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A critical appraisal of systemic treatment options for metastatic non-clear cell renal cell carcinoma

Salima Ismail [a,b,*,1], Malek Meskawi [a,1], Jens Hansen [a,c], Marco Bianchi [a,d], Zhe Tian [a], Mathieu Latour [e], Markus Graefen [c], Francesco Montorsi [d], Quoc-Dien Trinh [a,f], Paul Perrotte [b], Pierre I. Karakiewicz [a,b], Maxine Sun [a]

[a] *Cancer Prognostics and Health Outcomes Unit, University of Montreal Health Center, Montreal, Canada*
[b] *Department of Urology, University of Montreal Health Center, Montreal, Canada*
[c] *Martini-Klinic, Prostate Cancer Center Eppendorf-Hamburg, Hamburg, Germany*
[d] *Department of Urology, Urological Research Institute, Vita-Salute San Raffaele University, Milan, Italy*
[e] *Department of Pathology, University of Montreal, Montreal, Canada*
[f] *Vattikuti Urology Institute, Henry Ford Health System, Detroit, MI, USA*

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Abstract

Current guidelines provide most support for the use of temsirolimus in first line therapy for metastatic non-clear cell renal cell carcinoma (nccRCC). However, this recommendation is based on scant level 2a evidence. The objective of this review is to examine the evidence supporting first line temsirolimus use in patients with metastatic nccRCC as well as alternative first line treatment options. Six studies, that assessed the efficacy of five agents qualified for inclusion. Among recognized treatment options for metastatic nccRCC, mean weighted

* Corresponding author at: Cancer Prognostics and Health Outcomes Unit, University of Montreal Health Center (CHUM), 264 Boul. Rene-Levesque East, Suite 228, Montreal, QC, Canada H2X 1P1. Tel.: +1 514 890 8000x35336; fax: +1 514 227 5103.
E-mail address: ismail.salima@gmail.com (S. Ismail).
[1] Equally contributed.

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progression free survival values of 7.9 months for temsirolimus vs. 7.3 for sunitinib vs. 8.5 months for sorafenib vs. ≈4.1 months for erlotinib were recorded based on data from 10, 74, 33 and 51 patients respectively. In conclusion, the data supporting first line temsirolimus for metastatic nccRCC are based on a small patient sample. Sunitinib's efficacy is similar to that of temsirolimus but is based on a bigger patient sample that originates from phase II studies.

Keywords: Renal cell carcinoma; Non-clear cell; Metastatic; Papillary; Chromophobe; Systemic therapy; Targeted therapy; Temsirolimus; Sunitinib; Sorafenib

1. Introduction

In 2013, approximately 65,000 patients will be diagnosed with renal cell carcinoma (RCC) in the United States [1]. Of those, up to 30% will present with metastatic disease [2–9]. In the metastatic stage, non-clear cell RCC (nccRCC) is associated with worse prognosis compared to clear cell RCC (ccRCC) [10–13]. Specifically, it has been previously established that the biological basis of the treatment of nccRCC may be different than ccRCC, where alternative pathways could be targeted according to different nccRCC subtypes [9].

According to contemporary guidelines for the treatment of metastatic ccRCC, 4 molecules are available for first-line therapy (sunitinib, pazopanib, bevacizumab with interferon, and temsirolimus in the context of poor-risk patients) while 3 molecules are available for second-line therapy (everolimus, axitinib, sorafenib after tyrosine kinase inhibitor therapy), based on randomized phase III trials [8,14–22].

Unfortunately, the treatment recommendations for metastatic nccRCC are not as clear-cut. Indeed, due to the low prevalence of nccRCC, clinical trials focusing on metastatic patients with non-clear cell histological subtype are scarce and offer limited evidence supporting the use of available agents [23]. Therefore, contemporary guidelines strongly support participation in clinical trials as the standard option for 1st line nccRCC [21,22].

Alternatively, guidelines provide most support for the use of temsirolimus in first-line therapy for metastatic nccRCC for poor prognosis patients [22]. Such recommendations were based on results originating from a randomized controlled phase III trial examining the effect of temsirolimus relative to interferon, as well as temsirolimus in combination with interferon, in patients with poor or intermediate prognosis metastatic RCC of all histological subtypes, including nccRCC [15]. Additionally, other agents are also available: sunitinib (level of evidence 2A), sorafenib (level of evidence 2A), pazopanib (level of evidence 3), erlotinib (level of evidence 3), and axitinib (level of evidence 3) [22]. However, recommendations are not as evident and differ slightly from one guideline to another. For example, the National Comprehensive Cancer Network (NCCN) 2013 suggest temsirolimus as first choice and sunitinib and sorafenib as alternatives, whilst the European Society of Medical Oncology (ESMO) guidelines suggest temsirolimus, sunitinib and sorafenib with no preferences between agents [21,22].

These above observations and guidelines indicate that other agents than temsirolimus may represent valid alternatives as first-line therapies for metastatic nccRCC. We examined the data that may refute or substantiate this hypothesis.

2. Material and methods

A detailed literature review was performed using the PubMed (United States National Library of Medicine National Institutes of Health) database for articles published until October 1st 2012. Electronic articles published ahead of print were also considered. Search was conducted using the following key words: 'renal cell carcinoma', 'non-clear cell', 'metastatic', 'papillary', 'chromophobe', 'systemic therapy', 'targeted therapy', 'temsirolimus', 'sunitinib', 'sorafenib', 'erlotinib' and 'pazopanib'. The search was limited to English literature, humans, and persons aged 18 years and older. Subject and outcome of interest, pertinence, quality and detail of reporting were the indicators of manuscript quality. We included studies that focused on patients with papillary and/or chromophobe RCC (pRCC and chRCC, respectively) and reported progression free survival (PFS) after targeted therapy. The search was performed by one author (S.I.) and was validated by others (P.K., M.S., M.M.). All selected studies were grouped according to histological subtype and treatment type. When more than one PFS estimate was available, mean weighted PFS values were calculated.

Moreover, we examined the incidence trends of metastatic RCC (International Classification of Disease for Oncology (C67.0–C67.9)) in the Surveillance, Epidemiology and End Results (SEER) database in patients aged 18 years or older between years 1988 and 2008. Histological subtypes were grouped into four categories: clear cell, papillary, chromophobe and other. Death certificate only and/or autopsy cases were removed from our analyses.

3. Results

3.1. Incidence of metastatic papillary or chromophobe RCC

Since the exact incidence of metastatic nccRCC is unknown, we relied on the SEER database to better elucidate these rates in 20,456 patients with metastatic