Checkpoint Blockade – a New Treatment Paradigm in Renal Cell Carcinoma

Viktor Grünwald

Clinic for Hematology, Hemostasis, Oncology and Stem Cell Transplantation, Hanover Medical School, Hanover, Germany

Introduction

The medical treatment of renal cell carcinoma (RCC) has changed radically over the past decade. Previous treatment consisted of cytokine therapies and was associated with an overall survival (OS) of 13 months [1]. Targeted therapies have raised the bar to approximately 30 months in the metastatic setting [2, 3]. However, a ceiling effect has been reached with the current sequential use of vascular growth factor (VEGF) or mammalian target of rapamycin (mTOR) inhibitors. In order to further improve outcome, novel mechanisms of action have to be implemented in the treatment algorithm of RCC.

Quality of response has shown prognostic relevance for targeted therapies in metastatic RCC (mRCC). Superior outcome was detected in patients with any tumor shrinkage on targeted therapies, with an exceptional response in those with a tumor shrinkage of at least 60% [4]. This paves the way for novel concepts in mRCC trials, indicating that the enlargement of the fraction of patients with deep remission will improve survival. With the tyrosine kinase inhibitors (TKIs) currently available in the clinical setting, 25–31% partial or complete remissions were reported if used as first-line therapy [2]. In later lines of therapy, the objective response rate (ORR) is generally low and rarely exceeds 10% [5–7]. The prognostic role of the category of response with checkpoint inhibitors has not yet been defined. High-dose interleukin 2 (IL-2) was the first immunotherapy for which long-term response were reported when disease control was achieved upon treatment [8]. In this long-term follow-up, patients reporting partial or complete remission had favorable outcomes; however, disease stabilization also improved survival, albeit to a lesser extent. Despite its limitations, this report indicates the potential role of long-term tumor control which may be achieved with immunotherapies in the absence of continuous exposure to treatment. It is believed that a similar pattern may be seen with checkpoint inhibitors, but it is too early to draw any definite conclusions.

Keywords
Renal cell carcinoma · Kidney cancer · Immunotherapies · Checkpoint inhibition

Summary
Nivolumab is the first checkpoint inhibitor for the treatment of renal cell carcinoma (RCC), which is in line for approval in Europe. Despite its novelty in the treatment algorithm of RCC, it offers a whole new strategy of therapy management with safe applicability. The aim of this work was to review current data on checkpoint inhibitors in RCC and discuss future perspectives for this novel approach in RCC. A selective literature search was performed in the Pubmed database: Nivolumab is a first-in-class agent for the treatment of RCC, and its European label is anticipated for 2016. Contrary to many other agents, nivolumab was able to show a benefit in overall survival and health-related quality of life when compared to everolimus. Current trials focus on optimizing and expanding its use to metastatic RCC. In conclusion, nivolumab has already acquired a role in the treatment algorithm of RCC. However, which patient population derives the most benefit as well its optimal use in the treatment algorithm remain to be determined. A number of ongoing trials will provide novel insights and might help to untangle this novel network of therapy management for immunotherapies.
Based on these results, the quest for therapy optimization has led to the search for the optimal TKI in RCC. However, of those currently licensed, not one was able to significantly improve the outcomes. Recent studies have shown that the combination of everolimus and sunitinib (43%), for the first time indicating potential clinical benefit from a combination of 2 targeted agents. After a series of disappointing trials, a certain optimization of targeted therapies has been achieved, at least in the later lines of therapy.

More interestingly, therapies targeting immune checkpoints were recently added to the armamentarium of anticancer agents. Their clinical activity is diverse and has brought the clinical development of anticancer agents to a new level. Response to immunotherapies has been known to be persistent in a fraction of patients, with malignant melanoma taking the lead [11]. Based on the encouraging efficacy results from various indications [12–15], it is believed that similar effects will be detected in other malignancies.

A recent phase III trial with nivolumab reported positive results in previously treated mRCC patients, indicating superior efficacy and OS compared to everolimus [14]. For mRCC, this is the beginning of a new treatment era with room for improvement and development. Future concepts are being tested in clinical trials to either enhance or optimize the use of immunotherapies. This article reviews current data and future concepts in mRCC treatment.

The Prognostic Role of Checkpoints in RCC

Immune checkpoint ligand expression in the tumor or its environment has prognostic value in RCC. Programmed death receptor (PD)-1 regulates the T-cell effector axis and is activated via its ligands PD-L1 and PD-L2 [16, 17]. The prognostic role of PD-1 activation was explored in a number of studies. Among the first studies in patients undergoing nephrectomy, expression of PD-L1 was associated with a hazard ratio (HR) of 4.5 (95% confidence interval (CI) 1.94–10.56; p < 0.001) for death [18]. More recently, a meta-analysis of 6 studies revealed that PD-L1 expression is found in 24% of clear cell RCC and in only 11% of non-clear cell RCC specimens (p = 0.002) [19]. High PD-L1 expression levels were associated with risk of death (HR 1.81; 95% CI 1.31–2.49; p < 0.001), and this impact on prognosis was maintained in patients with metastatic disease. In addition, the analysis of a subgroup of patients from the COMPARZ trial confirmed these findings. PD-L1 positivity was found in 36% of patients with clear cell RCC, and high expression was associated with poor OS in patients treated with sunitinib or pazopanib (15.3 and 15.1 months compared to 27.8 and 35.6 months for PD-L1-negative disease) [20].

The dynamic changes of PD-L1 expression have rendered the assessment of its expression difficult in the clinic. Furthermore, variability of PD-L1 expression between primaries and metastases was seen in RCC. In a small cohort of 53 patients, a total of 11 (21%) cases was identified with discordant staining, but due to the small sample size this did not reach significance (p = 0.51) [21]. Furthermore, within a given lesion, PD-L1 expression was heterogeneous, underscoring the difficulties in PD-L1 detection.

Clinical Development

During the past decades, immune stimulation has been explored as a therapeutic avenue in mRCC. Cytokines were the cornerstone of such approaches and led to the approval of interferon alpha (IFN) and IL-2 in some parts of the world [22, 23]. ORR varied among patient cohorts tested and favored intravenous application in terms of efficacy (23% vs. 10%; p = 0.018) while failing to gain a survival advantage (17.5 vs. 13.0 months; p = 0.82) [23].

The largest trial for cytokine treatment in RCC involved 1,006 patients and explored IFN either with or without chemotherapy in the first-line setting. ORR and OS were 14 vs. 21% and 18.8 vs. 18.6 months (p = 0.55), respectively – not indicating any improvement through the addition of chemotherapy to IFN [22]. Overall, immune stimulation with cytokines only benefited a certain proportion of patients. Further improvement of cytokine therapy was sought by addition of targeted therapies in a number of trials but failed to achieve substantial benefit [24, 25].

Checkpoints are inhibitory regulators of immune cells, which are crucial to halt the natural immune response to an antigen [26]. The discovery that tumors employ certain checkpoints to escape the host’s immune surveillance has led to the development of a novel class of agents, which interfere with different checkpoints, thereby overcoming immune resistance.

After decades of exploration of immune stimulatory agents in clinical trials, checkpoint inhibitors were identified as key regulators of the tumor immune escape. Ipilimumab was the first-in-class checkpoint inhibitor inhibiting cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), developed in the setting of malignant melanoma [27]. Its ability to induce T-cell activation was associated with long-term responses in 21% of patients with malignant melanoma [11]. Another checkpoint is PD-1 which halts the effector axis of the T-cell response to tumor antigens [26]. Its pharmacologic inhibition is thought to induce a higher rate of response in cancers. A direct comparison of pembrolizumab to ipilimumab confirmed this hypothesis through higher ORR, better OS, and a lower incidence of grade 3–5 events in malignant melanoma [15].

Checkpoint inhibitors in mRCC were studied in a number of phase I trials which included RCC as a subgroup only [17]. However, a steady ORR has been reported in these trials and has spurred clinical development in mRCC (table 1). Given the uncertainty with regard to optimal dosing with the use of monoclonal antibodies, a randomized phase II study was recently launched. 168 patients were randomly allocated to doses of 0.3, 2, or 10 mg/kg nivolumab while employing a pick-the-winner design for the evolution of the dose-response relationship [28] (table 2). The ORR remained similar among all dose levels (20, 22, and 20%, respec-
while progression-free survival (PFS) favored dose levels of at least 2 mg/kg (2.7, 4.0, or 4.2 months). Response was sustained in 45–75% of patients, favoring the 0.3 mg/kg group. Median OS varied between groups, ranging from 18.2 to 25.5 months, indicating potential benefit in previously treated mRCC patients. Tolerability remained good overall, and treatment-related grade 3/4 adverse events (AEs) were reported in 5, 17, and 13% according to dose increase, indicating a ceiling effect at higher doses.

Based on these positive findings, a phase III study (Check-Mate025) was launched, which included 821 mRCC patients who had received a maximum of 2 TKI [14]. The study compared nivolumab 3 mg/kg every 2 weeks intravenous with everolimus 10 mg once daily, with OS being the primary endpoint. The primary endpoint of this study was met, and OS compared favorably for nivolumab (25.0 vs. 19.6 months; HR 0.73 (95% CI 0.57–0.93)) (table 2). However, PFS failed to reach significance (4.6 vs. 4.4 months; HR 0.88 (95% CI 0.75–1.03)) while the ORR favored nivolumab (25 vs. 5%; p < 0.001). This trial built the foundations for nivolumab treatment in mRCC and also raised the questions of how it compares to TKI treatment and what the best population would be to use this novel agent in. Currently, no subgroup has been identified that would not benefit from nivolumab compared to everolimus. However, patients with high-risk features derived the largest clinical benefit, indicating its outstanding clinical activity in a very difficult to treat patient population.

**Future Approaches**

**Dual Checkpoint Blockade**

While CTLA-4 has a major role in the process of building up an immune response, PD-(L)1 inhibition acts on the effector axis. As a prerequisite for clinical efficacy of PD-(L)1 inhibition, T-cell activation has to be in place. Therefore, these 2 checkpoint inhibitors introduce activity to the immune system at different levels. It seems conceivable that a combination of both inhibitors may boost the immune response and thereby improve clinical activity. An early clinical trial investigated this novel approach in RCC for the combination of ipilimumab and nivolumab. Based on the success of this combination in melanoma [29], 2 different doses (1 and 3 mg/kg) were tested for both drugs [30]. While the combination of nivolumab and ipilimumab at 3 mg/kg each was deemed too toxic for further clinical development, the combination of nivolumab and ipilimumab at 1 and 3 mg/kg was explored in 2 cohorts of 47 patients each. Not surprisingly, the ORR were improved by the combination, irrespective of the chosen dose. Nivolumab at 3 mg/kg and ipilimumab at 1 mg/kg achieved an ORR of 38% and nivolumab at 1 mg/kg and ipilimumab at 3 mg/kg of 40%, clearly indicating improved activity compared to single-agent treatment with either of these drugs (table 3). While PFS of 7.6 and 11 months, respectively, was promising, follow-up of approximately 1 year was too short to report on median OS.

<table>
<thead>
<tr>
<th>Table 1. Phase I efficacy of checkpoint inhibitors in renal cell carcinoma (RCC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCC cohort/total, n</td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td>BMS-936539 [34]</td>
</tr>
<tr>
<td>Atezolizumab [36]</td>
</tr>
<tr>
<td>MDX-1106 [37]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2. Phase II or III trials with checkpoint inhibition in renal cell carcinoma (RCC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibition of</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Ipilimumab [38]</td>
</tr>
<tr>
<td>Nivolumab [28]</td>
</tr>
<tr>
<td>Nivolumab [14]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3. Combination studies of checkpoint inhibitors with or without targeted agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agent + Partner compound</td>
</tr>
<tr>
<td>--------------------------</td>
</tr>
<tr>
<td>PD-L1 + VEGF</td>
</tr>
<tr>
<td>PD-1 + CTLA4</td>
</tr>
<tr>
<td>PD-1 + TKI</td>
</tr>
<tr>
<td>PD-1 + TKI</td>
</tr>
</tbody>
</table>

aNivolumab 3 mg/kg + ipilimumab 1mg/kg only.
bPazopanib subgroup in previously treated patients only.

VEGF = Vascular endothelial growth factor; TKI = tyrosine kinase inhibitor.
For further development in mRCC, a balance between tolerability and efficacy had to be achieved. While delivering similar efficacy and survival, the 2 doses varied substantially with regard to the toxicity derived from ipilimumab. Doses of ipilimumab at 3 mg/kg in the combination were associated with a rate of 64% of grade 3/4 AEs, while the lower dose of 1 mg/kg maintained a rate of only 34%. At the highest dose of 3 mg/kg for both agents, grade 3/4 AEs were reported in 83%, indicating the low tolerability of this regimen. Hence, for further clinical development, nivolumab 3 mg/kg and ipilimumab 1 mg/kg was chosen and its first-line activity tested in the CA209–214 trial in mRCC. Results of this study are anticipated for 2018.

**Combination with TKIs**

Targeted therapies are a milestone in mRCC treatment and are based on agents with the highest single-agent activity in mRCC. Due to the distinct mechanism of action, the combination of VEGF-targeting agents with checkpoint inhibitors is thought to have the potential to improve clinical efficacy. Early clinical development has tested a number of combinations which are listed in table 3. Overall, encouraging clinical activity has been detected during different clinical trials. Similar to the dual checkpoint blockade, an increase in toxicity has been noted, with a particular focus on hepatic toxicity detected with sunitinib or pazopanib combinations. A total of 18 out of 53 patients (34%) had an alanine transaminase (ALT) increase of any grade, and 10 out of 53 patients (19%) had a grade 3/4 elevation of ALT with such a combination [31]. A total of 17 out of 53 patients (32%) discontinued either the TKI or both agents due to toxicity, among which renal and hepatic toxicity prevailed.

**Axitinib** is a TKI that compares favorably with regard to hepatic toxicity (11% ALT increase [32]) to pazopanib (60% ALT increase) or sunitinib (43% ALT increase) in previously untreated patients [2]. A recent phase I study indicated the suitability of its combination with pembrolizumab (table 3).

In contrast to the combination of nivolumab with a TKI, bevacicizumab and atezolizumab were associated with an ALT increase in 8% only [33], clearly indicating a different toxicity profile. Data from a randomized phase II study is awaited, and a phase III trial in mRCC is ongoing.

**Discussion**

Inhibition of the PD-1 axis is already a clinical reality in a number of malignancies. Single-agent checkpoint inhibition exerts relevant clinical activity in mRCC. Its generally good tolerability has led to novel therapeutic approaches combining it with various different agents to treat cancer. Despite their exquisite response rates, the overall benefit of combination therapies remains unknown, underscoring the necessity to identify the best way to maximize future immunotherapy. The high rate of toxicity seen with combinations demands novel approaches such as pulsed therapy, maintenance, or early switch in order to optimize efficacy and tolerability of this novel therapeutic approach in cancer. Future trials are warranted to exploit this relationship in immunotherapies, not only in mRCC but other entities also.

**Disclosure Statement**

The author received honoraria from GSK, Novartis, Bayer, Pfizer, and BMS, consultancy fees from GSK, Novartis, Pfizer, Mologen, and BMS, and reimbursement of travel expenses from Novartis, Pfizer, Bayer, and BMS.

**References**


CheckPoint Blockade in Renal Cell Carcinoma


