The Natural History of Clinically Complete Responders to Neoadjuvant Chemotherapy for Urothelial Carcinoma of the Bladder

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Abbreviations and Acronyms

CSS = cancer specific survival

cT0 = clinical complete response

MIBC = muscle invasive bladder cancer

MVAC = methotrexate, vinblastine, doxorubicin and cisplatin

NC = neoadjuvant chemotherapy

NMIBC = nonMIBC

pT0 = pathologically free of cancer

RC = radical cystectomy

TURBT = transurethral bladder tumor resection

Accepted for publication March 13, 2014.

Study received institutional review board approval.

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Purpose: We describe the clinical course of patients who achieved cT0 status after neoadjuvant chemotherapy for muscle invasive bladder cancer. There is no established treatment paradigm for these patients.

Materials and Methods: We retrospectively reviewed the records of 109 patients with muscle invasive bladder cancer (T2 or greater urothelial carcinoma of the bladder) who underwent platinum based neoadjuvant chemotherapy at our institution from 1988 to 2012. Post-chemotherapy assessment of the response included cytology, cystoscopy with biopsy and cross-sectional imaging.

Results: Of 109 patients 32 (29.4%) achieved cT0 status after neoadjuvant chemotherapy. Mean ± SD age of the cohort was 68.3 ± 9.6 years. Of the patients 21 received MVAC, 8 received gemcitabine and cisplatin, and 3 received another regimen. Seven complete responders elected immediate radical cystectomy after the completion of neoadjuvant chemotherapy. Of 25 patients who refused radical cystectomy after achieving cT0 status 7 experienced relapse after the completion of neoadjuvant chemotherapy and proceeded to radical cystectomy. The remaining 18 patients (72%) retained the bladder, including 6 (18.8% of the cohort) in whom nonmuscle invasive relapses were managed conservatively and 12 (37.5%) with no recurrence. In the 25 patients who elected bladder preservation after achieving cT0 status following neoadjuvant chemotherapy 5-year cancer specific survival was 88%.

Conclusions: With proper counseling and identification of treatment goals patients with cT0 after neoadjuvant chemotherapy for muscle invasive bladder cancer may have the option to retain the bladder with durable survival. Larger studies are needed to identify possible predictors of response on the clinical, pathological and molecular levels.

Key Words: urinary bladder, carcinoma, drug therapy, neoplasm invasiveness, cystectomy

Bladder cancer was diagnosed in approximately 72,500 individuals in the United States in 2013 and 20% to 30% of patients have MIBC at presentation.[1,2] This is the fourth most common type of cancer in men.[3] The current standard of care for MIBC is RC but it has a high rate of morbidity and mortality, and a major impact on quality of life.

In 2003 the SWOG S8710 trial evaluated the efficacy of NC as treatment of locally advanced bladder cancer.[4] After neoadjuvant MVAC

0022-5347/14/1923-0696/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2014.03.078
Vol. 192, 696-701, September 2014
Printed in U.S.A.

38% of patients were rendered pT0 at cystectomy compared to a pT0 rate of 15% in the RC only arm. The contribution of RC in achieving long-term disease-free status in patients with pT0 in that trial is unknown since all patients underwent RC without prior cystoscopic assessment of the response to chemotherapy. Some patients treated with RC for pT0 cancer may have been cured by TURBT and NC alone so that RC may not have been necessary.[5,6]

In the later SWOG S0219 trial tumor status was evaluated in patients with cT0 after NC. In this carboplatin based trial cT0 was rejected as a correlate of pT0 after cystectomy.[7] However, Herr reported experience with patients who initially refused cystectomy after cisplatin based therapy with an encouraging rate of bladder preservation and a high correlation of cT0 with pT0 status.[8]

Because there are no validated treatments or surveillance protocols for patients who achieve cT0 following systemic platinum based NC and who wish to preserve the bladders, it is unknown whether any of them can forego RC without compromising oncologic outcomes. In this retrospective study we describe the natural history of a population of patients at a single institution with MIBC who achieved cT0 status after systemic platinum based NC. Patients elected cystoscopic surveillance or immediate RC after chemotherapy.

METHODS

We retrospectively reviewed the institutional review board approved urological oncology database at our institution. We identified all patients with MIBC who received platinum based chemotherapy from January 1988 to December 2012. Clinical stage was based on the pathology report after TURBT and on clinical and radiographic data. Patients who were not assessed for a response preoperatively and those who received chemotherapy in the adjuvant setting or for initial metastatic disease were excluded from analysis. Medical records of patients who met inclusion criteria were reviewed and initial pathology findings, chemotherapy regimen and response status were analyzed. The choice of NC regimen was at the discretion of the medical oncologist treating the patient based on changing criteria with time.

A complete clinical response to NC was defined as no evidence of residual disease at first followup on any abdominal and pelvic computerized tomography, urine cytology and cystoscopy with deep transurethral resection biopsies of the bladder mucosa down to the muscularis propria layer in all patients. Surveillance of those patients was based on institutional and widely accepted protocols of cytology and cystoscopy with or without biopsies every 3 months for the first 2 years, cross-sectional imaging every 4 months for the same period, cytology, cystoscopy with or without biopsies and cross-sectional imaging every 6 months for another 2 years, and yearly followup thereafter. Biopsies were performed at the first assessment after systemic treatment and as clinically indicated by positive cytology results or suspicious findings on cystoscopy. Patients who achieved initial cT0 as well as those with relapsed NMIBC were counseled regarding treatment options. RC was offered to all patients after NC as the best option based on the available literature throughout followup. All RCs included lymph node dissection and were performed by surgeons at our comprehensive cancer center.

Our study patients were evaluated based on their choice of immediate RC or cystoscopic surveillance and outcomes are reported accordingly. The Fisher exact test was used to compare complete response rates among chemotherapy regimens. Log rank tests and Kaplan-Meier survival plots were used to compare CSS among various combinations of immediate RC, delayed RC and no cystectomy cT0 cases.

RESULTS

A total of 129 patients treated with platinum based NC for urothelial carcinoma of the bladder were followed at our institution from January 1988 to December 2012. Of the 129 patients 109 received NC for MIBC, including 32 (29.4%) who were cT0 following NC. Table 1 lists the complete clinical

Table 1. *Patient demographic and clinical characteristics*

	Cohort	Conservative	Cystectomy	p Value
No. pts	32	18	14	—
No. male (%)	26 (81.3)	15 (83.3)	11 (78.6)	0.7457
Mean ± SD age at systemic NC	68.3 ± 9.6	68.6 ± 9.7	68.1 ± 9.8	0.8904
No. race (%):				0.5044
White	29 (90.6)	16 (88.9)	13 (92.9)	
Other	2 (6.3)	1 (5.6)	1 (7.1)	
Unknown	1 (3.1)	1 (5.6)	0	
No. clinical stage T2 or greater before systemic NC (%)	32 (100)	18 (100)	14 (100)	—
Median days diagnosis-systemic NC (range)	37.5 (1–121)	37.5 (3–121)	32.5 (1–103)	0.7038
No. regimen (%):				0.9828
MVAC	21 (65.6)	12 (66.6)	9 (64.3)	
Gemcitabine/cisplatin	8 (25.0)	5 (27.8)	3 (21.4)	
Gemcitabine/carboplatin	2 (6.3)	1 (5.6)	1 (7.1)	
Carboplatin	1 (3.1)	0	1 (7.1)	