Med Oncol (2012) 29:1914–1915
DOI 10.1007/s12032-011-0073-z

LETTER TO THE EDITOR

Sequential therapy in metastatic renal cell carcinoma: what comes next?

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Published online: 1 October 2011

Metastatic renal cell carcinoma (mRCC) is a fast-moving therapeutic field with multiple targeted agents approved and many more in development. In our expert agreement article [1], we evaluated available data together with our clinical experience to consider how we might optimize using targeted therapies in sequence, emphasizing the need continually to address the question, "what comes next?" Crucially, new phase III data presented at the American Society of Clinical Oncology (ASCO) 2011 annual meeting provide level 1 evidence that patients can receive continued clinical benefit when VEGF-targeted tyrosine kinase inhibitors (TKIs) are used sequentially [2, 3].

The randomized, open-label, phase III AXIS study compared second-line axitinib 5 mg bid (titrated to 7, then 10 mg bid, if tolerated) with sorafenib 400 mg bid in 723 patients with mRCC, more than half of whom had previously received the TKI sunitinib ($n = 389$) [2]. The study met the primary endpoint of superiority for axitinib, with median PFS 6.7 months, compared with 4.7 months for sorafenib ($P < 0.0001$).

Median PFS was lower in post-sunitinib than in the total patient population for both axitinib (4.8 months) and sorafenib (3.4 months; $P < 0.05$ versus axitinib). Notably, and as discussed in our expert agreement article, this phenomenon was also seen in the phase III RECORD-1 study of everolimus in patients previously treated with sorafenib and/or sunitinib—prior sunitinib was prognostic of lower PFS and overall survival in a multivariate analysis [1]. The AXIS and RECORD-1 data, therefore, suggest that pre-treatment with effective VEGF-TKI therapy, such as sunitinib, has a detrimental effect on subsequent outcome with both VEGF-TKI therapy and mTOR inhibition. Therefore, cross-resistance between these two classes may be apparent. A further noteworthy publication at ASCO 2011, from Dr. Mhd Al-Marrawi on behalf of the International mRCC Database Consortium, showed that response to initial TKI therapy did not predict response to further TKI therapy [4]. This study did not report whether the sequence of TKIs received was important, but this question could be addressed in part by performing a similar analysis using the AXIS data—i.e., were ORR/stable disease/PFS with axitinib or sorafenib related to ORR/stable disease/PFS with sunitinib and were there differences between axitinib and sorafenib in this regard?

Overall, the findings from AXIS, RECORD-1, and the International mRCC Database Consortium do not support the hypothesis that switching mode of action from VEGF inhibition to mTOR is the logical first step in the face of VEGF resistance. Re-challenging with VEGF-TKI therapy appears to be more attractive as the first treatment manipulation at present. Switching to mTOR as 3rd line or later, which is supported by randomized phase III data, gives us multiple lines of therapy with proven efficacy. On a further note, though it may be tempting to compare the efficacy data from AXIS with those for RECORD-1, there are a number of key differences between the studies, including patient population and study design, and so such comparisons are fundamentally flawed.

Patient-reported outcomes from AXIS were also presented at ASCO [3]. Dr. David Cella showed that

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health-related quality of life (HRQoL) was similar for sorafenib and axitinib, based on Functional Assessment of Cancer Therapy Kidney Symptom Index (FKSI)-15 and FKSI disease-related symptoms (DRS) scores. This similarity was observed, despite differences between sorafenib and axitinib in terms of their toxicity profiles—as reported by Dr. Brian Rini at ASCO, grade 3/4 AEs that were numerically more frequent in sorafenib-treated patients than in axitinib-treated patients were hand-foot syndrome (16% vs. 5%) and rash (4% vs. <1%), and grade 3/4 AEs numerically more frequent with axitinib than with sorafenib included diarrhea (11% vs. 7%), hypertension (16% vs. 11%), and fatigue (11% vs. 5%; for all AEs, the significance of between-treatment differences was not reported). All AEs can be troublesome, but their impact may vary between patients based on their individual needs and disease characteristics. For example, elderly patients, who make up the majority of patients with mRCC, are particularly prone to suffer from AEs that are usually more tolerated by younger patients (e.g., fatigue), reiterating the need for a patient-focused approach to treatment [5].

While the AXIS data answer some important questions and support the use of sequential TKI therapy in mRCC, there are still some unanswered considerations. These include the choice between VEGF-targeted therapy and an mTOR inhibitor in patients who have progressed on previous VEGF-targeted treatment, the identification of specific patients who benefit from each targeted agent, and what to use in axitinib-refractory disease. The implications for clinical practice of findings from ongoing studies will be of great interest.

Acknowledgments The authors are grateful to 7.4 Limited for providing editorial support, with unrestricted financial support from Bayer HealthCare Pharmaceuticals.

Conflict of interest CP has received research grants from Bayer HealthCare and Novartis Pharma and has acted as a paid consultant or speaker for Bayer HealthCare, Pfizer Oncology, Hoffmann-La Roche, Wyeth Pharmaceuticals, Novartis Pharma, and GlaxoSmithKline. TP has received research grants from Novartis, GlaxoSmithKline, Astra Zeneca, and Pfizer and has acted as a paid consultant or speaker for Pfizer, Astra Zeneca, Novartis, and GlaxoSmithKline.

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