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First-line antiangiogenics for metastatic renal cell carcinoma: A systematic review and network meta-analysis

Benoît Rousseau (MD, MSc)[a,b,c,*], Emmanuelle Kempf (MD, MSc)[a], Gaelle Desamericq (PharmD, PhD)[d], Emilie Boissier (MD, MSc)[a], Marie Chaubet-Houdu (MD)[a,b], Charlotte Joly (MD)[a,b], Carolina Saldana (MD, MSc)[a,b], Helene Boussion (MD)[a,b], Cindy Neuzillet (MD, MSc)[a,b], Isabelle Macquin-Mavier (MD, PhD)[a,b], Stéphane Oudard (MD, PhD)[e], Laurent Salomon (MD, PhD)[b,f], Alexandre de la Taille (MD, PhD)[b,f], Christophe Tournigand (MD, PhD)[a,b]

[a] Department of Medical Oncology, Henri Mondor Hospital, Assistance Publique-Hôpitaux de Paris, Créteil, France
[b] University of Paris-Est, Faculty of Medicine, Créteil, France
[c] INSERM, U955, Team 18, Créteil, France
[d] Huntington Center, Henri Mondor Hospital, Assistance Publique-Hôpitaux de Paris, France
[e] Department of Medical Oncology, European Georges Pompidou Hospital, Assistance Publique-Hôpitaux de Paris, Paris, France
[f] Department of Urology, Henri Mondor Hospital, Assistance Publique-Hôpitaux de Paris, Créteil, France

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* Corresponding author at: Pharmacologie Clinique, CHU Henri Mondor, 51 avenue du Maréchal de Lattre de Tassigny, 94100 Créteil, France.
E-mail addresses: benoit.rousseau@aphp.fr, ben.rousseau@gmail.com (B. Rousseau).

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ABSTRACT

Background: Sunitinib, pazopanib, sorafenib, axitinib and bevacizumab are the five recommended antiangiogenic agents in first-line therapy for metastatic renal cell carcinoma (mRCC). Because these drugs underwent simultaneous clinical development, no direct efficacy and safety comparison was ever conducted, thus preventing optimal therapy choices.
Methods: We performed a traditional and network meta-analysis to evaluate the efficacy and safety of mRCC-recommended first-line antiangiogenic agents. After a systematic review of Medline and Embase up to July 2014, we identified randomized clinical trials (RCTs) evaluating the outcomes of mRCC patients treated with sunitinib, pazopanib, sorafenib, axitinib and bevacizumab as first-line treatment. Endpoints of interest were response rate, progression-free survival (PFS), overall survival (OS), and safety.
Results: We screened 769 abstracts and included nine RCTs with a total of 4282 patients. In the weighted pooled analysis, first-line antiangiogenic agents showed significant improvement in PFS (HR = 0.6; 95% IC, 0.51–0.72) and OS (HR = 0.85; 95% IC, 0.78–0.93) compared to control (placebo or interferon-alpha2a (INF)). Network meta-analysis showed no significant differences among antiangiogenic drugs in 6-month PFS, 1-year OS, disease control rate and drug-related safety for all-grade hypertension, diarrhea, weight-loss, nausea or anorexia. However, pazopanib showed a lower incidence of fatigue, anemia and hand foot skin reaction.
Conclusions: This meta-analysis confirms the benefits of first-line antiangiogenic therapy in mRCC, with an improvement in OS. Sunitinib, pazopanib, axitinib and bevacizumab + INF offer similar efficacy but different safety profiles which can help clinicians to better personalize treatment decisions in patients with mRCC.

1. Introduction

Renal cell carcinoma (RCC) accounts for 80–85% of kidney cancers (Arai and Kanai, 2010). Clear cell carcinoma is the most frequent histological subtype accounting for 70–80% of RCC (Arai and Kanai, 2010). In the United States in 2014, 63,920 new cases of renal tumors were diagnosed and 13,860 patients died of the disease (Siegel et al., 2014). In Europe, incidence and mortality due to RCC was 115,200 and 49,000 cases in the year 2012 (Ferlay et al., 2013).

Clinical outcomes of kidney disease patients have significantly improved with the development of kinase inhibitors such as antiangiogenic drugs and mammalian target of rapamycin (mTOR) inhibitors. Since 2005, seven targeted agents – sunitinib (Motzer et al., 2007), sorafenib (Escudier et al., 2007a), pazopanib (Hutson et al., 2010), temsirolimus (Hudes et al., 2007), bevacizumab plus interferon alpha-2a (Rini et al., 2008; Escudier et al., 2007b), axitinib (Hutson et al., 2013; Motzer et al., 2013a), and everolimus (Motzer et al., 2008) – have been recommended in NCCN (Motzer et al., 2015a), ESMO-ESSO-ESTRO (Escudier et al., 2014a) and EAU guidelines (Ljungberg et al., 2015) for the treatment of mRCC (see web-appendix Table 1). The availability of these new drugs revolutionized the management of patients with mRCC (Motzer et al., 2015a; Escudier et al., 2014a; Ljungberg et al., 2015).

Pivotal (phase III) trials evaluating sunitinib (Motzer et al., 2007), sorafenib (Escudier et al., 2007a), pazopanib (Hutson et al., 2010), axitinib (Hutson et al., 2013) and bevacizumab (Rini et al., 2008; Escudier et al., 2007b) as first-line antiangiogenic drugs showed a significant improvement in response rate (RR) and progression-free survival (PFS), but failed to display any significant benefit in overall survival (OS). In these trials, mostly performed in the 2000s, experimental drugs were often compared with a historical control such as interferon alpha-2a or placebo. Since those trials were performed simultaneously and/or results in the same range, the new agents were not directly compared in terms of efficacy and safety, except for pazopanib vs. sunitinib (Motzer et al., 2013b), axitinib vs. sorafenib (Hutson et al., 2013), and sorafenib vs. pazopanib in first-line and/or cytokine-pretreated patients (Escudier et al., 2007a; Hutson et al., 2010). In addition, to our knowledge, no systematic review or meta-analysis has assessed the benefit/risk ratio of antiangiogenic drugs in first-line mRCC. Therefore, it remains unclear whether these treatments efficacy and safety profiles differ and clinicians lack data to define adequate first-line treatment for cytokine-naive mRCC patients.

This study aimed at performing a systematic review and network meta-analysis in order to compare clinical outcomes and safety profiles of five recommended first-line antiangiogenic drugs in cytokine-naive patients with mRCC.

2. Evidence acquisition

A systematic review of literature was performed to evaluate the efficacy and safety outcomes of first-line antiangiogenic therapies on cytokine-naive mRCC patients. We performed this study according to the Preferred Reported Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Moher et al., 2009).

2.1. Search strategy and study selection

We searched MEDLINE and EMBASE databases for relevant studies published between 1949 (MEDLINE) or 1974 (EMBASE) and July