

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) rated 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 recognizable 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).