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CLINICAL INVESTIGATION **Bladder**

RADIOCHEMOTHERAPY WITH CISPLATIN AND 5-FLUOROURACIL AFTER TRANSURETHRAL SURGERY IN PATIENTS WITH BLADDER CANCER

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Purpose: To give an update on the long-term outcome of an intensified protocol of combined radiochemotherapy (RCT) with 5-fluorouracil (5-FU) and cisplatin after initial transurethral resection of bladder tumor (TURBT) with selective organ preservation in bladder cancer.

Methods and Materials: One hundred twelve patients with muscle-invading or high-risk T1 (G3, associated Tis, multifocality, diameter >5 cm) bladder cancer were enrolled in a protocol of TURBT followed by concurrent cisplatin (20 mg/m^2/day as 30-min infusion) and 5-FU (600 mg/m^2/day as 120-h continuous infusion), administered on Days 1–5 and 29–33 of radiotherapy. Response to treatment was evaluated by restaging TURBT 4–6 weeks after RCT. In case of invasive residual tumor or recurrence, salvage cystectomy was recommended.

Results: Ninety-nine patients (88.4%) had no detectable tumor at restaging TURBT; 71 patients (72%) have been continuously free from local recurrence or distant metastasis. Superficial relapse occurred in 13 patients and muscle-invasive recurrence in 11 patients. Overall and cause-specific survival rates for all patients were 74% and 82% at 5 years, respectively. Of all surviving patients, 82% maintained their own bladder, 79% of whom were delighted or pleased with their urinary condition. Hematologic Grade 3/4 toxicity occurred in 23%/6% and Grade 3 diarrhea in 21% of patients. One patient required salvage cystectomy due to a shrinking bladder.

Conclusion: Concurrent RCT with 5-FU/cisplatin has been associated with acceptable acute and long-term toxicity. Overall and cause-specific survival rates are encouraging. More than 80% of patients preserved their well-functioning bladder. © 2007 Elsevier Inc.

Bladder cancer, Radiochemotherapy, 5-Fluorouracil, Cisplatin, Combined modality treatment.

INTRODUCTION

Trimodality treatment, including transurethral resection of bladder tumor (TURBT), radiation therapy (RT), and chemotherapy, is an alternative to primary cystectomy in high-risk T1 and muscle-invasive bladder cancer. Over the past 15 years, this approach has been investigated in prospective series from single centers and cooperative groups, with more than 1,000 patients included. Five-year overall survival rates in the range of 50–60% have been reported, and approximately three quarters of surviving patients maintained their bladder (1, 2).

The optimal regimen and combination of RT and chemotherapy, however, remains to be established. The only prospective, randomized comparison of RT alone vs. concomitant radiochemotherapy (RCT) in bladder cancer demonstrated an improved local control rate when cisplatin was given in conjunction with RT (3). However, this was a small study restricted to 99 patients and was not powered to detect even a 15% improvement in survival. In the Radiation Therapy Oncology Group (RTOG) series, a major effort was undertaken to determine the role of induction chemotherapy in studies 88-02 and, in a randomized design, in 89-03 (4, 5). In the latter study, treating patients with 2 cycles of induction MCV (methotrexate, cisplatin, and vinblastine) failed to improve complete response, local tumor control, and survival. Moreover, because of toxicity, only 67% of patients completed the MCV induction chemotherapy.

We designed a protocol of concomitant intensified RCT after initial TURBT using two well-established agents with radiosensitizing properties, cisplatin and 5-fluorouracil (5-FU), in an effort to improve both local and distant tumor control. Initial results of this trial on 45 patients were reported in 2002 (6). The present analysis on 112 patients so

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treated provides more mature data on local and distant control, 5-year survival rates, and acute and long-term toxicity, as well as patients' satisfaction with their preserved bladder.

METHODS AND MATERIALS

Patient eligibility

Between 1993 and 2006, a total of 112 patients with high-risk T1 (G3, associated Tis, multiple recurrences, >5 cm in diameter) or muscle-invasive T2–4 bladder cancer were entered into this prospective protocol. Initial evaluation included chest X-ray, computed tomography of the pelvis and abdomen, complete blood cell count and serum electrolytes, parameters of liver and kidney function, and creatinine clearance. White blood cell count >4,000/μL, platelet count >100,000/μL, bilirubin <1.5 mg/dL, and a creatinine clearance >60 mL/min were mandatory. Multiple TURBT before RCT, evidence of pelvic lymph node metastases, ureter obstruction successfully treated by a ureteral stent, or poor general physical condition with contraindications for radical cystectomy were not considered exclusion criteria. Patients were ineligible if there was evidence of distant metastases, including lymph node metastases above the bifurcation of the common iliac vessels, or prior pelvic irradiation, or contraindication for cisplatin, or 5-FU chemotherapy.

Treatment protocol

After written informed consent was obtained, initial TURBT was performed as thoroughly as was judged safely possible. Residual tumor was assessed histologically by biopsies from all resection margins and from the base of the resection. R0 indicated a microscopically complete TURBT, whereas R1 showed microscopic and R2 macroscopic tumor residual. Radiotherapy was initiated 4 weeks after TURBT using 6- to 10-MV photons and a four-field box technique with individually shaped portals and daily fractions of 1.8 Gy on 5 consecutive days. Patients were treated with empty bladder. The total dose to the whole bladder and pelvic lymph nodes ranged from 45 and 54 Gy. In case of R0 resection after TURBT, the whole bladder received a boost to 55.80 Gy with a 2-cm safety margin in all directions. After R1/2 resection, the boost dose to the whole bladder was increased to 59.4 Gy.

Concurrent chemotherapy was applied in Weeks 1 and 5 of RT and consisted of cisplatin (20 mg/m^2/day, 30-min i.v. infusion) and 5-FU (600 mg/m^2/day, 120-h continuous infusion). Hematologic and nonhematologic acute toxicities were recorded every week according to the National Cancer Institute Common Toxicity Criteria, version 2.0 (7).

Criteria for response, follow-up, and late toxicity

Six to eight weeks after completion of RCT, response was evaluated by restaging TURBT of the former tumor region. In case of histologically proven complete response, patients were followed up at 3-month intervals for the first 3 years, including urine cytology, cystoscopy, and biopsies of all suspected areas. For persistent or recurrent invasive tumor, salvage cystectomy was recommended. Evaluation of late toxicity was performed using a questionnaire based on the LENT-SOMA (late effects of normal tissue–subjective, objective, management, and analytic) grading system (8). In addition, the International Prostate Symptom Score (9) was used to assess patient satisfaction with their bladder function.

Table 1. Patient and tumor characteristics

Characteristic	No. of patients	Percentage
All patients	112	100
Gender		
Male	88	79
Female	24	21
Median age at diagnosis (y)	64	
Primary tumor	79	70
Recurrent tumor	33	30
Tumor status		
T1	54	48
T2	53	47
T3	3	3
T4	2	2
Grade		
1/2	47	42
3/4	65	58
Residual tumor status		
R0	61	55
R1	34	30
R2	11	10
Unknown	6	5
Multifocality		
Yes	44	39
No	67	60
Unknown	1	1
Associated Tis		
Yes	24	21
No	81	72
Unknown	7	7
Ureter obstruction		
Yes	23	20
No	89	80

Statistical analysis

Patients were followed up until January 2006. Actuarial survival rates were calculated from the end of RCT to the time of the last follow-up visit or death, using the method of Kaplan-Meier. Differences were analyzed using the log–rank test. The level of significance was 0.05 (two-sided) in all statistical testing. The statistical analysis was performed with SPSS for Windows, version 14.0 (SPSS, Chicago, IL).

RESULTS

Patient and tumor characteristics

Between 1993 and 2006, a total of 112 patients (24 women and 88 men) were recruited. Patient and tumor characteristics are shown in Table 1. At the time of analysis, the median follow-up time for all patients was 27 months (range, 3–191 months). Fifty patients have been followed for more than 3 years and 33 patients for more than 5 years.

Initial treatment response and early salvage treatment for nonresponders

Initial treatment response was assessed 4–6 weeks after completion of RCT by restaging TURBT. Ninety-nine of the entire cohort of 112 patients (88.4%) showed a complete pathologic response (CR) (Fig. 1). For the subgroups of