatment was repeated every 3 or 4 weeks, according to the chemotherapeutic protocol. In all patients, serum levels of inhibin B, FSH, and LH were measured before and after the completion of chemotherapy, and in half of the patients bilateral testicular volume also was measured at these stages. Bilateral testicular volume was determined as the sum of the right and left testicle volume.

All patients gave written informed consent before enrollment in the study. The study was approved by the University of Athens Ethics Committee.

Hormone Analysis

Blood samples were obtained between 7 and 9 AM, before the infusion of the chemotherapy, and were centrifuged after clotting. Single serum samples were stored at −80°C until analysis. Inhibin B concentrations were measured with use of a specific enzyme-linked immunosorbent assay (DSL-10-84100 active inhibin B ELISA; Diagnostic Systems Laboratories, Webster, TX) with an intra-assay variation of 4.1% and an interassay variation of 6.4%. The detection and captured antibodies used (two-site "sandwich" ELISA) are highly specific for the dimeric inhibin B molecule, with negligible cross-reactivity to the pro-alpha subunit, inhibin A, or activins. The detection limit was 7 pg/mL. Radioimmunoassays were used to measure serum FSH (intra-assay variation of 5.3%, interassay variation of 7.1%) and LH levels (intra-assay variation of 3.9%, interassay variation of 4.6%). The reference values of our laboratory were FSH 1.5 to 13 IU/L and LH 1.4 to 9 IU/L.

Testicular Volume

Testicular dimensions were measured with use of ultrasonography with a 7.5-MHz probe (Acuson Sequoia 512–Linear 8L5; Siemens Medical Solutions, Malvern, PA). This method is considered objective, accurate, and reproducible. The testicular volume was calculated with use of the formula: $V = (\pi/6) \times$ (Longitudinal axis) $\times$ (Transverse axis) $\times$ (Depth axis), where V = testis volume and $\pi/6 = 0.52$, which is the constant generally used in the assumption that the testicle resembles an ellipsoid in shape (18–20). The measurement was performed before and after the treatment by a single experienced radiologist who had no knowledge of the patient's hormone levels and cumulative dose of taxanes.

Statistical Analysis

All results are expressed as mean ± SEM or as median values. Data were computed by the SPSS statistical software package (version 15.0; SPSS, Inc., Chicago, IL). More specifically, statistical analysis of the values before and after chemotherapy