Intratumoral administration of hypoxic sensitizers in the radiotherapy of 494 uterine cancer patients: long-term results

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Purpose: In Kazakh Institute of Oncology and Radiology we made clinical trials of direct interstitial of metronidazole (later, also Sanazole-AK 2123) in patients treated with radiotherapy for cancer of uterine cervix and endometrial. The indicated treatment was completed in 435 uterine cervix and 97 endometrial cancer patients, the respective numbers of controls being 263 and 36. We were only able to carry out a limited number of randomized studies, as news about a novel method of treatment with unprecedentedly good results had spread widely and patients in an increasing number were requesting treatment with the new regime. All the patients were followed for a minimum of 5 years after termination of treatment. The last examination we made in 2001 year.

Patients characteristics: To the clinical investigation were admitted patients with cervix tumors in stages IIB and III, and patients with endometrial cancer in stages IB, IIB and III. Distant metastasis, neuropathy and liver and kidney dysfunction cases, or patients over 70 years of age were excluded. Assessment of long-term cervix tumor results was based exclusively on squamous cell data as the most highly representative morphological sample (Table 1). As can be seen here, in both subject and control groups, 80% of the cervix occurred in the locally advanced stage III, out of these, 54.6% had both of the parametric involved in the process. Clinical staging was done according to the FIGO system. Pretreatment evaluation consisted of physical examination, routine laboratory studies and cystoscopy. Lymphographic test were included as required. Stage allocation and the degree of tumors morphology differentiation appear to be comparable in two arms (Table 2). This was found to apply also to small group of patients that underwent treatment therapy in a randomized fashion. In about one third of all cases, the degree of differentiation was established to have reached grades I and II (Tables 1-2).

Methods: RT was performed using combined external and intracavitary irradiations, with total dose varying between 65 and 72 Gy at Point A, and between 55 and 60 Gy at Point B. The treatment started with 5 fractions each of 3-4 Gy given every second day on the whole pelvic from two opposing fields 18 × 15 cm. Treatment continued with intracavitary irradiation per 5 Gy twice a week, and completed with 2 Gy boosters given at 48 intervals on two opposing narrow fields (5 × 15 cm). A 0.5% solution of metronidazole was used. Injections were made from 3-4 points of fornix under ultrasound control about 15-20 minutes before each of the 3-5 initial irradiations with 4 Gy. About 20-40 ml, and in advanced cases up to 60-80 ml was administrated. The average content in neoplastic tissue was 1.5-2.5 mg/g wet weight. A 0.5% solution of metronidazole is equivalent to 21-29 Mmt and established drug content about 2 mg/6 of fissile (O.C.Scott). The plasma concentration of the drug, measured about 2 hours after the infusion varied between 10 and 30 mcg/ml. The concentration of metronidazole was determined spectrophotometrically (320 Nm) in ethanol extractions prepared from 32 biopsies taken 10 min after infusion. The treatment response was evaluated according the rate of complete regression of tumors and the grade of cytological damage. Local regression rate was determined by examination of visible and palpable tumors residues, aided by ultrasound provides the requisite topometric information concerning the state of tumor and surrounding tissue, especially with regard to the initial volume and subsequent change during treatment.

Results: Treatment results of radiotherapy combined with intratumoral sensitization are very high. The clearance rate of the tumors in the randomized and in the joint group of randomized and nonrandomized cases. Complete regression was achieved in 100% of stately patients treated by radiation therapy with metronidazole, compared to 81.3% of the same type of patients treated with RT alone. Of special note is the efficacy of the new regime in the case of stage III endometrial and cervix cancer: complete regression of the neoplasm and parametric metastases in 88.3% of cases (and as high as 95.3% for the randomized group) against 48.6% achieved with RT alone. In terms complete tumor regression criteria, the Dose-Modifying Effects (DIME) rate 0.83 when RT was combined with intratumoral injection of the hypoxic sensitized. The cytological damage caused by different modes of treatment was evaluated 1-2 weeks after completed therapy. A large proportion of MZ RT cases showed an increase in injuries. Grade III stromal elements were recognized in 86.4% of cases, with possible destroyed neoplastic cell rests and necrotic masses. The RT biopsies reverted a damage that in one half of cases rated grade II - on evidence from stromal elements with only a few severely damage tumor cells. The rate of grade II damages...
was 4-fold lower for MZ RT treatment. The MZ-treated patients displayed a considerably higher level of tumor radiosensitivity. The ultrasound measurements performed in the course of radiotherapy indicated that tumor reduction down to complete regression could in many instances take place upon the administration of the initial quarter of the total irradiation dose. In contrast, complete regression following the full irradiation course could only be achieved in one half of unmodified RT treatment cases (Tables 3-5).

Salvage brachytherapy for local recurrences of prostate cancer

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Purpose:

Radiation therapy for localized prostate cancer is a standard option of treatment. Local recurrences (biochemical and clinical) occurred in about 50% (depending on the initial stage and other prognostic factors). Usually local recurrences have ominous prognosis. The standard treatment is hormonotherapy.

Material and methods:

In MSC Memorial Cancer Center and Institute of Oncology, Gliwice Branch, a researched program on salvage HDR brachytherapy for local recurrences of prostate cancer treated earlier with radiotherapy has been opened since February 2008. Eligibility criteria: confirmed local recurrence after treatment for localized prostate cancer at least 2 years ago (transrectal ultrasound or MRI of the prostate, bone scan for occult metastases, biopsy of the prostate for histopathological confirmation of the recurrences). The earlier treatment were mainly external beam radiation but patients treated with external beam radiation with boost from brachytherapy are not excluded. Exclusion criteria was the same as for any HDR brachytherapy of prostate (volume > 60 cm³, TURP within 6 months, infiltration of the external sphincter of the bladder neck, significant urinary obstructive symptoms, pubic arch interference, litotomy position or anesthesia not possible). HDR brachytherapy was delivered using an Iridium-192 stepping source (MicroSelectron™, Nucletron NV). Treatment planning was performed intra-opertively. Needle applications were performed during spinal anesthesia. The treatment consisted of 3 fraction 10 Gy each given every 14 days. The dose was specificated on the prostate capsule or 2-3 mm from it (depending on clinical case). Generally homogenous needle distributions were applied with planed hot-spot in case of visible tumor. Maximal urethral doses (calculated at the centre of each urethral outline each 5 mm) were constrained to be 120% of prescribed dose. Maximal bladder and rectum doses were constrained to be 70% of prescribed dose.

Results:

Fifteen patients eligible were treated and analyzed from February 2008. All patients completed the treatment without major complication. The most common early complication were: macroscopic hematuria, pain in lower part of the abdomen, transient dysuria. During the first week after the procedure transient increase in IPPS score were noticed. A Foley catheter was removed on day 2nd to 5th. No complication after spinal anesthesia were observed. Acute toxicity according to EORTC/RTOG was low. For bladder EORTC/RTOG score was ranking from 0 to 2. Only in two patients grade 1 toxicity for rectum was observed. The follow up range from 4 to 14 months. In all patients early toxicity ceased quickly after treatment (lasting up to 3 weeks). No late toxicity were observed so far. In all patients but one decrease in PSA level were observed (one patients developed metastases in bones).

Conclusions:

Salvage brachytherapy for localized prostate cancer (10 Gy every 14 days) seems to be safe and well tolerated procedure. The efficiency of the procedure is yet to be established.

HDR Brachytherapy of prostate cancer – 2 years of treatment in Greater Poland Cancer Center

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Purpose:

External beam radiotherapy (EBRT) in prostate cancer treatment seems to be nowdays as effective as surgery procedure. Low dose rate brachytherapy (LDR-BT) can be applied as a single modality treatment in patients from low risk group with localized tumors. High dose rate brachytherapy (HDR-BT) is very useful in increasing prostate dose after EBRT (boost) which shortens whole radiation treatment. There is no clear recommendations about doses and schemes of combined radiation treatment (EBRT-BT). The aim of this work was to analyze the results and complications of three schemes in treatment of patients with initially localized prostate cancer and at least 2 years observation time.

Material and methods:

Sixty-three patients were enrolled to the study and divided to groups according to radiation schemes (I – EBRT 50/BRT 15, II – EBRT 46 Gy/BRT 2 × 10 Gy, III – BRT 3 × 15 Gy) Group I, II,