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Proceeding Paper

Ramucirumab as a Second-Line Treatment for Locally Advanced or Metastatic Urothelial Carcinoma: A Meta-Analysis of Randomized Clinical Trials †

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Abstract: Improvement of treatment outcomes in patients with locally advanced or metastatic urothelial carcinoma represents an important unmet need, since survival remains poor in patients who progress beyond first-line treatment. The purpose of this study was to investigate the effects of ramucirumab, a human monoclonal antibody that binds to VEGFR-2, in the treatment of locally advanced or metastatic urothelial carcinoma. A literature search of PubMed and CENTRAL was conducted. Outcomes of interest were overall survival (OS), progression-free survival (PFS) and the rate of adverse events. Time-to-event outcomes were combined using the generic inverse-variance method and presented as hazard ratio (HR) with 95% confidence intervals (95% CI), while dichotomous events were combined using the Mantel–Haenszel method and presented as odds ratio (OR) with 95% CI. All of the analyses were performed in RevMan 5.3. The literature search identified two randomized controlled trials. The addition of ramucirumab to docetaxel resulted in a statistically significant improvement in PFS (HR = 0.55, 95% CI 0.31–0.96, p = 0.030), while the difference was not significant for OS (HR = 0.86, 95%CI 0.71–1.04, p = 0.12). Subgroup analysis by sex, age (<65 and ≥65 years), baseline hemoglobin (<10 g/dL and ≥10 g/dL), presence of visceral metastases and presence of liver metastases did not identify a subgroup in which improvement in OS was present. The difference in treatment-related grade ≥ 3 adverse events was not significant (OR = 1.47, 95%CI 0.95–2.27, p = 0.08). Ramucirumab in addition to docetaxel significantly improved PFS in patients with locally advanced or metastatic urothelial carcinoma. Future studies are necessary to identify a subset of patients who might experience a significant improvement in OS.

Keywords: urothelial carcinoma; ramucirumab; overall survival; progression-free survival; meta-analysis

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1. Introduction

In 2017, 2.63 million people had bladder cancer and 200,000 died from this disease worldwide [1]. Global projections indicate that by 2030 many countries, including the most developed such as Switzerland, Germany, France, Japan, Canada, will experience a rise in bladder cancer incidence rates [2]. Therefore, stronger efforts aimed at prevention and improved treatment outcomes are of utmost importance.

Patients with locally advanced or metastatic urothelial carcinoma who have progressed following first-line platinum-based chemotherapy regimens have a poor prognosis with median survival of 5 to 7 months [3,4]. Options for second-line treatment most often include single-agent chemotherapy or immunotherapy. Currently, the National Cancer Comprehensive Network guidelines recommend pembrolizumab, nivolumab, avelumab or erdafitinib for second-line treatment in patients progressing after platinum-based regimens [4]. However, the reported objective response rates and survival benefits and safety profile of these targeted therapies warrant a need for other treatment options.

Ramucirumab is an IgG1 human monoclonal antibody that binds to the vascular endothelial growth factor receptor 2 (VEGFR-2) and inhibits the VEGF pathway [5]. Research shows a promising role for VEGF-inhibitors in a population of patients with platinum-refractory advanced urothelial carcinoma [6].

The purpose of this study was to investigate the effects of ramucirumab in the treatment of locally advanced or metastatic urothelial carcinoma in patients previously treated with platinum-based chemotherapy.

2. Materials and Methods

The present meta-analysis was conducted in accordance with Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) guidelines [7].

2.1. Literature Search

We performed a literature search of PubMed and CENTRAL from inception to February 2021. We searched these databases using the following keywords: "ramucirumab" AND "urothelial" AND ("cancer" OR "neoplasm" OR "tumour"). A snowballing technique was applied to further identify relevant studies by searching reference lists of retrieved studies and reviews. There were no language restrictions.

2.2. Inclusion and Exclusion Criteria

Both authors screened the titles and abstracts of all of the articles identified through the literature search. Full texts of relevant studies were independently assessed by both authors. The inclusion criteria were: study designed as a randomized controlled trial, conducted on humans. Studies conducted on animals, observational studies, case reports and reviews were excluded. Authors resolved disagreements through consensus. In cases of multiple published reports of the same study, the most recent publication and the one containing the most data was used.

2.3. Data Extraction and Study Quality Appraisal

The outcomes of interest were overall survival, progression-free survival and occurrence of treatment-related grade ≥ 3 adverse events. The quality of the included studies was assessed using the National Heart, Lung, and Blood Institute's study quality assessment tool for controlled intervention studies, which contains 14 questions regarding study design, statistical analysis and sources of bias [8].

2.4. Statistical Analysis

The time-to-event outcomes were combined using the generic inverse-variance method and presented as hazard ratio (HR) with 95% confidence intervals (95% CI). Dichotomous events were combined using the Mantel-Haenszel method and presented as odds ratio (OR) with 95% CI. Pooled HRs and ORs are graphically presented as forest plots. Based on the level of heterogeneity, a random effects model (DerSimonian and Liard) or a fixed effects model was applied. For heterogeneity assessment, I^2 statistic was used (moderate 30–60%, substantial 50–90% and considerable 75–100%) [9].

Subgroup analyses were planned for OS and PFS according to sex, age (<65 and $\geq$65 years), baseline hemoglobin (<10 g/dL and $\geq$10 g/dL), presence of visceral metastases and presence of liver metastases in order to further analyze heterogeneity. The p-value was considered significant at $p < 0.05$. All of the analyses were performed in RevMan 5.3 [10].

3. Results and Discussion

3.1. Literature Search and Study Characteristics

The literature search identified two randomized clinical trials. The flow diagram of literature search is shown in Figure 1. The study by Petrylak et al. (2016) was an open-label phase II trial that included 140 patients with locally advanced or metastatic urothelial carcinoma randomized to receive docetaxel, docetaxel plus ramucirumab or docetaxel plus

icrucumab [5]. The study by Petrylak et al. (2020) was a double-blind phase III trial that included 530 patients randomized to receive ramucirumab plus docetaxel or placebo plus docetaxel [3]. The quality of the included studies was satisfactory (Table 1).

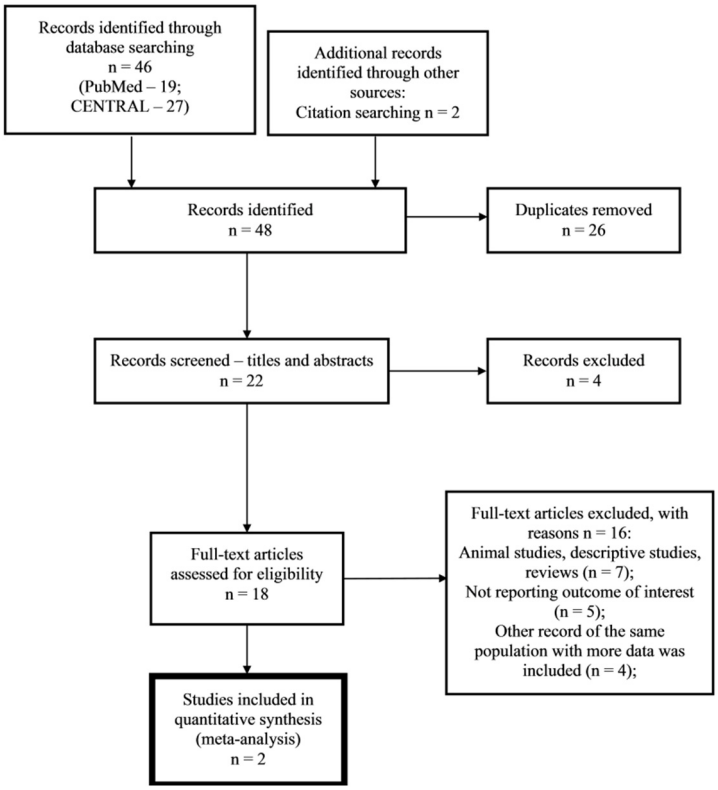

Figure 1. Flow diagram of literature search.

Table 1. Characteristics of included studies.

Author, Year [ref.]	Study Design	Experimental Group (No of Patients)	Control Group (No of Patients)	OS (Experimental vs. Control Group)	PFS (Experimental vs. Control Group)	Assessed Quality Score [1]
Petrylak, 2016 [5]	Randomized, controlled, open-label, phase II trial	Ramucirumab + docetaxel (46)	Docetaxel (45) [2]	10.4 vs. 9.2 months	5.4 vs. 2.8 months	10
Petrylak, 2020 [3]	Randomized, controlled, double-blind, phase III trial	Ramucirumab + docetaxel (263)	Placebo + docetaxel (267)	9.4 vs. 7.9 months	4.1 vs. 2.8 months	14

[1] According to the National Heart, Lung, and Blood Institute's study quality assessment tool for controlled intervention studies. [2] The trial had a third arm (docetaxel + icrucumab), the data of which were not included in the analysis because the published data outcomes of this group were given in reference to the control group (docetaxel), which did not contain ramucirumab. Legend: OS—overall survival; PFS—progression-free survival.

3.2. Overall Survival, Progression-Free Survival and Rate of Adverse Events

There was no statistically significant improvement in OS in patients receiving ramucirumab plus docetaxel compared to docetaxel alone (HR = 0.86 (95% CI 0.71–1.04), $p = 0.12$) (Figure 2a). Subgroup analysis by sex, age (<65 and ≥65 years), baseline hemoglobin (<10 g/dL and ≥10 g/dL), presence of visceral metastases and presence of liver metastases did not identify a subgroup in which improvement in OS was present (data not shown). The addition of ramucirumab significantly improved PFS in patients with advanced or

metastatic urothelial carcinoma (HR = 0.55 (95% CI 0.31–0.96), $p = 0.03$) (Figure 2b). Subgroup analysis for PFS was not possible because only one of the two studies reported this data. There was no statistically significant difference in the rate of treatment-related grade ≥3 adverse events with the addition of ramucirumab (OR = 1.47 (95% CI 0.95–2.27), $p = 0.08$) (Figure 2c).

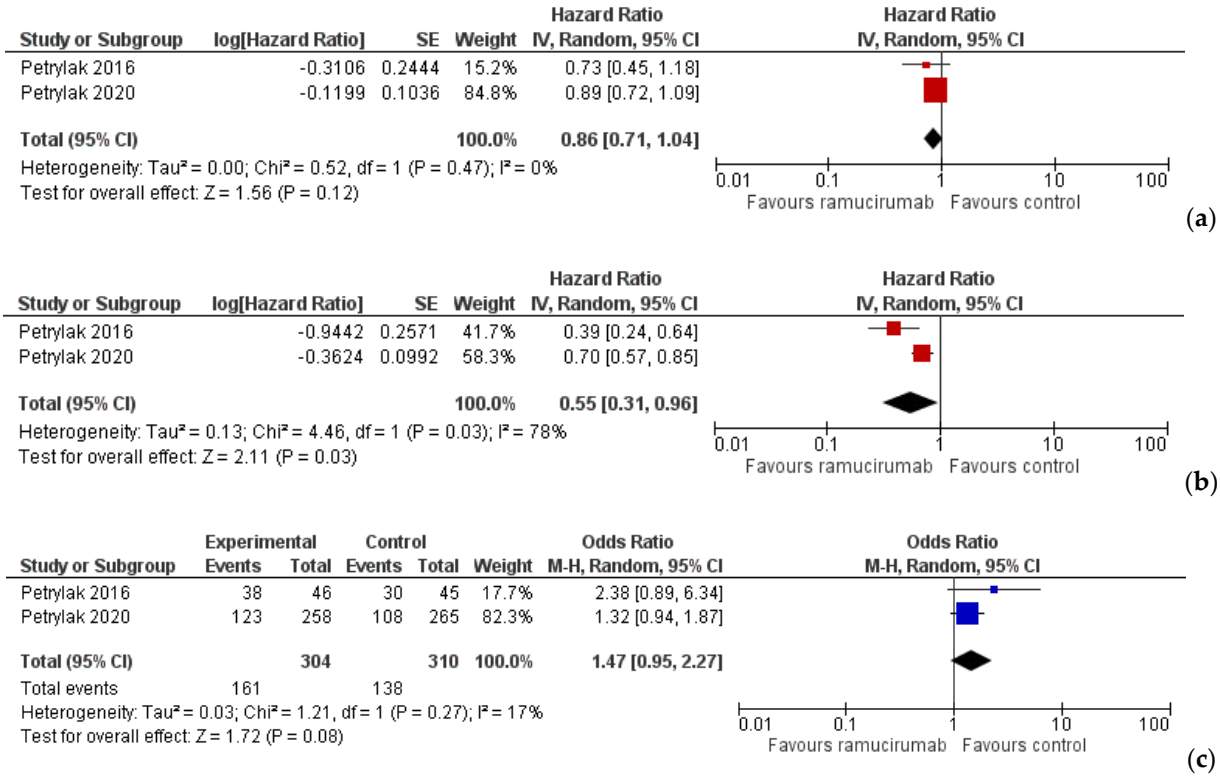

Figure 2. Forest plot of the effects of the addition of ramucirumab in the treatment of locally advanced or metastatic urothelial carcinoma on: (**a**) overall survival; (**b**) progression-free survival; (**c**) adverse events.

4. Discussion

Our study found a significant improvement in PFS (HR = 0.55 [95% CI 0.31–0.96], $p = 0.03$) with the addition of ramucirumab in patients with locally advanced or metastatic urothelial carcinoma without an increase in safety concerns (treatment-related grade ≥3 adverse events OR = 1.47 (95% CI 0.95–2.27), $p = 0.08$). However, the improvement in OS was not statistically significant (HR = 0.86 (95% CI 0.71–1.04), $p = 0.12$).

Approximately 5% of patients with urothelial carcinomas are diagnosed at the metastatic stage of disease, while approximately 50% of those are diagnosed at earlier stages and have received treatment relapse [4]. Given the poor prognosis in these patients, therapeutic options that enhance survival are necessary. Our study showed that the addition of ramucirumab to docetaxel increased PFS but showed no significant difference in OS compared to the control group. Similar results have been found for bevacizumab, which improved PFS but not OS when added to cisplatin and gemcitabine [11]. A possible explanation for not detecting a benefit in OS includes the fact that two trials were designed so that the sample size and study power were based on the detection of a PFS difference. The PFS benefit remained significant in all of the patients except those with ECOG PS 0, those with liver metastases and those with baseline hemoglobin < 10 g/dL [5]. Research shows that, in this group of patients, improvements in PFS predict improvements in OS [12]. However, another agent–pembrolizumab showed significant improvement in OS in this treatment setting, but no difference in median PFS [13]. Therefore, future research could go in the direction of investigating possibilities for the combination of VEGF-inhibitors and

immunotherapy. Currently, research shows an OS benefit for patients with locally advanced or metastatic urothelial carcinoma who have a platinum-refractory disease only with the use of single agent pembrolizumab [13], while ramucirumab combined with docetaxel increases PFS. Based on the results of combining bevacizumab with atezolizumab in patients with metastatic renal cell carcinoma, there is a potential for combining anti-VEGF agents with immune checkpoint inhibitors, since their mechanisms of action may be complementary in optimizing antitumor activity [14]. Therefore, identification of biomarkers which predict treatment response is crucial in the future analysis of trial results. Evidence from a phase 1a/b trial shows favorable outcomes in patients with previously treated advanced urothelial carcinoma treated with a combination of ramucirumab and pembrolizumab [15].

Our study did not show a significant increase in treatment-related grade $\geq$ 3 adverse events in patients receiving ramucirumab, compared to another anti-VEGF agent bevacizumab, which showed a statistically significant increase in occurrence of deep vein thrombosis and pulmonary embolism [6]. This is particularly important given that the median age at diagnosis of patients with bladder cancer is 73 years [4]; therefore, there are many concomitant medical conditions in these individuals that make treatment of this disease challenging.

Our results indicate a need for further research of biomarkers and patient characteristics that would help identify those subgroups who would benefit most from the addition of ramucirumab, as well as a need for research into the possibilities of combining VEGF-inhibitors such as ramucirumab and immunotherapy agents.

Strengths and Limitations

To the best of our knowledge, this is the first meta-analysis to investigate the effects of ramucirumab in patients with locally advanced or metastatic urothelial carcinoma. The quality of the included studies was satisfactory. However, our study had several limitations. Firstly, the number of included studies is only two due to the novelty of the investigated therapeutic regimen for this indication. Due to this, we could not analyze the presence of publication bias. Furthermore, we were not able to perform a planned subgroup analysis for PFS due to the lack of published data. Finally, although we have calculated the I^2 statistic to assess heterogeneity, this statistic can be biased in small meta-analyses.

5. Conclusions

The addition of ramucirumab to docetaxel in platinum-refractory patients with locally advanced or metastatic urothelial carcinoma improves PFS without increasing the rate of grade $\geq$ 3 adverse events. However, there was no benefit in OS. Further well-designed clinical trials are necessary to investigate the effects on OS and whether any subgroups of patients could see an improvement with this treatment regimen.

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Data Availability Statement: Data is contained within the article.

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Conflicts of Interest: The authors declare no conflict of interest.

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