European Journal of Cancer (2014) 50, 1321–1329

Available at www.sciencedirect.com

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journal homepage: www.ejcancer.com

Review

Controversies in renal cell carcinoma: Treatment choice after progression on vascular endothelial growth factor-targeted therapy

Emiliano Calvo [a,*], Viktor Grünwald [b], Joaquim Bellmunt [c]

[a] Centro Integral Oncológico Clara Campal and START Madrid, Madrid, Spain
[b] Clinic for Hematology, Hemostasis, Oncology and Stemcell Transplantation, Medical School Hannover, Germany
[c] University Hospital del Mar, Barcelona, Spain

Available online 1 March 2014

KEYWORDS
Quality of life
Renal cell carcinoma
Second-line
Sequencing
Treatment planning

Abstract The mammalian target of rapamycin inhibitor (mTORI) everolimus and the tyrosine kinase inhibitor (TKI) axitinib are the only two post-first-line treatment options for metastatic renal cell carcinoma (mRCC) licensed at present. Extrapolation of robust phase III studies suggests that median progression-free survival (PFS) is similar between agents. This presents a dilemma for the physician planning treatment for their patients with mRCC: should they be treated with a TKI–mTORI or a TKI–TKI sequence? The lack of direct comparison between axitinib and everolimus leaves the clinician without clear guidance on the optimal choice in second-line therapy. In phase III studies, both post first-line everolimus and axitinib have been shown to delay disease progression; however, cumulative toxicity with sequential use of TKIs may result in more treatment interruptions or dose reductions or increased likelihood of adverse events. While everolimus exerts a tolerability advantage, axitinib is associated with higher response rate and a similar PFS benefit. Proven superiority cannot be used to guide treatment sequence selection in mRCC. Instead, therapeutic planning requires us to take a long-term view of our patient's treatment that includes quality of life and a balance between symptom control, adverse event management and avoidance of unnecessary drug interruptions or dose reductions. In the absence of curative therapies, sustaining a patient's quality of life is a major goal throughout the course of treatment and choosing a second-line agent that is able to adequately achieve this by limiting adverse events should be a priority.

* *Corresponding author:* Address: START Madrid, Centro Integral Oncológico Clara Campal, Hospital Madrid Norte Sanchinarro, Calle Oña, 10, 28050 Madrid, Spain. Tel.: +34 91 7567825; fax: +34 91 7567931.
E-mail address: emiliano.calvo@start.stoh.com (E. Calvo).

http://dx.doi.org/10.1016/j.ejca.2014.02.007
0959-8049/

1. Introduction

Seven molecularly-targeted agents have been licensed for the treatment of metastatic renal cell carcinoma (mRCC), including the humanised anti-vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab (used in combination with interferon [IFN]-α); the multi-targeted receptor tyrosine kinase inhibitors (TKIs) sunitinib, pazopanib, axitinib and sorafenib; and the mammalian target of rapamycin inhibitors (mTORIs) everolimus and temsirolimus. In each line of mRCC therapy, the molecularly-targeted agents specifically approved for that setting have demonstrated similar efficacy, requiring oncologists to rely on factors other than clinical efficacy alone to select the optimal therapy for their mRCC patient and generating debate on the optimal therapy sequence in mRCC.

It is without doubt that initial treatment of low- or intermediate-risk mRCC patients with a VEGF-targeted agent significantly improves clinical outcomes compared with conventional immunotherapy [1–3], as reflected in current evidence-based guidelines (Table 1) [4,5]. A recent randomised non-inferiority trial (COMPARZ) suggested that pazopanib is non-inferior to sunitinib in the first-line setting, and may be more favourable than sunitinib in terms of safety and quality of life [6]. First-line temsirolimus has demonstrated efficacy in patients with poor prognosis [7].

Despite the clear benefits of targeted therapies in mRCC, most patients experience disease progression while on treatment [8]. Approved post first-line treatment options include everolimus [9,10] and axitinib [11,12], which are both active after treatment with VEGF-targeted therapy and are associated with median progression-free survival (PFS) durations in the range of 4–5 months.

This presents a dilemma for the physician planning the treatment sequence for their patient with mRCC: should they be treated with a TKI or an mTORI after failure of a VEGF-targeted therapy? In other tumour types, it is common practice to avoid cross-resistance by switching to a drug with a different mechanism of action after treatment failure. Do the same rules apply in mRCC? This review evaluates current evidence to guide post first-line drug selection in mRCC and considers how to optimise clinical outcome, patient quality of life and survival through therapy selection.

2. Treatment sequencing: what is the evidence from direct comparisons?

Until recently, there has been little evidence to guide treatment sequencing in mRCC, with most data generated from retrospective or non-comparative studies [13–26]. While these analyses indicate that some level of second-line activity is achieved when a TKI–mTORI or a TKI–TKI sequence is used, the quality of data makes it difficult to draw any greater conclusions. We need to extrapolate the robust data that we do have on individual agents into thoughtful and rational treatment decisions. One prospective study (INTORSECT) has recently been presented that directly compared agents with different mechanisms of action (temsirolimus and sorafenib) in mRCC patients who had progressed on first-line sunitinib [27]. There was no significant difference between treatments in the primary end-point of PFS (hazard ratio [HR] 0.87; 95% confidence interval [CI] 0.71–1.07); however, sorafenib afforded a significant overall survival (OS) advantage to temsirolimus (HR 1.31; 95% CI 1.05–0.63). The reasons for the discrepancy in PFS and OS are unclear. Data on post-second-line therapies were not collected, meaning that any potential contribution of between-group imbalances in salvage therapy cannot be elucidated. Irrespective of the findings of this study, it may be a red herring in unravelling the controversy surrounding

Table 1
ESMO recommendations for systemic treatment in clear-cell metastatic renal cell carcinoma (mRCC) [5].

Treatment line	Risk group	Previous therapy	Standard treatment	Alternative treatment
First	Good/ intermediate	None	• Sunitinib • Bevacizumab + IFN • Pazopanib	• Cytokines • Sorafenib
	Poor	None	• Temsirolimus	• Sunitinib • Sorafenib
Second	All	Vascular endothelial growth factor (VEGF)-targeted therapy Cytokines	• Everolimus • Axitinib • Sorafenib • Pazopanib • Axitinib	• Sorafenib • Sunitinib
Third	All	Two VEGF-targeted therapies VEGF-targeted therapy and mammalian target of rapamycin inhibitor (mTORI)	• Everolimus • Tyrosine kinase inhibitor (TKI)	

Adapted from Escudier B, Eisen T, Porta C, Patard JJ, Khoo V, Algaba F, et al. Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012;23 Suppl. 7:vii65–71.