A Retrospective Analysis of the Effect on Survival of Time from Diagnosis to Neoadjuvant Chemotherapy to Cystectomy for Muscle Invasive Bladder Cancer

Jong Chul Park,* Nilay M. Gandhi,* Michael A. Carducci,* Mario A. Eisenberger,* Alexander S. Baras,* George J. Netto,* Jen-Jane Liu,* Charles G. Drake,* Mark P. Schoenberg,† Trinity J. Bivalacqua* and Noah M. Hahn*,‡

From the Departments of Oncology (JCP, MAC, MAE, CGD, NMH), Urology (NMG, MAC, MAE, JJL, CGD, TJB, NMH), Pathology (ASB, GJN) and Immunology (CGD), Johns Hopkins University Sidney Kimmel Comprehensive Cancer Center, Baltimore, Maryland, and Department of Urology, Montefiore Medical Center and Albert Einstein College of Medicine, New York, New York (MPS)

Abbreviations and Acronyms

GC = gemcitabine and cisplatin

MIBC = muscle invasive bladder cancer

MVAC = methotrexate, vinblastine, doxorubicin and cisplatin

NAC = neoadjuvant chemotherapy

OS = overall survival

RC = radical cystectomy

TURBT = transurethral resection of bladder tumor

ypCR = complete pathological response after NAC

ypPR = partial pathological response after NAC

Purpose: We determine the impact of the timing of radical cystectomy from the diagnosis of muscle invasive bladder cancer on survival in patients also treated with neoadjuvant chemotherapy.

Materials and Methods: We performed a retrospective chart review of consecutive patients with muscle invasive bladder cancer who received neoadjuvant chemotherapy followed by cystectomy between 1996 and 2014 at a single institution. Cox proportional hazards regression models were used to investigate the effect of treatment time intervals on overall survival. Three treatment intervals were analyzed for survival impact, from diagnosis of muscle invasive bladder cancer to initiation of neoadjuvant chemotherapy, from initiation of neoadjuvant chemotherapy to cystectomy and from diagnosis to cystectomy. Other pretreatment and posttreatment clinicopathological parameters were also analyzed.

Results: Median time from the diagnosis of muscle invasive bladder cancer to radical cystectomy was 28 weeks. Cystectomy performed less than 28 weeks from the diagnosis did not result in significant improvement in overall survival outcomes (HR 0.68, 95% CI 0.28−1.63, p=0.388). Neither the timing of neoadjuvant chemotherapy initiation from diagnosis (median 6 weeks) nor the timing of cystectomy from neoadjuvant chemotherapy initiation (median 22 weeks) was associated with survival. Patient age, variant histology, extravesical and/or lymph node involvement (T3-4 and/or N1 or greater) were significantly associated with survival.

Accepted for publication November 9, 2015.

The corresponding author certifies that, when applicable, a statement(s) has been included in the manuscript documenting institutional review board, ethics committee or ethical review board study approval; principles of Helsinki Declaration were followed in lieu of formal ethics committee approval; institutional animal care and use committee approval; all human subjects provided written informed consent with guarantees of confidentiality; IRB approved protocol number; animal approved project number.

* No direct or indirect commercial incentive associated with publishing this article.

† Financial interest and/or other relationship with Elsevier, Photocure SA, Heat Biologics and Theracoat Ltd.

‡ Correspondence: Johns Hopkins University Sidney Kimmel Comprehensive Cancer Center, Bunting-Blaustein Cancer Research Building 1, Room 1M42, 1650 Orleans St., Baltimore, Maryland 21287 (telephone: 443-287-0553; FAX: 410-614-8397; e-mail: nhahn4@jhmi.edu).

See Editorial on page 821.

For another article on a related topic see page 1126.

0022-5347/16/1954-0880/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2015.11.024
Vol. 195, 880-885, April 2016
Printed in U.S.A.

Conclusions: The timing of radical cystectomy in relation to muscle invasive bladder cancer diagnosis date does not significantly impact overall survival in patients with muscle invasive bladder cancer receiving neoadjuvant chemotherapy.

Key Words: urinary bladder neoplasms, neoadjuvant therapy, cystectomy, time factors

RADICAL cystectomy is the mainstay treatment for muscle invasive bladder cancer. However, surgery alone is associated with a suboptimal disease control rate and survival due in part to micrometastases. Due to its proven improvement in overall survival in randomized trials, cisplatin based combination chemotherapy given before cystectomy is recommended for patients with MIBC eligible to receive cisplatin.[1]

Several studies have evaluated various clinical factors for the prognosis of MIBC. Extravesical tumor stage (T3-4), advanced age, nonurothelial variant histology and a reduced number of lymph nodes removed have been established as poor prognostic factors for patients treated with radical cystectomy.[2–6] In addition, the timing of radical cystectomy has been proposed to be another prognostic factor for MIBC.[7–10] Several studies suggested that delay of cystectomy by more than 12 weeks from the diagnosis date is associated with inferior survival.[11] However, these studies were performed before the wide acceptance of cisplatin based neoadjuvant chemotherapy. Thus, these efforts mainly evaluated patients who were treated with surgery alone or mixed populations with small proportions of patients receiving various perioperative therapies. Investigations examining the relationship between time from diagnosis to cystectomy in patients treated with NAC are lacking. Therefore, we conducted the current study to determine the effect on survival of the timing of radical cystectomy from the diagnosis of MIBC in patients who received NAC.

MATERIALS AND METHODS

Patient Population

The Johns Hopkins Hospital institutional review board approved (N0:03-03-07-02d) bladder cancer database was queried to identify patients who received NAC and underwent radical cystectomy between 1996 and 2014. Patients with known clinical metastatic disease or noninvasive disease, with tumor with small cell histology, who received concurrent chemoradiation therapy and whose data were incomplete for analysis, were excluded from the study.

Clinical and Pathological Data Evaluation

Patient charts were reviewed for 1) baseline pretreatment characteristics including demographics, clinical stage, histology and previous intravesical therapy history; 2) intervals between diagnosis of MIBC at TURBT and the initiation of NAC and radical cystectomy; and 3) post-treatment and treatment clinical and pathological characteristics.

Study End Points

Tumor staging was analyzed by standard American Joint Committee on Cancer TNM criteria.[12] Complete pathological response after NAC (ypCR) was defined as the complete absence of any viable remaining urothelial carcinoma (including Tis, Ta, T1) on pathological examination of the cystectomy tissues. Partial pathological response after NAC (ypPR) was defined as the absence of any muscle invasive urothelial carcinoma on pathological examination of the cystectomy tissues. Pathological response rate (ypRR) was defined as the total percentage of patients achieving a ypCR or ypPR after NAC. Overall survival was defined as the duration of time from the diagnosis of MIBC to death from any cause. Survival status was verified using clinical records, physician reports, the Social Security Death Index website and by other means (ie obituary) for any patients lost to followup.

Statistical Analysis

Data were analyzed using SPSS® Statistics version 22. Chi-square testing was used to analyze categorical variables and Student's t-test was used to analyze continuous variables. Associations between variables and OS were analyzed by Cox proportional hazards regression for survival analysis, with data summarized by hazard ratios with 95% CIs. A level of significance was set at $p < 0.05$ for all analyses.

RESULTS

Study Population

Between January 1996 and August 2014, 314 consecutive patients received NAC followed by cystectomy at the Johns Hopkins Hospital. Reasons for patient exclusion are summarized in figure 1. A total of 201 patients comprised the final study group. The majority of patients (193, 96%) were treated between 2004 and 2014. During this same time 232 patients with MIBC were treated at our institution with cystectomy alone. The NAC study population was characterized by a mean patient age of 61.8 years (range 39 to 83) with the majority being male (159 of 201, 79%) and Caucasian (185 of 201, 92%). More than a third of patients had extravesical disease at diagnosis, with 57 (28%) and 14 (7%) patients with clinical T3 and T4 disease, respectively. There were