Original Study

Feasibility of Cisplatin-Based Neoadjuvant Chemotherapy in Muscle-Invasive Bladder Cancer Patients With Diminished Renal Function

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Abstract

A retrospective analysis assessed chemotherapy tolerability and outcomes of patients with glomerular filtration rate (GFR) < 60 mL/min who received cisplatin-based neoadjuvant chemotherapy for muscle-invasive bladder cancer. Patients with impaired GFR had more treatment discontinuations and modifications relative to normal GFR patients, but most completed intended treatment cycles. For carefully selected patients with impaired GFR, cisplatin-based chemotherapy remains a treatment option.

Background: Cisplatin-based neoadjuvant chemotherapy (NAC) before radical cystectomy is the standard of care in muscle-invasive bladder cancer. There are limited data regarding chemotherapy tolerability and outcomes for patients with low glomerular filtration rate (GFR) who receive cisplatin-based NAC. **Patients and Methods:** A retrospective analysis of patients who received cisplatin-based NAC at Cleveland Clinic (2005-2016) was undertaken. Patients with pre-NAC GFR $<$ 60 mL/min by either Cockcroft-Gault (CG) or Modification of Diet in Renal Disease (MDRD) formula were compared to patients with GFR $\geq$ 60 mL/min for NAC tolerability, pathologic complete and partial response (pPR), and the ability to undergo radical cystectomy. **Results:** Thirty patients with low GFR (34-59 mL/min) and 94 patients with normal GFR ($\geq$ 60 mL/min) were identified. Low GFR patients were older (median, 71 vs. 65 years), but other demographic and transurethral resection of bladder tumor characteristics were comparable. Low GFR patients more frequently had early NAC discontinuation (30% vs. 13%), NAC modifications (delays, dose reduction, or discontinuation, 66% vs. 40%), and cisplatin-based NAC administered in split doses (37% vs. 16%). No differences in NAC tolerability or outcomes were noted among low GFR patients receiving split-dose versus standard regimens. No differences were noted between low and normal GFR patients in NAC cycles (median, 3 for each), cystectomy rates (93% for each), time to cystectomy, and GFR change from baseline to after NAC. Pathologic complete response was higher among normal GFR patients (24% vs. 14%). **Conclusion:** Patients with low GFR had more NAC discontinuations and modifications, but most completed planned NAC cycles. For carefully selected patients with GFR $<$ 60 mL/min, cisplatin-based NAC remains a treatment option.

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Introduction

It is estimated that 81,190 new cases of bladder cancer will occur in the United States in 2018, with approximately one third of patients presenting with muscle-invasive disease (MIBC).[1] A significant proportion of patients with non–muscle-invasive disease also progress to MIBC, resulting in 35,000 to 40,000 patients being diagnosed with MIBC annually.[2] The standard of care in MIBC is cisplatin-based neoadjuvant chemotherapy (NAC) followed by

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radical cystectomy with bilateral pelvic lymph node dissection and urinary diversion; however, approximately half of patients will experience relapse, commonly with distant metastases.[3-5]

Cisplatin, *cis*-diamminedichloroplatinum (II), is an alkylating antineoplastic agent, and it is probably the most effective agent in patients with bladder cancer.[6] Cisplatin-based NAC before radical cystectomy increases rates of pathologic complete response (pCR) and is associated with an overall survival benefit compared to surgery alone.[7-10] Several cisplatin-based regimens, including methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) as well as gemcitabine and cisplatin (GC), are commonly provided. Retrospective studies have not identified a meaningful difference between these regimens in the neoadjuvant setting, while prospective studies have also supported the benefit of dose-dense MVAC.[11-15] Major adverse events of cisplatin-based regimens include nephrotoxicity, neurotoxicity, ototoxicity, and bone marrow suppression, but renal impairment is the major dose-limiting toxicity and often requires significant hydration.[16]

A reported consensus definition of cisplatin ineligibility includes any of the following characteristics: Eastern Cooperative Oncology Group performance status (ECOG PS) $\geq$ 2, creatinine clearance $<$ 60 mL/min, grade 2 or higher neuropathy, grade 2 or higher hearing loss, and New York Heart Association class III or higher heart failure.[17] The proportion of patients ineligible for cisplatin based on renal function alone may be up to 50%.[13] The data for patients with glomerular filtration rate (GFR) $<$ 60 mL/min who receive cisplatin-based chemotherapy are limited, and most clinical trials exclude patients with impaired renal function, thus excluding a significant percentage of patients who could benefit from this treatment.[18,19] A recently published retrospective analysis assessed the impact of cisplatin-based treatment on the change in GFR for patients with baseline GFR $<$ 60 mL/min. It found that these patients did not experience a greater decline in GFR after cisplatin compared to patients with GFR $>$ 60 mL/min.[20]

Aside from the impact of cisplatin-based treatment on renal function, there are no data regarding tolerability of cisplatin-based chemotherapy and related outcomes in this patient population, and better selection of patients who may safely receive cisplatin-based NAC is needed to optimize outcomes in MIBC. The use of split-dose cisplatin regimens (cisplatin administered in split doses over 2 days in each cycle) as a treatment strategy in cisplatin-unfit bladder cancer patients in both (neo)adjuvant and advanced settings was shown to be both effective and well tolerated; however, this strategy was not directly compared to standard cisplatin regimens in these studies.[19,21-23] Additionally, to our knowledge, no studies have compared cisplatin-based NAC in MIBC patients with diminished renal function to a similar population with normal renal function.

We thus undertook a retrospective analysis to compare MIBC patients with diminished renal function (GFR $<$ 60 mL/min) to MIBC patients with normal renal function (GFR $\geq$ 60 mL/min) in their ability to tolerate cisplatin-based NAC, as well as the impact of NAC on subsequent surgical treatment and outcomes in both groups.

Patients and Methods

Patient Selection and Assessed Characteristics

All patient data were collected in accordance with the Cleveland Clinic institutional review board. Patients were identified retrospectively from an institutional database of bladder cancer patients who had transurethral resection of bladder tumor (TURBT) of at least clinical T2 stage, followed by NAC. Final analysis included data from 124 adult patients who initiated treatment at the Cleveland Clinic between December 1, 2005, and December 14, 2016, and received at least one cycle of cisplatin-based NAC. Patients who initiated cisplatin-based chemotherapy received intravenous fluids before and after cisplatin on days of cisplatin administration and did not receive mannitol. Among patients who received split-dose cisplatin for the GC regimen, cisplatin was split on days 1 and 8 of a 21-day treatment cycle. All pathology specimens were reviewed internally before start of treatment by experienced genitourinary cancer pathologists. Patient charts were reviewed to obtain relevant baseline patient characteristics (including confirmation of clinical T2 stage for patients with T1 stage documented on TURBT pathology report), NAC regimens received, treatment tolerance, pathologic responses, and clinical outcomes.

Laboratory values including creatinine, blood counts, and albumin were recorded at 3 different time points for all patients: (1) immediately before NAC, (2) immediately before cystectomy, and (3) 1 to 2 months after cystectomy for patients with available data. GFR was calculated at these 3 time points using both the Cockcroft-Gault (CG)[24] and Modification of Diet in Renal Disease (MDRD)[25] formulas for each patient. Formula yielding the lower GFR value at the initial pre-NAC time point for a particular patient was then used in the 2 subsequent GFR calculations for that patient.

End Points and Statistical Analysis

On the basis of the calculated pretreatment GFR of 124 patients, 94 patients had GFR $\geq$ 60 mL/min (normal GFR) and 30 patients had GFR $<$ 60 mL/min (low GFR). Primary analysis compared patient and treatment characteristics and outcomes between patients with normal and low GFR. Categorical variables were compared by the chi-square test or Fisher's exact test; continuous variables were compared by the Wilcoxon rank-sum test. A subset analysis was performed in 30 patients with low GFR ($<$ 60 mL/min) comparing 11 patients who received split-dose cisplatin to 19 who did not; the same methods were used as for primary analysis. All clinical outcomes were measured relative to the start of NAC. Recurrence was estimated by cumulative incidence and compared between groups by the Gray test. Overall survival and recurrence-free survival were estimated by Kaplan-Meier analysis and compared by log-rank test.

A secondary analysis was performed comparing 3 GFR groups: (1) 10 patients with very low GFR ($<$ 50 mL/min), (2) 20 patients with moderately impaired GFR (50-59 mL/min), and (3) 94 patients with normal GFR ($\geq$ 60 mL/min). Statistical methods were used to assess trends in the relevant characteristics and outcomes across the 3 GFR groups, looking for ordered patterns with GFR increase. Continuous, binary, and categorical variables were assessed relative to GFR using the Jonckheere-Terpstra, Cochran-Armitage, and Cochran-Mantel-Haenszel tests, respectively.

Data were analyzed by SAS 9.4 software (SAS Institute, Cary, NC). All statistical tests were 2 sided, and $P < .05$ was used to indicate significance.