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Phase II trial

Phase II study of radiochemotherapy with vinblastine in invasive bladder cancer

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Abstract

Concurrent vinablastine-based radiochemotherapy was evaluated in 84 bladder-cancer patients. It was effective in more than half: tumour-specific survival (51% 9-year), local control rate (55% 9-year). The drawback was the impaired function of the bladder (9-year prevalence SOMA G3-4 symptoms: 66%), indicating the need for treatment aimed at reducing chronic morbidity. © 2005 Published by Elsevier Ireland Ltd. Radiotherapy and Oncology 75 (2005) 44–47.

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Cystectomy is, as a rule, the standard treatment for the patients with invasive transitional cell carcinoma of the urinary bladder (TCCB). Conservative treatment involving basically transurethral resection (TURB) and radiation is, due to primarily insufficient local control, applied with restrictions, i.e. only in the treatment of patients with contraindications to radical surgery or of those who a priori decline radical surgery.

In order to improve the effect of irradiation and as a result of our experience with vinblastine at the Ljubljana Institute of Oncology, we used vinblastine-based concurrent radiochemotherapy (RChT) in treating the invasive TCCB [1,2,14]. In view of the acute toxicity and the age of patients, the first results proved favorable, more effective than radiotherapy alone, and, as to complete remission rate, comparable to cisplatin-based chemotherapy [14]. Based on these conclusions, we started a phase-II study on the patients with invasive TCCB in 1989.

Materials and methods

From 1989 to 1994, 84 patients were treated at the Ljubljana Institute of Oncology with concurrent vinblastine and radiotherapy. The study eligibility criteria were histologically proven muscle invasive TCCB (cT2–4), as well as recurrent, or with TURB unresectable high-grade (G3) lamina propria invasive TCCB (cT1), without cytologically or histologically proven regional or distant metastatic spread and no prior irradiation or major surgery in pelvic region. In the majority of patients, radiotherapy was indicated because they were not eligible for cystectomy due to poor performance status and several accompanying diseases. The pre-treatment characteristics of patients at the start of RChT are shown in Table 1.

The treatment started with maximal TURB, followed by concurrent radiation and chemotherapy, with weekly applications of 2 mg of vinblastine in 6 h-intravenous infusion. The patients were irradiated in the supine position by an 8- or 10-MV linear accelerator. A four-field box technique and individually shaped portals were used to irradiate the bladder and pelvic lymph nodes and a three-field beam arrangement (one posterior and two anterior oblique) coned down to the bladder or, rarely, bladder tumour. The patients were treated once daily, five times a week with 1.8–2.2 Gy per fraction. The ICRU 50 total dose was 63.8–64.0 Gy to the urinary bladder and 46.0–46.2 Gy to the pelvic lymph nodes. Single plane planning was used. Target volumes were defined on paper from X-ray pictures and CT scan. Planned target volume (PTV) of coned-down field included the bladder and eventual extravesical extension with 2-cm margin. Treatment volume was defined by the 95% isodose surface encompassing PTV; the dose variation of 10% or less was acceptable. Portal films taken at the start and every second week afterwards were used to assess the accuracy of the treatment.

Three to 4 months after completing the radiotherapy, restaging was performed. Follow-up examinations (including cystoscopy with bladder washing cytology) were performed every 4 months for 2 years and, thereafter, every 6 months.

Acute toxicity was assessed according to the RTOG scale. Symptoms of late treatment urinary bladder, urethral

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Table 1
Pre-treatment characteristics of patients with invasive transitional cell carcinoma of the urinary bladder

Total number of patients	84
Sex	
Male	75
Female	9
Age (years)	
Median (range)	68 (42–81)
T-stage	
T1, T2	58
T3, T4	25
Unknown	1
Histological grade	
1, 2	48
3	34
Unknown	2
Previous urothelial tumour	16
Multifocality	24
Ureteral obstruction	12
Haemoglobin ($\leq$126 g/L)	22
Incomplete TURB	28
Positive cytology after TURB	39

TURB, Transurethral resection.

and rectal morbidity were regularly assessed at each medical checkup in the majority of patients by the first author himself and, after 1995, with special attention to the subjective part of the SOMA scoring system [16] regarding urinary bladder/urethra and rectal morbidity. Elements of the objective and analytic parts of the SOMA scoring system were not gathered systematically and were therefore not included in the analysis. For the data processing, the grade of rectal and urinary bladder morbidity was defined by the most prominent symptom experienced by the patient and the associated management. The analysis of late effects included only the patients that were in complete remission for the period of interest, in order to avoid the concealment of morbidity that was due to the recurrence of the disease.

The Kaplan–Meier product limit method was used to calculate the probability of overall, tumour-specific, progression-free survival and local control rate [15]. The incidence rate of late effects was calculated for 3-, 5- and 9-year periods with regard to the initial number of patients, while the prevalence rate was calculated after 3, 5 and 9 years of follow-up, with regard to surviving patients at these points of observation. To evaluate late effects, the survival analysis method was also applied [3]. *P*-value 0.05 or less was considered significant in all statistical testing. The statistical analysis was performed by SPSS statistical package for Windows (Version 11.0, SPSS, Inc., Chicago, IL, USA).

The study has been approved by the Committee for Medical Ethics of the Institute of Oncology Ljubljana in 1988.

Results

Out of 84 patients, 54 (64%) completed treatment as specified. Modifications urged by acute side effects were the omission of concurrent chemotherapy in 17/84 (20%) patients, and RT treatment break or reduction of total tumour dose in 13/84 (15%) patients. On average, the patients received five applications of vinblastine and a mean total tumour dose of 63.6 Gy (mean dose per fraction was 2.1 Gy). Median treatment time was 50 days. Acute reactions attributable to RChT, defined as the most pronounced side effect in each patient, were completely absent or of only mild degree (RTOG grade 0–1) in 45/84 (54%), moderate (RTOG grade 2) in 27/84 (32%), and severe (RTOG grade 3) in 12/84 (14%) patients; none of the patients developed grade 4 acute toxicity. Acute reactions appeared as a consequence of urinary tract lesion in 13/84 (16%) patients, intestinal lesion in 18/84 (21%) or both in 8/84 (9%) of patients. Haematological toxicity was minimal and appeared as a grade 1 leucopenia in 16/84 (19%) of patients.

The median follow-up of the alive patients was 10.3 years. Out of the 84 patients entered into the study, 59 patients (70%) died, of whom 24/84 patients (29%) died of causes other than bladder cancer. The 9-year overall survival rate was 25% and tumour-specific survival was 51% (Fig. 1). Progression of carcinoma occurred in 40/84 (48%) patients—as a result of local failure in 26/40 (66%) patients, distant metastatic spread in 5/40 (13%) patients or both in 9/40 (23%) patients. The 9-year progression-free survival was 46%.

Complete remission of the urinary bladder tumour was acquired in 61/78 (78%) patients. Evaluation of response was omitted in six patients—due to distant metastatic spread and deterioration of general condition in five, and due to myocardial infarction and death in one patient. Local recurrence, as the sole site of tumour progression, or as a component of simultaneous local and distant failure, was the consequence of superficial recurrence in seven patients, and invasive recurrence in 11 patients. Local control rate, based on the 9-year rate of bladder preservation with persistent complete remission, without either superficial or invasive tumour recurrence, was 55% (Fig. 1). Salvage cystectomy was performed in only 4/28 patients with persistent or

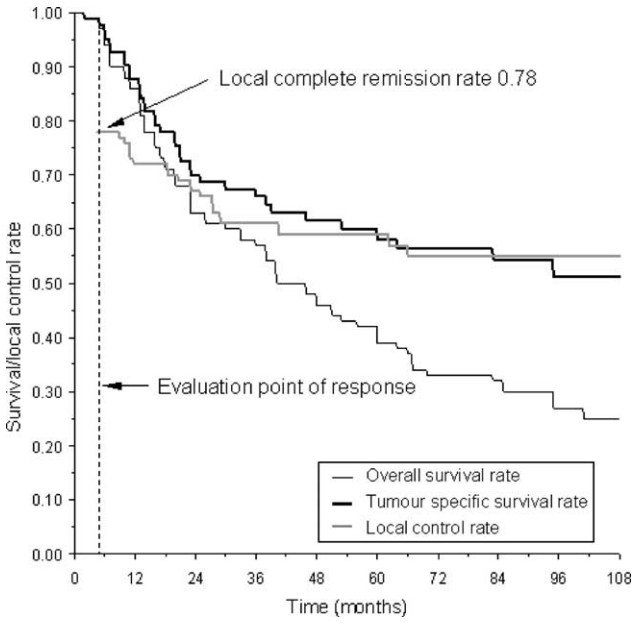

Fig. 1. Estimates of overall and tumour-specific survival rates, and local control rate in 84 patients with invasive transitional cell carcinoma of the urinary bladder.