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Evolution of randomized controlled trials and surrogacy of progression-free survival in advanced/metastatic urothelial cancer☆

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ABSTRACT

Background: Clinical trials in advanced/metastatic urothelial cancer have been difficult to perform. We review the current characteristics of randomized controlled trials (RCTs) and evaluate whether PFS could be a potential surrogate endpoint for overall survival (OS) in advanced/metastatic urothelial cancer.
Methods: We identified trials by a systematic review of Medline, Embase, and the Cochrane Central Register of Controlled Trials from inception to April 2017. We included RCTs of patients with locally advanced/metastatic urothelial cancer that involved systemic therapy as an intervention, and those with reported hazards ratios (HRs) and corresponding 95% confidence intervals (CIs) for both OS and PFS, or provided Kaplan–Meier curves from which HRs and 95% CI could be calculated. The correlation coefficient between log of HRs for OS and PFS was calculated using linear regression weighted by sample size.
Results: Forty eight trials that enrolled 7019 patients were included in the review and 24 RCTs were included in the surrogacy analysis. 27(56.3%) of identified 48 RCTs were phase II trials, and the median sample size was 107(range, 30–626) for all RCTs. The correlation coefficient between log HR for PFS and log HR for OS was 0.79 (95% CI, 0.58-0.91). The correlation coefficient increased to 0.87 (95% CI, 0.72-0.94) after excluding the only trial with immune checkpoint inhibitor. Multiple sensitivity analyses did not change the results..aph."/ >
Conclusions: PFS is strongly correlated with OS in trials of advanced/metastatic urothelial cancer assessing the treatment benefit of new drugs And PFS warrants further exploration as a surrogate endpoint in clinical trial datasets.

1. Introduction

Metastatic urothelial cancer is a disease with a poor prognosis. Platinum-based combination chemotherapy has been the standard front-line treatment for patients with advanced or metastatic urothelial carcinoma for three decades with median overall survival (OS) of 11–15 months (Sternberg et al., 1989; Loehrer et al., 1992; Saxman et al., 1997; von der Maase et al., 2000). In the second line setting, multiple agents have demonstrated only limited activity with a median OS of 6–9 months (Beer et al., 2008; Choueiri et al., 2012; Culine et al., 2006; Ko et al., 2013; Petrylak et al., 2010; Sternberg et al., 2001a; Vaughn et al., 2009; Bellmunt et al., 2009; Albers et al., 2011; Wong et al., 2012; Pili et al., 2013). Recently, immune-checkpoint inhibitors targeting the programmed cell death 1 protein (PD-1) and its ligand (PD-L1) have shown clinical activity in patients with platinum-refractory urothelial carcinoma (Plimack et al., 2017; Rosenberg et al., 2016; Sharma et al., 2016; Massard et al., 2016; Patel et al., 2017; Bellmunt et al., 2017a). However, a benefit was reported in only 20–30% of patients, highlighting that other targets and treatments are needed.

The development of new therapies for the urothelial cancer requires demonstration of statistically and clinically significant improvement in clinical meaningful outcomes in well-designed randomized controlled trials (RCTs), which is the gold standard assessment of treatment effect. The vast majority of contemporary clinical trials in metastatic urothelial cancer are small, non-randomized, phase II trials, which are generally not empowered, or intended to immediately advance current treatment standard (Galsky et al., 2013a). Major challenges for conducting RCTs in metastatic urothelial cancer include difficulty in patient accrual, limited funding opportunities, the co-morbidity and old age of the patients (Galsky et al., 2013a). A review of the current characteristics and evolution of RCTs in advance/metastatic urothelial cancer can provide insights about the problems that limit the evolution

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of new treatments for this disease.

Compared with OS, progression-free survival (PFS) events occur generally months to years earlier and therefore result in trials requiring smaller sample size, shorten follow-up time and completion at lower cost. But the surrogacy of PFS should be established if PFS can be used as a primary endpoint in RCTs of advance/metastatic urothelial cancer. Previous studies showed that in both first-line and second-line settings, an improvement in PFS can predict prolonged OS (Galsky et al., 2013b; Agarwal et al., 2014). However, the aims of these studies were to look for an intermediate endpoint for screening new agents in single-arm phase 2 trials. A surrogacy analysis that whether treatment effect of PFS can predict that of OS was never undertaken, although PFS has been used in phase III trials of this disease (Petrylak et al., 2017).

In this study, we systematically reviewed the current status/evolution of RCTs conducted in advance/metastatic urothelial cancer and evaluated the surrogacy of PFS for OS.

2. Methods

2.1. Identification of eligible studies

We searched MEDLINE, Embase, the Cochrane Central Register of Controlled Trials from inception to 15 April 2017 to identify all published RCTs in advanced/metastatic urothelial cancer. We also hand-searched conference abstracts from American Society of Clinical Oncology and the European Society for Medical Oncology to retrieve the latest studies. Finally, citations in reports of all eligible studies and related reviews were also hand searched for other relevant references. The detailed search strategy is shown in the Data Supplement.

We included RCTs of patients with locally advanced/metastatic urothelial cancer that involved systemic therapy as an intervention in at least one arm. We excluded reviews, meta-analyses, phase I and single arm phase II trials as well as secondary and pooled analysis.

To be included in the surrogacy analysis, trials were also required to report hazards ratios (HRs) and corresponding 95% confidence intervals (CIs) for both OS and PFS, or provide survival curves that HR and 95% CI can be estimated (Guyot et al., 2012). For trials with multiple arms, all comparisons between experimental therapy and control arm were included. For studies with multiple publications of different follow-up times, we extracted data from the primary report.

2.2. Data collection

For all eligible trials, we extracted the following baseline characteristics using standardized, predesigned forms: first author's name, year of publication, funding source, phase of the trial, line of treatment, treatment regimen in all arms, sample size, proportion of patients that crossed from control arm to treatment arm, median follow-up time, primary endpoints, whether histologic tumor type was used as inclusion criteria.

For trials included in the surrogacy analysis, we extracted the medians, HR, CIs, and P values for both PFS and OS. When HRs were unavailable, we calculated these data following established and widely used technique methods (Guyot et al., 2012). Specifically, we use digital software (DigitizeIt) to read in the time and survival probability coordinates of the PFS and OS Kaplan-Meier curves from the published graph; and we use the information on numbers at risk, and total number of events, where available, to reconstruct the Kaplan-Meier data for each arm. HRs and 95% CIs were estimated by a Cox proportional hazards regression model using reconstructed individual patient data.

Two authors (S.Z and F.L) independently screened trials for eligibility, and extracted data from each included trial using standardized forms. Any discrepancy was identified and resolved successfully by the consensus from of all authors this study. We used the κ coefficient to determine the degree of agreement between reviewers. Agreement between reviewers was high (κ = 0.91).

2.3. Statistical analysis

We conducted a descriptive analysis of all published RCTs in locally advanced/metastatic urothelial cancer. We also reported study characteristics of RCTs over two time periods: 1983–2000 and 2001–2017. The evolution of the characteristics of RCTs over two time periods were explored using independent sample *t*-test for continuous variables and Chi-square test or fisher's exact test for category variables. Due to the small datasets, the analysis was exploratory and no covariables were adjusted.

Trials-level surrogacy of PFS was assessed by correlations between treatment effect on PFS (log HR for PFS) and on OS (log HR for OS). Correlations coefficient was estimated using liner regression weighted by sample size. The correlation coefficient was also calculated via HR for PFS and OS, and the results were similar (data not shown). Given the constant findings have been observed with checkpoint inhibitors in many tumor types including urothelial cancer that PFS may not be a reliable surrogate endpoint for the clinical benefit of immunotherapy, we evaluated the surrogacy of PFS separately for two sets of trials: all trials including immunotherapy trials and trials without immunotherapy trials.

Since surrogacy of PFS is potentially affected by allowing for a crossover from control to experimental drugs at progression and the length of post-progression survival, we conducted two sensitivity analyses by including only studies without crossover and by inclusion of longer follow-up data. Other sensitivity analyses included analysis of only phase 3 trials, restriction of analyses to first line trials, trials with larger sample size (> 100 patients), trials using platinum-based controls, and including only trials that investigated cytotoxic drugs. All sensitivity analyses were done separately for all trials and trials without immunotherapy trials.

Statistical analyses were performed using R version 3.4.1 and SPSS 16.0 (SPSS Inc, Chicago, IL). All statistical tests were two sided, and $P < 0.05$ was used to indicate statistical significance. No corrections were made for multiple testing.

3. Results

After screening of 8364 initially identified reports and meeting abstracts, 48 RCTs that enrolled 7019 patients were eligible for analysis (Fig. 1). 27(56.3%) of the RCTs were phase II trials and 33(68.8%) were trials investigating first line therapies. Primary endpoints were identifiable in 40(83.3%) trials, with OS as the primary endpoint in 13(31.3%) RCTs. Transitional-cell carcinoma was explicitly reported as an eligible criterion in 24(50.0%) RCTs. Platinum-based controls were used in 62.5% of the trials. 36(75.0%) of the trials explored cytotoxic agents. Half of the RCTs were at least partially funded by industry. The characteristics of the included RCTs were detailed in Table 1.

The number of RCTs has increased substantially over time, with 18 trials published between 1983 and 2000 and 30 between 2001 and April 2017. There was significant increase in number of phase III trials in the period of 2001–2017 compared with that in 1983–2000 ($P = 0.002$). For trials published between 1983 and 2000, none investigated second line or beyond therapies, while 19 trials of second line or beyond were published after 2000 ($P = 0.001$). All trials published before 2000 explored cytotoxic agents, and 12(38.7%) trials published after 2000 explored targeted therapies ($P = 0.004$). There was an increase in the frequency of OS (odds ratio, 5.42; 95% CI, 1.05–27.89; $P = 0.031$) as primary endpoint. The frequency of PFS/TTP as primary endpoints increased from 0 to 35.5% ($P < 0.01$). Compared with trials published between 1983 and 2000, significant more multicenter trials and industry funded trials were published between 2001 and 2017.

Twenty-four RCTs (Loehrer et al., 1992; von der Maase et al., 2000; Choueiri et al., 2012; Bellmunt et al., 2009, 2017a; Bellmunt et al., 2017b; Mead et al., 1998; Noguchi et al., 2016; Bellmunt et al., 2017c;