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Critical Reviews in Oncology/Hematology 89 (2014) 386–393

CRITICAL REVIEWS IN
Oncology
Hematology
Incorporating Geriatric Oncology

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

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Accepted 18 September 2013

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

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http://dx.doi.org/10.1016/j.critrevonc.2013.09.002

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

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