

# Long-term safety of targeted agents used to treat metastatic renal cell carcinoma: the issue is not the rate of adverse events over time, but the expertise needed to manage them

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Targeted agents have revolutionized the treatment of advanced renal cell carcinoma (RCC), greatly improving the survival of patients affected with once orphan disease.

Although the median progression-free survival of patients treated in first-line, irrespective of the agent used, is between 9 to 11 months, a relevant number of patients do receive such a treatment for a longer period of time.

Thus, knowing not only acute, but also long-term toxicities of the agents we do use is mandatory and, given the data available for some of these agents (1,2), also reassuring (3).

However, in order to achieve even better results in terms of treatment duration, and thus disease control, we should try to increase the number of patients who are treated longterm.

However, one could argue that this is an almost impossible task, at least with presently available agents, since the development of acquired resistance appears to be ineluctable and tightly linked to the biology of the tumor itself (4).

Nevertheless, it is clear that too many patients discontinue first-line treatment (as well as subsequent lines), not for disease progression (or, if you want, before disease progression) due to toxicity. Is this again ineluctable?

We do think this is not the case.

When taking a look at the rates of treatment discontinuation due to adverse events reported in pivotal trials of agents used in first-line (*Table 1*), we recognize that this is a huge problem, despite the fact that this trials have

been conducted at experienced, referral, sites with time, experience and staff devoted to the management of these patients and their treatment.

Although it is difficult to demonstrate, the rate of treatment interruptions and discontinuations outside clinical trials is realistically higher, especially in low-volume centers.

Notwithstanding, all the above proved to have a detrimental effect on treatment's outcome; indeed, it has been previously demonstrated that a low dose-intensity correlates with a poor prognosis in metastatic RCC patients treated with different agents (5), strengthening, from a clinical viewpoint, informations we already gathered from pharmacokinetic studies (6).

This is all but strange, since we do know, form the old times of cytotoxic chemotherapy for metastatic breast cancer (7), that a direct relationship exist between a correct dose intensity (i.e., dose per unit of time) and treatment efficacy.

Finding agents endowed by a better therapeutic index is certainly mandatory in kidney cancer as well as in many other malignancies, but exploiting at its best what we presently have, in terms of treatment armamentarium, is even more important.

For sure, dose reductions, schedule modifications and even treatment discontinuations will continue to be necessary for many cancer patients with the present array of anticancer agents (and probably also with the next generation of them), but we should be brave enough not

Table 1Rates ofpatients	treatment discontinu	iations and/or dose m	odifications due to	adverse events in the pivot	al trials of targeted	l agents used to tre	at first-line me	tastatic kidn	sy cancer
Study (treatment arm)	Discontinuations due to AEs (%)	Dose interruptions due to AEs	Dose reductions due to AEs	Withdrawn from any component of T× before PD due to AEs (%)	Any study drug discontinuation due to AEs (%)	Tx delays of 4 to 6 days due to AEs (%)	Tx delays of >9 days due to AEs	≥1 dose	≥1 dose delay
Registrative trial (Sunitinib)	8%	38% (any length)	32%	1	I		I		
COMPARZ trial (Sunitinib)	20%	49% (≥7 days)	n.r.	1	I	I	I	I	
Registrative trial (Pazopanib)	12% (Tx-naive pts)	n.r	I	1	I	I	I	I	
COMPARZ trial (Pazopanib)	24%	44% (≥7 days)	I	I	I	I	I		
AVOREN trial (Bevacizumab + IFN)	ı.r	I	I	26.3%	28%	n.r.	n.r.		
CALGB 90206 (Bevacizumab + IFN)	24%	I	I	J.T.	n.r.	8.4%	19.9%		
ARCC trial (Temsirolimus)	7%	I	I	I	I	Ι	I	23%	8%
AFs adverse eve	nts. Tx_treatment.	PD progressive dise	ase. n r not renor	ted: IEN Interferon- $\alpha$					

treatment; PU, progressive disease; n.r., not reported; IFN, Interferon-a. AES, adverse events; Ix,

S614

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only to say to our patients to keep treatment going, because it will be realistically better tolerated over time, but also to teach them to prevent and manage, as much as possible (which definitely means not in every case), treatmentrelated adverse events, both acute and chronic.

To conclude, we cannot but recall Chris Ryan's words at the 2010 American Society of Medical Oncology annual meeting, words which were subsequently endorsed by many of us in the field of RCC (8), "*use any agent you want, but use it well*".

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