A Multi-Institutional Analysis of Outcomes of Patients with Clinically Node Positive Urothelial Bladder Cancer Treated with Induction Chemotherapy and Radical Cystectomy

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Purpose: Selected patients with bladder cancer with pelvic lymphadenopathy (cN1-3) are treated with induction chemotherapy followed by radical cystectomy. However, the data on clinical outcomes in these patients are limited. In this study we assess pathological and survival outcomes in patients with cN1-3 disease treated with induction chemotherapy and radical cystectomy.

Materials and Methods: Data were collected on patients from 19 North American and European centers with cT1-4aN1-N3 urothelial carcinoma who received chemotherapy followed by radical cystectomy between 2000 and 2013. The primary end points were pathological complete (pT0N0) and partial (pT1N0 or less) response rates, with overall survival as a secondary end point. Logistic regression and Cox proportional hazard ratios were used for multivariate analysis of factors predicting these outcomes.

Results: The total of 304 patients had clinical evidence of lymph node involvement (cN1-N3). Methotrexate/vinblastine/doxorubicin/cisplatin was used in 128 (42%), gemcitabine/cisplatin in 132 (43%) and other regimens in 44 (15%) patients. The pN0 rate was 48% (cN1—56%, cN2—39%, cN3—39%, p=0.03). The complete and partial pathological response rates for the entire cohort were 14.5% and 27%, respectively. The estimated median overall survival time for the cohort was 22 months (IQR 8.0, 54). On Cox regression analysis overall survival was associated with pN0, negative surgical margins, removal of 15 or more pelvic nodes and cisplatin therapy.

Conclusions: Complete pathological nodal response can be achieved in a proportion of patients with cN1-3 disease receiving induction chemotherapy. The best survival outcomes are observed in male patients on cisplatin regimens with subsequent negative radical cystectomy margins and complete nodal response (pN0) with excision of 15 or more pelvic nodes.

Key Words: urinary bladder neoplasms, cystectomy, neoadjuvant therapy, survival

Abbreviations and Acronyms

GC = gemcitabine/cisplatin

KM = Kaplan-Meier

MVAC = methotrexate/vinblastine/doxorubicin/cisplatin

NAC = neoadjuvant chemotherapy

OS = overall survival

pCR = pathological complete response

pPR = pathological partial response

RC = radical cystectomy

UC = urothelial carcinoma

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In patients with muscle invasive bladder cancer neoadjuvant chemotherapy before radical cystectomy has been shown to be associated with improved survival.[1–5] However, most studies assessing the efficacy of NAC

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have excluded patients with clinically node positive disease (cN1-3). In patients with cN1-3 disease systemic chemotherapy may be seen as the primary therapy and RC as consolidation in those with a major response to the induction chemotherapy. Thus, there are few data available to assess outcomes in this group of patients. The 5% improvement in overall survival with NAC observed in the landmark meta-analysis of 2,688 patients included only 4% with cN1-3 disease.[3] Thus, the reported results may not necessarily extend to cN1-3 cases.

Patients with cN1-3 disease are generally treated with the same regimens as those with cN0 disease.[6] MVAC (methotrexate/vinblastine/doxorubicin/cisplatin)[2] and cisplatin/methotrexate/vinblastine[5] have been established as effective NAC regimens in prospective randomized phase III clinical trials, but gemcitabine/cisplatin has been widely adopted as the favored regimen based on the lack of detected survival difference and less toxicity compared to MVAC.[7] Several retrospective data sets have also shown comparable pathological complete response rates with GC and MVAC in the neoadjuvant setting.[8,9] Carboplatin based regimens are widely believed to be inferior to cisplatin based regimens,[10–13] but are nonetheless administered by some providers in the NAC setting with the belief that suboptimal NAC is better than no NAC.[9,14–17]

We recently reported real-world outcomes of NAC in cN0 cases in a large retrospective multi-institutional series.[9] The aim of the current study is to extend this analysis to cN1-3 cases, and assess clinicopathological and survival outcomes after GC, MVAC and other noncisplatin based chemotherapy regimens in the same multi-institutional series.

PATIENTS AND METHODS

Study Population

A total of 19 European and North American institutions contributed to this study. Institutional review board approvals were obtained. Patients with cT1N1-3M0 and cT2-4aN0-3M0 bladder cancer who were treated with chemotherapy and RC between 2000 and 2013 were identified. Only patients with pure UC or mixed UC with squamous and/or glandular differentiation were included in the study. For this analysis patients with cT1-4aN1-3M0 disease were selected. Lymph node status was determined by the treating physician based on imaging criteria without specific requirement for biopsy confirmation. Patients were grouped according to the chemotherapy regimen they received into MVAC, GC and "other." The "other" group included patients who received gemcitabine/carboplatin, other carboplatin based regimens and taxanes, but not cisplatin. Patients who received chemotherapy but did not subsequently undergo cystectomy were not captured. The primary end point was pathological response to induction chemotherapy. Partial pathological response was defined as down staging to nonmuscle invasive disease, pT1N0 or less, and complete pathological response was defined as pT0N0. Median overall survival was a secondary end point.

Analysis

Information relating to demographics, clinical staging, chemotherapy, surgery, histopathology and survival outcomes were analyzed for the study population. Chemotherapy data incorporated type of regimen and number of cycles. Surgical variables included the extent of pelvic lymphadenectomy (standard vs extended, as categorized by the treating urologist as well as the number of nodes removed and subsequently identified by the pathologist). Histopathology assessment encompassed histological classification, presence of carcinoma in situ, and surgical soft tissue margin status and pathological TNM staging based on the 2010 American Joint Committee on Cancer classification. Duration of followup was measured from the date of RC.

Statistics

Categorical variables were compared using the chi-squared test. For variables with nonnormal distribution data were presented as median (range or interquartile range) and groups were compared using the Mann-Whitney U-test. Multivariable logistic regression analyses of selected variables were used to define factors predicting pCR and pPR. Survival analysis was performed using Kaplan-Meier analysis and groups were compared using the log rank test. A multivariable Cox proportional hazards regression model for overall survival was used to assess hazard ratios, and included relevant clinical and pathological variables. The number of removed nodes was examined using the minimal p value approach at different cutoff points (10-15).[18] Using Kaplan-Meier analysis and the log rank test the lowest cut point at which OS was significantly different between the 2 groups was used to dichotomize the data for inclusion in the Cox model. Analyses were performed using SPSS® v21 software and significance was set at $p < 0.05$.

RESULTS

Of 1,618 patients with bladder cancer receiving chemotherapy 304 (19%) had clinically node positive disease (cN1-3). Data on pathological nodal status (pN0-3) were available for 248 (82%) of these 304 patients.

Baseline Characteristics

The median age of the 304 patients in our cohort was 64 years (IQR 58–71) and pure UC (92%) was the dominant histological subtype on final pathology (see supplementary table, http://jurology.com/). GC (43%) and MVAC (42%) were used at equivalent rates in the cohort. Gemcitabine/carboplatin was administered in 89% of the remaining other regimen group (15%). The median number of chemotherapy cycles administered was 4 and 44 (14%) patients received more than 4 cycles.