Impact of the Number of Prior Lines of Therapy and Prior Perioperative Chemotherapy in Patients Receiving Salvage Therapy for Advanced Urothelial Carcinoma: Implications for Trial Design

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Abstract

This analysis of patients from prospective trials of salvage therapy for advanced urothelial carcinoma did not identify a prognostic effect for number of prior lines of therapy and prior perioperative chemotherapy. Performance status, hemoglobin, liver metastasis, and time from prior chemotherapy were prognostic for outcomes. These findings allow trials to use uniform eligibility criteria, which will enhance accrual and improve interpretability.

Background: The differential impact of the number of prior lines of therapy and the setting of prior therapy (perioperative or metastatic) is unclear in advanced urothelial carcinoma. **Patients and Methods:** Ten phase II trials of salvage chemotherapy, biologic agent therapy, or both, enrolling 731 patients, were available. Data on the number of prior lines of therapy and the setting of prior therapy were required in addition to known previously recognized prognostic factors: time from prior chemotherapy, hemoglobin level, performance status, and liver metastasis status. Cox proportional hazards regression was used to evaluate the association of the number of prior lines and prior perioperative therapy with overall survival (OS) as the primary clinical endpoint. Trial was a stratification factor. **Results:** A total of 711 patients were evaluable. The overall median progression-free survival and OS were 2.7 and 6.8 months, respectively. The number of prior lines was 1 in 559 patients (78.6%), 2 in 111 (15.6%), 3 in 29 (4.1%), 4 in 10 (1.4%), and 5 in 2 (0.3%). Prior perioperative chemotherapy was given to 277 (39.1%) and chemotherapy for metastatic disease to 454 (64.1%). The number of prior lines was not independently associated with OS (hazard ratio, 0.99; 95% CI, 0.86-1.14). Prior perioperative chemotherapy was a favorable factor for OS on univariate but not multivariate analysis. **Conclusion:** The number of prior lines of therapy and prior perioperative chemotherapy were not independently prognostic in patients with urothelial carcinoma receiving salvage therapy. Adoption of these data in salvage therapy trials should enhance accrual, the interpretability of results, and drug development.

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Introduction

The differential impact of the number of prior lines of therapy and the setting of prior therapy in patients receiving salvage systemic therapy for advanced urothelial carcinoma (UC) is unclear. Eligibility criteria for phase II trials conducted to identify the activity of new agents in the salvage setting have varied substantially. Some trials allow only 1 prior line of chemotherapy in any setting (perioperative or metastatic), whereas others require only 1 prior line for metastatic disease (and either disallow or permit prior perioperative chemotherapy). Few trials have allowed more than 1 prior line of therapy for metastatic disease.

Currently used agents yield limited activity in the second-line setting of advanced UC and yield a median progression-free survival (PFS) of 2 to 4 months and median overall survival (OS) of 6 to 9 months.[1] Survival outcomes of patients receiving salvage therapy for advanced UC differ based on a 3-factor prognostic model, derived from the sole large phase III trial evaluating vinflunine, consisting of Eastern Cooperative Oncology Group (ECOG) performance status (PS) > 0, hemoglobin level (Hb) < 10 g/dL, and liver metastasis (LM).[2,3] Another study reported that the addition of time from prior chemotherapy (TFPC) to the prognostic model enhances the ability to prognosticate for PFS compared with the aforementioned 3-factor model.[4] However, TFPC has not been externally validated for association with OS.

A rationale may be offered to investigate the prognostic impact of the number of prior lines of therapy and the setting of prior therapy (perioperative, metastatic, or both) in patients receiving salvage systemic therapy for advanced UC. Importantly, this information may facilitate the interpretation and conduct of phase II trials of salvage therapy. If these new variables affect outcomes, stratification to account for their impact will be necessary in randomized trials. Conversely, if these factors do not affect outcomes, uniform eligibility criteria may be advocated across trials, and accrual may be enhanced with more inclusive criteria. Therefore, this study retrospectively analyzed a large pooled data set of prospective phase II trials to evaluate the impact of the number of prior lines of therapy and the setting of prior therapy independent of Hb, PS, LM, and TFPC. The authors hypothesized that neither of these variables conferred an independent prognostic impact on OS.

Patients and Methods

Patient Population

Ten prospective phase II trials of salvage systemic chemotherapy, biologic agent therapy, or both for advanced UC were pooled.[5-14] These trials required previous pathologic confirmation of UC and the presence of measurable metastatic disease. Trials conducted after the year 2000 were selected based on the availability of individual patient–level data and the willingness of the respective principal investigators to provide these data. Data on the number of prior lines of therapy and the setting of prior therapy (perioperative, metastatic, or both) were required in addition to TFPC, Hb, PS, and LM status. 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 at Birmingham for retrospective analyses of such patients. The differences among these trials in patient eligibility criteria regarding the number of prior lines and prior perioperative chemotherapy are shown in Table 1.

Statistical Methods

Progression was defined as objective tumor progression or death from any cause and was calculated using the Kaplan-Meier method. OS was calculated from the date of study entry until death from any cause and was calculated using the Kaplan-Meier method. Objective tumor assessment was performed with the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 in all trials except the trial by Necchi et al[11] evaluating pazopanib, which used RECIST 1.1.[11,15,16] Cox proportional hazards regression was used to evaluate the association of the number of prior lines with OS, the primary clinical endpoint, and PFS, adjusted for the 3 validated prognostic factors along with TFPC. Trial was included as a stratification factor throughout. Patients in the trial by Choueiri et al[5] receiving docetaxel ± vandetanib were included as if on 1 trial when stratifying for the present analysis, given that there were no significant differences in OS and PFS between these arms. The trial by Gallagher et al[10] evaluated sunitinib administered in 2 doses and schedules (50 mg daily for 4 of every 6 weeks or 37.5 mg daily continuously), and the trial by Wong et al[8] evaluated cetuximab alone or with paclitaxel as 2 noncomparative arms; for both of these trials, the different regimens were assigned a separate stratification. A subanalysis examined the impact of prior perioperative chemotherapy. Internal validation was performed using bootstrap methods, with 95% bias-corrected and accelerated (BCa) confidence intervals (CIs), P values, and concordance statistics (c-index) calculated. All tests were 2-sided, and a value of $P \leq .05$ was considered statistically significant.

Results

Patient Characteristics

Of 731 patients, data for all factors were available for 711 (Table 2), and 3 patients from the volasertib study by Stadler et al[14] did not have data on prior chemotherapy setting (ie, for metastatic or perioperative disease) and were therefore excluded from that analysis. Trials evaluated vinflunine (n = 151), docetaxel ± vandetanib (n = 147), paclitaxel-gemcitabine (n = 83), sunitinib (n = 77), nanoparticle albumin-bound paclitaxel (nab paclitaxel) (n = 48), volasertib (n = 46), everolimus (n = 45), pazopanib (n = 43), cetuximab ± paclitaxel (n = 39), and paclitaxel-cyclophosphamide (n = 32). The number of prior lines of therapy, including perioperative chemotherapy as a line, was 1 in 559 patients (78.6%), 2 in 111 (15.6%), 3 in 29 (4.1%), 4 in 10 (1.4%), and 5 in 2 (0.3%). Prior perioperative chemotherapy was given to 277 patients (39.1%), chemotherapy for metastatic disease to 454 (64.1%), and prior chemotherapy in both perioperative and metastatic settings to 75 (27.1%).

Impact of the Number of Prior Lines of Therapy on PFS and OS

The overall median PFS and OS were 2.7 and 6.8 months, respectively (Table 3). Outcomes with different regimens exhibited a range but were uniformly dismal (see Table 3). TFPC, Hb, PS, and LM were significantly associated with OS