Radiotherapy with 16 Gy may fail to eradicate testicular intraepithelial neoplasia: preliminary communication of a dose-reduction trial of the German Testicular Cancer Study Group

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Low-dose radiotherapy to the testis is effective in eradicating testicular intraepithelial neoplasia (TIN, carcinoma in situ of the testis) at the risk of androgenic deficiency. The present trial was designed to define the lowest dose effective to control TIN assuming a dose–response relation of radiation-induced endocrinological damage. Patients with TIN in a solitary testicle or with bilateral TIN were treated with 18 Gy (14 patients) and 16 Gy (26 patients) (5 × 2 Gy per week). Biopsies to ascertain clearance of TIN were performed after 6 and 24 months. The median time of follow-up is 20.5 months. There were three adverse events. In one patient, relapse of TIN along with microinvasive seminoma was observed 2 years after 16 Gy irradiation. In two other patients, persistent spermatogonia were observed with the 16 and 18 Gy regimen after 6 and 24 months, respectively. All other post-treatment biopsies showed the Sertoli cell-only pattern. These results confirm that TIN is a radiosensitive lesion efficiently controlled in most cases with doses below 20 Gy. However, sporadic failures may occur. A dose of 16 Gy is probably unsafe and should no longer be used. Future investigations should not only focus on total dosage of irradiation but also on fractionation schedules.

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Testicular intraepithelial neoplasia (TIN; also called carcinoma in situ of the testis) is the uniform precursor of testicular germ cell tumours (Dieckmann and Skakkebaek, 1999). According to the current theory of the histogenesis of testicular tumours, TIN evolves from embryonic germ cells and thus it is present in the testicle many years before the tumour becomes invasive. Morphologically, TIN consists of large intratubular cells that closely resemble embryonic gonocytes (Rorth et al., 2000). Diagnosis is achieved by testicular biopsy and immunohistological examination with staining for placental alkaline phosphatase (PlAP). If TIN is left untreated after diagnosis, malignancy will develop in 50% of cases after 5 years and in 70% after 7 years, respectively. Probably, all cases of TIN will ultimately proceed to invasive testicular cancer (Skakkebaek et al., 1987). TIN can be effectively treated by low-dose radiotherapy. This treatment is appealing because TIN and thus the risk of testis cancer is eliminated without surgical castration. Moreover, the testosterone-producing Leydig cells are largely preserved and, consequently, hormone supplementation is usually not required in these individuals. So far, experience with radiotherapy of TIN is limited. According to early experience (von der Maase et al., 1986; Giwercman et al., 1991; Dieckmann et al., 1993), a total dose of 18–20 Gy is sufficient to clear the testis from TIN (Bamberg et al., 1997); however, it became obvious that this dosage also causes damage to the Leydig cells in at least one quarter of the patients (Dieckmann et al., 2001; Classen et al., 2001), rendering these patients dependent on androgen substitution. Therefore, a clinical trial was initiated to look for the most appropriate radiation dose that is still sufficient to eradicate TIN effectively, and that preserves Leydig cell function at the same time. Owing to unexpected outcomes, we here report interim results of this trial with respect to control of TIN by radiotherapy. The endocrinological data are still premature and will be reported later.

Patients and methods

A two-stage phase II study design was used for the trial (Simon, 1989). A stepwise dose-reduction schedule was employed starting at the 18 Gy level with dose-reduction steps of 2 Gy each. Dosage decrease was scheduled until treatment failure at any dose level was experienced or until the 12 Gy level was reached. According to the two-stage design of the trial, dose reduction on each dose level was employed after a minimum of seven patients had completed treatment on this level without adverse events, that is without persistence of TIN or germ cells, respectively, as evidenced by post-treatment biopsy (Simon, 1989). In the case of treatment failure at a given dose level, it was intended to confirm the safety of
Radiotherapy of TIN

J Classen et al

Enrolled for the trial
n=43

Excluded: • seminoma: n=1 • no TIN : n=2

Eligible
n=40

18 Gy: n=14

16 Gy: n=26

Control biopsies: n=12

Control biopsies: n=20

Control biopsies: n=5

Control biopsies: n=7

Patient accrual

Experimental treatment

6 months checkpoint

2 years checkpoint

Figure 1 Study population and follow-up biopsies after radiotherapy.

details are given in Figure 1. Histologically, three adverse events were encountered: one relapse of TIN, one patient with persistence of germ cells, and one other with reoccurrence of germ cells.

Overall, no persistence of TIN was observed in any post-treatment biopsy at the 6-month checkpoint. However, in one patient who had undergone the 16 Gy regimen, several vital spermatogonia were observed histologically. A second biopsy taken from this patient after 2 years was clear of TIN and germ cells. Currently, this patient is well and without clinical signs of malignancy.

At the 2-year checkpoint, 10 biopsies were clear of TIN and germ cells. However, TIN was detected in one patient who had been found free of TIN 6 months after completion of irradiation with 16 Gy. This patient subsequently underwent orchectomy. Histological evaluation confirmed the presence of TIN in numerous seminiferous tubules and, importantly, it also disclosed the presence of microinvasive seminoma (Figure 2). Germ cells were absent in the orchectomy specimen. In a second patient treated with 18 Gy, Sertoli cells only were found 6 months after completion of therapy, but isolated germ cells were detected in the second biopsy 2 years after radiotherapy. This patient is under continuous observation without clinical signs of testicular malignancy.

DISCUSSION

The finding of a TIN relapse after 16 Gy radiotherapy is clearly nonanticipted. At the outset of the present study, the expectation based on the cumulative international experience (Giwercman et al, 1991; Mumperow et al, 1992; Dieckmann et al, 1993; Classen et al, 1998; Kazem and Danella, 1999; Sedlmayer et al, 2001) had been that 14 Gy or possibly even 12 Gy radiotherapy would still be sufficient to eradicate TIN.

Failure of chemotherapy to eliminate TIN and likewise its inefficacy of preventing contralateral germ cell tumours has been observed in abundance (Hoff-Wanderas et al, 1997; Christensen et al, 1998; Ostau et al, 2001). Accordingly, there were five patients
with persistent TIN after chemotherapy in the present series. Primary resistance of TIN cells to chemotherapy, and possibly, protection from chemotherapy by the blood–testis barrier are the probable biological reasons for the inefficacy of chemotherapy to cure TIN.

The reasons for the relapse of TIN despite radiotherapy are unclear. Technical failure is improbable since in the present case the first post-treatment biopsy had demonstrated the absence of TIN and germ cells.

A feasible explanation would be the hypothesis that some of the TIN cells in the present patient were somehow radioresistant and thus escaped eradication. Presumably, in the present patient a few TIN cells had been present even at the 6-month checkpoint. Obviously, because of their low number and focal arrangement, they escaped detection by biopsy at that time. The surviving TIN cells resumed replication in the later course and were then large enough in number and topographic distribution to be detected by the biopsy at 2 years.

Further, the observation of persisting vital spermatogonia after 16 Gy and even after 18 Gy is incompletely understood, too. Such a finding has not been reported previously. Since spermatogonia and TIN cells share a number of biological features, it must be suspected that the persistence of germ cells after radiotherapy might herald also the persistence of TIN cells.

A further note is that the median follow-up is still low (20.5 months) in the present series. As the relapse has been found in a biopsy after 2 years and only 12 patients have passed this checkpoint to date, it could be suspected that even more relapses might be disclosed during longer follow-up. Thus, the adverse events reported here, although constituting only early experience, clearly indicate that the 16 Gy regimen involves a significant potential of treatment failure, and even the 18 Gy dose level may finally prove to be insufficient for safe eradication of TIN.

Recently, Petersen et al (2002) reported the recurrence of TIN after 14 Gy irradiation with a standard fractionation schedule. In analogy to our patient, that relapse was observed 2 years after completion of treatment. In contrast to our study, Petersen et al did not encounter relapse of TIN at the 16 Gy level. Furthermore, they did not observe persisting germ cells after the 16 and 18 Gy irradiation schedule. Possibly, small patient samples in both of the studies (the present one and the Petersen study) account for these incongruent findings. Interestingly, endocrinological compromise was present in many of the patients in the Petersen study with no significant differences between the various dose levels. In all, that report strongly accords with our observation that a dose reduction below 18 Gy involves a small but definite risk of treatment failure. In addition, it appears equivocal so far that a dose reduction of radiotherapy will ultimately translate into a substantial clinical benefit for the patient, that is, improved preservation of androgen synthesis.

Clearly, another important lesson to be learned from the present trial is that biopsies to control radiotherapeutic success are paramount. Moreover, late biopsies (e.g. after 2 years) are much more appropriate than early biopsies (i.e. after 6 months). Possibly, even very late biopsies after 3 or 4 years could be useful. If one assumes a persistence of TIN subsequent to radiotherapy, then this condition probably consists of a tiny focus, morphologically. A random biopsy taken 6 months thereafter probably has a large potential to miss that lesion. However, as TIN will inevitably resume replication, biopsies taken during later follow-up have a much higher chance of detecting the condition.

The dose–response relation of TIN is unknown so far. Owing to morphological similarity, it is assumed that TIN and spermatogonia are at least partly comparable with respect to radiosensitivity. Germ cells are highly vulnerable to radiotherapy. Even scatter doses from radiotherapy to abdominal or pelvic target organs can cause significant damage to the germinative epithelium (Classen and Bamberg, 1999). Depletion of germ cells is usually achieved after total doses exceed 12–14 Gy depending on the fractionation schedule (Shalet, 1993).

In contrast to other tissues, germ cells are particularly sensitive to fractionated irradiation. This phenomenon is because of different radiosensitivity of the various stages of germ cell maturation. Type A spermatogonia, the presumed stem cells of spermatogenesis, are rather radioresistant possibly due to their long cell cycle. Type B spermatogonia have a much shorter cycle time, which may be the reason for their increased radiosensitivity.

Based on the morphological and biological similarities of spermatogonia and TIN cells, it could thus be speculated that not only the total dose of radiation but also the fractionation schedule is critical for cure of TIN by radiotherapy. Accordingly, Sedlmayer et al (2001) reported the efficacy of a 13 Gy total dose applied in 10 fractions to eradicate TIN at least in a short time to follow-up and in a small cohort of patients.

According to standard fractionation regimens, a dose–response curve as shown in Figure 3 may be hypothesised for local radiotherapy of the testis (Figure 3). Total doses of 16 Gy or more will cure TIN in the majority of cases, but some of the cases will relapse or persist as demonstrated in the present study. Doses of 18–20 Gy will cure TIN in almost 100% of cases. However, sporadic relapse may occur even after standard dose treatment (Dötsch et al, 2000; Dieckmann et al, 2002). If higher doses are applied, no...
new growths have been observed (Read, 1987). With regard to the dose–response curve (Figure 3), it may be speculated that the curve could be shifted to the left by decreasing the daily dosage below the classical 2 Gy standard dose and by increasing the number of fractions at the same time. Thus, higher cure rates might be achieved with lower total doses. Furthermore, reduced single doses of treatment might contribute to protect androgen-producing Leydig cells from late sequelae of irradiation.

In conclusion, it becomes obvious that control of TIN by current radiotherapeutic strategies is not possible in virtually 100% of cases. High cure rates are achievable even with doses of radiotherapy just below or around the 20 Gy level, but sporadically, relapses may occur. The optimal dose of radiotherapy is yet to be found. Total doses of 16 Gy with standard fractionation is obviously not safe enough and should no longer be used. Conceivably, a schedule with higher fractionation may offer another convenient avenue to dose reduction and thus preservation of hormone-active Leydig cells.

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Figure 3 Dose–response curve hypothesised for radiotherapy of TIN. Increasing the number of fractions may shift the response curve to the left.

Radiotherapy of TIN

J Classen et al

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