Original Study

Cisplatin- Versus Non–Cisplatin-based First-Line Chemotherapy for Advanced Urothelial Carcinoma Previously Treated With Perioperative Cisplatin

Jennifer A. Locke,[1] Gregory Russell Pond,[2] Guru Sonpavde,[3] Andrea Necchi,[4] Patrizia Giannatempo,[4] Ravi Kumar Paluri,[3] Guenter Niegisch,[5] Peter Albers,[5] Carlo Buonerba,[6] Giuseppe Di Lorenzo,[6] Ulka N. Vaishampayan,[7] Scott A. North,[8] Neeraj Agarwal,[9] Syed A. Hussain,[10] Sumanta Pal,[11] Bernhard J. Eigl[12]

Abstract

To identify the optimal choice for first-line chemotherapy for advanced urothelial carcinoma (UC), we investigated the outcomes between cisplatin and non-cisplatin regimens in patients with metastatic UC after perioperative cisplatin-based chemotherapy (PCBC) in a multicenter retrospective study. In patients who had undergone previous PCBC for UC, a repeat challenge with cisplatin conferred poorer overall survival, especially in those with progression in < 1 year.

Introduction: The optimal choice of first-line chemotherapy for patients with relapse of urothelial carcinoma (UC) after perioperative cisplatin-based chemotherapy (PCBC) is unclear. We investigated the outcomes with cisplatin rechallenge versus a non-cisplatin regimen in patients with recurrent metastatic UC after PCBC in a multicenter retrospective study.

Patients and Methods: Individual patient-level data were collected for patients who had received various first-line chemotherapy regimens for advanced UC after previous PCBC. Cox proportional hazards models were used to investigate the prognostic ability of the type of perioperative and first-line chemotherapy to independently affect overall survival (OS) and progression-free survival (PFS) after accounting for known prognostic factors. **Results:** Data were available for 145 patients (12 centers). The mean age was 62 years; the Eastern Cooperative Oncology Group (ECOG) performance status (PS) was > 0 for 42.0% of the patients. Of the 145 patients, 63% had received cisplatin-based first-line chemotherapy. The median time from previous chemotherapy (TFPC) was 6.2 months (range, 1-154 months). The median OS was 22 months (95% confidence interval [CI], 18-27 months), and the median PFS was 6 months (95% CI, 5-7 months). A better ECOG PS and a longer TFPC ($>$ 12 months vs. $\leq$ 12 months; hazard ratio [HR], 0.32; 95% CI, 0.20-0.52; $P < .001$) was prognostic for OS and PFS. Cisplatin-based chemotherapy was associated with poor OS (HR, 1.86; 95% CI, 1.13-3.06; $P = .015$), which appeared to be pronounced in those patients with a TFPC of $\leq$ 12 months. Retreatment with cisplatin in the first-line setting was associated with worse OS (HR, 3.38; $P < .001$).

Conclusion: The results of the present retrospective analysis suggest that for patients who have undergone previous PCBC for UC, rechallenging with cisplatin might confer a poorer OS, especially for those with progression within $<$ 1 year.

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Keywords: Cisplatin rechallenge, Eastern Cooperative Oncology Group performance status, Metastatic urothelial carcinoma, Overall survival, Time from previous chemotherapy

[1]University of British Columbia, Vancouver, BC, Canada
[2]McMaster University, Hamilton, ON, Canada
[3]UAB Comprehensive Cancer Center, Birmingham, AL
[4]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
[5]Heinrich Heine University, Medical Faculty, Dusseldorf, Germany
[6]University Federico II, Naples, Italy
[7]Wayne State University Cancer Center, Detroit, MI
[8]Cross Cancer Institute, Edmonton, AB, Canada
[9]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT
[10]University of Liverpool, Liverpool, United Kingdom
[11]City of Hope Cancer Center, Duarte, CA
[12]British Columbia Cancer Agency, Vancouver, BC, Canada

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Address for correspondence: Bernhard J. Eigl, MD, BC Cancer Agency, Vancouver Centre, 600 West 10th Avenue, 4th Floor, Vancouver, BC V5Z 4E6, Canada
E-mail contact: Bernie.Eigl@bccancer.bc.ca

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Introduction

Despite the relatively high initial response rates to chemotherapy, the durability of the response has remained suboptimal, and the 5-year survival rates for patients with metastatic urothelial carcinoma (UC) of the bladder has been only 10% to 20%.[1,2] In both the perioperative and the first-line metastatic setting, cisplatin-combination chemotherapy (predominantly gemcitabine and cisplatin [GC] or methotrexate, vinblastine, doxorubicin, and cisplatin [MVAC]) has been the standard of care.[1-7] For those patients with disease progression after receiving perioperative cisplatin-based chemotherapy, however, no consensus has been reached for whether a cisplatin rechallenge or the use of a different regimen will be superior. The clinical trials[1-5] that established MVAC and GC as the standard of care for metastatic therapy included populations for whom perioperative chemotherapy was not yet an option or the trials did not allow previous systemic therapy.[8] However, contemporary trials evaluating these regimens in patients after PCBC are lacking. A key question therefore is whether advanced UC after PCBC should be retreated with cisplatin-based chemotherapy or should receive a different non-cisplatin or second-line regimen to improve efficacy.

To address this question, we initiated a multicenter retrospective study to investigate the differences in outcomes between patients with advanced UC who had received cisplatin-based first-line chemotherapy and those who had not received cisplatin-based first-line chemotherapy after previous perioperative (neoadjuvant or adjuvant) cisplatin-based chemotherapy (PCBC). It was hypothesized that patients with a longer time from previous chemotherapy (TFPC) would be reflective of those with platinum-sensitive disease and that these patients would have improved outcomes with cisplatin-based chemotherapy in the first-line setting. In contrast, the therapeutic index might be better when using a non-cisplatin regimen for those with a short TFPC after PCBC.

Patients and Methods

Patient Population

Individual patient-level data were collected from 12 regional referral centers in North America and Europe for consecutive patients who had received chemotherapy for advanced UC after previous PCBC. The data included age, gender, baseline visceral metastasis (defined as ≥ 1 of bone, brain, liver, and lung), Eastern Cooperative Oncology Group (ECOG) performance status (PS), TFPC, calculated creatinine clearance, hemoglobin (Hb), leukocyte count, and albumin. Perioperative and first-line chemotherapy information, such as the number of chemotherapy cycles, dose of cisplatin per cycle, setting of perioperative chemotherapy (neoadjuvant or adjuvant), and first-line regimen, were also collected. We also recorded the patient outcomes, specifically, the objective response rate, progression-free survival (PFS), and overall survival (OS), after first-line therapy. The ethics committee of the University of British Columbia (sponsor of the study) and each of the participating institutions approved the present study.

Statistical Analysis

Descriptive statistics were used to summarize the patient and treatment characteristics and outcomes. The study endpoints were PFS and OS. OS was the primary clinical endpoint of interest and was defined as the interval between the start of first-line therapy and death from any cause. The time was censored at the date of the last follow-up visit for patients remaining alive. PFS was defined as the interval between the start of first-line therapy and the date of disease progression or death without progression, whichever occurred first. The time was censored at the date of the last follow-up visit for patients alive without progression. TFPC was defined as the interval from the last date of perioperative chemotherapy to the first date of first-line therapy. The predefined cutpoints of TFPC were selected a priori at < 0.5 year (26 weeks), approximately 1 year (52 weeks), approximately 1.5 years (78 weeks), and approximately 2 years (104 weeks) for analysis. Anemia was defined as an Hb less than the lower limit of normal recorded by the local laboratory. Leukocytosis was defined as a white blood cell count (WBC) greater than the upper limit of normal at the local laboratory. Albumin was evaluated on a continuous scale.

The Kaplan-Meier method was used to estimate the time to event outcomes. Univariate Cox proportional hazards models were used to investigate the prognostic ability of all factors and clinical trial status (ie, whether the therapy was a part of a trial or not) on OS and PFS. The effect of treatment of metastatic disease (cisplatin-based chemotherapy vs. non–cisplatin-based chemotherapy) and specific perioperative chemotherapy (GC, MVAC, or others) was investigated in a univariate manner and in a multivariable model after adjusting for 4 known prognostic factors: ECOG PS (≥ 1 vs. 0), anemia, visceral metastases, and TFPC. Attempts to identify the optimal cutpoints for TFPC were performed by examining the martingale residuals, evaluating the results from multiple models based on the TFPC as a log-transformed continuous covariable, and using the a priori-defined cutpoints. All tests and confidence intervals (CIs) were 2-sided, and statistical significance was defined at $P = .05$.

Results

Patient Characteristics

The patient and treatment characteristics are summarized in Table 1. A total of 145 patients, treated from 1995 to 2014 (exception, 2007-2011 for the UAB Comprehensive Cancer Center), were included from 12 institutions in North America and Europe. The median age of the patients was 63 years (range, 32-81 years) at first-line chemotherapy, more than three quarters of patients were men, and 10.4% had an ECOG PS of 2 or 3. Most patients (n = 90; 63.8%) received adjuvant chemotherapy. Of the 145 patients, 81 (57.5%) received GC perioperative chemotherapy, 36 (25.5%) received MVAC, and 24 (17%) received another cisplatin-based regimen. The other cisplatin-based regimens consisted of 11 patients who had received methotrexate, vinblastine, epirubicin, and cisplatin, and 9 who had received methotrexate and cisplatin. The remaining 4 patients had received another cisplatin-based combination. Of the 145 patients, 91 (62.8%) underwent retreatment with cisplatin-based first-line chemotherapy (cisplatin with etoposide, methotrexate, vinblastine, and gemcitabine or doxorubicin), and 12 (8.3%) received first-line therapy as part of a clinical trial. The clinical trial therapies included AZD4877, OGX427, PZP, ramucirumab, sunitinib, vinflunine, vinblastine, and nab-paclitaxel. The remaining 42 patients (28.9%) received non–cisplatin-based first-line therapy regimens, including