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Chemoimmune Prophylaxis of Superficial Bladder Tumors: Results After Treatment of 130 Patients in 4 Years

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Summary. Since January 1978 we performed chemoimmune prophylaxis in 130 patients with superficial transitional cell carcinoma of the bladder. After complete tumor resection and exclusion of an urinary tract infection as well as an impaired global immune competence treatment consisted of one intravenous application of 700 mg Cyclophosphamide (CTX)/m^2 followed by 6 intravesical instillations of 120 mg BCG/50 ml saline together with BCG skin scarifications. In a total of 12.3% of the treated patients tumor recurrences were observed until the 18th month. These results compared favourably with the high recurrence rate in a group of 80 patients without CTX/BCG prophylaxis. In 48 patients with a history of recurrent tumors statistically significant treatment effects were noted after CTX/BCG ($p < 0.01$) using the Wilcoxontest. In 10% of the cases, inflammatory tumor-like lesions developed. Side effects of the treatment were generally well tolerable. From the presented data it is concluded that chemoimmune prophylaxis effectively prevents recurrences in superficial bladder cancer.

Key words: Superficial bladder cancer, Chemoimmune prophylaxis, Cyclophosphamide, BCG.

Introduction

During the last few years in increasing number of reports has been published on the beneficial effect of intracavitary BCG prophylaxis in superficial bladder cancer [4–6]. Since January 1978, we have performed chemoimmune prophylaxis with cyclophosphamide (CTX) and combined intravesical and systemic BCG [2]. On the basis of theoretical considerations and animal experiments this treatment is expected to act synergistically towards stimulating the cellular immune response [3]. We report here our treatment results after more than four years.

Material and Methods

1. Control Group

For comparison of the treatment results all charts of patients with urothelial bladder cancer who were treated in our department from 1972–1978 were reviewed. Eighty patients were selected for whom the strict criteria which have been published before [3] applied:

1. histologically confirmed complete resection of superficial transitional cell bladder cancer
2. complete documentation of all data
3. at least a 4-year follow-up.

2. Treatment Group

130 patients with primary or recurrent transitional cell bladder carcinoma staged pTA or pT1 according to the UICC were subjected to chemoimmune prophylaxis after complete tumor resection. The prerequisites for this treatment, the performance of chemoimmune prophylaxis as well as the follow-up control parameters remained unchanged [3].

In order to faciliate a comparison of both the untreated historical control group and the CTX/BCG treated group the known parameters which influence the recurrence rate or prognosis, such as anamnestically recurring tumors, stage, grade, multifocality, and size were determined.

In both groups the recurrence rate per time interval (6 or 12 months) was assessed. For each calculated percentage the 95% confidence intervals were determined. In a group of 48 patients with recurrent bladder tumors the following ratios, i.e. the number of tumors/month and the tumor episodes/month, before and after institution of chemoimmune prophylaxis were determined by comparing equal time intervals. In this particular group of patients, statistical differences were calculated using the Wilcoxon-test.

During the course of this clinical study, in some patients tumor-like lesions appeared which endoscopically were indistinguishable from tumor recurrences which, however, histologically proved to be benign. The incidence of these lesions was noted in relation to the same time intervals as applied for true recurrences.

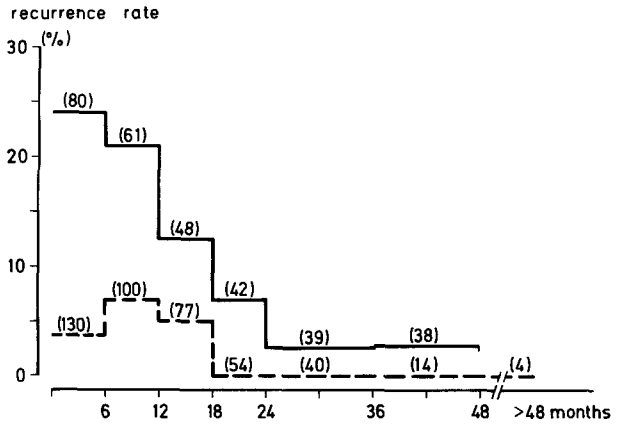

Fig. 1. Results of chemoimmune prophylaxis. —— recurrence rate after tumor resection without treatment; – – – recurrence rate after tumor resection followed by chemoimmune prophylaxis; ( ) number of patients at risk in the indicated time intervals

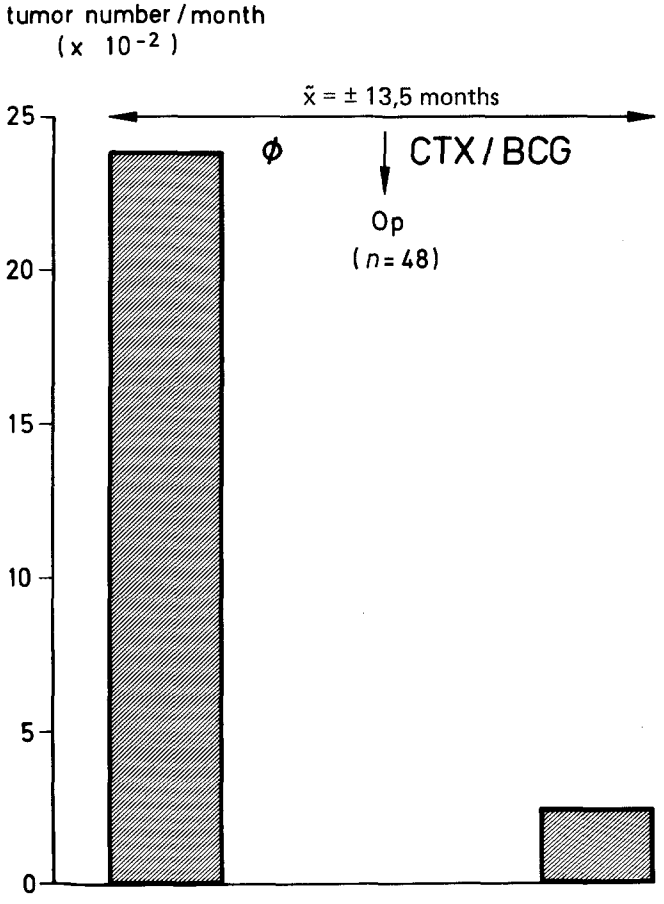

Fig. 2. Comparison of the ratios tumor number/month during equal time intervals (median observation time: 13.5 months) in 48 patients with recurrent tumors before and after CTX/BCG-treatment. The difference ist statistically significant ($p < 0.01$)

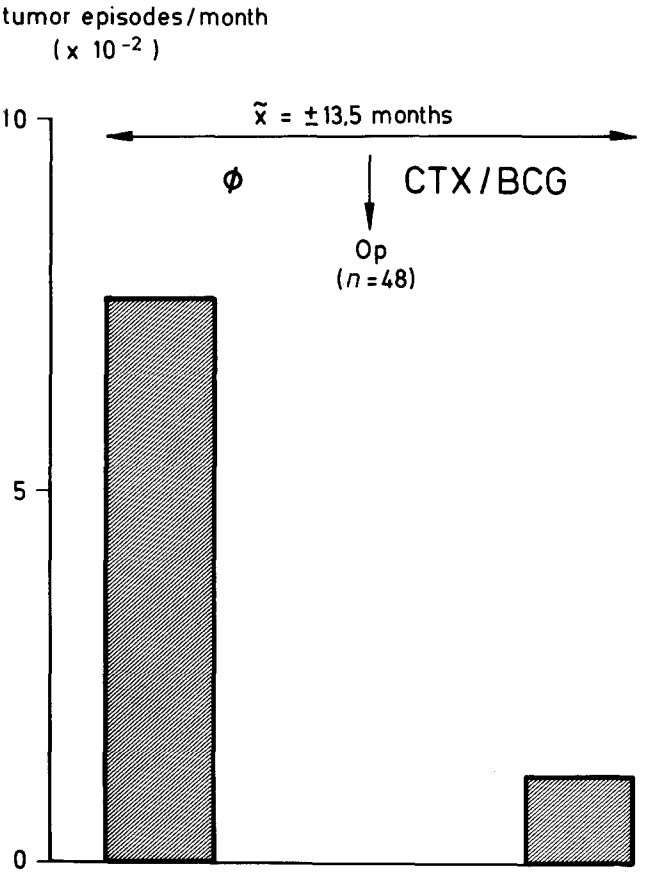

Fig. 3. Comparison of the ratios tumor episodes/month during equal time intervals (median observation time: 13.5 months) in 48 patients with recurrent tumors before and after CTX/BCG-treatment. The difference ist statistically significant ($p < 0.01$)

Results

The median age of the control group was 63 years (24–90 years) and in the CTX/BCG treated patients 67 years (24–82 years). In 16 of 130 individuals (12.3%) tumor recurrences of the bladder were observed during a median follow-up period of 13.5 months (4–52 months). In the control group 43 of 80 patients (54%) developed tumor recurrences during the total observation time of 4 years. Figure 1 represents the recurrence rates within the indicated time intervals. During the first postoperative year, the difference between both groups is most striking with the following confidence intervals:

from the 1st–6th month 1–9% (treated group) vs. 15–35% (untreated group)

from the 7th–12th month 3–14% (treated group) vs. 12–34% (untreated group).

After the 18th month in 54 treated patients no tumor recurrence was observed. Forty-eight patients suffered from recurrent tumors prior to the onset of chemoimmune prophylaxis. The course of disease after completion of CTX/GCG treatment was evaluated by determining the ratios of the number of tumors/month and tumor episodes/month for equal time intervals before and after chemoimmune prophylaxis. The results in Figs. 2 and 3 show for both the number and the episodes of tumors statistically significant differences ($p < 0.01$). Table 1 gives the details of

Table 1. Distribution of prognostically relevant tumor parameters in the untreated and CTX/BCG-treated group

tumor parameter	control group (n = 80) n(%)	CTX/BCG-treated group (n = 130) n(%)
stage		
pTA	19 (24)	52 (40)
pT1	61 (76)	78 (60)
grade		
1	48 (60)	83 (64)
2	31 (39)	41 (31)
3	1 (1)	6 (5)
recurrent	10 (13)	48 (37)
multifocal	28 (26)	43 (33)
large (tumor base > 3 cm ∅)	23 (29)	28 (22)

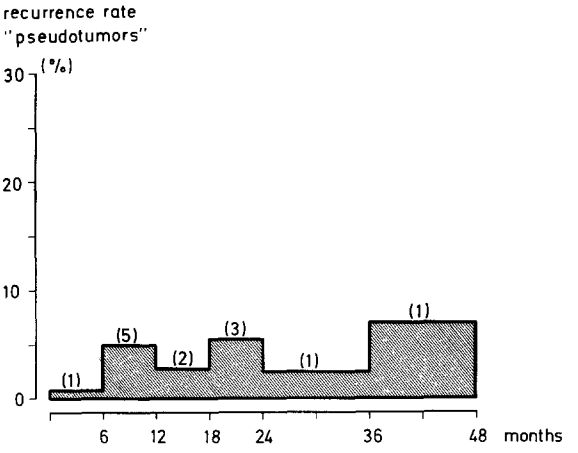

Fig. 4. Recurrence rate of "pseudotumors" in relation to the indicated time intervals. ( ), number of patients with "pseudotumors"

Table 2. Analysis of 16 patients with tumor recurrences after CTX/BCG. The prognostically relevant parameters, number of visible tumors, stage, and grade were assessed as to no change, improvement, or deterioration

alteration	No. of tumors	stage	grade
no change	7	9	13
improvement	8	4	1
deterioration			
minor	1	1	2
major	–	2	–

Table 3. Side effects of chemoimmune prophylaxis

side effect	n	%
nausea (after CTX)	74	57
dysuria	103	79
pollakisuria	76	58
fever	41	31
allergy	1	0,8
epididymitis	1	0,8

both patient groups as to the prognostically relevant tumor parameters.

The 16 patients with recurrences despite CTX/BCG treatment show stabilisation of those factors relevant for prognosis in most cases. In some of these patients improvement in this regard was noted whereas in 2 individuals a marked deterioration of the tumor stage was observed (Table 2). In both patients tumor progression occured during the first six months postoperatively. In one case with 6 primary tumors the recurrent tumor (stage pT3 N2 MO) developed in the bladder dome. Retrospectively, it cannot be excluded that this tumor had been overlooked at the time of primary operation. In the other patient with a large tumor originally (stage pT1, grade 2) lymphography revealed the possibility of a lymph node metastasis. However, a control roentgen film 4 weeks later did not confirm this suspicion so that CTX/BCG treatment was started. Six months later, a recurrent bladder cancer was diagnosed, staged T4 N2 M1 (lung metastasis). On retrospective analysis of this case it could be argued that at the time of primary surgery a lymph node metastasis was already present. On the basis of this assumption the observed clinical course of disease would be in accordance with the extremely bad prognosis well known in patients with proved positive pelvic lymph nodes [8].

During the follow-up, patients are not routinely checked for tumors of the renal pelvis or the ureter. As far as we know, in 2 patients transitional cell carcinomas of the renal pelvis developed, in one case with concomitant and in the other one *without* simultaneous bladder tumor recurrence.

The side effects of CTX/BCG treatment are shown in Table 3. Nausea was attributed to the cyclophosphamide injection, whereas the other symptoms were mainly the result of intravesical BCG instillations. The side effects generally were well tolerated and responded to symptomatic treatment. After termination of chemoimmune prophylaxis, all symptoms subsided. In no instance there was any pathological laboratory finding after treatment.

A very interesting phenomenon relates to certain tumor-like lesions, which histologically proved to be benign. Their predominant histological features were chronic inflammatory alterations of the stroma. The manifestion of these "pseudotumors" in relation to the same time intervals evaluated for the true recurrences are drawn in Fig. 4.

Discussion

Our favourable results of chemoimmune prophylaxis conform with reports of other authors using BCG treatment alone without preceding cyclophosphamide injection [4–7]. Moreover, in prospective randomized studies the benefical effect of BCG for the prevention of tumor recurrence has been demonstrated [4, 6]. The data summarized in Table 1 indicate that in our two patient groups the prognostically relevant parameters are comparable so that any significant bias of the treatment results can be excluded. Our group of 48 patients with recurrent bladder tumors offer an excellent possibility for valid statistical conclusions. Comparing the number of tumors as well as the tumor episodes before and after CTX/BCG treatment, the differences are statistically significant using the Wilcoxon test ($p < 0.01$). At present, we are unable to prove the hypothesis that – like in certain animal experiments [1] – cyclophosphamide acts synergistically to the immunostimulatory effect of BCG.

Analysing our patients with tumor recurrences despite CTX/BCG, there were only 2 cases exhibiting definite deterioration despite chemoimmune prophylaxis. Whether this represents BCG induced tumor enhancement remains very questionable on the basis of our clinical observations. In contrast to other authors [6], for that reason we still hesitate to use BCG in patients with tumors invading muscle which might be associated with regional lymph mode metastases. Further follow-up controls of BCG treated patients with special emphasis on possible recurrences of the renal pelvis and ureter are warranted to decide whether, after CTX/BCG treatment, the upper urinary tract becomes more vulnerable to cancerous lesions while the bladder itself remains protected. Benign tumor-like alterations of the mucosa (pseudotumors) are also of considerable interest since endoscopically they are indistinguishable from true tumor recurrences. The incidence of these lesions does not show any peak like the true recurrences in the untreated or CTX/BCG treated groups. At present, the biological significance of these "pseudotumors" remains obscure; albeit the appearance of these lesions does not imply any disadvantage to the patients as far as our longterm follow-up controls indicate.

The side effects of our treatment were essentially as previously described [6]. In a total of 130 treated patients no serious complications were observed nor did we encounter any abnormality in the routine laboratory analyses after CTX/BCG.

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