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Combination or sequencing strategies to improve the outcome of metastatic renal cell carcinoma patients: A critical review☆

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Abstract

The introduction of novel anti-angiogenic therapies has greatly improved the outcome of patients with metastatic renal cell carcinoma (mRCC). The use of these therapies in combination or sequentially is proposed to provide greater efficacy.

We have reviewed completed and ongoing clinical trials in mRCC that have reported efficacy and/or safety data of novel therapies used in combination or sequentially.

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Bevacizumab appears to be a useful partner when combined with interferon (IFN), while controversial results have been reported when combined with temsirolimus and everolimus. Other combinations appear to have unacceptable tolerability or require dose or schedule optimization. Sequencing data provide a clear indication that multiple lines of treatment may extend survival. The 'ideal' sequence, however, is still unknown.

In conclusion, novel therapies used in combination or sequentially have potential to provide optimised treatment and patient outcomes in mRCC. The results from ongoing/planned trials are expected to help shape future therapy.

Keywords: Angiogenesis inhibitors; Combination; Cytokines; Renal cell carcinoma; Sequencing

1. Introduction

Until recently, cytokine therapy provided the mainstay of treatment for metastatic renal cell carcinoma (mRCC), with interferon (IFN) and interleukin-2 (IL-2) providing clinical benefit based on response rates of <20% and median overall survival (OS) of ∼13 months [1]. However, the therapeutic benefit of cytokines was restricted to a limited number of patients [2], making new therapies a significant requirement in mRCC.

Treatment of mRCC has undergone a major transformation over the past 5 years with the emergence of novel targeted therapies proven to provide benefit in mRCC (Table 1). These include the multitargeted tyrosine kinase inhibitors (TKIs) sorafenib [3], sunitinib [4], and pazopanib [5], the humanised anti-vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab [6], and the mammalian target of rapamycin (mTOR) kinase inhibitors temsirolimus [7] and everolimus [8]. A number of other therapies are in late-stage clinical development, including the multitargeted TKI axitinib and tivozanib.

These therapies are generally classified as having anti-angiogenic activity through inhibition of VEGF pathway activity, but have different mechanisms of action: bevacizumab directly inhibits VEGF, whereas TKIs and mTOR inhibitors indirectly inhibit VEGF through targeting other factors.

The focus on VEGF is based on its role as the key mediator of tumor angiogenesis, which is essential for the growth and proliferation of most solid tumors [9,10]. Moreover, VEGF is particularly important in RCC because the *von-Hippel-Lindau* (*VHL*) tumor suppressor gene is inactivated in most patients with clear-cell carcinoma, the most common form of RCC [11], which leads to VEGF up-regulation.

Despite improvements in survival due to the introduction of these novel therapies, mRCC is still widely regarded as incurable. Therefore, ensuring that patients obtain optimal benefit from the available therapies to maximise survival is essential. Treatment needs to be tailored to the individual patient and the use of all therapies during the course of a patient's treatment may be a beneficial goal. However, few clinical trials have been conducted to specifically test the activity of these novel agents in combination or when used sequentially, an area in which there is considerable interest. While improvement in efficacy is clearly an important outcome for physicians and patients, tolerability is also another key issue. This paper reviews current data supporting combination and sequencing strategies and explores future perspectives.

2. Mechanism of action

Understanding the mechanism of action of therapies for the treatment of mRCC is important when considering combination and sequencing strategies.

2.1. Immunotherapy

IFN, the standard of care treatment for several decades, is believed to exert direct and indirect antitumor effects that appear to be dose-dependent [12]. Higher doses induce direct cytotoxic or anti-proliferative effects on tumor cells, while lower doses of IFN may stimulate the immune system or inhibit angiogenesis [13].

IL-2, the other commonly used cytokine in cancer therapy, acts by mainly stimulating CD8+ cytotoxic T lymphocytes and natural killer cells [14], although other mechanisms that are dose- and schedule-dependent have been proposed, including cell cycle perturbation [15], or the production of reactive oxygen species [16,17].

2.2. Molecularly targeted agents

The novel therapies available for mRCC do not have direct cytotoxic effects but inhibit one or more pathways, usually activated in RCC, and that are essential for tumor growth (Fig. 1).

Bevacizumab is a monoclonal antibody that binds to the VEGF ligand with high specificity and neutralises its activity [18].

Sunitinib, sorafenib and pazopanib are small molecules that inhibit multiple kinase receptors. These agents are non-specific and have the potential to interact with a large number of different ubiquitously expressed receptor-protein kinases with varying degrees of inhibition; the number of receptors inhibited by each of these drugs, as well as the degree of affinity for these receptors [19] – with potential implications in terms of activity and safety – could probably differentiate pazopanib (and especially newer molecules such as tivozanib or axitinib) from sunitinib and sorafenib.