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Intravesical chemotherapy in urinary bladder cancer

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Summary. *Monthly instillation therapy with Adriamycin in a standardized dose of 300 ng/ml/h together with a phosphate buffer at pH 7.4 seems to give satisfactory results in patients with primary bladder carcinoma in situ and in patients with secondary carcinoma in situ of the bladder who have previously received full courses of irradiation.*

The side-effects are transient and few.

During the last 10 years, the diagnosis and treatment of carcinoma in situ of the urinary bladder have attracted increasing interest.

In Stockholm, a group of 38 patients with primary and secondary carcinoma in situ (TIS) received intravesical treatment with adriamycin. Of these, 19 have primary TIS and 19 secondary TIS. Of the 19 with secondary TIS, 10 had received primary therapy with local coagulation for exophytic tumors, and 9 with a full course of irradiation for infiltrative tumors.

'Primary TIS' is used to mean no visible tumor at cystoscopy prior to instillation, and 'secondary TIS' to mean no tumor is visible prior to instillation, but these patients have previously been treated with local coagulation or a full course of irradiation.

All patients had cytologically and biopsy-proven TIS. They were followed-up by means of repeated DNA analyses together with bladder washing before every instillation of adriamycin.

For standardization of the intravesical chemotherapy the dose of adriamycin was calculated to give 300 ng per hour and ml.

The diuresis was approximately 50 ml/h if the patient did not have any fluid intake for 12 h before therapy. We used an instillation volume equal to the bladder capacity minus 50 ml. The instillation time was 1 h.

The cellular uptake of anthraquine glycoside is strongly dependent on pH, since such substances are protolytes. Consequently, a fixed pH value in the bladder – easily obtained by use of a pH buffer as drug solvent – is highly important in the standardization of intravesical therapy with adriamycin. We chose a phosphate buffer of pH 7.4 for this purpose, since under these circumstances adriamycin is largely in the non-charged form and has a sufficiently high stability.

High accuracy of the therapy was obtained and measured values for adriamycin showed no tendency to vary with the bladder capacity.

Analysis of plasma samples from patients during and after intravesical therapy with adriamycin in phosphate buffer at pH 7.4 did not reveal measurable concentrations of either adriamycin or adriamycinol (active metabolite), i.e., the plasma level was lower than 5 ng/ml. Hence, adriamycin can be instilled as described without the risk of side-effects.

The patients' bladder capacity was essentially unchanged during the instillation therapy. The duration of therapy ranged from more than 12 months to 5 years.

Urine cytology and peripheral blood count were monitored before each course of instillations. Cystoscopy, with bladder washings and DNA analyses, was performed every 4th month.

Cystoscopically and/or cytologically proven recurrences were defined as failure. *Complete remission* (CR) was defined as a complete disappearance of carcinoma cells (cytological remission). In *partial remission* (PR) severely atypical cells might be present but no carcinoma cells.

I. Primary carcinoma in situ

Nineteen patients were included in this study, 14 receiving monthly instillations and five different treatment modalities. Where monthly instillations were given the average number was 13.

A CR was seen in four of 14 or 29% and PR in six of 14 or 43% of the patients treated by monthly instillations. In the patients with CR there was an average follow-up time of 54 months and in those with PR, 35 months.

Patients with normalized benign cytology (CR) recovered well.

Two patients with PR (severe atypia after primary treatment) died of intercurrent diseases after 11 and 66 months. The autopsies did not reveal any signs of TIS or infiltrative growth in the bladder wall.

Of the four patients with recurrent cancer (cancer cells at cytology) two had cancer cells 6 and 16 months after instillation therapy. Preoperative irradiation was given, followed by cystectomy. TIS was only confirmed in one patient and no invasive growth was found in either of these patients.

A full course of irradiation was given to one patient, and in the other cytologic examination showed resistant cancer cells many times after instillation therapy. Eleven months later, without any therapy, the cytology changed to severe atypia but cancer cells were no longer present.

II. Secondary carcinoma in situ (previously irradiated)

All 9 patients in this group received a full course of irradiation as first-line treatment, with normalized cytologic on cystoscopic findings. Cancer cells were later detected on cytologic testing, but cytoscopic results remained normal. Random biopsies showed no infiltrative growth.

All 9 patients received instillation therapy monthly.

In this group of nine patients CR was achieved in six or 67% and PR in two or 22%. The average follow-up time for the CR group was 50 months and that for the PR group was 28 months.

On average nine courses were given.

In the eight patients with CR or PR the cytology had stabilized after three courses to a benign or in one case, severely atypical cell picture.

III. Secondary carcinoma in situ (previously coagulated)

Ten patients with secondary TIS received adriamycin instillations after previous local coagulation. The indication for the therapy given was the presence of cancer cells in repeated bladder washings without any sign of visible tumor at cystoscopy.

Ten patients received monthly instillations, and seven received more than two instillations. Of these ten, three (30%) achieved CR and three (30%) achieved PR. The number of courses was 14 on average. The only patient with PR or severe atypia at cytology had an aneuploidal cell pattern before therapy and a diploidal pattern afterwards. This patient is still living 46 months after the therapy.

Complications

In the group of patients with *primary TIS,* one patient had tenesmus during the second instillation. This normalized later.

In the group of patients with secondary *TIS previously irradiated,* one patient had the treatment broken off after the first instillation because of painful micturation with frequency and urgency. These disturbances were transient.

In one patient there was a slight reduction of bladder capacity. This disturbance was transient.

In the group of patients with secondary *TIS previously coagulated,* there was tenesmus in one patient. This came after 26 treatments and a break of 15 months, occurring after the first instillation in the new series. The condition normalized without discontinuation of the treatment.