Review

Efficacy and Safety of Gemcitabine Plus Either Taxane or Carboplatin in the First-Line Setting of Metastatic Urothelial Carcinoma: A Systematic Review and Meta-Analysis

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Abstract

Although gemcitabine plus carboplatin (GCa) is the conventional first-line chemotherapy for cisplatin-ineligible metastatic urothelial carcinoma, its results are suboptimal. A meta-analysis evaluated the results of gemcitabine with either carboplatin or a taxane (GT). Literature was searched for studies including GT (paclitaxel or docetaxel) and GCa. We pooled trial level data including response-rate, progression-free survival, overall survival (OS), and Grade 3 to 4 side effects. Trial characteristics and outcomes were univariably compared between GT and GCa. Those factors, which were recorded in > 12 trials, were analyzed. Multivariable regression models were used adjusting for Eastern Cooperative Oncology Group performance status 2 and the presence of visceral metastases. Each trial was weighted by its sample size. Twenty-seven arms of trials totaling 1032 patients were selected, of which 13 contained GT (n = 484) and 14 GCa (n = 548). The percentage of patients with Eastern Cooperative Oncology Group performance status 2 was statistically significantly different between the 2 groups (median, 8.7% vs. 23.9%; $P = .003$). No efficacy outcome was statistically significantly different. Median OS was 13.2 months (range, 10-15.8 months) for GT and 10 months (range, 3.3-20 months) for GCa ($P = .12$). However, statistically significant increases in the frequency of Grade 3 to 4 anemia ($P = .010$) and thrombocytopenia ($P = .010$) for GCa, and neuropathy ($P = .040$) for GT were observed. No difference in OS according to treatment was found multivariably ($P = .79$). In this analysis, a similar response rate and survival and worse neurotoxicity were observed with GT compared with GCa, for which hematologic toxicity was more frequent. GT is an alternative to GCa for advanced cisplatin-ineligible urothelial cancer.

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Introduction

Despite a remarkable incidence rate (the fourth most common malignancy in men in the United States), the progress in the therapeutic paradigm of urothelial cancer (UC), particularly for patients with stage IV UC, suffered a 2-decade delay characterized by numerous unsuccessful studies that accrued at a frustratingly slow rate.[1] The standard first-line chemotherapy for patients with metastatic UC is represented by cisplatin-based combinations with either methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) or gemcitabine-cisplatin as equally effective options.[2] The response rate (RR) with these regimens approximates 50%, and the median overall survival (OS) is in the range of 13 to 15 months. Many efforts have been made in the past decades with the aim of improving these results. In particular, the addition of paclitaxel to gemcitabine and cisplatin demonstrated a non-significant

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trend for overall survival improvement in a phase III trial, and potentially a larger trial may have attained statistical significance.[3,4]

Unfortunately, about 50% of patients with metastatic UC are ineligible for cisplatin treatment according to consensus criteria that account for renal function, performance status (PS), and comorbidities.[5,6] For these patients, there is no agreed upon the standard of care, although the administration of gemcitabine plus carboplatin (GCa) is the most frequently chosen option whenever patients are fit for combination chemotherapy. In the absence of any conclusive randomized study, the outcomes of carboplatin-based regimens seemed to be inferior to those with cisplatin-based chemotherapy.[7,8] For this reason, the regulatory authorities well recognize the treatment of cisplatin-ineligible patients as an unmet medical need.

Thus far, clinical trials in the second-line setting have required the failure of first-line platinum-based chemotherapy. This eligibility criterion is believed by the designers of these trials to be an essential prerequisite to access new drugs in the salvage setting, despite the lack of robust comparative data between carboplatin- and non−platinum-based regimens in cisplatin-unfit patients. A rational alternative to the use of platinum-based chemotherapy is represented by the use of gemcitabine and a taxane (GT, namely paclitaxel), that seemed to be equal in effectiveness to GCa in small, non-comparative phase II trials.

Also, a number of specialists may not routinely use GCa because of their clinical experience with the toxicities of GCa. We hypothesized that the GT combination may provide increments in outcomes with a different or favorable toxicity profile compared with GCa. Consequently, we conducted a trial-level meta-analysis of phase II and III studies that reported on GCa or GT in the first-line setting of metastatic UC, in order to compare efficacy and toxicities.

Patients and Methods

Search Strategy and Data Abstraction

From August to October 2015, we performed a systematic review and meta-analysis in accordance to the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines.[9]

Eligible randomized or non-randomized phase II and III 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 plus either carboplatin or 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-carboplatin/taxane + other chemotherapy or targeted compound. Also, trials that allowed the crossover between gemcitabine-carboplatin ± new drug were excluded (because new drugs may have unknown activity and benefit) as well as those where any agent had been administered sequentially or as a maintenance therapy, similarly to what we did in previous meta-analyses.[4]

The population, intervention, comparison, and outcome (question: which are the outcomes of gemcitabine/platinum vs. gemcitabine/taxane chemotherapy as first-line therapy for advanced or metastatic UC?) strategy was conducted, and the following search string was utilized: *'transitional cell carcinoma'/exp AND 'chemotherapy'/exp OR 'cancer combination chemotherapy'/exp OR 'combination chemotherapy'/exp AND 'gemcitabine'/exp AND 'carboplatin'/exp OR 'gemcitabine'/exp AND 'paclitaxel'/exp OR 'gemcitabine'/exp AND 'docetaxel'/exp AND 'clinical effectiveness'/exp OR 'overall survival'/exp OR 'progression free survival'/exp OR 'toxicity'/exp*. Other queries with relevant variants and filters were subsequently added and integrated by searching the American Society of Clinical Oncology website. Search results were independently reviewed by 2 authors (A.N., D.R.). Full articles were retrieved for further qualitative review.

Statistical Analyses

The primary objective was to compare the efficacy of GT and GCa studies, and the secondary objective was to compare the incidence of severe side effects in the respective groups. The primary endpoint was median OS, whereas secondary endpoints included 1-year OS, RR, median progression-free survival (PFS), and the rate of adverse events (AEs).

Outcomes were defined as per definitions of each study; however, PFS was commonly defined as the time from the date of starting treatment to the date of documented relapse or recurrence and censoring patients who have died without progression. OS was commonly 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 GT (docetaxel or paclitaxel) or GCa. Trial characteristics and outcomes were compared between trials using the Fisher 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 significance of the primary outcome result (ie, median OS). Only those characteristics and outcomes which were recorded in at least 12 trials were included for analysis.

Multivariable regression models were performed, adjusting for the percentage of patients with Eastern Cooperative Oncology Group (ECOG) PS 2 and the percentage of visceral metastases. Each trial was weighted by its sample size. A sub-analysis was performed including only those trials with no patients having received prior chemotherapy in the perioperative (ie, neoadjuvant/adjuvant) setting.

Publication bias was evaluated by visually inspecting funnel plots and using the Egger test for bias. Heterogeneity was assessed through visual inspection of forest plots, through the I^2 statistic, and through the Cochran Q test. Evaluations were assessed within each subgroup of interest (GT vs. GCa). Standard error of the median OS and median PFS was estimated as $1/\sqrt{(1/(\#\text{ of patients}/3))}$, as the true standard error was not available for most trials. Statistical significance was defined as a *P*-value of .05 or less, and all tests and confidence intervals were 2-sided. No adjustment for multiple testing was performed. Descriptive analyses were

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