Radiologic Heterogeneity in Responses to Anti–PD-1/PD-L1 Therapy in Metastatic Renal Cell Carcinoma

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Abstract

Radiologic assessment of tumor response remains a challenge in patients treated with immune checkpoint inhibitors. In metastatic melanoma, for example, a spectrum of imaging patterns in response to immunotherapies have been recognized and associated with clinical benefit. In metastatic renal cell carcinoma (mRCC), less than half of patients treated with immune checkpoint inhibitors achieve objective responses, but some of these responses have been durable. In this series, five different imaging patterns of response and progression are described in mRCC patients treated with anti–PD-1/PD-L1 agents: (i) early and complete response, (ii) pseudoprogression, (iii) disease stability before ultimate response, (iv) mixed response with new lesions, and (v) early progression/primary refractory disease. The implications of the different imaging patterns of patient responses on disease prognosis are discussed and highlight the need for individualized patient assessment when using these novel immune-targeted agents.

Introduction

The programmed death 1 (PD-1) pathway is a negative feedback system that represses immune responses, but if it is unregulated, it can damage the host, and it can contribute to autoimmune disease and cancer when dysregulated (1). The upregulation of the PD-1 pathway and associated complex interactions with the host have been seen in multiple cancers, and the blockade of this pathway has led to remarkable clinical responses in patients with advanced melanoma, non–small cell lung cancer (NSCLC), renal cell carcinoma (RCC), and several other types of cancer (2–4).

PD-L1 and PD-L2 are the major ligands for PD-1, which is a receptor expressed on T cells (1). PD-L1 binding to PD-1 negatively regulates the immune response and activity of antitumor T cells. Both PD-L1 and its ligand PD-L1 are targets of new immune therapies. Studies have shown that the expression of PD-L1 ligands on the surface of tumor cells or immune cells might be an important predictive biomarker of response to PD-1 blockade (5). Nivolumab is a new anti–PD-1 mAb that has been recently approved for metastatic melanoma (6) and NSCLC (7). Data from early studies in mRCC support current ongoing phase III clinical trials assessing nivolumab in first- and second-line therapy, both as a single agent and in combination with different anti–VEGF-targeted therapies (8). Another PD-1 inhibitor, pembrolizumab, is also being tested in combination with other agents such as ipilimumab in RCC (9).

Antibodies that also target the PD-L1 ligand are also under development for treatment of mRCC (5). Atezolizumab (MPDL3280A), a mAb against PD-L1, has been tested in a phase I trial with 69 mRCC patients, with a median progression-free survival (PFS) of 24 weeks (10). Durvalumab (MEDI4376), another anti–PD-L1 antibody, is being studied in combination with tremelimumab in patients with advanced solid tumors, including RCC (11).

As seen with ipilimumab, a CTLA-4 inhibitor approved for advanced melanoma, the kinetics of response to anti–PD-1 and anti–PD-L1 agents are rather heterogeneous and might be different from those for cytotoxic and targeted therapies (12). Objective responses can be observed in variable time frames, from a few weeks to several months after therapy initiation. Response or stable disease in mRCC may be preceded by apparent early disease progression, as has been seen in melanoma patients treated with ipilimumab (12). At this point, it is not clear whether a minimum amount of time is required to assess treatment response with anti–PD-1/PD-L1 therapy (13) or whether this new form of immunotherapy should be given continuously until progression or intermittently. Understanding the kinetics of response to immune-checkpoint inhibitors will help to improve the outcome of patients treated with anti–PD-1/PD-L1 therapies. Here, we discuss several cases illustrating the heterogeneous kinetics of radiologic response to PD-1/PD-L1–blocking agents in mRCC.

Case 1 (Early and Complete Response)

A 60-year-old man with excellent functional capacity and minimal symptoms was diagnosed with intermediate-risk
metastatic clear cell renal cell carcinoma (ccRCC) based on the
International Metastatic Renal Cell Carcinoma Database Consor-
tium (IMDC). Restaging scans after cytoreductive nephrectomy
showed increase in the size of several biopsy-proven pulmonary
and lymph node metastases in the thorax and abdomen (Fig. 1A
and B). The patient was started in a trial of anti–PD-1 treatment as
a first-line therapy. After only two doses of study drug, a follow-up
CT showed a complete response (CR). The patient tolerated this
therapy well and continued treatment for 14 months without
interruption. Ultimately, the patient stopped the drug due to the
late development of immune-related adverse effects (grade 2
uveitis). Despite 2 years without any treatment, the response
continues to be durable and the patient remains with no evidence
of disease.

Case 2 (Pseudoprogression)
A 54-year-old man presented with intermediate-IMDC risk
metastatic ccRCC (lung nodules and retroperitoneal lymphade-
nopathy). This patient’s first-line treatment was a sunitinib-based
combination [multitargeted tyrosine kinase inhibitor (TKI),
including VEGFRs and platelet-derived growth factor (PDGFR)]
as part of a phase II clinical trial, but he did not respond. For
second-line therapy, the patient was then entered into a clinical
trial assessing the combination of temsirolimus (inhibitor of
mTOR) and bevacizumab (anti-VEGF mAb), and he achieved a
partial response (PR) lasting 10 months. Progression with new
bone metastases as well as growth in lymph node and soft tissue
metastases made the patient eligible for a clinical trial with an
anti–PD-1 mAb. The scan at week 6 (Fig. 2B) showed a 19.6%
increase in tumor burden (stable disease according to RECIST
criteria). The patient continued in the study, especially in view of
his symptomatic improvement (resolution of asthenia and
anorexia). Subsequent scans at week 12 showed a PR, with target
lesions having decreased in size (Fig. 2C). This case illustrates that
despite images that show apparent early growth, continued treat-
ment may result in a clinical benefit to a particular patient.

Case 3 (Disease Stability before Ultimate
Response)
A 72-year-old woman, who presented initially with a large
right-sided kidney cancer, underwent nephrectomy for ccRCC.
Initial staging indicated good-IMDC risk metastatic disease. The
patient was treated first with pazopanib (a TKI that targets, among
other receptors, VEGFRs, PDGFRs, and c-kit) for 18 months until
progression, and then everolimus (mTOR inhibitor), which was
stopped after 1 month due to intolerance. Subsequently, the
patient received an anti–PD-1 mAb as part of a clinical trial.
Scans initially showed stable disease with no tumor growth or
shrinkage (Fig. 3B). After 8 months of treatment, there was mild to
moderate shrinkage of the target lesions (Fig. 3C). One year after
the start of treatment, retrocaval adenopathy had resolved and the
patient achieved a delayed PR (Fig. 3D). At cycle 31 (month 21),
the patient’s treatment was complicated by pneumonitis, neces-
sitating treatment discontinuation. The PR was maintained for 6
months after she stopped the anti–PD-1 inhibitor, and then the
patient’s disease progressed.

Case 4 (Mixed Response with New Lesion)
A 57-year-old woman was diagnosed with intermediate-IMDC
risk metastatic ccRCC with sarcomatoid features and underwent a
left radical nephrectomy showing ccRCC. Shortly thereafter, she
was started on single-agent anti–PD-L1 mAb as part of a clinical
trial. Her CT scan 8 weeks after the start of therapy showed that
several lung nodules had decreased in size (Fig. 4C) and lymph
nodes (not pictured); however, there was a new small (<1 cm)
indeterminate subcutaneous nodule in the left lower paravertebral area (Fig. 4D). Additional imaging 8 weeks later showed continued shrinkage of the lung nodule and lymph nodes (Fig. 4E), but with an increased size of the lesion in the lower back (Fig. 4F). Excisional biopsy of the growing lesion was consistent with RCC with sarcomatoid features.

**Case 5 (Early Progressive Disease/Primary Refractory Disease)**

A 49-year-old man was diagnosed with intermediate-IMDC risk metastatic ccRCC and underwent surgical debulking of a T11 lesion followed by radiation. Imaging showed pulmonary, adrenal, and liver metastases. The patient progressed on sunitinib and bevacizumab-based clinical trial combinations. He was subsequently started on an anti–PD-1 mAb as part of another clinical trial. The first CT scan after therapy initiation showed an increase in the size of liver lesions, with further increase on the second follow-up CT scan, as well as clinical deterioration, representing true progression (Fig. 5A–C).

**Discussion**

PD-1/PD-L1 pathway inhibitors have shown promising activity in the treatment of several advanced solid tumors (4, 5). Although RCC has been treated with cytokines—immunomodulating agents—for nearly 40 years (14), the imaging patterns and features of response to the new anti–PD-1/PD-L1 therapy need further characterization. In metastatic RCC, many clinical trials are currently ongoing in the first- and second-line setting as monotherapy, or in combination with targeted therapy or other immune-checkpoint blockers, such as CTLA-4 inhibitors. Indeed, a phase III clinical trial comparing nivolumab with everolimus (NCT01668784) has been stopped prematurely because the study has met the primary endpoint by demonstrating increased overall survival (OS) compared with the control arm in patients with previously treated mRCC (15).

In patients treated with these agents, interpretation of imaging results is challenging, considering the complexity of the immune response and underlying tumor heterogeneity (16). This case series illustrates some of the imaging patterns of response to PD-1/PD-L1–blocking agents being assessed for use in metastatic RCC.

Up to 29% of objective responses, as per RECIST criteria, were observed in a refractory cohort of mRCC included in a phase I clinical trial with nivolumab (2). In the same trial, 60% of patients with mRCC had some degree of tumor shrinkage and 9% had atypical immune-related response as described in Case 2. Variable expression of PD-L1, differences in T-cell content or T-cell
response, and intertumoral heterogeneity in treated patients are some of the possible explanations for these different patterns of response (5, 17): Patients experiencing benefit may have different timing of response as seen in Cases 1 to 4, and physicians must be familiar with the various patterns.

A CR, as shown in Case 1, is rarely seen in other targeted therapies (less than 1% in first-line sunitinib or pazopanib; ref. 18). It is impossible to predict which patients will achieve such a good response as there are no validated predictive biomarkers despite intense research in this field (17). Furthermore, the durable response in Case 1, with continued benefit extending more than 2 years after treatment was stopped, is extraordinary. This long-lasting response, without treatment, is in contrast with clinical experience with TKIs, the current standard of care in RCC, a setting in which treatment discontinuation is usually associated with growth or even growth acceleration in some reports (19).

In terms of the timing and kinetics of tumor shrinkage and response, it remains unknown whether patients with the best outcomes will be those who respond immediately to the first few doses of therapy or those who require a longer period of time on treatment, as seen in Case 3. If a longer time to produce response with the PD-1 pathway blockade is needed in some patients, we could argue for a rational combinatorial approach with addition of another immune checkpoint blocker (e.g., CTLA-4 inhibitors) or a VEGF-targeted agent that may lead to a faster, and perhaps more durable, response.

Genomic heterogeneity of tumors, a phenomenon well described in mRCC (20) and common in patients treated with targeted therapy, may explain the mixed response seen in Case 4. Although some of the lesions were responding, a dominant resistant population of cells may have been present at baseline (soft tissue nodule, Fig. 4F) and was only appreciated after starting therapy. This scenario suggests that genomic heterogeneity may result in a mixed response, as assessed by CT scans. It is not unreasonable that anti–PD-1 therapy be continued beyond "progression," while addressing the "resistant clone" with a local therapy such as surgery (20).

A challenging pattern of response is demonstrated in Case 2. The size of metastases may increase significantly before regression.
or response is detected, as previously described with ipilimumab treatment in melanoma (12). "Pseudoprogression" might lead to premature withdrawal of the treatment, which may not be in the patient’s best interest, particularly if the treatment is well tolerated. A subsequent scan showed the delayed response. This is the rationale for the recommendation of follow-up confirmatory imaging, as described in the Immune-Related Response Criteria (irRC, ref. 21). The use of traditional imaging methods to assess response during the first few weeks may therefore be challenging. The immune response generated by these agents may produce “tumor inflammation,” possibly due to a massive T-cell infiltration in the target lesions, resulting in apparent tumor growth (12).

Careful evaluation of each patient’s clinical situation is important to avoid premature discontinuation or a continuation of therapy when the patient is not actually benefiting. Comprehensive evaluation of new or enlarging lesions early in the course of therapy should also include assessment of location of the lesion and the amount of growth, to decide upon the need for a complementary intervention or a change in systemic treatment.

The symptomatic improvement in our patient led us to continue systemic therapy. The irRC, still under development, may play a major role in guiding response assessment in mRCC patients treated with PD-1/PD-L1 inhibitors (22).

Another unanswered question in the use of checkpoint immune therapies in mRCC involves the optimum length of treatment. Everolimus can provide clinical benefit/disease stabilization regardless of whether treated patients experience a significant decrease in tumor burden (23). This has been well captured with PFS as the endpoint, a strategy used for the approval of most targeted agents in mRCC. However, use of PFS as an endpoint in mRCC patients treated with immune checkpoint blockers may not be ideal. Motzer and colleagues (24) used median PFS from nivolumab as the endpoint in their study of mRCC. PFS ranged between 2.7 and 4.2 months, despite a very promising OS ranging between 18 and 25 months in a highly refractory mRCC population. The PFS in these reports suggests a moderate benefit at best, so it does not necessarily reflect the efficacy of PD-1/PD-L1 inhibitors for some patients with mRCC. Median OS would more accurately describe antitumor activity. In this series, PFS in Case 2 might have been reported in as short a time as 6 weeks.

As highlighted in Case 1, patients may achieve an immediate CR as a durable event after stopping treatment. Even in this early stage of development, durable responses with PD-1 inhibitors have already been reported in mRCC (2). Conversely, Case 3 illustrates a prolonged time to achieve PR, though the clinical benefits and CT scans continued for more than 2 years. It is possible that intermittent treatment, whether by reinstituting therapy upon progression or instituting a treatment break after an optimal response is achieved, has a place in certain subsets of patients who achieve an exceptional initial response, with the advantage of less potential toxicity and cost savings. Genome sequencing analysis of tumor biopsy samples could help to define the escape resistance mechanisms, which may be due to complex immune mechanisms or merely “de novo” mutations, as seen with some forms of targeted therapy (25).

**Conclusions**

The response to anti–PD-1/PD-L1 agents may be very heterogeneous, with a spectrum of patterns seen on imaging. Careful assessment of the responses of patients treated with these immune checkpoint inhibitors is needed, and multidisciplinary awareness of the commonly observed patterns and potential pitfalls in interpretation (i.e., “pseudoprogression”) is necessary. Observed durable responses to treatment represent a great source of optimism and hope in the management of advanced RCC.

**Disclosure of Potential Conflicts of Interest**

L. Albige serves in a consulting or advisory role for Bristol-Myers Squibb, Pfizer, Novartis, and Bayer. J. Bellmunt serves in a consulting or advisory role for Pfizer, GlaxoSmithKline, Novartis, Bristol-Myers Squibb, and Genentech. F.S. Hodi is a consultant at Merck and Genentech, reports receiving a commercial research grant from Bristol-Myers Squibb and has ownership interest (including patents) in MICA Related Disorders IP as per institutional policy. T.K. Choueiri serves in an advisory role for Bristol-Myers Squibb, Merck, and Roche.

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**References**


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