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The role novel targeted agents in the treatment of previously treated patients with advanced urothelial carcinoma (UC): a meta-analysis

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Abstract. – OBJECTIVE: Second-line treatment options for advanced urothelial carcinoma (UC) patients are limited. We aim to investigate the efficacy and toxicities of novel targeted agents (TAs) as salvage treatment for advanced UC by using a meta-analysis.

MATERIALS AND METHODS: Relevant trials published from 1994 to 2017 were identified by an electronic search of public databases. Demographic data, treatment regimens, objective response rate (ORR), disease control rate (DCR), median progression-free and overall survival (PFS, OS) and grade 3/4 toxicities were extracted and analyzed using open Meta-Analyst software version 4.16.12 (Tufts University, URL http://tuftscaes.org/open_meta/).

RESULTS: Eleven trials with 1,630 previously treated UC patients were included for analysis. The pooled ORR, DCR and 1-year OS for single targeted agent in pre-treated UC patients was 10.7% (95% CI: 10.7-19.6%), 33.2% (95% CI: 25-41.4%), and 31% (95%: 23.6-39.4%), respectively. Sub-group analysis based on specific targeted agents showed that the efficacy of immune checkpoints inhibitors (ICIs) was significantly higher than that of small molecular tyrosine-kinase inhibitors (TKIs) concerning ORR and 1-year OS. Also, a meta-analysis of three randomized controlled trials showed that the use of TAs in advanced UC patients significantly improved ORR, but not for DCR. As for grade 3 and 4 toxicities, more incidences of severe anemia, fatigue, and diarrhea were observed in the TKIs group than in ICIs group, but not for hypertension.

CONCLUSIONS: Our findings support the use of immune checkpoints inhibitors, but not for tyrosine kinase inhibitors as salvage treatment for previously treated UC patients due to its potential survival benefits.

Key Words

Advanced urothelial cancer, Targeted agents, Previously treated, Meta-analysis.

Introduction

Urothelial cancer (UC) is the most common cancer of urinary tract, which accounts for more than 90% of bladder cancers. It has been reported that more than 350,000 newly UC cases are diagnosed annually worldwide[1-3], although, approximately 75-80% of UC cases are non-muscle invasive diseases at diagnosis and could be cured with definitive local treatments. However, nearly two-thirds of those with muscle-invasive disease show regional or systematic disease recurrence. The prognosis for advanced or metastatic UC patients remains very poor with 5-year survival less than 5%[4,5]. Currently, cisplatin-based chemotherapy is the standard first-line treatment for advanced or metastatic UC, and around half of these patients would respond to this chemotherapy regimen. However, response duration of first-line chemotherapy is very short, and most of UC patients would finally experience disease progression. For advanced/metastatic UC patients who are refractory to the first-line platinum-containing regimen, treatment options are limited[6,7]. Until now, the only approved second-line therapy in UC patients by EMA (European Medicines Agency) is vinflunine, which demonstrates a 8.6% response rate with a 2.3-month survival benefit compared with the best supportive care alone[8,9]. Therefore, there is an urgent need for an effective and well-tolerated treatment for previously treated UC patients.

During the past decade, several molecular targeted agents (TAs) have been extensively investigated as candidate second-line regimens for advanced UC. Vascular endothelial growth factor (VEGF), tyrosine kinase inhibitors (TKIs) and immune checkpoints inhibitors (ICIs) are the most investigated in advanced UC patients[2,5]. However,

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to our best knowledge, this is no systematic review to investigate the overall efficacy and toxicities of TAs as salvage treatment for advanced UC patients. Therefore, we perform the present study to determine the role of TAs as a second-line treatment for advanced UC patients, and compare treatment outcomes of VEGFR-TKIs *versus* ICIS in this setting.

Materials and Methods

Study Design

We performed the present meta-analysis adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements[10].

Identification and Selection of Studies

We conducted a broad search of four databases, including Embase, Medline, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews, to identify relevant trials. The following terms were used: "urothelial neoplasms", "urothelial carcinoma", "urothelial cancer", "targeted agents", "previously treated", "refractory", "salvage therapy", and "clinical trials". Additional references were searched through manual searches of the reference lists and specialist journals. No language restrictions were applied.

To be eligible for inclusion in our study, study populations (referred to hereafter as cohorts) had to meet all the following criteria: 1) patients with urothelial carcinoma refractory to previous chemotherapy; 2) treatment with a single targeted agent or randomized controlled trials comparing therapy with or without TAs. Patients received chemotherapy plus molecular targeted agents were excluded for analysis in our study; 3) reported outcomes of interest (i.e., objective response rate, disease control rate, and 1-year OS); and 4) from an original study (i.e., randomized controlled trial, non-randomized clinical trial, observational studies, or case series).

Data Extraction

Two investigators screened the titles and abstracts of potentially relevant studies. The same two reviewers retrieved the full text of relevant studies for further review. A third senior investigator resolved any discrepancies between reviewers. If reviewers suspected an overlap of cohorts in a report, they contacted the corresponding author for clarification; we excluded studies with a clear overlap.

The same pair of reviewers extracted study details independently, using a standardized pilot-tested form. We extracted the following data: author, study design, study period, median age, interventions (treatment regimens and dose), sample size, and outcomes of interest. We defined outcomes of interest as objective response rate (ORR), disease control rate (DCR), and 1-year overall survival (OS). To assess quality, since we included non-comparative (uncontrolled) studies in our systematic review and meta-analysis, we used the Newcastle-Ottawa quality assessment scale[11]. We selected items that focused on the representativeness of study patients, a demonstration that the outcome of interest was not present at the start of the study, adequate assessment of outcome, sufficient length of follow-up to allow outcomes to arise, and adequacy of follow-up.

Statistical Analysis

We analyzed all patients who started a single targeted agent regardless of their adherence to treatment. We calculated event rates of outcome (the proportion of patients who developed outcomes of interest) from the included cohorts for a single targeted agent. We pooled log-transformed event rates with DerSimonian and Laird random-effect models and assessed heterogeneity using the X^2-based Q statistic test[12]. We used the test of interaction proposed by Altman and Bland[13] to compare log-transformed rates of outcomes between VEGFR-TKIs and ICIs. A statistical test with a p-value less than 0.05 was considered significant. To measure overall heterogeneity across the included cohorts, we calculated the I^2 statistic, with I^2 greater than 50% indicating high heterogeneity. We did all statistical analyses with open Meta-Analyst software version 4.16.12 (Tufts University, URL http://tuftscaes.org/open_meta/).

Results

Search Results

A total of 240 studies were identified from the database search, of which 60 reports were retrieved for full-text evaluation. A total of 11 trials met the inclusion criteria and were included in this systematic review (Figure 1)[14-24]. Table I showed the characteristics of the included studies. Overall, 1,630 previously treated patients with advanced UC were included. The median OS was higher in ICIs cohorts than VEGFR-TKIs cohorts, while the median PFS did not significantly differ between groups (Table I).

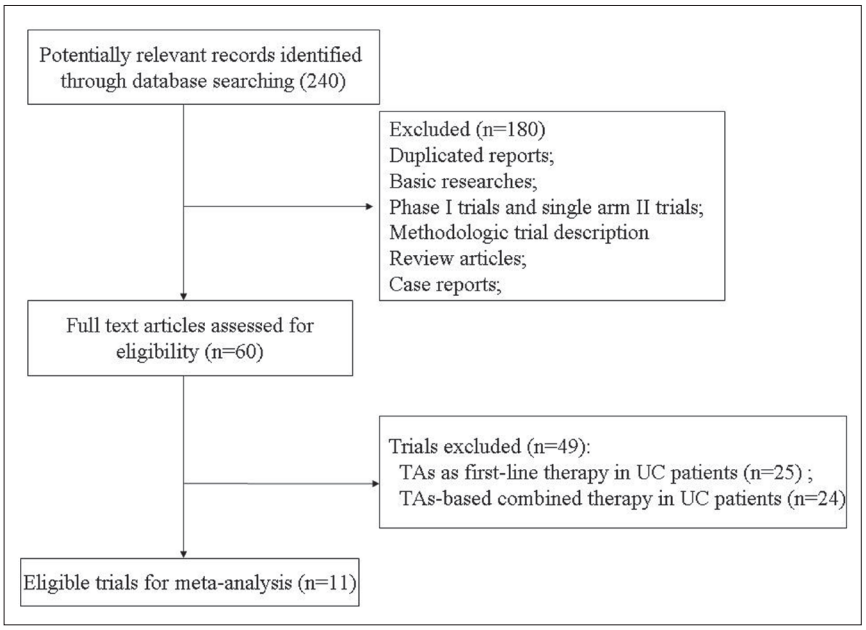

Figure 1. Selection process for clinical trials included in the meta-analysis.

Pooled Incidence of Primary Outcomes

A total of 1,043 patients were included for ORR analysis. The pooled event rate of ORR for ICIs was higher than that of TKIs (18.2% versus 4.9%, Table II). In addition, a higher incidence of 1-year OS was observed in ICIs groups in comparison with TKIs (39.7% versus 18.3% respectively), while a comparable incidence of DCR was found between TKIs and ICIs (31.6% *versus* 35.9%, Table II).

Table I. Baseline characteristics of included 11 trials.

Author	Patient enrolled	Type of study	Treatment regimens	Median age, y	Median OS, m	Median PFS, m
Dreicer et al/2009	27	P	Sorafenib 400 mg bid po	66	6.8	2.2
Gallagher et al/2010	45	P	Sunitinib 50 mg qd po	64	7.1	2.4
	32	P	Sunitinib 37.5 mg qd po	68	6	2.3
Choueiri et al/2012	70	P	Vandetanib 100 mg qd po +Docetaxel	NR	5.85	2.56
	72	P	Placebo+Docetaxel	NR	7.03	1.58
Necchi et al/2012	41	P	Pazopanib 800 mg qd po	67	4.7	2.6
Wong et al/2012	11	P	Cetuximab 250 mg	70	17 weeks	7.6 weeks
	28	P	Cetuximab 250 mg+paxlitaxel	69	42 weeks	16.4 weeks
Pili et al/2013	19	P	Pazopanib 800 mg qd po	65.6	NR	1.9
Choudhury et al/2016	23	P	Afatinib 40 mg qd po	67	5.3	1.4
Petrylak et al/2016	140	P	Docetaxel	69	9.2	2.8
			Docetaxel+ramucirumab	67.5	10.4	5.4
			Docetaxel+icrucumab	66	6.7	1.6
Rosenberg et al/2016	310	P	Atezolizumab 1200 mg q.3.w	66	7.9	2.1
Bellmunt et al/2017	542	P	Pembrolizumab 200 mg q.3.w	67	10.3	2.1
			Chemotherapy	65	7.4	3.3
Sharma et al/2017	270	P	Nivolumab 3 mg/kg q.2.w	66	8.74	2

Abbreviations: P, prospective; OS, overall survival; PFS, progression-free survival; NR, not reported.

Table II. Comparison of primary outcomes for single TKIs versus ICIs alone.

Groups	Cohorts (n)	Patients (n)	Events (95%)	I^2	Relative risk (95%)	p
ORR						
TKIs	13	198	4.9 (1.4-8.3%)	25	1	
ICIs	154	845	18.2 (14.1-22.3%)	60	3.71 (1.48-9.31)	0.002
DCR						
TKIs	69	186	31.6 (15.7-47.6)	84	1	
ICIs	208	580	35.9 (31-40.7)	35	0.88 (0.50-1.56)	0.33
1-year OS						
TKIs	33	184	18.3 (9.3-32.7%)	66	1	
ICIs	337	850	39.7 (34.5-45.2%)	62	2.17 (1.14-4.13)	0.009

$I^2 \geq 50\%$ suggests high heterogeneity across studies.
Abbreviation: TKIs, tyrosine kinase inhibitors; ICIs, immune checkpoint inhibitors; ORR, objective response rate; DCR, disease control rate; OS, overall survival.

Efficacy Comparison Between ICIs and TKIs

The pooled event rate of overall survival for ICIs was significantly higher than that for TKIs at 1 year (relative risk 2.17, 95% CI 1.14-4.13; p=0.009, Table II). Additionally, ORR was significantly different between ICIs and TKIs (RR 3.71, 95% CI: 1.48-9.31, p=0.002), but not for DCR (RR 0.88, 95% CI: 0.50-1.56, p=0.33) (Table II).

Meta-Analysis of Randomized Controlled Trials

Three randomized controlled trials were available for analysis. The pooled result showed that the addition of TAs to chemotherapy significantly improved ORR (RR1.84, 95% CI: 1.29-2.62, p<0.001, Figure 2) by using fixed-effect model (I^2=0%, p=0.94), while no significantly improved DCR was observed in combined therapy (RR 0.95, 95% CI: 0.81-1.10, p=0.47).

Toxicity

Table III showed the overall occurrence of high-grade (≥grade 3) toxic effects with a single targeted agent. There were significantly more incidences of high-grade anemia, fatigue, and diarrhea in the TKIs group than that in ICIs group (p=0.002, p<0.001 and p=0.001, respectively). While equivalent frequencies of hypertension were found between TKIs and ICIs (p=0.53, Table III).

Discussion

Despite initial sensitivity to standard first-line platinum-based chemotherapy in advanced UC patients, the majority of these patients would be refractory to chemotherapy, and the prognosis of these patients is very poor[5,26]. Until now, there is no established treatment for these patients with progressive disease after first-line platinum-based chemotherapy. Although taxanes are widely used

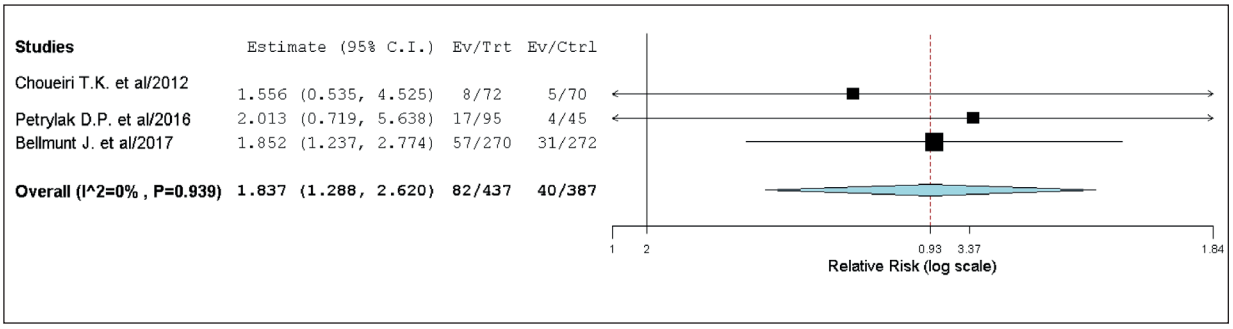

Figure 2. Meta-analysis of randomized controlled trials comparing therapies with or without TAs.

Table III. Comparison of ≥ grade 3 toxic effect event rates for single targeted agent.

	Included study	Events	Total	Events rate (95% CI)	I^2	RR (95% CI)	p
Anemia							
TKIs	6	15	209	5.9% (1.8-17.9%)	68%	1	
ICIs	2	5	852	0.7% (0.3-1.6%)	11%	8.43 (2.03-34.9)	0.002
Fatigue							
TKIs	7	23	236	10.8% (7.3-15.8%)	0%	1	
ICIs	3	13	1122	1.3% (0.6-2.5%)	35%	8.31 (3.69-18.7)	<0.001
Diarrhea							
TKIs	6	11	209	6.9% (3.8-12.2%)	3%	1	
ICIs	3	9	1122	0.8% (0.3-2.4%)	58%	8.63 (2.62-28.4)	0.001
Hypertension							
TKIs	6	12	209	5.3% (2.3-8.3%)	0%	1	
ICIs	1	3	310	10% (0.3%-30%)	0%	0.53 (0.05-5.65)	0.30
Hand-foot reaction							
TKIs	5	7	155	4.9% (1.4-15.7%)	10%	1	

Abbreviations: TKIs, tyrosine kinase inhibitors; ICIs, immune checkpoint inhibitors; RR, relative risk.

in cisplatin-refractory patients, the efficacy is modest. Vinflunine is the only approved for relapsed/refractory UC in Europe but not in the United States[9]. As a result, there is an urgent need for effective and well-tolerated agents for previously treated UC patients. In the past decades, several novel agents, including angiogenesis inhibitors and ICIs, have been extensively investigated in pre-treated UC patients. However, to our best knowledge, there is no available systematic review to specially assess the efficacy and toxicities of novel targeted agents in the treatment of relapsed/refractory UC patients.

A total of 1,630 previously treated UC patients from 11 trials are included for analysis. Our pooled results show that the efficacy of immune checkpoints inhibitors (ICIs) is significantly higher than that of small molecular tyrosine-kinase inhibitors (TKIs) regarding ORR and 1-year OS. In addition, a meta-analysis of three randomized controlled trials shows that the use of TAs in advanced UC patients significantly improves ORR, but not for DCR. As for grade 3 and 4 toxicities, more incidences of high-grade anemia, fatigue, and diarrhea are found in the TKIs group than in ICIs group, but not for hypertension. Based on our findings, ICIs could be recommended as salvage treatment for previously treated UC patients. However, prospective trials are still required to confirm our findings and identify patients who will most likely benefit from ICIs treatment.

There are some limitations need to be mentioned. First and most importantly, the application of formal meta-analytic methods to observational studies has been controversial. One of the most important reasons for this is that the designs and populations of the studies are diverse, and that these differences may influence the pooled estimates. However, when no head-to-head comparison data available for TKIs versus ICIs, a meta-analysis of observational studies is one of the few methods for assessing efficacy and toxicities[25]. Second, patients in trials have adequate organ and hematological function, which may not be the case in common oncology practice. All of these might cause potential selection bias. Finally, this is a meta-analysis of published data, and lack of individual patient data prevents us from adjusting the treatment effect according to previous treatment and patient variables.

Conclusions

With available clinical evidence for advanced UC patients, ICIs might be a more efficient than TKIs alone for previously treated UC patients. However, since the overall quantity and quality of data regarding ICIs and TKIs is poor and considering the risk of bias in comparisons between observation studies, the reported results do not allow for definite conclusions. Thus, prospective randomized studies, definitively comparing the survival and treatment toxicity between TKIs and ICIs, are strongly recommended to clearly determine the role of ICIs as salvage treatment for previously treated UC patients.

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Conflict of Interests:

All authors declare that they have no potential conflicts of interests.

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