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Original article

Gemcitabine and cisplatin neoadjuvant chemotherapy for muscle-invasive urothelial carcinoma: Predicting response and assessing outcomes

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Abstract

Purpose: To evaluate gemcitabine-cisplatin (GC) neoadjuvant cisplatin-based chemotherapy (NAC) for pathologic response (pR) and cancer-specific outcomes following radical cystectomy (RC) for muscle-invasive bladder cancer and identify clinical parameters associated with pR.

Materials and methods: We studied 150 consecutive cases of muscle-invasive bladder cancer that received GC NAC followed by open RC (2000–2013). A cohort of 121 patients treated by RC alone was used for comparison. Pathologic response and cancer-specific survival (CSS) were compared. We created the Johns Hopkins Hospital Dose Index to characterize chemotherapeutic dosing regimens and accurately assess sufficient neoadjuvant dosing regarding patient tolerance.

Results: No significant difference was noted in 5-year CSS between GC NAC (58%) and non-NAC cohorts (61%). The median follow-up was 19.6 months (GC NAC) and 106.5 months (non-NAC). Patients with residual non–muscle-invasive disease after GC NAC exhibit similar 5-year CSS relative to patients with no residual carcinoma ($P = 0.99$). NAC pR ($\leq$pT1) demonstrated improved 5-year CSS rates (90.6% vs. 27.1%, $P < 0.01$) and decreased nodal positivity rates (0% vs. 41.3%, $P < 0.01$) when compared with nonresponders ($\geq$pT2). Clinicopathologic outcomes were inferior in NAC pathologic nonresponders when compared with the entire RC-only–treated cohort. A lower pathologic nonresponder rate was seen in patients tolerating sufficient dosing of NAC as stratified by the Johns Hopkins Hospital Dose Index ($P = 0.049$), congruent with the National Comprehensive Cancer Network guidelines. A multivariate classification tree model demonstrated 60 years of age or younger and clinical stage cT2 as significant of NAC response ($P < 0.05$).

Conclusions: Pathologic nonresponders fare worse than patients proceeding directly to RC alone do. Multiple predictive models incorporating clinical, histopathologic, and molecular features are currently being developed to identify patients who are most likely to benefit from GC NAC.

Keywords: Urothelial carcinoma; Bladder cancer; Neoadjuvant chemotherapy; Gemcitabine-cisplatin; Pathologic response

1. Introduction

Neoadjuvant cisplatin-based chemotherapy (NAC) in combination with radical cystectomy (RC) for the treatment of muscle-invasive bladder cancer (MIBC) is supported by level 1 evidence [1–4]; however, it remains underutilized

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nationally [5,6]. Methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) is an established standard neoadjuvant regimen [1]. Dose-dense MVAC (DD-MVAC) [7] and gemcitabine plus cisplatin (GC) [8] have demonstrated similar overall survival rates when compared with those of MVAC in patients with metastatic urothelial carcinoma (UC). Although no definitive evidence demonstrates superiority of GC over MVAC, GC has increasingly been used in the NAC setting because of a more favorable side effect profile.

The National Cancer Database reported increasing use of NAC, from 10.2% in 2006 to 20.9% in 2010 [9]. Almost 80% of the Bladder Cancer Advocacy Network oncologists offer NAC with GC, which is the most used regimen (90%), followed by MVAC (30%) and DD-MVAC (20%) [10]. A prospective multicenter abstract of Bladder Cancer Advocacy Network investigators identified a 47% cisplatin-based neoadjuvant regimen utilization rate [11]. Despite its widespread use, there is a paucity of data assessing long-term patient outcomes following neoadjuvant GC.

To evaluate the effect of GC NAC on long-term outcomes and identify clinical parameters predictive of response, we present the largest single-institution, retrospective study of solely GC NAC–treated patients. Pathologic response and cancer-specific survival (CSS) were compared with a series of RC-only–treated patients over a similar period at our institution.

2. Materials and methods

2.1. Patient cohorts

The Johns Hopkins Hospital (JHH) Institutional Review Board–approved (N0:03-03-07-02d) bladder cancer database was queried to identify all patients who received any NAC followed by open RC between 2000 and 2013. Only patients who underwent open RC following GC NAC were included in the study; all other forms of NAC were excluded. GC regimens that were assessed included (1) the traditional 1,000 mg/m^2 of gemcitabine on days 1, 8, and 15 along with 70 mg/m^2 of cisplatin on day 1 of a 28-day cycle for 3 to 4 cycles, (2) 1,000 mg/m^2 of gemcitabine on days 1 and 8 along with 70 mg/m^2 of cisplatin on day 1 of a 21-day cycle for 4 cycles, or (3) 1,000 mg/m^2 of gemcitabine and 35 mg/m^2 of cisplatin given on days 1 and 8. Each NAC patient underwent a prechemotherapy staging computed tomography or magnetic resonance imaging. Following NAC, a restaging examination was performed within 1 month before RC, comprising diagnostic cystoscopy without transurethral resection [12] and computed tomography or magnetic resonance imaging of the chest, abdomen, and pelvis. NAC patients with clinical node-positive disease (before or after chemotherapy) were included if their disease was deemed surgically resectable or lymph node (LN) enlargement was confined to the pelvis.

Consecutive MIBC patients treated by RC alone (non-NAC) beginning in the year 2000 were identified and used for comparison. These patients were either not offered NAC, as it was not currently standard of care at our institution during that period, or chose not to pursue NAC. Patients with unknown follow-up or cause of death were excluded. These 2 cohorts did not differ significantly regarding clinical stage (cStage), age, clinical nodal stage, and smoking status. All patients underwent preoperative imaging, and all non-NAC patients with LN disease/metastasis were excluded and recommended to receive systemic chemotherapy, unless deemed surgically resectable. Pelvic lymphadenectomy followed a standard surgical template including LN of the obturator fossa and those along the internal and external iliac arteries up to and including the common iliac artery and vein.

2.2. Response and survival evaluations

All post-NAC cystectomy pathologic evaluations were performed at JHH by expert pathologists. We defined NAC pathologic responders (pR) as the absence of residual MIBC ($\leq$pT1) at the time of RC [13]; pathologic nonresponders (pNR) were defined by the presence of muscle-invasive, extravesical, and metastatic disease ($\geq$pT2). CSS was defined according to review of death certificates by the JHH Cancer Registry or biopsy of metastatic lesions confirming UC and was updated for all patients by review of clinical medical records and query of the Social Security Death Database. For cases without evidence of cancer-specific death, survival was censored at the date of last clinic visit.

2.3. JHH dose index

According to the National Comprehensive Cancer Network 2014 guidelines, MIBC patients should receive 4 cycles of neoadjuvant GC. However, patients commonly have missed/held doses or fail to complete treatment cycles owing to intolerance, renal impairment, or hematological complications [14]. Currently, no standardized terminology exists within the genitourinary oncology literature to classify the amount of NAC received when interpreting pR to a given therapeutic modality. As RCTs assessing NAC used 3-cycle MVAC regimens, 3 or 4 cycles are regarded as adequate therapy [15]. The effect of missed or reduced doses is not accounted for when assessing true pR. We created the JHH Dose Index (JHH-DI) to characterize patient tolerance to NAC (Table 1). The medical record review that was performed for all patients receiving NAC determines dosing amount and total number of cycles received. Dose reduction was defined as a reduction in either gemcitabine or cisplatin dose owing to patient intolerance. Each patient was given a dose index score summarizing the total amount of chemotherapy tolerated.