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Platinum Priority – Review – Urothelial Cancer

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The Impact of Adding Taxanes to Gemcitabine and Platinum Chemotherapy for the First-Line Therapy of Advanced or Metastatic Urothelial Cancer: A Systematic Review and Meta-analysis

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Abstract

Context: Gemcitabine/platinum chemotherapy is the most widely used first-line regimen for metastatic urothelial carcinoma, and the potential improvement of adding taxanes needs to be clarified.
Objective: To study the survival impact of taxane plus gemcitabine/platinum compared with gemcitabine/platinum alone as upfront therapy.
Evidence acquisition: Literature was searched for studies including gemcitabine/platinum ± taxanes (paclitaxel or docetaxel only). We pooled trial level data including the median, proportions, and confidence intervals on response-rate, progression-free survival, overall survival (OS), and side effects. Univariable and multivariable regression models evaluated the prognostic role of addition of taxanes after adjusting for platinum type, performance status 2, and the presence of visceral metastases. Data were weighted by the logarithm of the trial sample size.
Evidence synthesis: Thirty-five arms of trials including 2,365 patients were selected (seven with taxanes [$n = 617$], and 28 arms without taxanes [$n = 1,748$]). Median OS was univariably significantly different ($p = 0.019$) between trials with and without taxanes. Across trials, the median 'median OS' amongst trials containing taxanes was 15.5 mo, compared with 12.5 mo in trials which did not. Multivariably, visceral disease and performance status were significantly associated with OS, and the addition of taxanes trended toward significantly better OS ($p = 0.056$) and increase in grade ≥ 3 neurotoxicity ($p = 0.051$), regardless of specific platinum agent used.
Conclusions: In this meta-analysis, adding taxanes to gemcitabine and platinum showed a trend for improved OS and higher grade ≥ 3 neurotoxicity. Improvements in patient selection and the evaluation of a more potent and tolerable tubulin inhibitor in combination with gemcitabine/platinum in a well-powered trial are the critical next steps.
Patient summary: In this report, a trend for improved overall survival and worse neurotoxicity was observed for adding a taxane to first-line gemcitabine/platinum chemotherapy for metastatic urothelial carcinoma. More effective taxanes should be investigated further in urothelial carcinoma in combination with gemcitabine/platinum.

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1. Introduction

Despite the remarkable progress in the therapeutic paradigm of urothelial cancer (UC), particularly in advanced stages, UC has suffered a 2-decade delay characterized by plenty of unsuccessful systemic treatments that have resulted from negative trials, often plagued by early closure due to poor accrual. With the use of methotrexate, cisplatin, doxorubicin, and vinblastine combination and gemcitabine/cisplatin (GC) doublet, despite an overall objective response-rate of about 50%, the median progression-free survival (PFS) and overall survival (OS) attained are approximately 8 mo and 14 mo, respectively [1]. Furthermore, cisplatin is being administered in less than half of patients once they are diagnosed with advanced UC, and GC doublet is the alternative option; although, its efficacy seems to be inferior to that of cisplatin-based therapy [2–5].

In the attempt to improve the available results, the addition of a third drug to platinum doublets has been investigated. In particular, given the single agent activity of taxanes [6,7], the combination of GC with paclitaxel has been investigated in a phase 3 trial of 626 patients led by the European Organization for the Research and Treatment of Cancer (EORTC) [8]. A nonsignificant trend ($p = 0.075$) towards a better OS with the triple combination regimen was observed, although a larger trial may have potentially identified a statistically significant difference. Additional smaller phase 2 studies have reported results with either gemcitabine or platinum alone or in combination with paclitaxel or docetaxel [9–35]. Results with gemcitabine-platinum doublet as the standard arm of randomized phase 3 studies were also available [36–39].

Although promising new agents are emerging, there remains a role for combinations of chemotherapeutic drugs with proven single agent activity. Given that the aforementioned single phase 3 EORTC 30987 trial showed a trend for improved survival by the addition of paclitaxel to GC, we hypothesized that a pooled analysis of multiple trials will increase the power to identify a significant increment in OS. Hence, we conducted a systematic review and meta-analysis of the results from prospective studies which either did or did not contain paclitaxel or docetaxel in combination with gemcitabine plus platinum.

2. Evidence acquisition

2.1. Search strategy and data abstraction

From December 2014 to April 2015, we performed a systematic review and meta-analysis in accordance to the preferred reporting items for systematic reviews and meta-analyses guidelines [40].

Eligible randomized or nonrandomized phase 2 and 3 studies were searched in PubMed, EMBASE, and meeting abstracts presented at congresses of the American Society of Clinical Oncology, European Society for Medical Oncology, American Association of Cancer Research, and Genitourinary Cancers Symposiums.

The following inclusion criteria have been adopted: period of publication between 1990 and 2014, English language, retrospective and prospective trials/studies reporting data on gemcitabine and platinum doublet, alone or with a taxane (including paclitaxel or docetaxel only). The administration of prior perioperative chemotherapy was allowed. Principal exclusion criteria were overlapping publications, lack of relevant outcome data, less than 15 patients, studies entirely reporting on patients treated prior to 1990, and studies reporting on either gemcitabine/platinum + nontaxane combination regimens. Also, trials that allowed the crossover between gemcitabine/platinum ± new drugs were excluded (since new drugs may have unknown activity and benefit), as well as those where any agent had been administered sequentially or as a maintenance (since this approach is not standard).

The population, intervention, comparison, and outcome (question: which are the outcomes of gemcitabine/platinum chemotherapy or gemcitabine/platinum plus a taxane as first-line therapy for advanced or metastatic UC?) strategy was conducted and the following search string was utilized: 'transitional cell carcinoma'/exp OR transitional AND cell AND carcinoma:ab,ti AND 'chemotherapy'/exp OR 'salvage therapy'/exp OR 'single drug dose'/exp OR 'cancer combination chemotherapy'/exp OR 'salvage therapy':ab,ti OR 'combination chemotherapy':ab,ti OR 'single drug dose':ab,ti AND 'clinical effectiveness'/exp OR 'overall survival'/exp OR 'progression free survival'/exp OR 'cancer staging'/exp OR 'toxicity'/exp. Additional queries with relevant variants and filters have been added up, integrated by the search through the American Society of Clinical Oncology portal. Search results were independently reviewed by two authors (DR, AN). Full articles were retrieved for further qualitative review.

2.2. Statistical analyses

The primary objective was to compare taxane- versus nontaxane studies, and the secondary objective was to compare cisplatin versus carboplatin studies. The primary endpoint was median OS, while secondary endpoints included 1-yr OS, response-rate, median PFS, and the rate of adverse events.

Outcomes were defined as per each study definitions, however, PFS was commonly defined as the time from the date of starting treatment to the date of documented relapse, recurrence, and censoring patients who have died without progression, while OS was defined as the time from treatment start to death for any reason, with censoring alive patients at the date of last contact.

Descriptive statistics were used to summarize information across all trials, and grouped by whether the treatment contained a taxane (docetaxel vs paclitaxel) and by platinum status (carboplatin vs cisplatin). Trial characteristics and outcomes were compared between trials using the Fisher's exact test (dichotomous characteristics) or Wilcoxon rank sum test (continuous characteristics and outcomes). These analyses were univariable only. Bootstrapping was performed to evaluate the sensitivity of the