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GOAL: An inverse toxicity-related algorithm for daily clinical practice decision making in advanced kidney cancer

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Contents

Abstract

Metastatic renal cell carcinoma (mRCC), considered almost an orphan disease only six years ago, appears today a very dynamic pathology. The recently switch to the actual overcrowded scenario defined by seven active drugs has driven physicians to an incertitude status, due to difficulties in defining the best possible treatment strategy. This situation is mainly related to the absence of predictive biomarkers for any available or new therapy. Such issue, associated with the nearly absence of published face-to-face studies, draws a complex picture frame. In order to solve this dilemma, decisional algorithms tailored on drug efficacy data and patient profile are recognized as very useful tools. These approaches try to select the best therapy suitable for every patient profile. On the contrary, the present review has the "goal" to suggest a reverse approach: basing on the pivotal studies, post-marketing surveillance reports and our experience, we defined the polarizing toxicity (the most frequent toxicity in the light of clinical experience) for every single therapy, creating a new algorithm able to identify the patient profile, mainly comorbidities, unquestionably unsuitable for each single agent presently available for either the first- or the second-line therapy. The GOAL inverse decision-making algorithm, proposed at the end of this review, allows to select the best therapy for mRCC by reducing the risk of limiting toxicities.

Keywords: Renal cell carcinoma; Sorafenib; Pazopanib; Everolimus; Sunitinib; Bevacizumab; Axitinib; Antiangiogenic therapy; Treatment algorithm

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1. Introduction

The new molecular targeted therapies offer new and unexpected therapeutic tools for the treatment of tumours previously resistant to conventional chemotherapy. Patients with metastatic renal cell carcinoma (mRCC) can take particularly good advantage of these new therapeutic approaches. While mRCC was considered for many years as an orphan disease, seven new targeted agents for the treatment of this condition are now available. Sunitinib, sorafenib, pazopanib, and axitinib are oral multi-targeted agents commonly defined as tyrosine kinase inhibitors (TKIs). Physicians can also rely on the anti-vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab intravenously administered in combination with interferon (IFN) alfa 2a, and on two mammalian target of rapamycin (mTOR) inhibitors: everolimus (oral) and temsirolimus (intravenous).

However, differing from other tumour types such as breast, colon, and lung in which the therapeutic choice is frequently driven by the presence of specific identified tumour biomarkers (HER2+, B-Raf, ALK) which, if properly considered, may help improve the clinical outcomes, no evidence of a relation between biomarker expression and the activity of targeted therapies in mRCC exists. All the pivotal studies carried out with the different new agents showed the capability to achieve the predefined clinical endpoints without clearly indicating if the activity profile could be identified on the basis of the possible biologic and/or molecular characteristics of the disease. In clinical practice, this lack gave rise to a series of issues and queries. With the exception of temsirolimus, indicated for the first-line treatment of patients with a poor prognosis on the basis of a modified Memorial Sloan-Kettering Cancer Center (MSKCC) score, several other approaches display overlapping indications both for the first-line treatment as well as for subsequent lines. Such situations could likely be ascribed to the fact that most pivotal studies have been undertaken in different patient populations and different settings of disease in comparison with placebo or immunotherapy [1], and only scanty information from head-to-head studies comparing new targeted agents is presently available. In fact, only recently head-to-head phase III studies were designed: axitinb vs. sorafenib, tivozanib vs. sorafenib, temsirolimus vs. sorafenib and the non-inferiority study pazopanib vs. sunitinib. Therefore, the possibility of performing the best choice in terms of efficacy and tolerability for a given patient population or disease characteristics remains strongly limited or even unattainable.

To settle this ambiguous and challenging situation, several algorithms for the most appropriate treatment have been proposed. Whereas for first-line treatment most suggestions aim at identifying a well-defined efficacy and toxicity profile suitable for a given patient population, for patients who have relapsed some algorithms have recommended the choice of second-line treatment on the basis of the behaviour of the tumour burden and of the toxicity of the previous treatment [1–3]. Consequently, at the present time several physicians recognize that the only possible suggestion for the most suitable choice lies in Ryan's unbiased, reasonable, and simple suggestion: at least for the time being, all the available targeted agents are equivalent in terms of efficacy, therefore we can use any of them provided it is administered correctly [4,5]. This review identifies a "reverse-road" map to establish the most appropriate treatment. Instead of defining the optimal patient profile suitable for a given therapy, we try to identify the patient profile unquestionably unsuitable for a given agent for both first- and second-line therapy.

Our objective was to define a decision-making algorithm allowing us to identify which patient should be excluded from the treatment with a given targeted agent on the basis of the comorbidities of the patient and the specific toxicity profile of the drug toxicity. It has been established that no drug currently available for the treatment of RCC is free from toxicities, and several agents share common toxicities. In addition, the possibility of inducing a polarized toxicity, which is characteristic of the molecule, has been evaluated for each single agent.

2. Sources and methods

Data from phase 3 clinical studies, summary product characteristics (SPCs), and post-marketing surveillance reports concerning the drugs approved by the European Medicines Agency (EMA) such as sunitinib, sorafenib, bevacizumab plus IFN, everolimus, pazopanib, and axitinib were taken into consideration and analyzed. Temsirolimus was excluded from the analysis because the drug has already been clearly positioned through a modified MSKCC algorithm for the first-line treatment of patients with a poor prognosis.

2.1. Polarizing toxicity

Polarizing toxicity, which represents the basis of this paper, has been considered and defined as follows: the most frequent toxicities reported in literature or presented at the main congresses for each targeted agent, revised by the Authors, and adjusted at the light of our clinical experience.

2.2. Features of the drugs

For an overall view of the toxicities related to the targeted agents described here, Tables 1 and 2 report the frequency of the most important adverse events recorded in first- and second-line phase 3 trials.

2.3. Sunitinib

Along with sorafenib, sunitinib was the first TKI available for the treatment of patients with RCC. Therefore, a large amount of efficacy and toxicity data has been gathered. In Europe, it has been approved for the treatment of

Table 1
Treatment associated adverse events reported in first line phase III trial RCC drug currently approved.

	Sunitinib				Sorafenib		Bevacizumab+IFN				Pazopanib			
	(Motzer 2007) *Grades*		COMPARZ *Grades*		TIVO1[a] *Grades*		AVOREN *Grades*		CALGB *Grades*		(Sternberg 2012) *Grades*		COMPARZ *Grades*	
	All	*3–4*	*All*	*3–4*	*All*	*3–4*	*All*	*3–4*	*All*	*3–4*	*All*	*3–4*	*All*	*3–4*
Fatigue	51	11	55	10			33	12	35	2	14	3	63	17
Dyspnoea	10	2					13	<1	5	1				
Endocrinological														
Hypothyroidism	14	2									<10	<1		
Hyperglycaemia			57	4							41	<1	54	5
Hypophosphatemia	31	6	52	8	70	25					34	4	36	4
CV														
Hypertension	30	12	41	15	34	17	26	3	9	1	13	<1	46	15
Decline in LVF	13	3					<1	<1						
Bleeding							33	3	1	1				
Thrombosis/embolism							3	2	1	1				
Gastro-hepatological														
Anorexia	34	2			8		36	3	17	0	22	2		
Nausea	44	3	45	2	6					7	26	<1	46	2
Vomiting	44	3									21	2		
Diarrhoea	53	5	57	7	27	6	20	2			62	3	63	9
Proteinuria							15	18			<10	<1		
Hypercreatininemia	66	1	46	1							<10	<1	32	<1
Hyperbilirubinemia	19	1	27	2							36	3	36	3
ALT levels	46	3	43	4							53	12	60	17
AST levels	52	2	60	3							53	7	61	12
Dermatological														
Mucositis	20	2			7						<10	<1		
HSFR	20	5	50	11	53	17					<10	<1	29	6
Rash	19	2			11						<10	<1		

[a] TIVO1 trial was conducted for the 70% in first line patients and 30% in cytokine pretreated patients.

advanced RCC in any line of treatment [6]. The major treatment toxicities affect liver, kidney, thyroid, and, in particular, are represented by arterial hypertension and cardiac function impairments [6]. A black box warning in the SPC against hepatotoxic risks was requested by the US health authorities due to liver function insufficiency, sometimes even fatal, observed during clinical trials and post-marketing surveillance [7]. In addition, the European SPC recommends careful monitoring of clinical signs and symptoms concerning heart failure, particularly for patients with cardiac risk factors or a history of coronary disease [6]. This could be attributed to the fact that such toxicity had been underestimated in the registration trials, which excluded patients displaying cardiac events during the last 12 months [6–9]. Subsequent spontaneous reports coming from post-marketing surveillance data and retrospective analyses carried out on limited sample sizes of patients underlined the risks of reduced ejection fraction both in patients with RCC during treatment as well as in other groups of patients [10–13]. In some cases, severe cardiac myopathy and/or QTc interval prolongation were noted [14,15]. A study carried out on 6935 patients documented an incidence of all-grade congestive heart failure equal to 4.1%, with 1.5% of them high grade [16]. Although this adverse event seems reversible, available evidence recommends caution in the treatment of patients with hypertension, cardiac diseases, or in combination with other cardiotoxic agents [17]. In addition, sunitinib cannot be recommended, according to available evidence, in patients with serious liver impairment.

2.4. Sorafenib

The EMA approved sorafenib for the treatment of patients with mRCC who have relapsed after cytokines or for those considered unsuitable for cytokine therapy [18]. In contrast to other TKIs, besides targeting VEGF 1, 2, and 3 receptors responsible for angiogenic activity, in vitro data also showed an activity of sorafenib against showed an activity of sorafenib against B-raf serine–threonine kinase factor [19]. Similarly to other B-raf inhibitors which are associated to dermatological events (e.g. vemurafenib), sorafenib is mainly characterized by a skin toxicity profile that may involve up to 90% of patients [20,21]. According to the literature, more than 60% of patients display the typical hand-foot-skin reaction, particularly affecting contact areas such as the hand, palm, and sole of the foot [18,21]. This reaction arises within 2–3 weeks since the initiation of therapy and, if not correctly managed, can even lead to immobility [22,23]. Another skin toxicity frequently related to sorafenib therapy consisted of up to 40% of patients experiencing cutaneous rash of all

Table 2
Treatment associated adverse events reported in second and/or later lines phase III trial RCC drug currently approved.

	Sorafenib						Everolimus		Axitinib	
	TARGET *Grades*		AXIS *Grades*		INTORSECT *Grades*		RECORD1[a] *Grades*		AXIS *Grades*	
	All	*3–4*	*All*	*3–4*	*All*	*3–4*	*All*	*3–4*	*All*	*3–4*
Fatigue	29	3	32	5	34	7	31	5	39	11
Endocrinological										
Hypothyroidism			8	0					19	1
Hyperglycaemia					6	2	57	15		
Hypercholesterolemia							77	4		
Hypertriglyceridemia							73	1		
Hypophosphatemia		13			12	7	37	6		
CV										
Hypertension	17	4	29	11					40	16
Bleeding	15	3								
Respiratory										
Dyspnoea	14	4			18		24	7		
Pneumonitis							14	4		
Infections							37	10		
Gastro-hepatological										
Anorexia	14	<1	14	3			22	2	21	5
Nausea	23	6	22	1	28		15	0	32	3
Vomiting	16	6	17	1			12	0	24	3
Diarrhoea	43	12	53	7	63	2	17	1	55	11
Proteinuria							7			
Hypercreatininemia			41	1			46	<1	55	0
Hyperbilirubinemia							3	<1		
ALT levels					34	3	18	<1		
AST levels					49	3	21	<1		
Dermatological										
Mucositis	5	0	12	1	14		14	1	15	1
HSFR	30	12	51	16	52	15			27	5
Rash	40	13	32	4	35		25	<1	13	1

[a] RECORD1 trial was conducted for the 21% in second line patients and for 79% in following line patients.

grades, with 12% of those grades 3 and 4 [24]. Although the drug has shown other lower grade toxicities, skin toxicity remains the major problem of sorafenib. With respect to the possibility of onset of cardiotoxic events, the results of phase 3 registration study [25] showed an incidence of these events that do not appear particularly marked. This trial was carried out in a highly selected patient population; however, a prospective study on the cardiac safety of the drug did not show any difference before and after treatment with sorafenib [26].

2.5. Bevacizumab plus interferon

The treatment of patients with mRCC with the combination bevacizumab plus IFN is restricted to the first line [27]. The analysis of the profile of drug-related adverse events identifies hypertension, thromboembolism, bleeding, and proteinuria [27]. These events have also been observed when using the drug in other tumour types [28]. Therefore, the use of bevacizumab should be avoided in patients with a history of haemorrhage or thromboembolism and in those with uncontrolled hypertension. This could lead to the hypothesis that the combination bevacizumab plus IFN should not be the treatment of choice for this patient population.

2.6. Everolimus

Since the pivotal trial for registration was undertaken in patients with mRCC progressing after one or more therapy lines, everolimus was approved for the treatment of patients who relapsed after previous and/or repeated treatments with VEGF inhibitors [29,30]. Due to the particular mechanism of action of mTOR inhibitors, the toxicities of everolimus are characterized by impairments of metabolism and the development of infections. Preclinical investigations established that the mTOR pathway is strictly related to metabolic sign modulation, and an activation of this path results in an increase of glucose uptake, glycolysis, and lipid synthesis [31]. Similar effects were observed in clinical studies of both everolimus and temsirolimus [24]. Therefore, when patients display uncontrolled metabolic alterations at baseline, the actual need to use mTOR inhibitors should be

carefully evaluated. In addition, when used at different doses and schedules in settings other that oncology, it was also shown that the mTOR pathway plays an important role in the modulation of the immune response resulting in immunosuppressive activity, which could explain the possible onset of interstitial pneumonia [32]. Data following the treatment of patients with RCC with everolimus report a 37% incidence of infections of any grade and 10% of grades 3 and 4 [28]. Data coming from a retrospective analysis carried out on 237 patients treated with everolimus report a 13.5% incidence of clinically diagnosed pneumonia [9,33]. It must also be kept in mind that latent infections such as those related to the hepatitis B and C viruses could endanger patients treated with everolimus [24]. Consequently, special caution should be used when treating elderly patients (almost 50% of all RCC patients [34]) or those with impaired immune function.

2.7. Pazopanib

Pazopanib, an oral TKI, received EMA approval for the first-line treatment of patients with advanced RCC and for those relapsed from cytokines [35]. Data from clinical trials indicate a rate of dose reductions and treatment interruptions ranging from 36% to 42% [35]. In the non-inferiority phase 3 study vs. sunitinib (COMPARZ trial), treatment withdrawals of 24% of patients were recorded [36]. The overall safety profile of pazopanib appears similar to that of other drugs with antiangiogenic activity, with the exception of a higher incidence of liver enzyme impairment, hypertension, and hair discoloration [37]. The rate of hypertension observed with pazopanib accounted for 40% [35]. In addition, because in the pivotal registration phase 3 study vs. placebo about 10% of patients included in the experimental arm complained of at least one cardiac and/or vascular adverse event [9,36], EMA required a special post-marketing programme aimed at monitoring the cardiovascular risk induced by pazopanib [38]. Regarding liver toxicity, the drug received a black-box warning by the US health authorities after fatal cases of liver insufficiency were observed [39]. Therefore, in addition to not being recommended in patients with severe liver insufficiency, close monitoring is also suggested of patients with normal liver function at baseline. It recently emerged that the combination of pazopanib with cholesterol synthesis inhibitors such as statins (particularly simvastatin) seems to further increase alanine aminotransferase serum levels [35].

2.8. Axitinib

Axitinib was approved by the EMA for the treatment of patients with mRCC who relapsed after a previous therapy line consisting of sunitinib or cytokines [40]. Data concerning toxicity of the drug came from a pivotal registration phase 3 trial (AXIS study), and were further collected in the recent AGILE 1051 study, so far published only in abstract form [41,42]. In the AXIS study, patients previously treated with cytokines and sunitinib were compared with those on sorafenib, selected as a reference drug for second-line treatment [41]. The peculiarity of this study lies in the fact that no fixed dosage for axitinib was established. Starting from an initial dose of 5 mg, if no particular and serious toxicity was observed, an escalation to 7 mg was applied after 2 weeks, and then administering a final dose of 10 mg was considered [39]. With this approach, the most important adverse events were diarrhoea (55% all grades; 11% grades 3–4), hypertension (40% all grades; 16% grades 3–4), and fatigue (39% all grades; 11% grades 3–4) [41]. A similar approach was tested during the early phases of development of sorafenib, but led to poor results. Only by applying the data of this study to clinical practice, it would be possible to verify whether this escalation strategy is helpful, and whether high rates of grade 3–4 hypertension could represent a limiting factor.

3. "GOAL": an inverse decision-making algorithm for daily clinical practice

Considering the most important serious toxicities potentially associated with the use of targeted agents in mRCC, and crossing them with the more important comorbidities or clinical conditions of treated patients, in our experience about 1 out of 3 patients could be defined as "no-preferred", i.e. not preferentially suitable for a given agent. Concerning patients aged over 65 or 70 years, in absence of head-to-head studies comparing the safety of different targeted agents in this population, current evidence seems to indicate that elderly patients do not experience more frequent or severe toxicity than younger subjects [43]. However, a continuous surveillance of patients with important history of comorbidities (mainly metabolic and cardiovascular) or at risk of drug interactions (a more frequent condition in aged patients) should be recommended [43]. A complete list of drug-related main toxicities is reported in Tables 1 and 2, while potential contraindications to treatment and potential drug alternatives are reported in Table 3. Of note, "GOAL" aims to identify the worst drug(s) for a given patient profile, and not to suggest the most suitable treatment.

Of course, the interest of this inverse algorithm, clearly reported in Table 3, is related to the potential selection of a single patient with specific comorbidities, and to the identification of agents with comparable efficacy data and indications but different toxicity profiles: an important "grey area" with overlapping treatment indications where the "GOAL" algorithm could make easier a proper drug indication. A limit of the "GOAL" is that it is based on registrative trials that are di per se biased. In fact phase 3 studies often enrol patient populations that are different from that observed in everyday clinical practice. Therefore, an update of this algorithm with data deriving from EAPs or post marketing surveillance studies would be important when such data will be available.

Table 3
Suggested inverse algorithm in decision making for first and later lines of therapy in RCC.

Comorbidity or relevant clinical condition	Potential polarizing toxicity	Drug to avoid 1st line	Drug to avoid 2nd line or later
Serious pre-existing cardiac problems	Serious cardiotoxicity	*sunitinib* *pazopanib (?)*	*sunitinib*
Serious liver impairment	Liver toxicity	*pazopanib*, *sunitinib*	*pazopanib*, *sunitinib*
Uncontrolled hypertension	Hypertension	*sunitinib-* *bevacizumab+ifn*	*axitinib*
Uncontrolled diabetes and dyslipidemia	Metabolic toxicities	–	*everolimus*
Important respiratory tract diseases (e.g. COPD)	Pulmonary toxicity	–	*everolimus*
Viral latent infections (e.g. active HBV, HCV infections)	Viral reactivation	–	*everolimus*
Some job situations	Dermatological toxicity	*sorafenib*	*sorafenib*
History of thromboembolisms or hemorrhages	Vascular events	*bevacizumab+ifn*	–

4. Discussion and conclusions

When the new targeted agents first came into the therapeutic armamentarium for the treatment of mRCC, the urgency to meet the medical needs of consumers (both patients and physicians), on the one hand, and the immediate need of investment remuneration and commercial competition among the pharmaceutical companies, on the other hand, led to early utilization with only incomplete scientific evidence [44]. Although clearly approved by the regulatory authorities, this evidence was still based on limited or not fully explored evidence-based recommendations. Indeed, data from phase 3 clinical trials, mostly aiming at demonstrating efficacy and safety in highly selected patient populations, somehow disregarded the role and the weight of particular comorbidities, thus preventing physicians in clinical practice from fully administering the recommended doses and schedules to the global patient population. Consequently, treatment decisions have often depended on the ability of each physician to identify the most appropriate agent for a given patient. When analysing the pivotal phase 3 clinical trials carried out for the registration of the most important targeted agents currently used for the treatment of advanced RCC, it immediately appears that most of these trials did not consider different patient characteristics and/or an important subgroup of patients was frequently excluded or not fully represented. Paradigmatic, in this regard, seems to be the pivotal trial with sunitinib that excluded patients with uncontrolled hypertension or clinically significant cardiovascular events in the last 12 months before treatment, as well as the phase 3 trial of sorafenib that excluded patients with impaired liver, pancreatic, and renal function [8,9]. Collectively, such situations resulted in a sort of gap between the results of clinical trials and daily practice, and new evidence and experience appeared required to fill this gap.

The large experience subsequently gathered by physicians now allows a more correct analysis of toxicities characterizing each of the six therapeutic agents presently available for the treatment of mRCC. On the basis of different patient clinical profiles, this might pave the way for new guidelines for both first- and second-line therapy. As the matter now stands, the question arises of whether it is still correct or convenient to use therapeutic approaches based on the algorithms so far proposed, that place at the forefront the value or the importance of the efficacy of different drugs. Keeping in the statement by Ryan's, who said that all the targeted agents so far available are more or less similar in terms of efficacy, is it still acceptable to make a fine distinction between first- and second-line treatment while placing the drug toxicity in subordinate position as the unavoidable price to pay? If this is true – and a number of clinical experiences seem to support this – we suggest that the therapeutic approach for mRCC patients could be improved by turning to a reverse one based on the clinical profile of each single patient, characterized by different and more or less severe comorbidities, thus preventing them from being treated with a particular agent.

In case of patients for whom different therapies are equivalent, the new approach (Table 3) allows to select the best therapy which presents the most limiting toxicity, therefore improving treatment compliance. Indeed, since each patient represents the focal point for any therapeutic approach, ethical principles suggest avoiding the toxic effects of a given drug in a patient not considered suitable for that treatment. Conversely, the deep evaluation of patient comorbidities could be a valid way to maintain a good efficacy profile or even attain better results (e.g. increased probability of maintaining sufficient drug dose levels). However, additional evidence is necessary to cover all the 'grey areas' still remaining undetermined at the light of available evidence, such as the potential existence of 'class toxicities' like hypertension for TKIs. The achievement and maintenance of a good efficacy profile in order to maximize treatment outcomes should be our daily ethical "GOAL" in treating advanced kidney cancer.

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Biography

Sergio Bracarda is currently the Director of Medical Oncology, Department of Oncology, Istituto Toscano Tumori (ITT), Azienda USL8. Ospedale San Donato, Arezzo. Dr. Bracarda graduated from the School of Medicine, University of Perugia in 1986, where he also received the Italian Anti-Tumour League Award for his thesis for tumour prevention. Following this, he firstly specialized in medical oncology at the "Sacro Cuore" Catholic University of Rome, Italy, and following in urology at the University of Perugia, where he later became a Resident in the Department of Medical Oncology. Prior to taking up his current position, Dr. Bracarda was Junior and following Senior Registrar/Consultant Oncologist, in the Department of Urology of Perugia University, then Senior Oncologist and Section Chief of Oncology-Urology in the Medical Oncology Division, Policlinico Hospital, Perugia.

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