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Single-agent Taxane Versus Taxane-containing Combination Chemotherapy as Salvage Therapy for Advanced Urothelial Carcinoma

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Abstract

Background: Single-agent taxanes are commonly used as salvage systemic therapy for patients with advanced urothelial carcinoma (UC).
Objective: To study the impact of combination chemotherapy delivering a taxane plus other chemotherapeutic agents compared with single-agent taxane as salvage therapy.
Design, setting, and participants: Individual patient-level data from phase 2 trials of salvage systemic therapy were used.
Interventions: Trials evaluating either single agents (paclitaxel or docetaxel) or combination chemotherapy (taxane plus one other chemotherapeutic agent or more) following prior platinum-based therapy were used.
Outcome measurements and statistical analysis: Information regarding the known major baseline prognostic factors was required: time from prior chemotherapy, hemoglobin, performance status, albumin, and liver metastasis status. Cox proportional hazards regression was used to evaluate the association of prognostic factors and combination versus single-agent chemotherapy with overall survival (OS).
Results and limitations: Data were available from eight trials including 370 patients; two trials ($n = 109$) evaluated single-agent chemotherapy with docetaxel ($n = 72$) and cremophor-free paclitaxel ($n = 37$), and six trials ($n = 261$) evaluated combination chemotherapy with gemcitabine–paclitaxel (two trials, with $n = 99$ and $n = 24$), paclitaxel–cyclophosphamide ($n = 32$), paclitaxel–ifosfamide–nedaplatin ($n = 45$), docetaxel–ifosfamide–cisplatin ($n = 26$), and paclitaxel–epirubicin ($n = 35$). On multivariable analysis after adjustment for baseline prognostic factors, combination chemotherapy was independently and significantly associated with improved OS (hazard ratio: 0.60; 95% confidence interval, 0.45–0.82; $p = 0.001$). The retrospective design of this analysis and the trial-eligible population were inherent limitations.
Conclusions: Patients enrolled in trials of combination chemotherapy exhibited improved OS compared with patients enrolled in trials of single-agent chemotherapy as

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salvage therapy for advanced UC. Prospective randomized trials are required to validate a potential role for rational and tolerable combination chemotherapeutic regimens for the salvage therapy of advanced UC.

Patient summary: This retrospective study suggests that a combination of chemotherapy agents may extend survival compared with single-agent chemotherapy in selected patients with metastatic urothelial cancer progressing after prior chemotherapy.

1. Introduction

Single-agent taxane chemotherapy is the most common agent used to treat metastatic urothelial carcinoma (UC) progressing after prior chemotherapy [1]. Although vinflunine is approved in Europe and other countries (but not the United States), single-agent taxanes are widely used as standard alternatives, given similar outcomes when compared across trials [2]. Median progression-free survival (PFS) and overall survival (OS) of 2–4 mo and 6–9 mo, respectively, suggest that new agents and strategies are required for the salvage therapy of metastatic UC.

Indeed, some new agents are showing promise, such as programmed cell death 1 (PD1) and programmed death ligand 1 (PD-L1) inhibitors, vascular endothelial growth factor receptor inhibitors, and tubulin-inhibiting cytotoxic chemotherapeutic agents [3–5]. However, these agents may be expected to confer incremental benefits, and thus room remains for evaluating other strategies such as combinations of chemotherapeutic agents known to exhibit single-agent activity. Very few trials have investigated combination chemotherapy as salvage therapy for metastatic UC [6–11]. We conducted a retrospective study to identify whether combination chemotherapy including a taxane confers incremental outcomes over single-agent taxanes.

2. Patients and methods

2.1. Patient population

Trials were selected based on the availability of individual patient-level data and willingness of the respective principal investigators to provide data. Two prospective phase 2 trials of salvage systemic single-agent taxane chemotherapy following platinum-based chemotherapy for advanced UC were available (Table 1) [12,13]. Six phase 2 trials of salvage combination chemotherapy that combined a taxane with one or two other chemotherapeutic agents were available [6–11]. All trials required prior platinum, and prior taxane chemotherapy was not allowed or administered except in the docetaxel plus vandetanib/placebo trial by Choueiri et al [12] and the paclitaxel plus gemcitabine trial by Albers et al, which had few patients previously exposed to paclitaxel [10]; in addition, approximately 57% of patients in the trial of paclitaxel plus gemcitabine by Albers et al had been exposed to gemcitabine. The trial of paclitaxel plus epirubicin by Rozzi et al did not allow prior anthracycline [6]. The trial of paclitaxel plus gemcitabine by Ikeda et al had no patients exposed to gemcitabine [7]. The trial of paclitaxel plus ifosfamide plus nedaplatin by Kitamura et al did not have patients exposed to ifosfamide or nedaplatin [8]. The trial of docetaxel plus ifosfamide plus cisplatin by Kakutani et al did not have patients exposed to ifosfamide [9]. The trial of paclitaxel plus cyclophosphamide by Di Lorenzo et al had no patients exposed to cyclophosphamide [11].

All trials required previous pathological confirmation of UC and measurable metastatic disease. Data regarding known baseline prognostic factors in the context of salvage systemic therapy including time from prior chemotherapy (TFPC), hemoglobin (Hb), Eastern Cooperative Oncology Group (ECOG) performance status (PS), albumin, and liver metastasis (LM) status were requested [14–16]. The data were deidentified and provided in an Excel spreadsheet (Microsoft, Redmond, WA, USA) by all investigators. All of the individual trials were approved by the respective institutional review boards (IRBs) of the institutions at which they were conducted, and our retrospective study was IRB approved by the University of Alabama, Birmingham.

2.2. Statistical methods

OS was the primary clinical end point, calculated from the date of study entry until death from any cause, and PFS was the secondary end point, calculated until objective disease progression or the date of

Table 1 – Eligibility criteria of trials included in analysis

Trial regimen	Enrolled, *n*	Performance status allowed	Prior taxane allowed	Required only one prior regimen	Required prior therapy for metastatic disease	Required prior platinum	Allowed prior perioperative chemotherapy as only prior regimen	Period allowed between prior perioperative chemotherapy and salvage therapy regimen
Docetaxel plus placebo [12]	72	0–1	Yes	No	No	Yes	Yes	2 yr
Cremophor-free paclitaxel [13]	37	0–2	No	No	No	Yes	Yes	No limitation
Paclitaxel plus epirubicin [6]	35	0–1	No	Yes	Yes	Yes	No	Not applicable
Paclitaxel plus gemcitabine [7]	24	0–2	No	No	No	Yes	Yes	1 yr
Paclitaxel plus ifosfamide plus nedaplatin [8]	45	0–2	No	Yes	No	Yes	Yes	No
Docetaxel plus ifosfamide plus cisplatin [9]	26	0–2	No	No	Yes	Yes	No	Not applicable
Paclitaxel plus gemcitabine [10]	99	0–2	Yes	Yes	No	Yes	Yes	No limitation
Paclitaxel plus cyclophosphamide [11]	32	0–2	No	No	Yes	Yes	No	Not applicable

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