Impact of therapy and androgen receptor polymorphism on sperm concentration in men treated for testicular germ cell cancer: a longitudinal study

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BACKGROUND: Testicular cancer (TC) patients have a high survival rate, and the question of post-therapy recovery of sperm production and its dependence on genetic predisposition is of major interest. METHODS: Ejaculates were obtained from 112 TC patients at one or more of the following time points: post-orchidectomy, or 6, 12, 24, 36 and 60 months post-therapy. The lengths of the androgen receptor (AR) function modulating CAG and GGN repeats in leukocyte DNA were also analysed. RESULTS: No significant decrease in sperm concentration was seen in men who received 1±2 cycles of adjuvant chemotherapy (ACT). Radiotherapy (RT) or more than two cycles of chemotherapy (HCT) caused an initial decline in sperm concentration, which returned to pre-treatment levels 2±5 years after therapy. In the HCT group, sperm concentration 12±24 months post-treatment (T12±24) was inversely correlated with CAG length (r = ±0.72, P = 0.03). The type of treatment, but not the concentration at T0, was an independent predictor of sperm concentration at T6 (P < 0.0005) and T12±24 (P = 0.004). CONCLUSION: ACT did not induce a significant decline in sperm concentration. After HCT and RT, a significant reduction of sperm concentration was observed, recovering to pre-treatment levels 2±5 years post-treatment. In HCT-treated patients, the AR CAG length influenced the recovery of spermatogenesis.

Key words: androgen receptor/chemotherapy/radiotherapy/semen quality/testicular cancer

Introduction

Testicular germ cell cancer (TGCC) is the most common cancer disease in males aged 20–40 years. Since the introduction of cisplatinum-based chemotherapy (CT), the survival rate has approached 95% (Dearnaley et al., 2001). The question of long-term toxicity of the treatment and quality of life, including reproductive function, has therefore become increasingly important (Arai et al., 1997; Hartmann et al., 1999). However, the consequences of TGCC treatment for reproductive function are not fully understood. Longitudinal data are still scarce, the majority of studies being cross-sectional (Kuczyk et al., 2000) generally lacking properly matched control groups (Kuczyk et al., 2000).

Although available data show that testicular cancer is associated with impaired sperm production as well as decreased fertility potential (Møller and Skakkebæk, 1999; Petersen et al., 1999), many studies do not discriminate between the effects of different treatment modes including orchidectomy, radiotherapy (RT), CT or retroperitoneal lymph node dissection (RPLND) (Hendry et al., 1983; Fossà et al., 1985; Hansen et al., 1990; Stephenson et al., 1995; Joos et al., 1997; Lampe et al., 1997; Pont and Albrecht, 1997) and do not take the intensity of the treatment into account (Hansen et al., 1990; Stephenson et al., 1995; Bokemeyer et al., 1996). Information regarding the time course and the degree of the recovery of sperm production as well as the proportion of males becoming permanently azoospermic is also limited.

Some studies have indicated that pre-treatment FSH levels, sperm concentration and the sperm chromatin structure predict post-treatment recovery of spermatogenesis (Fossà et al., 1985, 1990, 1997; Aass et al., 1991; Lampe et al., 1997). However, no attention has yet been paid to the impact of genetic factors. Androgens are crucial for spermatogenesis, the concentration of testosterone being 100 times higher in the testis than in serum (Maddocks et al., 1993). Recent animal studies (Meistrich, 1999; Shetty et al., 2001) have shown that the intra-testicular steroid balance probably plays a crucial role for post-treatment recovery of spermatogenesis. Androgen action is the sum effect of available testosterone and 5α-dihydrotestosterone, and the responsiveness of the androgen receptor
(AR) in target cells. One critical function of the AR gene product is to activate the expression of other genes. Two polymorphic sequences of CAG and GGN repeats have been shown to be important for the transactivation of other genes and thus play an important role for the fine-tuning of AR function (Tut et al., 1997; Hsing et al., 2000; von Eckardstein et al., 2001).

The aim of this prospective, longitudinal study was to provide data on the effect of CT and RT on semen quality of TGCC patients, with special focus on the dose–response effect and the time course of recovery. Furthermore, we have investigated the impact of the variation in the lengths of the CAG and GGN repeats of the AR gene on pre-treatment sperm characteristics and as a predictor of sperm regeneration post-treatment.

Materials and methods

Patients

The study was initiated on March 1, 2001, and all men below the age of 50 with TGCC diagnosed ≤5 years prior to inclusion were eligible for the study. Six time points for delivery of ejaculates were defined: after orchidectomy but prior to further measures (T₀), and 6 (T₆), 12 (T₁₂), 24 (T₂₄), 36 (T₃₆) and 60 (T₆₀) months after completion of RT or CT. The patients could enter the study at any time between T₀ and T₆₀ and were asked to deliver samples at the remaining time points.

Up to April 1, 2003, 112 of 144 eligible patients were included in the study. Nineteen men declined to participate and 13 were excluded for the following reasons: five due to bilateral TGCC; three for psychiatric/psychological reasons; two due to linguistic difficulties; two because of hepatitis C; and one because of physical handicap. Eleven patients developed retrograde ejaculation due to retroperitoneal lymph node dissection. One died in progressive disease and one developed bilateral disease after inclusion (Figure 1). After primary inclusion, none of the men has left the study due to unwillingness to deliver a semen sample.

All men gave written informed consent to participate. The protocol was approved by the ethical review board of Lund University.

The characteristics of the study population are given in Table I.

Cancer treatment

All patients were managed according to the Swedish/Norwegian Testicular Cancer Group (SWENOTECa) protocols (Klep et al., 1997; Laguna et al., 2001). Patients with clinical stage I (CSI) non-seminoma (NSGCT) were offered either adjuvant chemotherapy (ACT) or surveillance. Patients with CSI seminoma (SGCT) could choose between RT and surveillance. Seven patients were in the surveillance group. Patients with metastases or elevated tumour markers (Mk+) only were treated with CT.

Standard chemotherapy of NSGCT was the BEP regimen (bleomycin 30 000 IU days 1, 5 and 15; etoposide 100 mg/m² days 1–5; cisplatinum 20 mg/m² days 1–5, given every third week). In six patients given ACT diagnosed before 1998, the etoposide was replaced with vinblastine 0.15 mg/kg, maximum 11 mg/day, days 1 and 2 (CVB regimen).

ACT (BEP/CVB) was given to 32 patients. Among these, 27 patients had one and five had two CT cycles.

Forty-two patients with metastatic disease received three or more CT cycles (HCT). Among patients with NSGCT, 14 received three cycles of BEP, 15 four cycles of BEP and one died in progressive disease during treatment. Four cycles of EP (BEP minus bleomycin) were given to seven patients with advanced SGCT. Five patients (three NSGCT and two SGCT) received more intensive CT.

RT was administered to para-aortic and ipsilateral iliacal lymph nodes. A target dose of 25.2 Gy was given in 14 fractions. In order to obtain an estimate of the magnitude of the scattered irradiation of the gonad, the total dose to the remaining testicle was estimated retrospectively in seven randomly selected men to be 0.04–0.43 Gy.

Biological samples

The patients delivered a blood sample for DNA analysis at the first control after inclusion in the study and semen samples at the fixed time points between T₀ and T₆₀. An overview of sample delivery in relation to treatment and follow-up time is given in Figure 2.

The assessments of ejaculate volume, sperm concentration and motility were performed according to the 1999 recommendations of the World Health Organization (WHO) (World Health Organization, 1999) with use of positive displacement pipettes for diluting the samples and with an improved Neubauer chamber for counting. For motility assessment, the sperm were divided into four categories, A–D, ranging from rapidly, progressive motile to immotile spermatozoa. In our analysis, sperm motility was assessed as the total proportion of sperm in categories A, B and C.

The laboratory participates in the external quality control programme of the Nordic Association for Andrology and the European Society of Human Reproduction and Embryology (Cooper et al., 2002). The data have been expanded with results of analysis of samples delivered for cryopreservation, after orchidectomy but prior to inclusion in this study.

All samples collected after inclusion were analysed in one laboratory (Fertility Centre, Malmö University Hospital). However, the cryopreservation samples were analysed by two different laboratories (Fertility Centre, Malmö University Hospital and Fertility Laboratory, Lund University Hospital). Both laboratories
were performing semen analysis according to the most recent WHO recommendations (World Health Organization, 1992, 1999).

**DNA analysis**

Blood samples for DNA analysis were available from the first 83 men included in the study. These subjects did not differ from the remaining 29 with regard to age, sperm concentration at T0, disease, stage, histological type or treatment given (data not shown). Genomic DNA was prepared from peripheral leukocytes, and the CAG and GGN repeats (in 81 subjects) were amplified by PCR and subsequently analysed externally on a Beckman Coulter CEQ 2000XL (Beckman Coulter, Bromma, Sweden) sequencing gear as previously described (Lundin et al., 2003).

**Statistical analysis**

Statistical analysis was performed using the SPSS 11.0 software (SPSS Inc., Chicago, IL). Longitudinal analysis of data was performed (Figure 2). Additionally, comparison of semen parameters between groups defined according to the treatment and follow-up time (cross-sectional analysis) was done. In order to obtain sufficient numbers of individuals, the results of samples collected at T24, T36 and T60 were combined into one category (T24±60). If a patient delivered more than...
one sample during this time interval, the one with the highest sperm concentration was included in the analysis. For longitudinal comparisons of more than two samples, Friedman’s test was used. For intra-individual comparison of values at two time points only, the Wilcoxon test for paired data was applied. In the cross-sectional analyses, Kruskal-Wallis test and Mann-Whitney test for unpaired data were used.

Spearman’s rho was calculated in order to find the correlation between the CAG or GGN repeat length and the sperm concentration at any of the following time points: T0, T6, T12–24 and T36–60. These calculations were performed for the randomly selected group of 83 TGCC patients from whom the DNA data were available and separately for the therapy groups ACT, HCT and RT.

Subsequently, in these 83 men, in order to calculate the predictive value on the sperm concentration at T0, multivariate linear regression analysis was used with the type of tumour as the discrete variable, and age and CAG repeat length as continuous variables. A similar type of analysis was done for sperm concentration at T6, T12–24 and T36–60, with type of therapy as the discrete variable, and CAG repeat lengths and age as well as sperm concentration at T0 as continuous independent variables. Sperm concentrations were log transformed (after adding 0.1 to all sperm concentrations in order to be able to transform 0 values) prior to the analysis. The numbers of patients providing semen analysis data were 56, 23, 42 and 31 for T0, T6, T12–24 and T36–60, respectively. All statistical tests were two-sided, and P < 0.05 was considered statistically significant.

Results

Azoospermia

In total, 73 men delivered samples at T0. Among those, four [5.5%, 95% confidence interval (CI) 1.5–13%] were azoospermic. Two of them had no further follow-up, one continued to be azoospermic at T6 and one had a few sperm in the ejaculate at T12. Of the 69 men having spermatozoa in the ejaculate after orchidectomy, 16 have not yet delivered any post-treatment samples. Among the remaining 53, five became azoospermic after CT or RT treatment (9.4%, 95% CI 3.1–21%). None of the 26 men in the ACT group became azoospermic (0%, 95% CI 0–13%). Of 17 patients in the HCT group from whom post-treatment samples were available, two were azoospermic at T0 and one at T60 (18%, 95% CI 3.8–43%). From these three patients, only one post-treatment sample was available. Two of 10 men in the RT group (20%, 95% CI 2.5–56%) were azoospermic at T6 after treatment, one regaining sperm secretion at T12, whereas the other did not have further follow-up.

Sperm concentration

The data are summarized in Table II and Figure 3.

In eight patients in the ACT group investigated at T0, T6 and T12, the longitudinal changes in sperm concentration were not statistically significant (P = 0.20). However, there was a decrease from median 29 × 10⁶/ml at T0 to 14 × 10⁶/ml at T6 (P = 0.09) and a recovery to 29 × 10⁶/ml at T12 (P = 0.02) for comparison between T6 and T12 (Table II). In 14 patients, investigated at baseline, T0, sperm concentration was also analysed after 2–5 years (T24–60) and no difference compared with baseline was found, 22 versus 26 × 10⁶/ml (P = 0.42). No difference in the pattern of sperm concentration was found when the five men in the ACT group who received two cycles of CT were excluded leaving only those treated with one cycle of CT.

In the HCT group, the longitudinal comparison showed that the median sperm concentrations at T6 and T12 were significantly lower than at T0, 0.05 × 10⁶/ml at T6 compared with the baseline value of 3.4 × 10⁶/ml (P = 0.043), and 2.4 × 10⁶/ml at T12 compared with 18 × 10⁶/ml at T0 (P = 0.046) (Table II). At T24–60, the sperm concentration had recovered to 19 × 10⁶/ml, not different from the T0 value of 12 × 10⁶/ml (P = 0.8).

In the SGCT group treated with RT, the sperm concentration was lower at T6 compared with T0, 0.1 versus 48 × 10⁶/ml (P = 0.04), while the T12 value was significantly higher compared with T6 (6.8 versus 0.9 × 10⁶/ml, P = 0.03). The difference between T12 and T0 levels (median: 6.3 versus 36 × 10⁶/ml, respectively) was close to the level of statistical significance (P = 0.08). Sperm concentration at T24–60 in four

<table>
<thead>
<tr>
<th>Table II. Changes in sperm concentration in relation to time after treatment and type of therapy in testicular cancer patients with longitudinal data</th>
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<tbody>
<tr>
<td>Median (range) sperm concentration in 10⁶/ml P for difference between the groupsb</td>
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<tr>
<td>ACT</td>
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<tr>
<td>T0 versus T6</td>
</tr>
<tr>
<td>n = 11</td>
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<tr>
<td>T0 versus T12</td>
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<tr>
<td>n = 12</td>
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<tr>
<td>T0 versus T24–60</td>
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<tr>
<td>n = 14</td>
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<tr>
<td>T6 versus T12</td>
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<tr>
<td>P = 0.021</td>
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<td>n = 9</td>
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</tbody>
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ACT = 1–2 cycles of chemotherapy; HCT = >2 cycles of chemotherapy; RT = radiotherapy; ND = statistical analysis not done because of insufficient number of subjects included.

*The earliest period mentioned first.

aWilcoxon test for paired data.
males, also investigated at baseline, was not different from the T₀ value, 47 versus 32 ± 10⁶/ml (P = 0.27) (Table II).

There was no significant difference in median sperm concentration at T₀ between the NSGCT and SGCT patients (median: 19.6 versus 10.0 ± 10⁶/ml, respectively) (P = 0.24). Comparing the different treatment groups at T₀, no statistical difference was seen. At T₆ and T₁₂, there was a significant difference between the groups (P = 0.0001), the ACT group having significantly higher sperm concentration than both the HCT (P = 0.0001) and the RT group (P = 0.001). T₂₄±₆₀ concentrations did not differ between the therapy groups.

The number of observations in the surveillance group was too low to allow statistical analysis.

Data on the period of ejaculation abstinence were available for 91 of the 177 samples. No significant difference in abstinence time was found when T₀ samples were compared with samples collected at the other time points (P = 0.11).

**Length of CAG repeat, correlation with sperm concentration recovery**

There was a significant negative correlation between CAG repeat and sperm concentration after 12–24 months (ρ = -0.72; P = 0.03) (Figure 4) in men treated with three or four cycles of CT. The repeat number did not correlate with sperm concentration for the other therapy forms or at other time points.

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Figure 3. Sperm concentration: longitudinal data: ACT, HCT, RT are as defined in the text. Bars correspond to median value, boxes to the interquartile interval and whiskers to the 95% CI. (A) T₀ versus T₆; (B) T₀ versus T₁₂; (C) T₀ versus T₂₄±₆₀. Black boxes represent T₀. P-values <0.05 are given.

Figure 4. Correlation between CAG repeat length and sperm concentration in patients treated with 3–4 cycles of chemotherapy 12–24 months after treatment. Spearman's ρ = -0.72; P = 0.03.
including at T₀. No significant correlation was found for GGN length.

Factors predicting sperm concentration

When applying a multiple linear regression model, in the whole group of patients, neither the tumour type, CAG length nor age was significantly associated with sperm concentration at T₀. Using type of therapy, CAG length and pre-treatment sperm concentration as independent variables, the type of therapy was the only significant predictor of sperm concentration at T₀ (adjusted \( R^2 = 0.69; P < 0.0005 \)). Also at T₁₂-twenty-four, the association with the type of therapy (adjusted \( R^2 = 0.31; P = 0.004 \)), but not with any of the other variables included in the model, was statistically significant. No statistically significant associations were found at T₃₆-sixty. When analysing the group of patients, neither the tumour type, CAG length nor age, was significant in predicting the concentration after 12–24 months.

Sperm motility

The only significant finding was a lower percentage of motile sperm at T₁₂ compared with T₀, found in the RT group, 38 versus 68% (\( P = 0.03 \)). However, for several comparisons, the number of patients included was not sufficient to perform statistical analysis (see Table III).

Discussion

The major findings of this study were the therapy-dependent recovery of sperm concentration over time after treatment for TGCC and the impact of the AR CAG length on sperm concentration 1–2 years after HCT. This is, to our knowledge, the first study reporting an impact of genetic factors on the recovery of spermatogenesis after cancer therapy.

Novel for this study, compared with those already published (Giwercman and Petersen, 2000), is the combination of discrimination between treatment modes and post-treatment sample collection at well-defined time points, in principle allowing for more precise mapping of the process of spermatogenesis recovery (Kuczyk et al., 2000). The participation rate was close to 80%, reducing the risk of selection bias. From 65% of these men, pre-treatment sperm parameters were available, and 80% of them delivered further samples, allowing a longitudinal follow-up.

Four of the 73 men from whom a pre-treatment semen sample was available had azoospermia already after orchidectomy. None of the patients treated with ACT developed azoospermia. However, the number of patients, especially those given two chemotherapy cycles, is still limited, and until more data are available, we recommend cryopreservation to men receiving ACT. The risk of developing azoospermia was significantly higher for those receiving RT or HCT. Unfortunately, we did not have enough longitudinal observations to allow detailed analysis of the recovery from azoospermia. Previous studies (Hansen et al., 1989) have indicated that 5 years after treatment, the risk of permanent azoospermia is negligible even in men treated with more than two cycles of BEP chemotherapy.

In agreement with earlier reports, we found the negative impact of CT on spermatogenesis to be dose dependent (Petersen et al., 1994). ACT did not have any significant influence on sperm production (Cullen et al., 1996). The time course of the recovery of sperm production was similar in men treated with RT and HCT. Apart from the already mentioned risk of azoospermia, the pre-treatment levels of sperm concentration were seen after 24–60 months. Since the reproductive period of a couple is limited, a prolonged period of azoospermia or very low sperm concentration may seriously reduce the possibility of having a child.

Potentially, the results of our study could be influenced by variation in the length of the abstinence period. Such data were only available for 91 of the 177 samples. However, there was no statistically significant difference between the lengths of the abstinence period at the different time points, and these

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Table III. Changes in sperm motility in relation to time after treatment and type of therapy in testicular cancer patients with longitudinal data.

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<th></th>
<th>ACT</th>
<th>HCT</th>
<th>RT</th>
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<tbody>
<tr>
<td>Median (range)</td>
<td>Median (range)</td>
<td>Median (range)</td>
<td>Median (range)</td>
</tr>
<tr>
<td>T₀ versus T₆</td>
<td>72 (44–90)</td>
<td>–</td>
<td>62 (20–76)</td>
</tr>
<tr>
<td>( n = 10 )</td>
<td>( P = 0.51 )</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>T₀ versus T₁₂</td>
<td>68 (50–90)</td>
<td>64 (50–70)</td>
<td>68 (20–76)</td>
</tr>
<tr>
<td>( n = 10 )</td>
<td>( P = 0.074 )</td>
<td>( P = 0.71 )</td>
<td>( P = 0.028 )</td>
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<tr>
<td>T₀ versus T₃₆-sixty</td>
<td>70 (69–70)</td>
<td>70 (57–87)</td>
<td>69 (67–71)</td>
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<tr>
<td>( n = 4 )</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
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<tr>
<td>T₀ versus T₁₂</td>
<td>75 (58–83)</td>
<td>ND</td>
<td>47 (30–60)</td>
</tr>
<tr>
<td>( n = 9 )</td>
<td>( P = 0.12 )</td>
<td>ND</td>
<td>27 (10–42)</td>
</tr>
</tbody>
</table>

ACT = 1–2 cycles of chemotherapy; HCT = >2 cycles of chemotherapy; RT = radiotherapy; ND = statistical analysis not done because of insufficient number of subjects included.

*The earliest period mentioned first.

Wilcoxon test for paired data.
parameters were therefore not taken into consideration in the analysis of data. Concerning inter-laboratory variation in evaluation of sperm parameters, 41 samples analysed at the time of cryopreservation at another laboratory were included in order to increase the amount of data available for analysis. Both laboratories followed the WHO guidelines for performing semen analysis, and previous studies have shown that assessments of sperm concentration and total percentage of motile sperms are rather robust to inter-laboratory variation, when the same protocols (WHO) are applied (Jørgensen et al., 1997; Giwercman et al., 1999).

The major conclusions of the study regarding the recovery of sperm concentration are based on longitudinal data and, for some of the analyses, the number of patients was fairly low. Inclusion of additional patients and prolonged follow-up of those who have already entered the study will give more precise information about the post-treatment recovery of spermatogenesis.

We found a negative correlation between the length of CAG repeat in the AR gene and sperm concentration after 12–24 months in men who were treated with 3–4 cycles of BEP; the shorter the CAG stretch, the higher the sperm concentration. Furthermore, in a multivariate analysis, together with sperm concentration at T0, the CAG length was shown to be a significant, independent, predictor of sperm concentration at T12–24. Previous in vitro and in vivo studies have shown that the length of the CAG repeat is inversely correlated with the transcriptional activity of the AR and with the sensitivity to the male sex hormones (Tut et al., 1997). Some studies have demonstrated longer CAG repeats in infertile men (Dowsing et al., 1999) and an inverse correlation between sperm concentration and CAG length (von Eckardstein et al., 2001). We did not find any correlation between CAG lengths and pre-treatment sperm concentration. Furthermore, the results of the multivariate analysis indicated that the effect of this AR polymorphism is not exerted through regulation of the pre-treatment state of spermatogenesis but rather is implicated in the process of recovery. We did not find any effect of the other repetitive sequence of the AR, i.e. the GGN repeat.

The finding of an association between the CAG segment and recovery of spermatogenesis is intriguing, not only from a clinic, but also from a biological point of view. The impact of androgen action on the rapidity of recovery of spermatogenesis indicates that after HCT, late stages of spermatogenesis (Zhang et al., 2003) play an important role for reaching pre-treatment levels of sperm concentration. Our findings should also be seen in view of the recent (Meistrich et al., 1999) finding showing that in rats, recovery of spermatogenesis after procarbazine or irradiation treatment could be stimulated by use of GnRH agonists or antagonists. Further, it was shown (Shetty et al., 2000) that this effect of hormonal treatment was due to lowering intratesticular testosterone levels. Our study indicates that decreased androgen action after BEP treatment rather delays the recovery of sperm production. This apparent discrepancy might be due to one or a combination of interspecies difference, use of another treatment mode or the fact that men with TGCC might also have Leydig cell dysfunction (Willemsen et al., 1983), leading to a relative hypoandrogenic intratesticular milieu of such patients. However, inclusion of larger groups of men is necessary to draw any firm conclusions regarding this issue.

In conclusion, we found a non-significant decrease in sperm concentration with full recovery after 12 months in TGCC patients treated with 1–2 cycles of cisplatin-based chemotherapy. In those who received RT or more than two cycles of CT, the dip in sperm concentration was more prolonged, not reaching pre-treatment levels until 2–5 years after completion of therapy. We also found that the AR CAG polymorphism is a significant predictor of the rapidity of recovery after 3–4 cycles of CT. Future studies including more patients and additional genetic markers may provide us with new powerful tools for an individualized prediction of the gonadotoxic effects of therapy in young males undergoing cancer treatment.

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