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Acceptability of simultaneous irradiation and mono/polichemotherapy with cis/carboplatin

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By improving local and systemic control of the disease, simultaneous polychemotherapy and radiotherapy could exert a favorable effect on the curability of patients with locally advanced tumors of the urinary bladder. The question remains, however, how to adjust both therapeutic schedules so as to keep the associated toxic side effects within acceptable limits. Our retrospective study was aimed to assess the toxicity of concurrent chemotherapy with cis- or carboplatin and with/without vinblastine and methotrexate in combination with irradiation in 14 patients with locally advanced carcinomas of the urinary bladder or symptoms of obstructive uropathy. As compared to irradiation alone, the combined therapy was associated with greater - particularly gastrointestinal - toxicity (in 8/14 patients grade 2,3) and low tolerability, which required adjustment of chemo- or radiotherapy in more than half of the patients (8/14). Considering the indicated dependence of toxic side effects from the type of cytotoxic therapy, and the fact that the peak of side effects occurs within 3-4 weeks of therapy, perhaps an acceptable level of combined-treatment-related toxicity could be achieved by daily applications of lower doses of cytotoxic drugs and a split-course irradiation regimen, with discontinuation of irradiation during the acute phase of side effects.

Key words: bladder neoplasms-drug therapy-radiotherapy; invasive bladder cancer, tolerability of chemoradiotherapy

Introduction

Although cystectomy represents a standard therapy for invasive carcinoma of the urinary bladder, the so-called conservative approach - i.e. transurethral tumor removal with chemotherapy (ChT) and irradiation (RT)- offers equal chances of cure as cystectomy.[1,2] As to the success of local control of disease in the bladder and pelvis, the conservative therapy by enabling bladder preservation in 2/3 of patients yields results comparable to those obtained by radical cystectomy using modern surgical techniques, which ensures 70-85% probability of local disease-free survival.[3,4] Local control with conservative therapy depends on T stage and patency of the ureters; the risk group consisting of the tumors which penetrate through the bladder wall and/or cause blockage of the ureters.[2,5] Apart from worse local control, patients with such tumors run a higher risk of metastatic dissemination.[6] Treatment results could be

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improved by immediate simultaneous application of chemotherapy and irradiation, which would result in a better local control attributable to the interaction between chemo- and radiotherapy, as well as to the systemic control exerted by chemotherapy. This was also the main objective of our study which was aimed to assess the acceptability of such treatment.

Material and methods

Our retrospective study was carried out on a series of patients with carcinoma of the urinary bladder invading the bladder wall or blocking the ureters, who were treated by irradiation and simultaneous cisplatin or carboplatin based mono- or polychemotherapy in the period from 1994 to 1997.

The decision about treatment with either one or both cytotoxic drugs depended on the preservation of renal function. The latter was assessed on the basis of the evaluation of serum levels of creatinine and blood urea nitrogen, as well as on the evaluation of endogenous creatinine and/or ^{125}J hippuran clearance; with increased serum creatinine values or with more than half reduced creatinine or ^{125}J hippuran elimination, the patients received carboplatin-based chemotherapy, while in other cases cisplatin was used instead. Sometimes the schedule would also include vinblastine or vinblastine and methotrexate. Two different methods of chemotherapy application were used: 1) low doses of cytotoxic drugs were given regularly every week throughout the duration of radiotherapy (continued chemotherapy - CChT), or 2) ChT schedule was applied in standard 3-week intervals (intermittent chemotherapy - IChT).

Irradiation was carried out on linear accelerators, using the 4-field technique and standard regimen: the patients were irradiated once daily for 5 days weekly, in 2-2.2 Gy doses. In the case of disseminated disease, the irradiation field included the urinary bladder alone, while with the disease limited to the urinary bladder the field also included regional lymph nodes. The planned target doses were as follows: 46 Gy for the areas of microscopic disease, and 63.4 to 66 Gy for macroscopically visible tumors. In the case of disseminated disease, the target dose was limited to 50 Gy, also for the area of macroscopic disease.

The extent of disease was evaluated according to TNM classification (modified in 1997).

Treatment related side effects, i.e. acute hemo- and nephrotoxicity, were assessed according to WHO recommendations; acute proctitis, enteritis and cystitis were evaluated by means of RTOG scale for the assessment of acute irradiation-related side effects: acute proctitis grade II was further classified as grade IIA in the cases when the acute difficulties persisted despite the supportive therapy given.

Symptoms of postirradiation cystitis and proctoenteritis was also assessed with respect to the radiation dose received, and the time interval from the beginning of irradiation to the onset of difficulties.

Problems associated with postirradiation cystitis were also evaluated against the signs of already present cystitis at the beginning of irradiation, attributable either to tumor growth, previous surgeries or to chemotherapy.

Acceptability was assessed according to a possible need for discontinuation of chemo- and/or radiotherapy or premature cessation of treatment.

Side effects as well as acceptability of treatment were assessed according to the type of therapy: mono / polychemotherapy, intermittent / continued and more (MChT) / less intensive (LChT) chemotherapy with cisplatin or carboplatin. The latter two groups were determined by the median cumulative dose of carbo- or cisplatin per m2 of body

surface / week, which was (in the case of more intensive ChT) or was not exceeded (less intensive ChT).

Results

The study included 14 patients, 10 males and 4 females, aged 62-75 years (median age 65 years). The stage was assessed as T2 N0-x M0 in 5/14 patients, and as T3 N0-x M0 in 7/14 patients; in one the stage was defined as T4 N2 MO and T2 No-x M1 respectively. Histological findings were as follows: transitiocellular ca. in 10/14 patients (grade 2 in 6/10, grade 2-3 in 2/10 and grade 3 in 2/10 patients), non-differentiated anaplastic carcinoma in 3/14 and microcellular carcinoma in 1 patient. Signs of obstructive uropathy were present in 7/14 patients, of these 3 presented with bilateral ureteral obstruction. Renal dysfunction was observed in 8/14 patients; in all 7 with obstructive uropathy, and in one due to previous nephrectomy.

The method of therapy is presented in Table 1. In 9/14 patients ChT was based on cisplatin, while in 5/14 it was based on carboplatin.

Either cisplatin or carboplatin was used as mono-ChT in 5/14, and as poly-ChT in 9/14 patients - vinblastine was added to the schedule in 4/9 and vinblastine plus methotrexate in 5/9 patients.

As to the mode of application, CChT was used in 11/14, and IChT in 3/14 patients.

The intensity of ChT applied simultaneously with irradiation was as follows: platinol 22.2 - 40 mg/m^2/week (median 26.2 mg/m^2/week), carboplatin 65-181 mg/m^2/week (median 136 mg/m^2/week), vinblastine 0.8-1 mg/m^2/week (median 1 mg/m^2/week) and methotrexate 4.5-15 mg/m^2/week (median 8mg/m^2/week).

All patients were irradiated on linear accelerators, using four-field technique. Target doses (TD) applied to the urinary bladder ranged between 28 Gy - 66 Gy (median 60 Gy), delivered in 2-2.5 Gy fractions (median 2 Gy).

Treatment related side effects are presented in Table 2. These were most frequently associated with postirradiation proctitis, the difficulties being present in 13/14 patients. The problems occurred within the 2nd - 5th week of therapy, in the majority of patients (9/13) within the 3rd - 4th week of therapy. In 8/13 patients the problems considerably influenced the patients' quality of life, and were actually intolerable, despite the supportive therapy (grade 2A-4), the patient's performance status being directly affected in 3/8 cases (grade 3, 4); in one of the latter three patients, side effects were an indirect cause of the patient's death. With respect to mono- or poly-ChT, the intensity of proctitis related difficulties was comparable: grade 2A, 3 problems were established in 3/5 patients with mono-ChT and in 5/8 patients with poly-ChT. The difference related to the mode and intensity of chemotherapy was more obvious: grade 2A-4 problems were observed in all (3/3) patients with IChT and in 4/11 with CChT, and in 6/7 and 2/7 with with MChT or LChT.

Postirradiation cystitis related problems were less frequent. Cystitis symptoms prior to the onset of chemo-radiotherapy were present in 12/14 patients. Worsening of the symptoms during therapy occurred in 6/14 patients after 3-5 weeks from the beginning of treatment, in the majority of these (5/6) within the 4th - 5th week of therapy. All 6 patients presented with grade 3,4 side effects. There were no differences in the intensity of side effects noted with respect to mono vs. polychemotherapy, continuous vs. intermittent ChT,, and more intensive vs. less intensive ChT: thus grade 2A-4 difficulties were observed in 3/5 and 3/9 patients receiving either mono- or polychemotherapy, in 1/3 and 5/11 with IChT or CChT, and in 3/7 and 3/7 with MChT or LChT.

Table 1. Treatment of 14 patients receiving concurrent ChT and RT by intensity of treatment with platinol and carboplatin, type of adjuvant ChT, tumor dose (TD) of irradiation and duration of RT.

Pts. No.	Platinol		Other ChT	RT	
	mg/m^2/week	No. doses/weeks		Dose	Time
1	27	3/3 w.		66 Gy	66 days
2	23	5/5 w.		58.5 Gy	43 days
3	25	4/4 w.		64 Gy	44 days
4	26	5/5 w.	Vlb	65.2 Gy	64 days
5	30	2/2 w.	Vlb	28 Gy	12 days
6	26.2	2/2 w.	Vlb	66 Gy	42 days
7	34	3/5 w.	Vlb, Mtx	60 Gy	47 days
8*	40	3/5 w.	Vlb, Mtx	66 Gy	57 days
9*	22.2	1/3 w.	Vlb, Mtx	60 Gy	43 days

Pts. No.	Carboplatin		Other ChT	RT	
	mg/m^2/week	No. doses/weeks		Dose	Time
10	148	2/3 w.		50 Gy	40 days
11	83	4/4 w.		46 Gy	36 days
12	65	4/6 w.	Vlb, Mtx	64 Gy	47 days
13*	181	2/4 w.	Vlb, Mtx	59.4 Gy	42 days
14	136	3/4 w.	Vlb	55 Gy	44 days

Mtx:methotrexate; Vlb: vinblastine, w.: week, *: intermittent chemotherapy (IChT)

Table 2. Acute treatment related toxicity by acceptability of therapy, need for discontinuation of ChT/RT and the cause for discontinuation, as well as by grade and time of side effect occurrence (proctoenteritis, cystitis, also with respect to presence of symptoms before the beginning of chemotherapy), and by signs of leukopenia, thrombo topenia, anemia and renal failure

Pts No.	Decontinuation		Proctoenterites		Cystitis		Leuko-cytes	Hemo-gobin	Trombo-cytes	Creatine
	Type	Cause	Grade	Week	Grade#	Week	Grade	Grade	Grade	Grade
1	RT,ChT	PS	2A	3	2/2		0	0	0	1
2	0	0	1	2	3/3		0	0	0	0
3	ChT	P,C	2A	4	1/4	4/5	0	0	0	0
4	0	0	2	3	1/1		1	0	0	0
5	RT,ChT	P	3	3	0/0		0	0	0	1
6	ChT	RF	2	3	1/1		0	0	1	2
7	ChT	P,C	2A	4	1/3	3	0	0	0	0
8	RT, ChT	P	3	(2)*5	1/1		1	0	0	0
9	RT,ChT	P	2A	(2)*5	1/1		1	0	0	0
10	0		3	4	1/3	5/6	0	3	2	0
11	0		1	4	1/4	5	0	0	1	0
12	0		0	0	1/3	4	2	1	2	0
13	RT,ChT	P,C	2A	(2)*6	1/3	5	2	2	3	1
14	RT,ChT**	P	2	1′	4/4		0	2	1	0

RT: radoitherapy, ChT: chemotherapy, P: proctitis, C: cystitis, PS: performance status, RF: renal failure, # grade of cystitis symptoms at the beginning / during irradiation, ()* interval from IChT to the onset of symptoms,
**: planed 2-week discontinuation of radio- and chemotherapy

Signs of more expressed hemotoxicity (grade 2,3) were present in 4/14 patients: in 4/5 receiving carboplatin and in none of those receiving cisplatin. Leukopenia was observed in 2/5 patients, while anemia and thrombocytopenia occurred in 3/5 patients each. Hematological side effects did not require moderation of therapy. A severe renal dysfunction was found in one patient. This particular case required discontinuation of concurrent chemotherapy (Table 2).

The previously planned treatment had to be changed in 8/14 patients: while 3/8 required cessation of chemotherapy only, in 5/14 patients radiotherapy had to be discontinued as well. The reasons for discontinuation were as follows: postirradiation proctitis (4 patients), postirradiation proctitis and cystitis (3 patients) and renal failure (1 patient). In 5/8 patients treatment had to be changed in the 5th week of chemotherapy, in 1/8 in the 4th week, and in 2/8 patients in the 3rd week of chemotherapy. Radiotherapy had to be completed prematurely in 3/14 patients.

Discontinuation of therapy occurred in altogether 5/13 patients in whome no treatment break was planned. Also in this group the patients with intermittent and more intensive chemotherapy were prevailing: thus, discontinuation of both irradiation and chemotherapy was necessary in 3/3 and 2/10 patients with IChT/CChT, and in 4/6 and 1/7 patients with MChT/LChT.

By the end of follow up which lasted from 6 to 34 months (median 12 months) 7/14 patients are still alive, 5/7 without evidence of disease and 2/7 with residual tumor of the urinary bladder. Seven patients have died, of these 5 due to dissemination, 1 with evidence of dissemination and local recurrence, while one patient with total remission of the disease in the bladder died of an unknown cause. One patient died due to treatment related toxicity.

Discussion

Our study was aimed to define new starting points in the treatment of patients with advanced carcinoma of the urinary bladder. So far, the results of concurrent (mono) chemotherapy and irradiation have not been encouraging, particularly in terms of the survival of patients with advanced carcinoma of the urinary bladder. A meta-analysis of randomized studies concerned with neoadjuvant or concurrent monochemotherapy with cisplatin also failed to evidence better survival results.[9] Although simultaneous use of cisplatin and irradiation has the potential of improving local control of the disease,[10] it cannot ensure control of distant dissemination. A higher rate of cures could be achieved through better systemic control of the disease, which is known to be significantly better with polychemotherapy combining vinblastine, methotrexate, adriablastin and cisplatin, than with cisplatin alone[11] The question remains how to achieve an optimal combination of polychemotherapy and irradiation. The experience with treatment of ORL tumors[12] as well as our own poor results achieved in the treatment of advanced

Table 3. Unplanned discontinuation of ChT or ChT + RT by mono- vs. poly-ChT, continued vs. intermittent ChT, and by less vs. more intensive ChT

Type of ChT	Discontinuation of ChT	Discontinuation of ChT and RT
Mono-ChT	2/5 pts.	1/5 pts.
Poly-Cht	6/8 pts.	4/8 pts.
Continued ChT (CChT)	5/8 pts.	2/10 pts.
Intrmittent ChT (IChT)	3/3 pts.	3/3 pts.
Less intensive ChT (LChT)	3/7 pts.	1/7 pts.
More intensive ChT (MChT)	5/6 pts.	5/6 pts.

tumors by means of sequential chemo-radiotherapy,[13] seem to speak in favor of the use of imediate concomitant radio and chemotherapy. The key problem that remains to be solved is related to the toxicity of concomitant polychemotherapy and irradiation: to what extent can the expectedly increased toxicity limit the acceptability of such treatment?

The toxicity of concomitant chemo-radiotherapy in our study was considerable. The comparison of acute side effects resulting from irradiation as single-modality treatment vs. irradiation as part of sequential chemoradiotherapy showed no statistically significant difference,[13] while the comparison of toxicity of concurrent chemo-radiotherapy vs. radiotherapy alone showed that the combined treatment was associated with greater toxicity, which renders such treatment less acceptable.

The main difficulties which restricted the acceptability of concomitant chemo-radiotherapy were associated with acute postirradiation proctoenteritis. They occurred in 87% of patients treated by chemo-radiotherapy, in 35% of these being so severe that the treatment had to be discontinued. In the comparable group of patients treated by radiotherapy alone, the difficulties (frequent stools, flatulence and mucous discharge) occurred in 46% of patients, while discontinuation of therapy was required in 23%.

Otherwise, the development of postirradiation proctoenteritis in patients treated by chemoradiotherapy is comparable to that seen in patients treated by irradiation alone. In a majority of patients, the difficulties occurred within the third week of irradiation, and mostly started to regress after the fifth week of therapy in both groups of patients, i.e. those receiving chemoradiotherapy as well as in those treated by radiotherapy alone.

Likewise proctitis problems, the symptoms of postirradiation cystitis following either concomitant chemoradiotherapy or irradiation alone were similar. This could perhaps be attributed to the preexisting cystic symptoms at the beginning of irradiation. In a majority of patients this could be due to previous surgical interventions or due to tumor growth in the urinary bladder. More prominent difficulties with voiding of urine at less than one-hour intervals occurred in approximately 1/3 of patients of both groups. These, however, never required cessation of therapy.

As compared to irradiation alone, higher toxicity of concomitant chemoradiotherapy is the main reason for lower acceptability of the combined therapy. In only 38% of patients receiving concomitant chemoradiotherapy, the treatment could be carried out without any adjustments in the therapeutic schedule. In the remaining 62% of patients, however, the adjustments were required, mostly of the chemotherapy part only, although in 35% of the patients radiotherapy had to be disrupted as well. In the group of patients treated by radiotherapy alone, the treatment related side effects did not require discontinuation or cessation of irradiation in 77%. In both groups of patients, i.e. those treated by chemoradiotherapy as well as those receiving irradiation alone, the main reason for change of therapy was attributable to the difficulties associated with postirradiation inflammation of the rectum and small intestine. The three-week interval to the development of proctitis symptoms, and 4-5-week interval to cessation or radiotherapy is similar in both groups. The majority of therapy discontinuations occurred within the appointed time period.

When paralleled with experience reported by other centers, the proctitis-related difficulties in our group of patients with concomitant chemoradiotherapy show some specific features, while the cystitis-related difficulties are comparable. With comparable irradiation regimens and concomitant chemotherapy with platinol, other authors report 26-47% incidence of proctitis symptoms.[7,8] The dif-

ference is probably not attributable to the mode of therapy with platinol - in most studies this was carried out in 2 - 3 -week intervals, with doses of 70 - 100 mg/m^2 - since the majority of our patients treated in a similar way (by the so-called intermittent chemotherapy) had more difficulties than others. Therefore it seems more likely that the cause lies in other cytotoxic drugs in the schedule, particularly methotrexate. Severe difficulties, which persisted despite the anti-diarrheic therapy, were present in all patients (4/4) receiving methotrexate as part of the concomitant chemotherapy.

Is it possible that a higher intensity of concomitant treatment with cis/carboplatin-based chemotherapy and irradiation could be associated with more postirradiation proctitis-related difficulties? In our study, the degree of difficulties increased by the intensity of chemotherapy, although the small number of patients and possible overlapping toxicity of methotrexate render any definitive conclusions questionable. The lower rate of proctoenteritis-related difficulties at a higher intensity mono-chemotherapy with cisplatin reported by other authors (in the majority of studies it ranged between 28-49mg/m^2/-week), speaks against the synergistic intestinal toxicity of radio- and chemotherapy with cis/carboplatin.[6,7,8,10]

Conclusions

1. The main reason for poor acceptability are the toxic side effects related to postirradiation proctoenteritis.
2. These typically occur only after the 2nd week of irradiation, and generally become more prominent within the 3rd - 4th week of irradiation, with interruption of chemotherapy or chemo- and radiotherapy in the 4th - 5th week of therapy.
3. Continuous chemotherapy seems to be more acceptable than intermittent chemotherapy.
4. The acceptability of polychemotherapy is worse than that of monochemotherapy, which could be attributed to the synergistic toxicity of methotrexate and radiotherapy exerted on the gastrointestinal tract.

The study points out the possibility of combined polychemotherapy and irradiation. Based on the facts that an optimal fractionation of chemotherapy within an irradiation schedule has not been clarified yet, and that possible interruptions and associated with that prolonged duration of irradiation within the framework of chemoradiotherapy probably do not diminish the success of local therapy,[14] an acceptable combination of both treatment modalities could be based on the following principles:

1. repeated applications of lower doses of cytotoxic drugs during the course of radiotherapy;
2. irradiation split into two courses, with an interruption during the time when the peak of toxic side effects is expected, i.e. in the 3rd and 4th week of therapy.

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