Nivolumab in renal cancer

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Abstract
Renal cell carcinoma (RCC) is a chemoresistant tumor, characterized by a poor response and lack of survival benefit with conventional cytotoxic agents. Furthermore, the complexity and heterogeneity of RCC limit the biologic targets for novel agents to manage RCC. Expression of the multiple drug resistance (MDR) protein (ATP-binding cassette P-glycoprotein) is increased in RCC, while the Von Hippel Lindau protein is mutated or silenced in approximately half of sporadic RCC, resulting in high levels of hypoxia inhibiting factor (HIF) and the activation of several genes codifying growth factors and growth factors receptors, such as vascular endothelial growth factor (VEGF), platelet-derived growth factor B (PDGF-B), and transforming growth factor alpha (TGFα). Consequently, immunodrugs targeting pathways related to these proteins have been evaluated for the management of metastatic RCC (mRCC). This review provides an overview of drugs that have been evaluated or are under investigation for the treatment of mRCC, including the multi-tyrosine kinase inhibitors (TKIs) sunitinib, pazopanib, axitinib, the mammalian target of rapamycin (mTOR) inhibitors everolimus and temsirolimus, and nivolumab, which targets the programmed death-1/programmed death-ligand 1 (PD-1/PD-L1) pathway. Promising results have been obtained with nivolumab, alone or in combination with TKIs such as sunitinib and pazopanib, and with ipilimumab, an immune checkpoint inhibitor which acts on the CTLA-4 pathway. Although much progress has been made, research with these and other agents is ongoing, and there is a need to identify makers of response to "tailor" the most suitable therapy, or sequence of therapies, to the individual patient, with the aim of improving outcomes and reducing unneeded toxicity.

Key words: renal cell carcinoma, multi-tyrosine kinase inhibitors, mTOR inhibitors, nivolumab, combination therapy

Introduction

Renal cell carcinoma (RCC) has always been considered a chemoresistant tumor, related to a poor response rate and lack of clear survival benefit from therapy with cytotoxic agents. The biological features underlying this unfavorable clinical outcome involve increased expression of the multiple drug resistance (MDR) protein (ATP-binding cassette P-glycoprotein), which can expel drugs out from tumor cells, reducing their cytotoxic efficacy [1]. Von Hippel Lindau protein is mutated or silenced in about half of sporadic RCC: cancer cells lacking this protein, which usually turns cell replication off in the presence of oxygen, produce high levels of hypoxia inhibiting factor (HIF), then activating the transcription of several genes, almost all codifying growth factors and growth factors receptors, such as vascular endothelial growth factor (VEGF), platelet-derived growth factor B (PDGF-B), and transforming growth factor alpha (TGFα) [2-4]. For these reasons, new agents targeting pathways related to these proteins have been evaluated for the management of metastatic RCC (mRCC). Sunitinib was the first multi-tyrosine kinase inhibitor (TKI) approved in 2006, improving the survival of patients suffering from mRCC compared to interferon alpha (IFN-α), the standard of care until then [5]. Later, pazopanib and axitinib were approved for first and second line therapy, respectively [6, 7]. These molecules share a similar mechanism of action, which consists of inhibition of several tyrosine kinase receptors (RTKi), mostly VEGFR and PDGFR: these proteins are steadily activated in renal cancer cells, at least as long as new mutations arise in the tumor ge-

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nome, turning off the addiction of cancer cells to these oncogenic pathways, and so developing resistance to these drugs. The phosphatidyl-inositol-3 kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway proved to be another molecular target of clinical interest in mRCC. Indeed, mTOR plays a pivotal role in many cellular "devices", as well as regulating the synthesis of HIF and VEGF [8, 9]. mTOR inhibiting agents, such as everolimus and temsirolimus, are currently approved for second line use after TKI therapy failure, and for untreated patients with poor-intermediate prognosis renal tumors, respectively [10, 11]. Therefore, efforts have been made to "open" new therapeutic scenarios, and the most interesting one represents a kind of "back to the past" journey, to the time when the only therapy tools were the immunostimulating agents, such as interleukin 2 (IL-2) and IFN-α, which were, until the TKI era, the standard of care for mRCC [12].

Return to the past: back to immunotherapy

Until the middle of the 2000s, few therapeutic options were available in mRCC management, and these were mostly represented by IL-2 and IFN-α. Unfortunately, these agents are burdened by excessive toxicity and limited effectiveness [13, 14]. An interesting attempt was made to "merge" therapy with anti-VEGF agents, of which at that time there was only bevacizumab, a humanized antibody directed against circulating VEGF, and IFN-α, but even this combination therapy did not significantly improve survival for patients with mRCC [15]. Nevertheless, a renewed interest in this pharmacological approach arose with the advent of a new class of immunotherapy agents, targeting programmed death-1/programmed death-ligand 1 pathway (PD-1/PD-L1). In fact, as well as melanoma, renal cancer shows a massive infiltration of immune cells, consisting mostly of T cells, natural killer (NK) and dendritic cells: these cells cannot exert their functions because of being induced to a state of anergy [16], and PD-1/PD-L1 was shown to have a preeminent role in this. As stated, melanoma and RCC share similar features, such as great infiltration of immune cells and extensive chemoresistance, and these reasons underlie the clinical interest in drugs targeting immune checkpoints. CD4+/CD8+ T cells, NK cells, B cells and monocytes express PD-1 on induction of several cytokines, such as IL-2, IL-7, IL-15 and IL-21 [17, 18], and patients whose tumors contain PD-1 positive tumor-infiltrating lymphocytes (TILs) having a poorer outcome than patients with PD-1 negative lymphocytes [19]. On the other hand, PD-1 ligands, namely PD-L1 (also called B7-H1), and PD-L2 (also known as B7-DC), are expressed not only by several immune-regulating cells, but also by cancer cells: PD-L1 expression has been detected in up to two-thirds of clear cell renal carcinomas, with significantly worse cancer-specific survival of patients suffering from PD-L1 overexpressing disease. Furthermore, PD-L1-enriched TILs infiltrating primary RCC correlate with advanced stage and shorter progression-free survival (PFS) [20, 21], thus providing the biological foundations for PD-1/PD-L1 blockade in order to increase the reactivity of the host immune system against the tumor.

Targeting the PD-1/PD-L1 pathway

Nivolumab is a fully humanized antibody directed against PD-1 which acts by breaking the PD-1/PD-L1 interaction, so preventing the latter from "turning off" TILs and other immune cells, which otherwise would be induced into a state of anergy [22, 23]. Because of its high affinity to the target, nivolumab rapidly disappears from the bloodstream, nevertheless persisting in occupying PD-1 receptors for up to 3 months after infusion [24]. Since the catabolic pathway of nivolumab is the same as that of regular immunoglobulin G (IgG), no dose adjustment is needed in patients with mild or moderate renal impairment or mild hepatic impairment; limited data are available from patients with severe renal or moderate-to-severe liver impairment [25]. After the encouraging results of phase I trials recruiting patients with metastatic melanoma, non-small cell lung carcinoma and RCC [26, 27], a phase II trial showed median PFS and overall survival (OS) of 4.2 and 24.7 months, respectively, for patients with mRCC treated with nivolumab at a dose of 10 mg/kg, after having received no more than three previous therapy lines with at least one VEGFR TKI [28]. More recently, the CheckMate 025 trial, an open-label, phase III study, compared nivolumab 3 mg/kg every two weeks with everolimus 10 mg/day in patients with mRCC who progressed on at least one TKI therapy line (no more than three previous treatments). Nivolumab-treated patients had a longer OS compared with everolimus (median OS 25 *vs* 19.6 months; hazard ratio [HR] for risk of death 0.73), with no difference in terms of PFS (4.6 *vs* 4.4 months). Of note, a subgroup analysis of patients with OS and PFS longer than 6 months revealed a statistically significant difference in PFS between patients who received nivolumab and those who took oral everolimus: nivolumab median PFS 15.6 months *vs* 11.7 months for the everolimus group (HR for progression risk 0.64), irrespective of PD-L1 expression [29]. At the 2016 Genitourinary Cancers Symposium, authors presented a subgroup analysis further supporting the use of nivolumab as a new standard of care in patients with

previously treated mRCC, regardless of Memorial Sloan Kettering Cancer Center (MSKCC) and International Metastatic Renal Cell Carcinoma Database Consortium (IMRCC) prognostic score, number or duration of prior therapies (sunitinib, pazopanib, or IL-2 therapy), age and sex, with a lower incidence of grade 3 or 4 treatment-related adverse events (AEs). Of interest, patients with poor MSKCC risk seem to benefit more from nivolumab than everolimus (HR 0.48, 95% confidence interval 0.32-0.70) [30].

In a large expanded access program (EAP) that enrolled 389 patients across 95 Italian sites, clear-cell histology was the most common (92% of cases), and half of the patients had bone metastases. Only 18 patients (5%) discontinued treatment because of an AE. The disease control rate (DCR) was 48% (17% objective response; one complete and 66 partial responses), while 121 patients (31%) had stable disease [31]. Brain metastases occur quite rarely in renal cancer (approximately 10% of mRCC) and the ability of monoclonal antibodies to cross the blood-brain barrier (BBB) is a hot topic. Furthermore, the administration of steroids often becomes necessary due to neurologic symptoms triggered by metastatic lesions and peripheral edema, thereby decreasing the efficacy of immunodrugs. Fifty-three patients with mRCC and brain metastases from GETUG-AFU 26 (Nivoren) Study were treated with nivolumab after having received previous mTOR inhibitor as systemic therapy. Five had had previous brain surgery and 17 brain radiation. Forty-four patients were evaluated for response on brain metastases, with 10 achieving an objective response (response rate 23%), while 21 had locally progressive disease. Nevertheless, neurologic symptoms required steroids administration in 15 patients [32].

Combination therapy: can efficacy be improved?

As has been shown in other malignancies, therapies combining multiple drugs have been shown to be more effective, resulting in a synergistic, rather than additive, effect compared with monotherapy alone, although with an associated increase in the incidence of AEs. In this regard, nivolumab has been administered both in combination with TKIs, such sunitinib, and pazopanib and with ipilimumab, another immunotherapy agent acting on the CTLA-4 pathway. The biological rationale underlying the association of immune checkpoint inhibitors with TKIs rely on the ability of the latter to modulate the immune microenvironment, with a decrement of circulating regulatory T cells (T-regs) and myeloid-derived suppressor cells [33, 34]. In a first-line treatment-naïve setting, the nivolumab plus pazopanib combination was associated with dose-limiting liver toxicity, while the nivolumab plus sunitinib combination was well tolerated to a higher nivolumab dose. Although both drugs proved to be effective when combined with nivolumab in terms of encouraging antitumor activity, data from randomized trials are needed to evaluate the efficacy of combination *versus* monotherapy [35].

As expected, further studies were designed to assess combinations of TKIs and other anti-PD-1 agents, such as axitinib plus pembrolizumab [36] or axitinib plus anti PD-L1 agents, such as avelumab [37]. These latter agents, when administered together, did not show an increased incidence of AEs compared with single agent therapy, with two deaths during the study period (1 disease-related and 1 treatment-related). AEs led to discontinuation of avelumab in 5 patients (9.1%) and axitinib in 4 patients (7.3%). The overall response rate was 54.5%, consisting of two complete responses and 28 partial responses [37].

As already noted, multiple immune checkpoint inhibition is also an attractive option. The CheckMate 016 phase I trial combined nivolumab with ipilimumab in patients with mRCC with encouraging results [38]. Therefore, this combination is under evaluation compared with sunitinib monotherapy in the first-line setting in a phase III trial (CheckMate 214; ClinicalTrials.gov identifier: NCT02231749). Combination of antibodies targeting PD-L1 and circulating VEGF have also been investigated. Atezolizumab/bevacizumab showed a decreased risk of disease progression in previously untreated patients with mRCC, although not statistically significant, compared to sunitinib. Of note, the HR for PFS decreased concomitantly with the percentage of PD-L1-expressing cells (HR 0.87 for tumors with ≥1% and <5% PD-L1 expressing cells, HR 0.5 for ≥5% and <10% and HR 0.23 for tumors expressing PD-L1 in ≥10%). Finally, there was a statistically significant risk reduction for disease progression in patients with high T-effector count [39].

How can the best drug for the best patient be chosen?

Unlike some malignancies, for which we have the right drug for the right neoplastic aberration, RCC lacks a singular oncogene addiction that can form the target for immunotherapy agents. Nevertheless, the choice of patients who could take the most advantage of immunodrugs is definitely an unmet need. Already known from the use of IFN-α and IL-2 is that patients treated with these immunostimulating agents benefit from a longer OS after

undergoing nephrectomy [40], although some evidence suggests that surgical removal of the primary tumor may result in a decrease of PD-1 and PDL-1 expression, thus decreasing the targets for immunodrugs [41, 42]. Therefore, clinicians are looking for possible predictive markers of response, in order to "tailor" the most suitable therapy for each patient, preventing unneeded toxicity and reducing costs. PD-L1 expression on cancer cells seems to affect outcome and response to PD-1 pathway inhibitors [43, 44], but, importantly, the activity of TKIs (either pazopanib or sunitinib) was reduced in patients whose tumors overexpressed PD-L1, resulting in significantly shorter OS [45]. In addition to PD-L1, the presence of >300 intratumoral CD8+ T cells also proved to be a marker of poor prognosis [45]. This has been confirmed by other authors. The detection of high counts of CD8+ T cells close to the neoplastic invasion margin, along with the presence of immune cells expressing PD-1 and cancer cells expressing PD-L1, is evidence of immune-editing that the cancer exerts on the microenvironment, "turning off" T cells by inducing them into a state of anergy [46], and thus preventing them from properly triggering an immune response. In addition to PD-1/PD-L1 expression and infiltration of tumor by T cells, levels of genomic aberrations correlate with response to immunodrugs. Indeed, the more mutations cancer cells accumulate in their genomes, the more they are likely to express aberrant, and therefore immunogenic, proteins. Loss of DNA mismatch repair genes, such as MLH1 and MSH2, makes RCC a genetically unstable malignancy, leading to an increased PD-L1 expression on RCC cells and concomitant PD-1 expression by TILs [47], but further clinical evidence is needed to support a strong correlation between these features and effectiveness of PD-1/PD-L1 antibodies. Histology does not seem to help us in recognizing patients more likely to benefit from immunodrugs; indeed, nivolumab has also proved to be effective in non-clear cell renal cancers, such as papillary histotype, with a 29% partial response rate and 19% of stable disease [48].

Is immunotherapy more toxic than TKIs?

The excellent safety profile of nivolumab in patients with advanced RCC has been highlighted in many studies [24, 27, 28], with a lower incidence of treatment-related side effects than everolimus [29]. In the CheckMate 025 trial, almost 80% of patients treated with nivolumab and 88% of everolimus patients experienced AEs of any grade, although grade 3 or 4 AEs were reported in only in 19% and 37% of patients, respectively, with the most common AEs consisting of fatigue (33%), nausea (14%), and pruritus (14%) among patients undergoing nivolumab, and fatigue (34%), stomatitis (29%), and anemia (24%) among patients who received everolimus. This led to a slightly greater percentage of drug discontinuation with everolimus compared to nivolumab (13% *vs* 8%). Given its distinguishing mechanism of action, nivolumab is associated with immune-mediated adverse reactions which, although rare, include immune-mediated pneumonitis, colitis, hepatitis, nephritis, and thyroiditis [25, 28]. An intriguing issue is obviously the change of therapeutic index in combination strategies. Adding a VEGF-TKI to nivolumab resulted in an increased incidence of grade 3-4 AEs (82% of nivolumab plus sunitinib treated patients) with alanine aminotransferase (ALT) elevation and hypertension in 18%. Toxicity-related therapy discontinuation was necessary in one third of patients. The combination of nivolumab and pazopanib led to grade 3-4 liver toxicity in 20% of subjects, with ALT and aspartate aminotransferase (AST) elevation which, in addition to grade 3-4 fatigue in 15%, was the reason for stopping recruitment into this arm [35]. Similar results were found with the pazopanib/pembrolizumab combination, with concomitant therapy burdened by significant hepatotoxicity. Conversely, the sequential schedule of pazopanib for nine weeks, followed by pembrolizumab plus pazopanib, showed reduced hepatotoxicity, with preliminary signs of efficacy but overall limited tolerability [49].

For patients undergoing nivolumab/ipilimumab in combination, grade 3-4 AEs were reported in 43% of patients, mostly elevated lipase and ALT (16% and 11% respectively), diarrhea (9%), and colitis (5%). Treatment discontinuation was necessary for 16% of patients [38].

Conclusions

Since the early 1990s much progress has been made in the understanding of the biology of RCC, coupled with outstanding results in terms of survival and quality of life. Combination therapy in this malignancy is a hot topic. Acting on multiple targets, both immune checkpoints and VEGF/mTOR pathways could be an effective strategy in order to better (and for longer) control disease progression, although the cost to pay for these improvements is an increased incidence of AEs. Furthermore, the importance of the correct sequencing cannot be disregarded, which will need to be defined by future clinical trials. The complexity and heterogeneity of the cancer slow down our progress, but also provide new tools and therapy options. Therapy "tailored" to fit individual characteristics, both of the host and the cancer, represents a real challenge, and future perspectives will see

proper use of these opportunities, by identifying patients most likely to benefit from each specific drug.

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Conflicts of Interest

The Authors declare there are no conflicts of interest in relation to this article.

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