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Review

Systematic review and survival meta-analysis of real world evidence on first-line pazopanib for metastatic renal cell carcinoma

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ABSTRACT

A systematic review was conducted to identify real world studies reporting outcomes after first-line pazopanib in patients with metastatic renal cell carcinoma. Studies had to be observational and report survival data in terms of progression-free survival and overall survival in order to conduct meta-analysis techniques. These real-world data were compared to those obtained in the phase II and III randomized controlled trials of pazopanib. Real world evidence showed that the clinical and safety outcomes were consistent with those observed in the clinical trials despite the inclusion of unselected patients with a wide spectrum of prognostic features and comorbidities. Similarly to the results of the pivotal studies, good prognosis patients had the most benefit from pazopanib. Further investigation is needed to complement evidence from clinical trials, in particular focused on patient-centered outcomes.

1. Introduction

Renal cell carcinoma (RCC) represents approximately 90% of all renal cancers, with 85% of RCC tumors classified as clear cell subtype. Almost one third of the affected patients are initially diagnosed with advanced or metastatic disease (mRCC). Even in patients with localized disease, relapse rate is high despite initial curative surgery (Ljungberg et al., 2011). Over the last decade, the introduction of targeted therapies has greatly improved the prognosis of patients with mRCC. These therapies include small-molecule tyrosine kinase inhibitors (TKIs) (sorafenib, sunitinib, pazopanib, axitinib, and cabozantinib), mammalian target of rapamycin (mTOR) inhibitors (temsirolimus and everolimus), checkpoint inhibitors (nivolumab), and an anti-angiogenic antibody (bevacizumab, usually in combination with interferon alpha).

Pazopanib (Votrient®, Novartis) inhibits different kinase receptors such as VEGF receptors 1, 2, and 3, platelet-derived growth factor receptors alpha and beta, and c-Kit (CD117), exerting an anti-angiogenic effect that reduces the processes of cell proliferation and metastasis (Pick and Nystrom, 2012). The safety and efficacy of pazopanib were evaluated in a randomized double-blind, placebo-controlled phase III trial in both treatment-naive and cytokine-pretreated patients, demonstrating superior efficacy compared to placebo (Sternberg et al., 2010). The open-label COMPARZ trial compared the efficacy and safety of pazopanib and sunitinib as first-line therapy in patients with clear-cell mRCC and demonstrated the noninferiority of pazopanib to sunitinib in terms of progression-free survival (PFS) and overall survival (OS), but the safety and quality of life profiles favoring pazopanib (Motzer et al., 2013; Motzer et al., 2014). Pazopanib is recommended in the clinical guidelines for first-line treatment of advanced RCC (Escudier et al., 2014a; Ljungberg et al., 2015). The National Comprehensive Cancer Network (NCCN) guidelines gave pazopanib a category 1 recommendation for first-line therapy for relapsed or stage IV surgically unresectable predominantly clear-cell RCC (Motzer et al., 2009).

Although randomized controlled trials (RCTs) are regarded as the gold standard for determining the efficacy of medical interventions, there are several concerns about the external validity (or generalizability) of their results (Rothwell, 2005). It has been shown that patients with mRCC treated with TKIs in real-world clinical practice were older and had poorer prognosis and performance status than those enrolled onto the pivotal studies, being more than one third trial ineligible (Mitchell et al., 2015). Real-world studies may complement RCTs by investigating a more diverse group of patients than those

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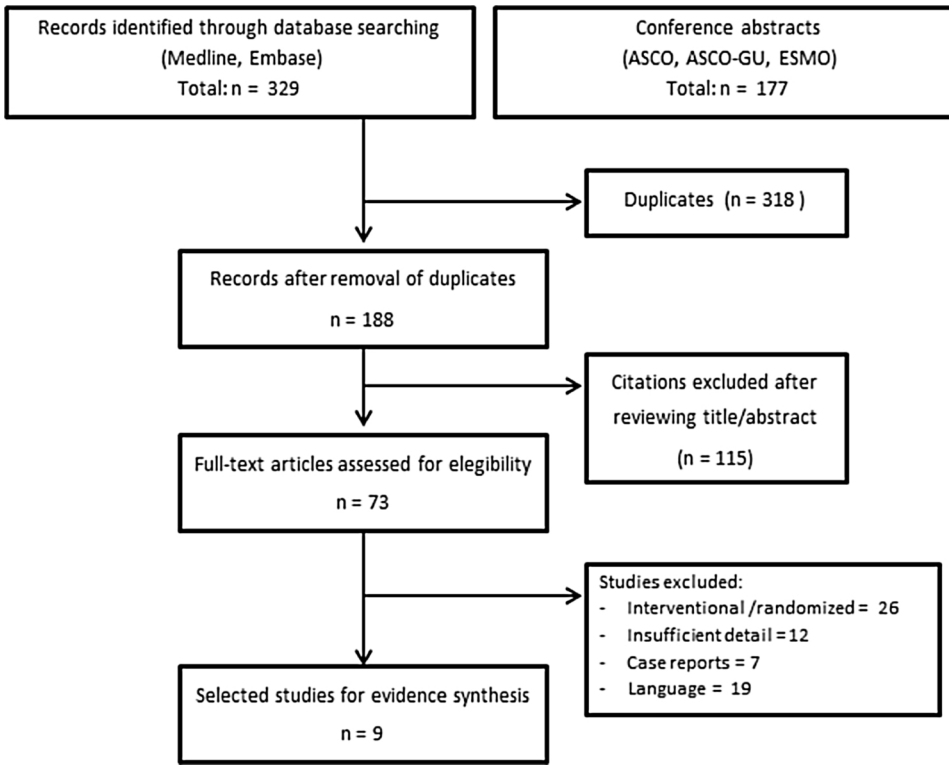

Fig. 1. Flowchart of literature search and study selection.

included in clinical trials, improving the quantity and quality of evidence used in guidelines and guidance (Oyinlola et al., 2016). The aim of this systematic review and meta-analysis was to examine the published real-world studies evaluating the outcomes of mRCC patients that received pazopanib as first-line treatment and summarize survival outcomes using meta-analysis techniques. The secondary objective was to qualitatively compare these real-world data to those obtained in the phase II and III RCTs.

2. Methods

2.1. Search strategy and study selection

A systematic review of literature using MEDLINE and EMBASE was conducted to identify publications that reported RWE on pazopanib in mRCC patients. The search terms included 'renal cell carcinoma' and 'pazopanib'. Since pazopanib for this indication was approved in 2010, studies published between 1 January 2011 and 31 December 2016 were considered. Supplementary searching of congress abstracts published between 2011 and 2016 was also carried out for the American Society of Clinical Oncology (ASCO), ASCO Genitourinary Cancers Symposium (ASCO-GU), and European Society for Medical Oncology (ESMO) annual meetings. References from systematic reviews and meta-analyses were screened to ensure search sensitivity.

All identified citations were reviewed (title and abstract) on first pass and those considered unrelated were excluded. Full papers were obtained for remaining references and assessed independently by three researchers (JM, LB, and CS). Included studies were required to: 1) be observational (i.e., non-randomized), 2) evaluate pazopanib as first-line treatment for mRCC, 3) at least report PFS and OS outcomes, and 4) be published in English. Case reports, economic evaluations, randomized trials, and other studies not reporting analyses of real-world data were excluded. Disputes as to eligibility were discussed within the project team, including a fourth reviewer (MAC), and resolved by consensus.

2.2. Data extraction and analysis

A pre-prepared data extraction table was created in Microsoft® Excel. Baseline demographic and clinicopathological features of patients were summarized. The study outcomes extracted included median PFS and OS with 95% confidence intervals (95% CI), response rates, adverse events (AEs), and discontinuation rates. Data were cumulated and weighted by taking into account each study sample.

Combined survival data was calculated using a random- or fixed-effects models, depending on the heterogeneity of the included studies. When there was no substantial heterogeneity, the pooled estimate survival was calculated based on the Mantel-Haenszel fixed-effects model. When substantial heterogeneity was observed, the pooled estimate survival was calculated based on the DerSimonian and Laird random-effects model, which considers both within- and between-study variations (DerSimonian and Laird, 1986). Statistical heterogeneity between the studies included in the meta-analysis was assessed using Cochrane's Q statistic, and inconsistency was quantified with the Higgins I2-statistic. For Cochran's Q-statistic, we considered a P-value of < 0.1 for a chi-squared value to be indicative of heterogeneity. We defined a Higgins I2-statistic of $< 25\%$ as low heterogeneity, 25–50% as moderate heterogeneity, and $> 50\%$ as high heterogeneity (Higgins and Thompson, 2002).

In order to align baseline patient characteristics, the two studies reporting on non-clear cell RCC outcomes (Vogelzang et al., 2015; Ruiz-Morales et al., 2016) and one study that did not report the 95% CI of PFS and OS (Chow et al., 2016) were excluded from the survival meta-analysis. The discussion about the pooled real world evidence (RWE) and the results of pazopanib RTCs (Sternberg et al., 2010; Motzer et al., 2013; Hutson et al., 2010) was restricted to unadjusted, qualitative comparisons.

3. Results

The systematic search of the literature identified 9 studies meeting the selection criteria (Fig. 1): 7 peer-reviewed journal publications