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Platinum Priority – Editorial

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Slow and Steady Wins the Race: Practical (and Philosophical) Considerations of Treatment Activity Evaluation When Novel Anticancer Agents Just Slow Neoplastic Progression

Camillo Porta [a,b,*], *Alessandro Vercelli* [c], *Chiara Paglino* [a,b]

[a] *Medical Oncology, I.R.C.C.S. San Matteo University Hospital Foundation, Pavia, Italy;* [b] *Italian Nephro-Oncology Group (Gruppo Italiano di Oncologia Nefrologica – G.I.O.N.), Italy;* [c] *Radiology, I.R.C.C.S. San Matteo University Hospital Foundation, Pavia, Italy*

The question of how to measure antitumor treatment activity in the era of molecularly targeted agents is anything but trivial. This is especially so in diseases like kidney cancer, where, because of the availability of a number of active agents that are often used sequentially, progression-free survival (PFS) has replaced overall survival (OS)—once the holy grail of oncology—as the most reasonable, although not ideal, primary end point of clinical trials [1].

We have learned over the years that many of these novel agents exert more cytostatic than cytotoxic activity or, at least, that they induce limited, albeit discrete, tumor shrinkage. This does not take into account the issue of pseudoprogression (or initial progression followed by tumor shrinkage), a phenomenon once dramatically relevant only in relatively rare cancers such as gastrointestinal stromal tumors [2] but now of interest after the first experiences with novel immunotherapeutics (eg, anti-CTLA-4, anti-PD-1, and anti-PD-L1 antibodies) [3], regardless of tumor type. These issues have raised questions about the usefulness of commonly accepted Response Evaluation Criteria in Solid Tumors (RECIST) for patients receiving targeted or novel immunologic agents [3–5].

In this month's issue of the Platinum Journal, Ferté and colleagues provide evidence that the *tumor growth rate* (TGR) is associated with prognosis (PFS and OS) in kidney cancer patients treated with two different targeted agents (ie, sorafenib and everolimus), allowing for early and precise evaluation of drug activity compared with RECIST evaluation [6]. TGR is a relatively complex computation that combines the RECIST sums of the target lesions and the time between tumor imaging, including pretreatment, off-treatment, and postprogression periods. Notably, with this method, the authors demonstrated persistent activity of sorafenib at progression and an apparent flare-up effect after drug discontinuation; this pattern was not observed in everolimus-treated patients [6].

Given this finding, a difficult key question arises: When should we really stop treatment if, with some agents (eg, sorafenib), slowing of tumor growth may be observed beyond progression but tumor flare may occur at treatment discontinuation?

This pattern of drug activity over time seems to support a very practical approach of some kidney cancer specialists (although not common practice among general oncologists), namely, to continue treatment beyond (limited) progression, changing the drug only in case of numerical or massive dimensional progression. However, those of us who acted this way did not take into account those putative differences between agents suggested in the paper by Ferté and colleagues [6].

Continuing treatment beyond progression is quite difficult, although not impossible, to perform and to explain to patients, especially in the presence of several alternatives; however, this approach could help us optimize some of the drugs within our cancer armamentarium. Yet, the practical application of this strategy is hampered not by the art of medicine but by health economics. In some countries (eg, Italy), the national health system reimburses high-cost targeted agents only until progression is documented and definitely not beyond. Consequently, continuing treatment despite progression could be quite complicated at best.

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* Corresponding author. Medical Oncology, I.R.C.C.S. San Matteo University Hospital Foundation, Piazzale C. Golgi, 19, 27100 Pavia, Italy.
Tel. +39 0382 501355; Fax: +39 0382 501223.
E-mail addresses: c.porta@smatteo.pv.it, camillo.porta@gmail.com (C. Porta).

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In conclusion, although the provocative paper by Ferté and colleagues [6] needs validation and probably is not applicable outside referral centers like Institut Gustave Roussy, the authors raise some key questions about how best to evaluate tumor response to targeted agents, when to stop treatment, and how to integrate such decisions with economic issues. To date, none of these questions has a clear-cut, evidence-based answer.

Fortunately, medicine is still more art than pure science.

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