Clinical outcomes in patients receiving three lines of targeted therapy for metastatic renal cell carcinoma: Results from a large patient cohort

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Abstract

Aim
A number of targeted therapies (TTs) are effective in metastatic renal cell carcinoma (mRCC) but clinical outcomes with the sequential use of three TTs have been poorly investigated, this study evaluates their outcome.

Methods
Patients with clear cells mRCC treated with three TTs were retrospectively studied. Therapies were classified as vascular endothelial growth factor (VEGF)/vascular endothelial growth factor receptor (VEGFR) or mammalian target of rapamycin inhibitors (mTORi). Progression free survival (PFS), overall survival (OS) and total PFS (tPFS) – defined as the time from start of first-line to progression on third-line treatment – were estimated using the Kaplan–Meier method and curves were compared with log-rank test.

Results
A total of 2065 patients with mRCC were consecutively treated with first-line TT in 23 centres in Italy. Overall 281/2065 patients (13%) were treated with three TTs. Median OS and tPFS were 44.7 and 34.1 months, respectively and were longer in patients receiving the sequence vascular endothelial growth factor inhibitors (VEGFi)–VEGFi–mTORi compared with those receiving VEGFi–mTORi–VEGFi with a statistical difference in OS (50.7 versus 37.8 months, $p = 0.004$; 36.5 versus 29.3 months, $p = 0.059$, respectively).

Conclusions
Few patients received three lines of TTs. The sequence VEGFi–VEGFi–mTORi was associated with improved survival with respect to VEGFi–mTORi–VEGFi and primary resistance to first-line was a negative predictive and prognostic factor.

1. Introduction
Metastatic renal cell carcinoma (mRCC) is a fatal urological cancer with a 5-year survival rate of approximately 10%.[1 and 2] During the last decade, five vascular endothelial growth factor (VEGF)/VEGF receptor (VEGFR) inhibitors (VEGFi) – sorafenib, sunitinib, pazopanib, axitinib and bevacizumab (in combination with interferon) – and two mammalian targets of rapamycin inhibitors (mTORi) – temsirolimus and everolimus – have been approved for the treatment of mRCC. Despite the evident benefits of TTs in terms of increased control of disease and response rate, complete responses are rare, with most patients eventually experiencing progression during treatment, leading to subsequent-lines of therapy in attempts for disease control.[3] Use of sorafenib and sunitinib sequentially is now a common clinical practice due to the growing body of evidence for non-minimal cross-resistance between VEGFR inhibitors. In addition, efficacy has been demonstrated by shifting to a drug with another mechanism of action such as mTOR inhibitors.[4, 5, and 6] There are to date limited published data on the sequential use of three TTs in the treatment of mRCC.[7, 8, and 9] Of these, one retrospective study reported that patients who received third-line sorafenib after sunitinib and everolimus or temsirolimus showed a disease control rate (complete responses plus partial responses plus stable disease) of 44% with a favourable toxicity profile.[9]

The aims of this study were to: investigate the numbers of patients receiving three TTs in some of the

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