Original Study

Six-Month Progression-Free Survival as the Primary Endpoint to Evaluate the Activity of New Agents as Second-line Therapy for Advanced Urothelial Carcinoma

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Abstract

This study examined the association of progression-free survival at 6 months with overall survival in the context of second-line therapy of advanced urothelial carcinoma in pooled patient-level data from 10 phase II trials and then externally validated in a large phase III trial. Progression-free survival at 6 months was significantly correlated with overall survival and is an innovative primary endpoint to evaluate new agents in this setting.

Objective: Second-line systemic therapy for advanced urothelial carcinoma (UC) has substantial unmet needs, and current agents show dismal activity. Second-line trials of metastatic UC have used response rate (RR) and median progression-free survival (PFS) as primary endpoints, which may not reflect durable benefits. A more robust endpoint to identify signals of durable benefits when investigating new agents in second-line trials may expedite drug development. PFS at 6 months (PFS6) is a candidate endpoint, which may correlate with overall survival (OS) at 12 months (OS12) and may be applicable across cytostatic and cytotoxic agents. **Methods:** Ten second-line phase II trials with individual patient outcomes data evaluating chemotherapy or biologics were combined for discovery, followed by external validation in a phase III trial. The relationship between PFS6/RR and OS12 was assessed at the trial level using Pearson correlation and weighted linear regression, and at the individual level using Pearson chi-square test with Yates continuity correction. **Results:** In the discovery dataset, a significant correlation was observed between PFS6 and OS12 at the trial ($R^2 = 0.55$, Pearson correlation = 0.66) and individual levels (82%, $\kappa = 0.45$). Response correlated with OS12 at the individual level less robustly (78%, $\kappa = 0.36$), and the trial level association was not statistically significant ($R^2 = 0.16$, Pearson correlation = 0.37). The correlation of PFS6 (81%, $\kappa = 0.44$) appeared

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stronger than the correlation of response (76%, $\kappa = 0.17$) with OS12 in the external validation dataset. **Conclusions:** PFS6 is strongly associated with OS12 and appears more optimal than RR to identify active second-line agents for advanced UC.

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Introduction

Advanced urothelial carcinoma (UC) has not had major improvements in outcomes for more than 2 decades. Despite initial high response rates (RRs) of 40% to 70% with cisplatin-based frontline combination chemotherapy, these regimens are generally not curative and yield a 5-year overall survival (OS) of 4% to 20%.[1-3] Multiple agents have demonstrated limited activity in the second-line setting, with RRs of 5% to 20%, median progression-free survival (PFS) of 2 to 4 months, and median OS of 6 to 9 months.[4-14] Thus, there are significant unmet medical needs, particularly in the second-line setting.

Trials of metastatic UC in the second-line setting have commonly used RR or median PFS as the primary endpoint to evaluate activity and as a surrogate for OS. However, response may not capture the activity of cytostatic agents, and both of these endpoints do not lend confidence with regard to the durability of benefits. PFS at a fixed time point beyond the usual median PFS at 6 months (PFS6) may warrant further study as an intermediate endpoint for OS at 12 months (OS12). Indeed, a strong association between PFS6 and OS has been found in similar aggressive malignancies, glioblastoma multiforme, and small-cell lung cancer.[15-17] We hypothesized that PFS6 correlates with OS12 in the context of second-line therapy for advanced UC and may be a robust endpoint to identify signals of durable benefits when investigating new agents.

Patients and Methods

Eligible Trials and Patients

Individual patient-level data were pooled from 10 phase II trials (8 single arm and 2 randomized) evaluating second-line chemotherapy or biologics (except the trial by Choueiri et al,[5] which allowed ≤ 3 prior lines of therapy after enrolling 65 of 149 patients) (Table 1). Prior therapy may have been administered in the metastatic or perioperative setting. The study by Wong et al[14] was a noncomparative randomized trial that randomized patients to 2 arms (cetuximab and cetuximab-paclitaxel) but discontinued enrollment on cetuximab after accruing 11 patients because of futility. Patients with available progression data by 6 months and survival data by 12 months were eligible for analysis, and others were censored.[4-10,12-14] Progression was defined as objective tumor progression (by Response Evaluation Criteria in Solid Tumors [RECIST] 1.0 in 9 trials and World Health Organization criteria in 1 trial by Sternberg et al[9]), or death from any cause.

A second-line phase III trial of patients with advanced UC was used for external validation.[11] In this trial, 370 patients who had received 1 prior regimen for metastatic disease were treated with vinflunine plus best supportive care (BSC) (n = 253) or BSC alone (n = 117). This trial used central radiology review and RECIST 1.0 for objective tumor assessment.

Statistical Analysis

Unadjusted and adjusted binomial confidence intervals (CIs) for PFS6, OS12, and response were reported, with adjustment for variability between trials using random effects models. To get an estimate of PFS6 with an appropriate estimate of standard error, we fit generalized linear mixed models with normal random effects for trial, using a penalized quasi-likelihood estimation approach as implemented in the glmmPQL function of the MASS package in "R".[18,19] The relationship between PFS6/RR and OS12 was assessed at the trial level using weighted linear regression, with larger studies having more influence and Pearson correlation. For the weighted linear regression correlation, the fitted line is from a weighted least-squares regression model with weights proportional to the study size. The circles are proportional to the study size. The equation for the regression model is $y = 0.07694 + 0.5685*x$. If there was perfect agreement between OS12 and PFS6, the slope would be 1.00. In contrast, the Pearson correlation treats all trials as equal regardless of size. For the Pearson correlation, values from 0.3 to 0.5 generally indicate a large positive association.

The relationship between PFS6/RR and OS12 at the individual level was assessed using Pearson chi-square test with Yates continuity correction. Statistical analyses used "R" statistical computing software, version 2.8.0. A secondary analysis was conducted to examine the trial and individual-level associations of PFS6 and OS12 based on prior chemotherapy in the perioperative disease or metastatic settings. The second-line phase III trial comparing BSC with vinflunine plus BSC was used for external validation.[11]

Results

Trial and Patient Characteristics

Of 689 patients enrolled in 10 phase II trials used as the discovery dataset, 646 were evaluable for PFS analysis (with available trial-defined progression and survival data). Patients were censored because of loss to follow-up and removal from trial for reasons other than progression (eg, toxicities or patient decision). A total of 560 were evaluable for response (with available baseline measurable disease and survival data) (Table 1). The agents evaluated in these trials included chemotherapy (gemcitabine-paclitaxel, nanoparticle-albumin-bound (nab)- paclitaxel, irinotecan, docetaxel, vinflunine), biologic agents (gefitinib, pazopanib, cetuximab), and the combination of chemotherapeutic and