Original Study

Incomplete Cross-Resistance Between Taxanes for Advanced Urothelial Carcinoma: Implications for Clinical Practice and Trial Design

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Abstract

In this retrospective study, docetaxel treatment after previous paclitaxel treatment and the reverse sequence demonstrated outcomes and activity similar to salvage therapy for advanced urothelial carcinoma (UC). The clinical implications are that trials using a taxane can probably allow previous exposure to a different taxane, and patients treated off protocol may receive a taxane after previous exposure to a different taxane.

Background: Taxanes such as paclitaxel and docetaxel are commonly used for second- or third-line salvage systemic therapy for metastatic UC. Although trials have generally excluded previous exposure to taxanes when using a taxane in a salvage therapy trial, taxanes might not be completely cross-resistant. Hence, we aimed to study outcomes with docetaxel after previous paclitaxel and the reverse sequence, to identify the level of cross-resistance between these taxanes. **Patients and Methods:** Data from a randomized phase II trial that compared salvage therapy with docetaxel combined with either placebo or vandetanib for advanced UC were analyzed. Both arms were combined for analysis because no differences in any outcomes were observed. Data were also requested from institutions for patients who received paclitaxel after previous docetaxel treatment. Descriptive statistics were used to summarize patient and treatment characteristics and outcomes. The primary clinical end point of interest was overall survival (OS). **Results:** Of 148 patients who received docetaxel with either vandetanib or placebo, 21 had received previous paclitaxel treatment. No difference in OS, progression-free survival, or response rate was observed with docetaxel based on previous paclitaxel treatment after adjusting for known prognostic factors. Among the 8 patients who received paclitaxel after previous docetaxel treatment, partial response was observed in 1 patient (12.5%) and stable disease in 2 patients (25%). **Conclusion:** Docetaxel treatment after previous paclitaxel treatment and the reverse sequence demonstrates activity in advanced UC. There is no strong evidence to disallow patients with previous exposure to a taxane to enroll in a clinical trial involving another taxane.

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Introduction

The salvage systemic therapy of advanced urothelial carcinoma (UC) has substantial unmet needs.[1] Vinflunine is approved in Europe and multiple other countries based on a phase III trial that accrued 370 patients who demonstrated improved overall survival (OS) in the eligible population compared with best supportive care, albeit not using intention to treat analysis.[2] In the United States, taxanes such as paclitaxel and docetaxel are commonly used as a community standard for second-line or third-line salvage systemic therapy based on phase II data.[3] The median progression-free

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survival (PFS) and OS are 2 to 4 months and 6 to 9 months, respectively, with salvage systemic therapy.

Multiple trials that evaluated novel taxanes (eg, nanoparticle albumin bound [nab]-paclitaxel) and the combination of biologic agents with taxanes as salvage therapy have not permitted previous exposure to any taxane.[4] However, because of the difficulties of accrual of the advanced UC population, we hypothesized that patients previously exposed to a different taxane may be permitted to participate in trials (eg, those exposed to paclitaxel may be allowed to participate in trials using docetaxel as the platform of therapy and vice versa). Our rationale was based on differences in structure, solvent vehicle, metabolism, central nervous system penetration, and susceptibility to resistance mechanisms (eg, p-glycoprotein) between taxanes that might translate to lack of complete cross-resistance.[5,6] For example, docetaxel is more water soluble than paclitaxel because of differences in 2 positions in its chemical structure and is delivered in polysorbate 80 as the solvent instead of cremophor.[7] Hence, we performed a retrospective analysis to evaluate outcomes when docetaxel was used with or without previous treatment with paclitaxel, and also to describe outcomes when paclitaxel was used after previous treatment with docetaxel.

Patients and Methods

Patient Population

Data were requested from a multicenter randomized phase II trial managed by the Dana Farber Cancer Institute that compared salvage therapy with docetaxel every 3 weeks combined with either placebo or vandetanib for advanced UC.[3] Up to 3 previous systemic regimens were allowed including previous paclitaxel, after an amendment because of slow accrual. Data were requested for previous paclitaxel treatment, PFS, and OS in addition to major prognostic factors (ie, liver metastasis [LM], Eastern Cooperative Oncology Group [ECOG] performance status [PS], time from previous perioperative chemotherapy [TFPC], and hemoglobin [Hb]).

Data were also requested from 13 institutions (that did not participate in the aforementioned randomized phase II trial), known to treat large numbers of advanced UC for patients, on patients who received paclitaxel after previous exposure to docetaxel. Data regarding previous docetaxel usage, previous prognostic factors and response, PFS, and OS outcomes were requested. All data were deidentified and provided in an Excel spreadsheet by all investigators and this study was conducted after institutional review board approval.

Statistical Methods

For the analysis of outcomes with docetaxel after exposure to paclitaxel, both arms of the randomized phase II trial that compared docetaxel combined with either vandetanib or placebo were combined because no differences in overall outcomes were demonstrated between the arms, and there is no biological rationale to believe that previous paclitaxel treatment will differentially affect outcomes of patients treated with either vandetanib or placebo.[3] Descriptive statistics were used to summarize patient and treatment characteristics and outcomes. The primary clinical end point of interest was OS and the secondary end points were PFS and response rate (RR). The Kaplan–Meier method was used to estimate time to event outcomes. OS and PFS were defined according to the study protocol. Fisher exact tests, Cochran–Armitage tests for trend, Wilcoxon rank sum tests, and log-rank tests were used to investigate differences between patients exposed and not exposed to previous paclitaxel for categorical, ordinal, continuous, and time-to-event outcomes, respectively. Cox proportional hazards regression models were used to investigate the prognostic ability of previous paclitaxel exposure, after adjusting for major factors (LM, ECOG-PS, TFPC, and Hb) known to affect OS and PFS. All tests and confidence intervals were 2-sided and set at a $P = .05$ level of significance. For analysis of patients who received paclitaxel after previous exposure to docetaxel, descriptive statistics were used to summarize patient and treatment characteristics and outcomes.

Results

Patient Characteristics

The randomized phase II trial that compared docetaxel combined with vandetanib or placebo as salvage systemic therapy has been published.[3] Table 1A shows the baseline characteristics of patients who received docetaxel with either vandetanib or placebo and received and did not receive previous paclitaxel treatment. Of 148 patients, 21 had been exposed to previous paclitaxel treatment. Patients with previous paclitaxel treatment were more likely to have received previous carboplatin, a greater number of previous chemotherapy regimens, and previous chemotherapy regimens for metastatic disease ($P < .001$ for all).

Table 1B shows baseline characteristics of patients who received paclitaxel after previous docetaxel. Of 13 institutions that were requested data for patients who received paclitaxel after previous docetaxel, 3 institutions were able to identify 8 patients overall: University Federico II, Naples, Italy (n = 4), Istituto Ospedaliero del Sud and Coleman, Napoli, Italy (n = 2), and Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy (n = 2).

Effect of Previous Paclitaxel Treatment on Outcomes With Docetaxel Treatment

No difference in OS (Figure 1) or PFS (Figure 2) was observed based on previous paclitaxel treatment. Patients with previous paclitaxel had a median PFS and OS of 1.9 (95% confidence interval [CI], 1.4-2.9) and 4.0 (95% CI, 2.7-7.0) months respectively, which compared similarly with patients without previous exposure to paclitaxel who had median PFS and OS of 1.8 (95% CI, 1.5-2.5) and 5.3 (95% CI, 4.4-6.8) months, respectively. Table 2 shows results of an evaluation as to whether patients with previous paclitaxel had different OS or PFS after adjusting for known prognostic factors. No significant effect or trend was observed ($P = .86$ for OS and $P = .29$ for PFS). Because TFPC and performance status were both significant in this model, it was interesting to evaluate whether there was any differential effect of previous paclitaxel treatment within each subgroup. An interaction effect was not significant for previous paclitaxel with TFPC $\geq$ 3 months or with ECOG PS $>$ 0, although power was limited. The results were therefore plotted for visual inspection (Figures 3 and 4) with no obvious pattern.

Docetaxel-based therapy induced responses in 3 of 21 patients (14.3%) exposed to previous paclitaxel treatment, including 1 complete response (CR). The single patient who demonstrated a CR received docetaxel with vandetanib, and the other 2 patients who