Original Study

Cisplatin-Based First-Line Therapy for Advanced Urothelial Carcinoma After Previous Perioperative Cisplatin-Based Therapy

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Abstract

Longer time from previous perioperative chemotherapy (TFPC) ≥ 78 weeks and Eastern Cooperative Oncology Group (ECOG) performance status (PS) = 0 were independently prognostic for better survival with cisplatin-based first-line chemotherapy for advanced urothelial carcinoma (UC) after previous perioperative cisplatin-based chemotherapy. Because of particularly poor outcomes in those with TFPC < 52 weeks, the data support using TFPC ≥ 52 weeks to rechallenge with cisplatin-based first-line chemotherapy for metastatic disease.

Background: Outcomes with cisplatin-based first-line therapy for advanced UC after previous perioperative cisplatin-based chemotherapy are unclear. In this study we evaluated outcomes with a focus on the effect of time from previous cisplatin-based perioperative chemotherapy. **Patients and Methods:** Data were collected for patients who received cisplatin-based first-line therapy for advanced UC after previous perioperative cisplatin-based therapy. Cox proportional hazards models were used to investigate the prognostic ability of visceral metastasis, ECOG PS, TFPC, anemia, leukocytosis, and albumin on overall survival (OS). **Results:** Data were available for 41 patients from 8 institutions including 31 men (75.6%). The median age was 61 (range, 41-77) years, most received gemcitabine plus cisplatin (n = 26; 63.4%), and the median number of cycles was 4 (range, 1-8). The median OS was 68 weeks (95% confidence interval [CI], 48.0-81.0). Multivariable Cox regression analysis results showed an independent prognostic effect on OS for PS > 0 versus 0 (hazard ratio [HR], 4.56 [95% CI, 1.66-12.52]; $P = .003$) and TFPC ≥ 78 weeks versus < 78 weeks (HR, 0.48 [95% CI, 0.21-1.07]; $P = .072$). The prognostic model for OS was internally validated with c-index = 0.68. Patients with TFPC < 52 weeks, 52 to 104 weeks, and ≥ 104 weeks had median survival of 42, 70, and 162 weeks, respectively. **Conclusion:** Longer TFPC ≥ 78 weeks and ECOG PS = 0 were independently prognostic for better survival with cisplatin-based first-line chemotherapy for advanced UC after previous perioperative cisplatin-based chemotherapy. The data support using TFPC ≥ 52 weeks to rechallenge with cisplatin-based first-line chemotherapy for metastatic disease.

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Introduction

Cisplatin-based chemotherapy is established as a standard first-line therapy for metastatic urothelial carcinoma (UC).[1-4] Gemcitabine with cisplatin (GC), MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin), or dose-dense (DD) MVAC are all acceptable regimens and yield a median overall survival (OS) of 12 to 15 months. However, these trials were conducted in an era before definitive evidence supporting the role of neoadjuvant cisplatin-based chemotherapy was adopted in the community.[5-7] Indeed, the phase III trials that established cisplatin-based chemotherapy as first-line therapy did not enroll patients who had received previous perioperative chemotherapy. Although data supporting the role of adjuvant cisplatin-based chemotherapy for high-risk disease after radical cystectomy are still controversial, adjuvant chemotherapy is often more frequently used.[8-14]

The effect of previous perioperative cisplatin-based chemotherapy on outcomes when repeating cisplatin-based chemotherapy as first-line therapy for subsequent recurrent or metastatic disease is unclear. Major known prognostic factors across different studies in the setting of first-line chemotherapy include visceral metastasis, performance status (PS), hemoglobin (Hb), leukocyte count, and albumin.[15-17] We hypothesized that longer time from previous perioperative cisplatin-based chemotherapy might be an additional prognostic factor, which concurs with recently reported first-line phase II trials and an ongoing important phase III trial (Cancer and Leukemia Group B [CALGB]-90601 trial), which restricted inclusion of patients to those with > 52 weeks from previous perioperative cisplatin-based chemotherapy. Hence, we conducted a retrospective analysis of patients with advanced UC who received first-line cisplatin-based chemotherapy after previous perioperative cisplatin-based chemotherapy to study outcomes and evaluate the effect of time from perioperative cisplatin-based chemotherapy after controlling for known prognostic factors.

Patients and Methods

Patient Population

Data were requested from 10 collaborating institutions regarding patients who received cisplatin-based first-line therapy for advanced UC after previous perioperative cisplatin-based therapy. Data were requested for baseline visceral metastasis, Eastern Cooperative Oncology Group (ECOG) PS, time from previous perioperative chemotherapy (TFPC), Hb, leukocyte count, and albumin. Patient outcomes, specifically best response, progression-free survival (PFS), and OS, from first-line therapy were also requested. The data were deidentified and provided in an Excel spreadsheet by all investigators. The study was conducted after institutional review board approval at the University of Alabama, Birmingham for retrospective analyses of such patients.

Statistical Methods

Descriptive statistics was used to summarize patient and treatment characteristics and outcomes. The primary clinical end point of interest was OS from the date of beginning first-line chemotherapy. The Kaplan–Meier method was used to estimate time to event outcomes. OS was defined according to those alive with or without disease, and PFS was defined according to those alive and free from disease progression, from the first date the patient received first-line therapy. Univariable Cox proportional hazards models were used to investigate the prognostic ability of age, sex, number of cycles of chemotherapy, dose of cisplatin per 3- to 4-week cycle, calculated creatinine clearance, setting of previous perioperative chemotherapy (neoadjuvant or adjuvant), first-line regimen (GC or other), visceral metastasis, ECOG-PS, Hb, leukocyte count, albumin, and TFPC to initiating first-line chemotherapy on OS and PFS. Predefined cutoff points of TFPC were assessed for prognostic effect including 52 weeks (approximately 1 year), 78 weeks (approximately 1.5 years), and 104 weeks (approximately 2 years). Anemia was defined as Hb < the lower limit of normal according to sex as recorded by the local laboratory. Leukocytosis was defined as a white blood cell count > the upper limit of normal (ULN) based on the local laboratory. Albumin was evaluated on a continuous scale. A forward stepwise selection method was used to create an optimal multivariable model of prognostic factors. Albumin was excluded from the multivariable model selection because of a large number of missing data, but all other factors were included. Because stepwise selection requires complete case data, results for the final multivariable model were calculated based on data from all patients with complete data on the selected factors. All tests and confidence intervals (CIs) were 2-sided and set at $P = .05$ level of significance. Internal validation of the final multivariate models were performed by performing 2000 bootstrap replications and calculating the estimated median and 95% bias-corrected and accelerated (BCa) CIs for the hazard ratio (HR) estimates of each factor, and for the concordance-statistic (c-statistic).

Results

Patient Characteristics

Individual level data for 41 patients from 8 institutions who were treated between the years 1999 and 2013 were obtained (Table 1). Two institutions could not identify any eligible patients. The evaluable patients came from Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy (n = 16), University Federico II Napoli, Italy (n = 13), British Columbia Cancer Agency, Vancouver, Canada (n = 3), City of Hope, CA (n = 3), University of Utah, Salt Lake City, UT (n = 3), Wayne State University Cancer Center, Detroit, MI, Heinrich Heine University, Dusseldorf, Germany, University of Liverpool, Liverpool, United Kingdom (n = 1 each). The cohort included 31 men (75.6%), the median age was 61 (range, 41 to 77) years, and 46.3% had visceral disease. Most had an ECOG-PS of 0 (n = 32; 78.1%) and only 1 patient had an ECOG-PS of 2. Most received first-line GC (n = 28; 68.3%), the median number of cycles was 4 (range, 2-8), and the median time from previous perioperative cisplatin-based chemotherapy to first-line therapy was 68 weeks. The previous perioperative cisplatin-based chemotherapy was administered in the adjuvant setting in most patients (63.4%). Pathologic T0 (pT0) disease was observed in 1 of the 30 patients for whom pathologic staging at the time of radical cystectomy was available. This patient had received neoadjuvant chemotherapy.

Effect of Potential Prognostic Factors on OS

Of the 41 patients, 30 (73.2%) were known to have died at a median of 68.0 (95% CI, 48.0-81.0) weeks. In univariate analyses (Table 2), ECOG-PS > 0 (HR, 4.96 [95% CI, 1.80-13.68]; $P = .002$), leukocytosis (HR, 2.82 [95% CI, 1.27-6.23]; $P = .011$), and