Clinical practice of renal cell carcinoma treatment with nivolumab

ABSTRACT

Nivolumab alike other immune checkpoint inhibitors has been intensively developed during the last decade. Kidney cancer is among the neoplasm in treatment of which we have accumulated the most experience regarding nivolumab. As improves our understanding of the mechanisms underlying specific cellular immune response, thus improves our understanding of the place the nivolumab holds among other therapeutic options. Recent years brought development of innovative immunotherapy combinations as a method for improving immunotherapy efficacy. This review aims at providing practicing oncologists with key aspects of renal cell carcinoma treatment with nivolumab.

Key words: kidney cancer, renal cell carcinoma; nivolumab, anti-PD-1, immunotherapy; checkpoint inhibitor

Introduction

Rare cases of spontaneous complete remissions due to potential immunological anti-tumour responses have been drawing the attention of researchers for centuries. Well-documented cases of attempts at inducing such response have been undertaken as early as in the 17th and 18th centuries. Back then, spontaneous remission was most commonly seen along with severe infection. Nineteenth century research led to the formulation of the first standardised therapies based on attenuated encapsulated bacteria [1]. However, it was only the developments in molecular biology in the second half of the 20th century that brought about the opportunity to develop a modern immunotherapeutic approach, with its rapid expansion during the last decade.

According to the Global Cancer Observatory report, in 2018 about 400 thousand new renal cell carcinoma (RCC) cases were diagnosed worldwide, with over 175 thousand RCC-related deaths [2]. The progress in RCC treatment seen in the 21st century is based on the understanding of RCC core pathomechanisms: induction of angiogenesis and deregulation of immune response (overactivation of innate inflammatory response with deficient adaptive immune response). Several new therapeutic approaches for advanced disease have been developed: inhibitors of vascular endothelial growth factor (VEGF)-dependent angiogenesis; inhibitors of mammalian target of rapamycin (mTOR) — an another protein involved in RCC pathogenesis; cytokines that induce adaptive response; and finally the immune checkpoint inhibitors — innovative particles that activate suppressed mechanism of antigen presentation and enable cytotoxic T-cell activity.


The presented article aims at providing practicing oncologists with current data regarding the activity and safety profile of nivolumab in the treatment of RCC as well as valuable insights into clinical aspects of immune response in the pathophysiology of RCC.

Immune system and carcinogenesis

The immune system plays an important and multifactorial role in the aetiopathogenesis of cancer. From
the one side, some aspects of immune response may promote carcinogenesis, enabling survival of cancer cells in a metastatic niche or leading to inefficient protein and energy metabolism. From the other side, the immune system is the most important defence line against cancer development.

We currently know that immune cells from myeloid and lymphatic lines, both present in direct tumour microenvironment as well as distant ones, are responsible for several characteristic traits of cancer called “hallmarks of cancer”. These arise through several feedback loops: stimulation of proliferation; resistance to antiproliferative signalling; evasion of cell death; stimulation of angiogenesis; local invasion and metastases formation; and escape from immunosurveillance (Table 1) [4]. Additionally, overactivation of nonspecific inflammatory response is an important driver of cachexia, one of the most common cancer complications.

Immunosurveillance and mechanisms responsible for evasion from it are among the key factors in oncology [5]. Adaptive antitumour immune response requires a difference in antigens between cancer and healthy tissue. These so-called neoantigens are released from the cancer cell and then captured and presented to the immune system by dendritic cells (DC). For proper functioning, DCs have to go through a process of activation and maturation, which enable expression of specific co-stimulatory factors required by naïve T cells (Tn). If a mature DC presents detected antigen within proper major histocompatibility complex (MHC) class I and II and with adequate co-stimulation, antigen-specific Tn are selected and activated. As a result, Tn differentiate and proliferate into cytotoxic (Tc) and memory (Tm) clones.

Activated Tc clone have to reach cancer tissue and infiltrate it. Cancer cell destruction requires Tc cell to recognize its specific antigen, presented through class I MHC, in the absence of additional signals supressing cytotoxicity (either by cytokines or immunosuppressive cell-membrane molecules present in the tumour microenvironment).

Destroyed cancer cells release new portions of neoantigens, again detected and presented by DC, closing the cycle of immune antitumour response (Fig. 1) [6]. Each cycle iteration may promote additional clones of Tc lymphocytes active against subsequent neoantigens, potentially resulting in more and more effective response.

It is well acknowledged that evasion from immunosurveillance through disruption of at least one part of the described cycle is a necessary condition for the cancer to develop. To achieve effective and persistent tumour control by the immune system — and therefore long-term remission — we have to facilitate closing of the cycle. This requires recognition of its weak spots and potential methods for strengthening them.

**Selected mechanisms of immunosurveillance evasion — clinical aspects**

Systematic review of mechanisms used by cancer to evade immunosurveillance surpasses the limits of this manuscript. An excerpt of this complex landscape, significant in terms of the immune feedback loop described above, is presented in Table 2. Analysis of the aforementioned mechanisms at each stage of cytotoxic antitumour immune response provide practical insights...
Figure 1. Cycle of immunological antineoplastic response (based on [6]). APC — antigen-presenting cells; DC — dendritic cells; Tn — lymphocytes T-naive; Tc — lymphocytes T-cytotoxic

Table 2. Mechanisms impacting different stages of immunosurveillance [6, 11, 34, 35]

<table>
<thead>
<tr>
<th>Stage</th>
<th>Mechanisms impairing immunosurveillance</th>
<th>Mechanisms promoting immunosurveillance</th>
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<tbody>
<tr>
<td>1. Cancer cell death — release of antigens</td>
<td>Low cell antigenicity (low TMB)</td>
<td>High cell antigenicity (high TMB, mutagens)</td>
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<tr>
<td></td>
<td>Non-immunogenic cell death</td>
<td>Immunogenic cell death</td>
</tr>
<tr>
<td>2. Neoantigen presentation</td>
<td>Immunosuppressive cytokines (IL-10; IL-4; IL-13)</td>
<td>Activating cytokines (TNF-α, IL-1, IFN-γ)</td>
</tr>
<tr>
<td></td>
<td>Low DC availability</td>
<td>PRR activation (DAMPs, PAMPs)</td>
</tr>
<tr>
<td></td>
<td>Suppressing cytokines — prostaglandins</td>
<td>Activating cytokines (IL-2; IL-12)</td>
</tr>
<tr>
<td></td>
<td>Availability and variability of Tn Treg</td>
<td></td>
</tr>
<tr>
<td>4. Migration of Tc</td>
<td>Chemokines engaging Treg and MDSC</td>
<td>Chemokines engaging Tc (CCL2; CCL3; CCL4; CCL5; CXCL9; CXCL10)</td>
</tr>
<tr>
<td>5. Tumour Tc infiltration</td>
<td>Angiogenesis (especially VEGF-dependent)</td>
<td>Adhesive particles (ICAM1, selectins)</td>
</tr>
<tr>
<td>6. Cancer cell recognition by Tc</td>
<td>Low cell antigenicity (low TMB)</td>
<td>High cell antigenicity</td>
</tr>
<tr>
<td></td>
<td>Decreased expression of MHC</td>
<td>Proper TCR expression</td>
</tr>
<tr>
<td></td>
<td>Low number of Tc clones</td>
<td>High affinity of TCR to antigen</td>
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<tr>
<td>7. Destruction of cancer cell by Tc and other immune cells</td>
<td>Immunosuppressive co-stimulation (PD-L1:PD-1; PD-L1:B7.1; MICA:MICB; BTLa; LAG-3)</td>
<td>IFN-γ</td>
</tr>
</tbody>
</table>

BTLa — B- and T-lymphocyte attenuator; CCL — CC class chemokine; CTLA4 — cytotoxic lymphocyte antigen-4; CXCL — CXC class chemokine; DAMPs — damage associated molecular patterns; IFN — interferon; IL — interleukin; LAG-3 — lymphocyte-activating gene (protein product of its’ transcription); MDC — myeloid-derived suppressor cell; MHC — major histocompatibility complex; PAMPs — pathogen associated molecular patterns; PD-1 — programmed cell death 1 receptor; PD-L1 — programmed cell death 1 receptor ligand; PRR — pattern-recognizing receptor; Tc — T-cytotoxic lymphocyte; TCR — T lymphocyte receptor; TMB — tumour mutational burden; Tn — T-naive lymphocytes; TNF — tumour necrosis factor; Treg — T-regulatory lymphocyte; VEGF — vascular endothelial growth factor
into the mechanism of action of novel therapeutic approaches. Below we describe those that are most important to understand the clinical application of immune checkpoint inhibitors.

Expression of programmed death receptor 1 (PD-1) is present mostly on mature Tc lymphocytes. Interaction of PD-1 with specific ligands, PD-L1 and PD-L2, suppresses cytotoxic activity of lymphocytes. Several signalling pathways, existing in the tumour microenvironment, induce expression of PD-1 ligands on the surface of different types of cells present in the microenvironment because the interaction between PD-1 and PD-L1/2 is a common mechanism behind immunosurveillance evasion [7, 8]. Nivolumab acts through the inhibition of this signalling. Additionally, PD-1 might play a role in the activation of Tn lymphocytes by DC, but available data suggest that this effect is not crucial for immune checkpoint inhibitor effectiveness.

Immunogenicity of cancer cells can be assessed in two categories: quantity and quality of neoantigens present in the cancer cell and the actual availability of neoantigens for DC. Tumour mutational burden (TMB), defined as the number of mutations per thousand DNA base pairs, is a rising biomarker for immunogenicity prediction. The more mutations, the more altered proteins and therefore the more neoantigens. Several reports confirm the predictive value of TMB for immunotherapy effectiveness, in terms of both overall survival and depth of response [9, 10].

The second factor defining immunogenicity of cancer cells is the actual availability of its neoantigens for DC and Tc cells. This depends on several factors, including: MHC expression; expression of neoantigens themselves; mechanisms of cancer cell death and its effective (immunogenic death) or non-effective (non-immunogenic death) neoantigen release [11].

Therapeutic influence on TMB is not yet available, but the strategy of combining immune checkpoint inhibitors with therapies aimed at increasing neoantigen expression and inducting immunogenic cancer cell death are intensively studied [12]. One of most successful approaches, often described in the literature, is the combination of immunotherapy with radiotherapy, especially valuable in oligometastatic diseases or in the presence of tumours in difficult localisations [13–15]. Practicing oncologists should be aware of numerous clinical trials evaluating the combination of immunotherapy with other drugs, including chemotherapy, and about the potentially beneficial role of palliative radiotherapy in patients receiving immune checkpoint inhibitors (these data, although arising from low numbers of cases or singular case reports, are extremely promising).

Antigen presentation by DC and recruitment of Tn lymphocytes are, besides the cytotoxic response itself, part of one of the two main phases of immune response activated by immune checkpoint inhibitors. This complex mechanism will not be fully covered, but some of its aspects have strong implications for clinical practice. Dendritic cells, in order to efficiently stimulate Tc clone proliferation, have to go properly through the activation and maturation processes. Presentation of antigens by non-activated DC fails to recruit Tn or, even worse, recruitment of Tn simultaneously with additional signalling through co-stimulatory molecules may be responsible for inducing immune tolerance.

Maturation of dendritic cells requires the coexistence of several signals. From a functionary perspective, we can divide them into two groups: cytokines and ligands of pattern-recognition receptors (PRR). PRR ligands include damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs). DAMPs are mostly products of cell lysis and stroma damage: HSP, calreticulin, nucleic acids, and products of their degradation. PAMPs are mostly substances being common denominators of pathogenic microorganisms, such as evolutionary conservative parts of bacterial cell wall or viral RNA. DAMPs and PAMPs circulate in blood in the presence of tissue damage or infection and are a warning signal required for initiation of DC maturation. Lack of proper PRR stimulation dampens activation of cellular response, preventing auto-immunogenicity in normal conditions but concurrently allowing evasion of immunosurveillance during oncogenesis [16].

Gut microbiome is a significant source of PAMPs, which draws attention to the connection between gut microbiome, immunological response, and carcinogenesis. Beside its effect on DC maturation, several mechanisms of interaction between gut microbiome, and cellular and inflammatory response have been described. Numerous reports tie phenotype of commensal microbiota with effectiveness of immunotherapy — both in animal models and in humans [17–21]. Connecting negative impact of antibiotics on bacterial microflora, additional reports showed strong negative correlation between antibiotics administration and effectiveness of immune checkpoint inhibitors. Significantly worse outcomes of checkpoint inhibitor therapy (both overall survival [OS] and progression-free survival [PFS]) was shown in patients pretreated with antibiotics as compared to patients not exposed to antibiotics (Table 3). Oncologists administering immunotherapy should be aware of this connection and avoid needless antibiotics. This includes adequate differential diagnosis between infections and autoimmunological adverse events associated with immunotherapy (e.g. bacterial pneumonitis vs. autoimmune pneumonitis; Clostridium difficile infection vs. autoimmunological colitis). Available data do not support attempts to modify the composition of gut microbiome in patients outside of clinical trials.

Cachexia is a multifactorial disease that includes protein and energy malnutrition in mechanisms of both
inadequate intake and excessive expenditure, non-specific systemic inflammation and increased catabolism. Cachexia develops in 80% of cancer cases and is the leading cause of death in nearly 20% of cancer patients. The incidence and intensity of cachexia are related to stage of disease and cancer biology. Cachexia develops commonly in patients with gastric, pancreatic, and lung cancers as well as in patients with genitourinary, lymphatic and gynaecological malignancies [22]. The presence of cachexia is a factor associated with poor prognosis.

Additionally, cachexia is a negative prognostic factor for immune checkpoint therapy in animal models and in human clinical trials [23, 24]. This may be due to promotion of immunosurveillance evasion through the following: induction of immunosuppression (interleukin-6 [IL-6], glucocorticosteroids, depletion of immune cells); limitation of metabolic support for highly-energetic processes associated with Tc clone activation; and increase in clearance of therapeutic monoclonal antibodies due to protein deficiency [25].

Despite common knowledge regarding the benefits of treating cachexia — mostly through adequate nutritional support [26] — we lack prospective data that allow optimisation of cachexia management in patients undergoing immune checkpoint therapy. Although promising interventions exist (e.g. non-steroidal anti-inflammatory drugs, direct and indirect IL-6 antagonists), their combination with immune checkpoint inhibitors remains a domain of research. Oncologists should be aware of decreased immunotherapy effectiveness in patients with cachexia (alternative therapies might be advised), and they should recognise that immune response requires a significant amount of energy and thus treat cachexia intensively according to current guidelines.

**Nivolumab in renal cell carcinoma refractory to antiangiogenic treatment**

In November 2015 nivolumab gained registration by Food and Drug Administration (FDA) in the USA and in April 2016 by the European Medicine Agency (EMA) in the indication “treatment of advanced renal cell carcinoma in patients who received prior treatment”. The registration was based on the results of the phase III trial CheckMate 025 (NCT01668784) trial. This international study recruited adult patients with advanced RCC after failure of one or two lines of antiangiogenic treatment. Between October 2012 and March 2014, 821 patients were randomised to either nivolumab or everolimus in standard continuous dosing of 10 mg per day (Fig. 2) [27].

The newest, three-year update of the study results [28] showed data after a median observation time of 24 months in the nivolumab arm and 19 months in the everolimus arm (Table 4). The response rate was, respectively, 26% and 5%, although nearly 35% of patients receiving nivolumab were refractory to the treatment and had progressive disease as their best response. Typically for the immunotherapy, not all responses were seen in the first scanning, and some were obtained later. Median OS was 25.8 months in the nivolumab arm and 19.7 months in the everolimus arm (hazard ratio [HR] 0.74; p = 0.0005). Rates of two-year survival were, respectively, 52% and 42%, and rates of three-year survival were 39% and 30%, respectively. Median progression-free survival times (4.2 vs. 4.5 months) and median duration of response (12.3 vs. 12.0 months) did not differ between patients receiving nivolumab and everolimus, respectively. Durable responses were more
### Table 4. Summary of CheckMate025 trial

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab</th>
<th>Everolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (CR+PR)</td>
<td>26%</td>
<td>5%</td>
</tr>
<tr>
<td>mPFS</td>
<td>4.2 months</td>
<td>4.5 months</td>
</tr>
<tr>
<td>mOS</td>
<td>25.8 months</td>
<td>19.7 months</td>
</tr>
<tr>
<td>2-year survival rate</td>
<td>53%</td>
<td>42%</td>
</tr>
<tr>
<td>3-year survival rate</td>
<td>39%</td>
<td>30%</td>
</tr>
<tr>
<td>Rate of G1–4 toxicity</td>
<td>80%</td>
<td>89%</td>
</tr>
<tr>
<td>Rate of G3–4 toxicity</td>
<td>21%</td>
<td>37%</td>
</tr>
</tbody>
</table>

ORR — objective response rate; CR — complete response; mOS — median overall survival; mPFS — median progression-free survival; PR — partial response

Figure 2. Scheme of CheckMate025 trial. mRCC — metastatic renal cell cancer; KPS — Karnofsky Performance Status

common in patients receiving nivolumab (18% vs. 6%). Toxicity profile was also in favour of nivolumab, with a rate of all treatment-related adverse events of 80% in the nivolumab arm and 89% in the everolimus arm with grade 3–4 adverse events present in, respectively, 21% and 37% of patients.

In the subgroup analysis [29] the benefit from nivolumab was irrespective of either MSKCC or IMDC prognostic group, number of prior treatment lines, and localisation of metastases. The only subgroup of patients with limited benefit from nivolumab were patients aged over 75 years. A trend in favour of nivolumab was seen in subgroups of patients with lung metastases and without bone or liver metastases.

### Choice of optimal therapy after progression of anti-VEGF TKI — the place of nivolumab

In Poland, majority of patients with advanced RCC treated outside of clinical trials receive tyrosine kinase inhibitors (sunitinib or pazopanib) as a first-line therapy. The median progression-free survival achieved with TKI reaches 9–11 months [30, 31], and second-line treatment is inevitable in the majority of patients. In this setting options include the following: alternative TKI with a different affinity to key receptors (axitinib); mTOR inhibitor (everolimus); multi-kinase inhibitor with additional activity against MET and AXL kinases (cabozantinib); and immune checkpoint inhibitors aimed at PD-1 (nivolumab). Only some of these options were compared head-to-head in randomised clinical trials, yet knowledge regarding different modes of action, expected efficiency, and toxicity profile allows optimisation of therapy for each patient (Table 5).

In an indirect comparison of response rates, both nivolumab and cabozantinib exhibit similar activity (25% vs. 5% for, respectively, nivolumab and everolimus in the CheckMate 025 trial and 17% vs. 3% for, respectively, cabozantinib and everolimus in the METEOR trial). However, nivolumab is associated with the highest rate of progressive disease as the best response — about 35% of cases compared with only 12% treated with cabozantinib. This suggest that nivolumab may not be an optimal choice for symptomatic patients or those in whom moderate progression may be life threatening. As mentioned previously, nivolumab might also be less active in elderly patients (> 75 years old) and in patients with cachexia [24].

Compared with everolimus, nivolumab is characterised by favourable toxicity profile and a beneficial impact on quality of life. Direct comparison of its toxicity profile with TKI is difficult due to the different methods of safety assessment used in each trial. It is well recognised that adverse event profiles differ between TKI and immune checkpoint inhibitors, and this difference can affect patients’ and physicians’ treatment preferences.
Table 5. Comparison of activity of drugs used in the second-line treatment of renal cell carcinoma after progression on tyrosine kinase inhibitors aimed at VEGF

<table>
<thead>
<tr>
<th>Drug</th>
<th>Axitinib [40]</th>
<th>Everolimus [27, 28]</th>
<th>Cabozantinib [41]</th>
<th>Nivolumab [27, 28]</th>
</tr>
</thead>
<tbody>
<tr>
<td>mOS (months)</td>
<td>20.1</td>
<td>19.7</td>
<td>21.4</td>
<td>25.8</td>
</tr>
<tr>
<td>mPFS (months)</td>
<td>8.3</td>
<td>4.5</td>
<td>7.4</td>
<td>4.2</td>
</tr>
<tr>
<td>ORR (CR + PR)</td>
<td>19%</td>
<td>5%</td>
<td>17%</td>
<td>26%</td>
</tr>
<tr>
<td>CBR (CR + PR + SD)</td>
<td>76%</td>
<td>61%</td>
<td>87%</td>
<td>59%</td>
</tr>
<tr>
<td>PD as best response</td>
<td>17%</td>
<td>28%</td>
<td>12%</td>
<td>35%</td>
</tr>
</tbody>
</table>

CBR — clinical benefit rate; mOS — median overall survival; mPFS — median progression-free survival; ORR — objective response rate; CR — complete response; PR — partial response; SD — stable disease; PD — progressive disease.

Figure 3. Trends in recruitment in trials assessing combination of immunotherapy with other therapies (based on [12]).

Concluding, second-line treatment of advance RCC with nivolumab can be considered in patients: under 75 years old; optimally asymptomatic or mildly symptomatic; without critical tumour mass; without significant cachexia; and capable of withstanding autoimmunological adverse events (e.g. without contraindication to steroids).

Future of immuno-oncology — perspectives for innovative combinational therapies

Comparison of toxicity profile of anti-PD1 and anti-PD-L1 immunotherapies and their comparators within clinical trials strongly favours immunotherapy [32]. Low toxicity and increased activity, as well as potential synergy of combinational therapy, encourage research assessing combinations of both immuno-oncologic drugs and immunotherapy with other anticancer therapies and treatment modalities.

These and other factors result in growing numbers of studies dedicated to combinational therapies (Fig. 3). Between 2014 and 2017 the number of new clinical trials assessing immunotherapy combinations increased eight-fold and the number of recruited patients over four-fold [12]. As a result, a trend towards reduced population size in trials can be seen, probably due to several factors, including large numbers of innovative combinational therapies assessed in early phases on limited populations, and improved selection of patients in more advanced trials that enable sufficient statistical power with lower numbers of patients per trial.
It is difficult to predict when trial results will be published because this is affected by numerous factors: recruitment time; assessed end-points; pace of maturing data; sources of financing; and others. According to a large analysis performed by American researchers the estimated median time from recruitment closure to publication is about 47 months – nearly four years [33]. Assuming that the recruitment for trials presented in Figure 3 require 12 months on average, we may estimate that half of the trials initiated in 2014 will be published before 2020. Moreover, based on this calculation, we may anticipate results from over 500 trials assessing immunotherapy combination in the next five years.

Summary

The immunological system is a key component of both pathogenesis and treatment of RCC. Understanding of complex mechanisms that take part in activation and in effector phase of adaptive cellular immune response allows the development of more efficient therapies and leads to their effective implementation in clinical practice.

Nivolumab acts mostly through modification of the effector phase of immune response. It proved activity in several cancer types, becoming the standard of care in many. As the number of patients potentially qualifying for treatment with immune checkpoint inhibitors grows, so should the knowledge regarding their strong and weak points, subpopulations with increased or decreased treatment efficiency, and about their interactions with other therapies.

European patients with renal cell carcinoma may be treated with nivolumab after failure of at least one line of prior systemic therapy*. Nivolumab offers promising activity in terms of response rate and median overall survival, along with a favourable toxicity profile. Unfortunately, nivolumab is limited by high rates of primary resistance and decreased activity in older patients and in the presence of cachexia.

A large number of new trials assessing immunotherapy in combinations with other therapies is a consequence of encouraging results achieved with immune checkpoint monotherapy. Analysis of trends in numbers of such trials gives hope that the best in immuno-oncology is yet to come.

Conflict of interests

Paweł Potocki — fees and travel grants — BMS, Ipsen, MSD, Pfizer, Roche.

Piotr Wysocki — fees and travel grants — Roche, BMS, Pfizer, Novartis, Ipsen.

References


*On January 14, 2019, the EMA approved the nivolumab plus ipilimumab combination for first-line treatment.