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EDITORIAL

Sorafenib tosylate for advanced kidney cancer: lucky loser and magic box at the same time

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Despite being the very first molecular targeted agents registered for the treatment of advanced kidney cancer (in the post-cytokines setting) [1], Sorafenib seemed to lose its momentum as a credible first-line treatment option, when it proved not to be superior to Interferon within a randomized phase II trial [2].

Even though the results of that trial have been highly criticized—mainly due to patient selection bias—these negative results, together with the concomitant availability of other highly active treatments, such as Sunitinib, the combination of Bevacizumab plus Interferon, Temsirolimus (for poor risk patients) and, more recently, also Pazopanib, greatly limited its front-line use almost only to those few patients still treated first-line with cytokines, or to ill-defined, special situations (e.g., elderly patients, patients with cardiovascular co-morbidities, etc.) [3].

As far as second-line, where its use is supported by almost only retrospective, studies [4], the publication of the randomized controlled, phase III trial of Everolimus [5] seemed to have moved Sorafenib back to third, or even subsequent, line.

Recent data—surprisingly gathered from non-Bayer-sponsored trials—seem to have someway revitalized this drug in its very first oncological indication, i.e., kidney cancer.

Indeed, in the recently presented first-line AMG 386 trial [6], Sorafenib—which was used as a control arm—yielded a progression-free survival (PFS) of 9.0 months, almost doubling the PFS reported in the first-line trial against Interferon [2], moving Sorafenib closer to the other treatment options commonly used in first-line treatment options that, as in the case of Sunitinib, saw their performance someway resized when tested, similar to the two above-mentioned Sorafenib studies, within smaller (and therefore more biased), randomized phase II studies [7].

Similarly, when the results of the Axitinib AXIS trial were disclosed [8], Sorafenib gained further momentum also in the second-line setting; how is it possible, given that Sorafenib was the loser against Axitinib?

It happened that Sorafenib, given after a first-line treatment (mainly Sunitinib), yielded a PFS that was almost superimposable to the one observed for Everolimus after Sunitinib.

Even though it should be noted that, in the vast majority of cases, Everolimus-treated patients were not pure second-line patients, the results achieved with Sorafenib in the AXIS trial do support the option of its use in a second-line setting, as a partial alternative to Everolimus, at least until Axitinib registration.

Indeed, the level of evidence of the two putative options (i.e., Sorafenib and Everolimus) is now the same.

At this point, second-line treatment should be tailored on a patient-to-patient basis, taking into account patients' characteristics (especially co-morbidities), disease characteristics, as well as treatment aim [9].

Furthermore, a recent report from a Japanese group [10] clearly suggests that the concept of re-challenge may also apply to Sorafenib, and not just to Sunitinib [11].

Indeed, the authors showed—even though in a retrospective way—that clinical benefit may be achieved with Sorafenib also in patients already treated with this same multikinase inhibitor [10].

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Even though, for sure, the lack of alternative treatment options is definitely not an issue in kidney cancer nowadays, Sorafenib (and Sunitinib) re-challenge could be a reasonable treatment option where alternative therapies are not available (and where regulatory authorities do allow it).

More interestingly, both the prospective AXIS data, as well the retrospective Japanese report do suggest that a continuous inhibition of the VEGFR(s) pathway could be of benefit for advanced kidney cancer patients.

The activity of the mTOR inhibitor Everolimus in patients failing a first or second-line treatment with an anti-VEGF pathway tyrosine kinase inhibitor do not necessarily contradict this hypothesis. Indeed, due to the peculiar molecular pathogenesis of kidney cancer—so dependent on angiogenesis, due to the frequent mutation of the VHL gene also in sporadic cases [12]—it is also possible that presently available mTOR inhibitors also (which indeed are just TORC1 complex inhibitors) could be active due to their indirect inhibition of angiogenesis [13].

As a whole, it is clear that we still have a lot to know about the presently available treatments for kidney cancer (Sorafenib in primis), and that the phase III trials performed to date simply cannot address all the issues still on the table.

Finally, I cannot but agree with the strong statement made by Chris Ryan during the educational session at the 2010 annual meeting of the American Society of Medical Oncology (ASCO), when he provocatively proposed his personal (and simplified) algorithm with the strong sentence: *choose any agent You want. Use it well*.

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