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IMMUNOTHERAPY IN RENAL CANCER:
Immune Checkpoint Modulators for the Treatment of Metastatic Renal Cancer

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Introduction

The responsiveness of metastatic renal cancer (mRCC) to immune stimulating agents has been known for many years. Low rates of objective tumor regression have been reported consistently in clinical trials of cancer vaccines and various cytokines. Of the cytokines, interferon-alpha and interleukin-2 (IL-2) appear to demonstrate the highest response rates, in the range of 5-20%, and therefore have been studied extensively alone and in combination with other agents. As discussed above, high dose IL-2 in particular produces very durable complete remissions in approximately 5% of patients with mRCC , including patients with large tumor burdens, and thus provides important proof-of-concept for the therapeutic potential of immunotherapy in this disease.[1]

The immunologic mechanisms by which IL-2 produces tumor regression in mRCC are not fully understood. Nevertheless, it seems reasonable to assume that IL-2 and other immune therapies are activating or expanding T-lymphocytes that specifically recognize antigens expressed by renal carcinoma. Further promoting the development, expansion, and effector function of these tumor-specific lymphocytes could lead to even better anti-tumor responses. In line with this hypothesis, several groups have attempted to immunize patients against their tumor. Only a limited number of broadly expressed defined cancer-associated antigens have been identified in renal carcinoma, therefore several cancer vaccines have used allogeneic or autologous tumor cells as the source of antigen, and have relied on advances in immunology (for example, derivation of autologous heat shock protein containing potential peptide antigens, or fusions of dendritic cells with tumor cells) to produce more effective T-cell responses to the vaccine antigens.[2-5]

The minimal to modest success of cancer vaccines and cytokine therapy to date is not surprising, when viewed in the context of a more modern understanding of the extensive and complex regulation of immune responses, and the immune inhibitory influences within the tumor microenvironment. The identification of multiple positive and negative regulators of T-cell activation and function provides new opportunities for effectively modulating anti-tumor immune responses in mRCC. These new agents may provide key agonist and survival signals to T-cells, or more importantly block regulatory checkpoints for T-cell expansion and function. Although a logical use of the checkpoint modulators is in combination with cancer vaccines, many patients may already have ongoing antigen presentation and immune responses against their cancer, thus the checkpoint modulators alone may be sufficient to induce tumor regression, similar to and perhaps more effectively than interferon or IL-2.

Three immune checkpoint modulators have received limited evaluation in metastatic renal cancer, including:

- antibodies to CTLA-4 (ipilimumab)
- agonist antibody to CD137
- PD1 blockade

Because these molecules are found on more than one immune cell type, and because expression may be time and context dependent, the exact mechanisms contributing to their anti-tumor activity in animal models or patients will be difficult to define. Consequently, selection of patients most likely to respond to any individual agent may also prove challenging.

Antibodies to CTLA4

CTLA4 is brought to the surface of activated T-cells, and upon binding to its ligands CD80 or CD86 on antigen-presenting cells, inhibits further lymphocyte proliferation.[6] CTLA4 is also expressed on T-regulatory cells.[7] Two blocking antibodies to CTLA4, ipilimumab and tremelimumab, were advanced into clinical development, mostly focused on metastatic melanoma.

Ipilimumab. The largest experience with ipilimumab in mRCC was published from the Surgery Branch, NCI.[8] The first cohort of 21 patients had all received prior high dose IL-2 and received a loading dose of 3 mg/kg, followed by 1 mg/kg every 3 weeks. One patient (4.7%) developed a partial response (PR) in lung and adrenal metastases that lasted 18 months, but progressed in a single bone site. The second cohort of 40 patients received 3 mg/kg every 3 weeks. Three of 14 (21.4%) patients without prior high dose IL-2 and 2 of 26 (7.7%) with prior high dose IL-2 achieved PR. Responding sites included liver, bone, and lung. Response durations at the time of publication were 7, 8, 12, 17 and 21+ months. Two of the partial responders progressed only in a single new site. Similar to the experience with ipilimumab in patients with melanoma, one of the partial responders initially showed disease progression after 2 doses, before lesions began to regress. Autoimmune adverse events including colitis, hypophysitis, rash, and adrenal insufficiency were observed similar to those reported for ipilimumab administration in patients with melanoma. Three patients developed a bowel perforation. There was strong correlation in this study between occurrence of autoimmune adverse events and tumor response.

The results of the ipilimumab trial in patients with mRCC can now be placed in context of mature and extensive data generated in patients with metastatic melanoma.[9-13] The overall objective response rate to ipilimumab in the small phase II trial in patients with mRCC is similar to response rates observed in patients with metastatic melanoma. In the NCI trial, although no patient achieved a complete response and only one patient had an ongoing response at the time of publication, three of the patients progressed only at a single site that could be managed with radiation or surgery. The study reported from NCI also did not describe patients who may have had mixed responses or regression that did not meet partial response criteria, although the investigators alluded to at least one patient with a mixed response. In data generated for ipilimumab in patients with metastatic melanoma, those achieving mixed responses, or developing progression in a single site after a good response, were felt to derive survival benefit from treatment. In addition, overall survival in patients with metastatic melanoma is increased by ipilimumab despite low objective response rates and minimal to no effect on median time to progression.[9] Surprisingly, no other trials of ipilimumab or tremelimumab in patients mRCC are reported in the literature. The results of the NCI trial and the similarities in activity of ipilimumab in melanoma and mRCC support further study of ipilimumab in patients with mRCC.

Antibody to CD137

CD137 (4-1BB) is expressed after activation of several different types of immune cells.[14,15] An agonist signal through CD137 can provide co-stimulation for T-cells, increase T-cell survival, promote cytokine production and increase T-cell cytotoxicity. A phase I trial of a fully human IgG4 agonist antibody to CD137 administered every 3 weeks was conducted, followed by randomization of 30 metastatic renal cancer patients to the 1, 3 and 10 mg/kg dose levels.[16] At the time of data presentation, none of 22 patients with mRCC had achieved an objective response. Despite the lack of clear activity in this small trial, because of the important role of CD137 signaling in T-cell activation and survival, additional studies of anti-CD137 in patients with mRCC should be considered, possibly in combination with other agents.

PD1 blockade

PD1 is expressed by activated T-cells, memory T-cells and regulatory T-cells, and downregulates T-cell function upon binding to its ligands.[17] Blockade of PD1 in vitro enhances T-cell proliferation and cytokine production in response to a challenge by specific antigen targets or by allogeneic cells in mixed lymphocyte reactions. Thompson et al reported that one ligand for PD1, (PD-L1 or B7-H1) was expressed on tumor cells or on tumor-infiltrating T-cells in 44% of clear cell renal cancers, and was associated with worse survival, regional node involvement, distant metastases, and advanced nuclear grade.[18] In a subsequent analysis of 306 nephrectomy specimens of clear cell cancer, 23.9 % expressed B7-H1 in tumor cells by immunohistochemistry staining, and similar to the prior study, expression correlated with worse survival and higher nuclear grade.[19] The same group also studied 267 nephrectomy specimens of clear cell renal cancer for both T-cell infiltration and PD1 expression by the tumor infiltrating lymphocytes.[20] Immune cell infiltrates were absent in 49% of patients. In the other 51%, PD1 expression was correlated with the extent of tumor immune cell infiltration. These preclinical studies provided a compelling rationale to study blocking antibodies against PD1 or PD-L1 in patients with metastatic renal cancer.

MDX1106.

The initial phase I trial of a blocking antibody to PD1 (MDX 1106, BMS 936558, ONO4538) demonstrated that single doses of 0.3 to 10 mg/kg were well tolerated and associated with a low rate of adverse events.[21] Limited re-treatment was allowed in this trial, given as 2 doses spaced 4 weeks apart at intervals of 3 months. The single patient with mRCC enrolled to the study, with disease in multiple sites, and previously treated with sunitinib, sorafenib, and an HDAC inhibitor, achieved an unmaintained ongoing PR that now exceeds 24 months. The pre-treatment tumor specimen from this patient demonstrated substantial expression of B7-H1. In a subsequent phase I trial, doses of 1, 3, and 10 mg/kg administered every 2 weeks were evaluated, and similar to the initial study, anti-PD1 was well tolerated at all dose levels with a low incidence of grade 3 or grade 4 adverse events.[22]

All patients enrolled were required to demonstrate disease progression on or after a prior treatment. At the time of the latest data analysis, 16 patients with clear cell mRCC were evaluable for response, 2 treated at 1 mg/kg and 14 at 10 mg/kg. At the 1 mg/kg level, one patient achieved a complete response of lung, pleural-based, and lymph node metastases. Four of the 14 evaluable patients at 10 mg/kg achieved confirmed or unconfirmed PR. Overall, 5/16 (31%) achieved objective responses. Regression was observed in large lesions, including a large intact primary tumor. All of the responders (confirmed and unconfirmed) remain progression-free from 7+ to 17+ months since beginning treatment. Although the analysis is not fully complete, activity was also observed in some of the patients with mRCC not meeting criteria for PR; for example, tumor regression in one patient treated at 1 mg/kg only met criteria for stable disease but he remains progression-free 20+ months from first dose on trial. Similar to ipilimumab, patients demonstrated varying kinetics of tumor response, including initial mixed responses subsequently followed by reduction in size of the growing lesions.

Conclusion

Overall, results from the limited studies of the checkpoint inhibitors ipilimumab and anti-PD1 in patients with mRCC suggest clinically important anti-tumor activity. The value of these agents, similar to IL-2, is likely to be in the induction of very durable responses and possibly cure of metastatic disease, in contrast to the small molecule targeted agents. Many questions remain, for example, the activity of the agents in different subtypes of clear cell cancer and other histologic types of renal carcinoma is not yet known. Identification of predictive biomarkers for response will be an important component of the clinical development of the agents. Although finding predictive biomarkers may prove difficult for ipilimumab, tumor expression of the ligand B7-H1 may be associated with response to anti-PD1 or anti-PD-L1.

For subsequent development and ultimately in clinical practice, we will need to address when and how to use these agents in patients with metastatic disease, and how to integrate their use with the approved anti-angiogenesis and mTOR inhibitors. Future studies will also likely be initiated to determine the activity of combinations, for example of anti-PD1 with anti-CTLA4, or of either of these agents with IL-2.[23] Similarly, combinations of anti-PD1 or ipilimumab with agents such as sunitinib or bevacizumab that have high rates of tumor regression may lead to synergistic clinical activity. Other immune checkpoint modulators will enter clinical development in the near future, and should be studied in patients with mRCC. Because of the potential for these therapies to improve outcomes for patients with metastatic renal cancer, clinical trials should be considered for appropriate patients with metastatic disease ahead of standard treatment with approved non-curative agents.

Discussion

Dr. Atkins: So, let us just fantasize for a second that you are in charge of the development of this drug and you have the ability to do what you want. What would you do?

Dr. Sznol: I would try to get this in on the market for kidney cancer as quickly as possible. I think we could propose a single-arm study third-line for patients whose disease failed VEGF pathway and mTOR pathway inhibitors. If you observe a 15 or 20-percent durable remission rate in 100 patients, there is no reason why this agent should not be approved, especially with a toxicity profile that we have seen so far. It depends on how you define durable response, but if you define a durable remission as six plus months or more, or even a year or more, you may see a 15 to 20-percent rate in that population. Some of the responses have been observed in patients who have progressed on prior sunitinib or both sunitinib and sorafenib therapy.

Dr. Atkins: If you are sitting on ODAC, would you consider this an unmet need, in which case you could get an accelerated approval for response rate alone? Or would this drug have to show an improved survival in a randomized trial?

Dr. Hutson: There is going to be a shifting in ODAC's interpretation of new drugs for kidney cancer. Hopefully Pfizer, who has the largest database now with temsirolimus, axitinib and

sunitinib, can prospectively validate the most rigorous way of defining the impact of PFS on overall survival. We do not have enough patients to do the trials,
so there are going to have to be well-defined endpoints.

Dr. Sznol: I understand that argument. But everolimus does not have a proven survival benefit. Sunitinib seems to have a survival advantage, but not definitively proven because of the crossover. So neither the front-line nor the second-line agents have clearly defined survival advantages in Phase 3 trials. If you go to a third-line setting for which there is no approved agent, and you have a drug with a reasonable durable response rate with a good risk-to-benefit ratio that includes improvement in symptoms, I think it would be difficult for a regulatory body to turn the drug down. Now if the real response rate was 5-percent, it would be more difficult to use this strategy.

Dr. McDermott: But it is just 16 patients so far.

Dr. Stadler: We are getting ahead of ourselves. We need to get some more experience with this drug in renal cancer.

Dr. Sznol: I agree completely that a lot more Phase 2 work needs to be done—and that dosing schedule and looking at the different types of histology, all are really important. But concurrently with that, I would begin a 100-150 patient Phase 2 study in a previously treated group in the hope that if significant activity is seen similar to the very impressive preliminary experience, it might be a short track to drug approval and getting this agent available to patients in need.

Dr. Atkins: Since this is an agent that has a target, I think it is a good opportunity to also think about the biology of tumor response Why are more aggressive looking tumors potentially more likely to benefit from this approach? For example, PDL1 expression on the cell surface can inhibit the PI3 kinase/ AKT pathway. It is essentially a TOR inhibitor. So does that mean that expression of PDL1 by tumor cells creates a profoundly immune-suppressive environment that can be reversed with the PD1Ab? In addition, we should consider what is known about the causes of upregulation of PDL1 on tumor cells.

Dr. Sznol: It is possible that the PD1-PDL1 interaction makes the cell more resistant to apoptosis. If you block the interaction you also might make the cell more sensitive to, for example, cell death from other agents, chemotherapy or targeted agents, whatever the case might be. What causes PDL1 upregulation is not completely clear. It may actually result from T-cells infiltrating the tumor, and intra-tumoral production of interferon-gamma. All of that needs to be worked out. Selecting out for responders may be difficult. The easy guess is that the patients who respond will have T-cell infiltrates and tumors over-expressing PDL1, and possibly poorly differentiated tumors, but I would evaluate these biomarkers retrospectively in a Phase 2 trial.

Dr. George: Is it is worth building in mandatory biopsies of metastatic disease? Patients will want to get on these studies, and these are the opportunities that we typically miss because we do not want to slow accrual.

Dr. Sznol: Absolutely.

Dr. Stadler: The complexity of doing these biopsies correctly is completely underappreciated by the clinical researcher.

Dr. Atkins: Once a drug is approved, it is hard to get patients to agree to go on a study that requires a biopsy when they can get the drug without the biopsy. So, this is a time to do it so we can learn what we need to learn to use this drug optimally.

References

Immune Checkpoint Modulators for the Treatment of Metastatic Renal Cancer

1. Fyfe G, Fisher RI, Rosenberg SA, et al: Results of treatment of 255 patients with metastatic renal cell carcinoma who received high-dose recombinant interleukin-2 therapy. J Clin Oncol. 1995; 13: 688-96.
2. Jonasch E, Wood C, Tamboli P, et al: Vaccination of metastatic renal cell carcinoma patients with autologous tumour-derived vitespen vaccine: clinical findings. Br J Cancer. 2008; 98: 1336-41.
3. Avigan DE, Vasir B, George DJ, et al: Phase I/II study of vaccination with electrofused allogeneic dendritic cells/autologous tumor-derived cells in patients with stage IV renal cell carcinoma. J Immunother. 2007; 30: 749-61.
4. Su Z, Dannull J, Heiser A, et al: Immunological and clinical responses in metastatic renal cancer patients vaccinated with tumor RNA-transfected dendritic cells. Cancer Res. 2003; 63: 2127-33.
5. Neumann E, Engelsberg A, Decker J, et al: Heterogeneous expression of the tumor-associated antigens RAGE-1, PRAME, and glycoprotein 75 in human renal cell carcinoma: candidates for T-cell-based immunotherapies? Cancer Res. 1998; 58: 4090-5.
6. Egen JG, Kuhns MS, Allison JP. CTLA-4: new insights into its biological function and use in tumor immunotherapy. Nat Immunol. 2002; 3: 611-8.
7. Peggs KS, Quezada SA, Chambers CA, et al: Blockade of CTLA-4 on both effector and regulatory T cell compartments contributes to the antitumor activity of anti-CTLA-4 antibodies. J Exp Med. 2009; 206: 1717-25.
8. Yang JC, Hughes M, Kammula U, et al: Ipilimumab (anti-CTLA4 antibody) causes regression of metastatic renal cell cancer associated with enteritis and hypophysitis. J Immunother. 2007; 30: 825-30.
9. Hodi FS, O'Day SJ, McDermott DF, et al: Improved Survival with Ipilimumab in Patients with Metastatic Melanoma. N Engl J Med. 2010;363(8):711-23.
10. O'Day SJ, Maio M, Chiarion-Sileni V, et al: Efficacy and safety of ipilimumab monotherapy in patients with pretreated advanced melanoma: a multicenter single-arm phase II study. Ann Oncol. 2010;21:1712-7.
11. Hersh EM, O'Day SJ, Powderly J, et al: A phase II multicenter study of ipilimumab with or without dacarbazine in chemotherapy-naive patients with advanced melanoma. Invest New Drugs. 2010 Jan 16. [Epub ahead of print].
12. Wolchok JD, Neyns B, Linette G, et al: Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind, multicentre, phase 2, dose-ranging study. Lancet Oncol. 2010; 11: 155-64.
13. Weber J, Thompson JA, Hamid O, et al: A randomized, double-blind, placebo-controlled, phase II study comparing the tolerability and efficacy of ipilimumab administered with or without prophylactic budesonide in patients with unresectable stage III or IV melanoma. Clin Cancer Res. 2009; 15: 5591-8.
14. Lee SW, Croft M. 4-1BB as a therapeutic target for human disease. Adv Exp Med Biol. 2009; 647: 120-9.
15. Melero I, Shuford WW, Newby SA, et al: Monoclonal antibodies against the 4-1BB T-cell activation molecule eradicate established tumors. Nat Med. 1997; 3: 682-5.
16. Sznol M, Hodi FS, Margolin K, et al: Phase I study of BMS-663513, a fully human anti-CD137 agonist monoclonal antibody, in patients (pts) with advanced cancer (CA). J Clin Oncol. 2008; 26: Abstract 3007.
17. Fife BT, Bluestone JA. Control of peripheral T-cell tolerance and autoimmunity via the CTLA-4 and PD-1 pathways. Immunol Rev. 2008; 224: 166-82.
18. Thompson RH, Gillett MD, Cheville JC, et al: Costimulatory B7-H1 in renal cell carcinoma patients: Indicator of tumor aggressiveness and potential therapeutic target. Proc Natl Acad Sci USA. 2004; 101: 17174-9.
19. Thompson RH, Kuntz SM, Leibovich BC, et al: Tumor B7-H1 is associated with poor prognosis in renal cell carcinoma patients with long-term follow-up. Cancer Res. 2006; 66: 3381-5.
20. Thompson RH, Dong H, Lohse CM, et al: PD-1 is expressed by tumor-infiltrating immune cells and is associated with poor outcome for patients with renal cell carcinoma. Clin Cancer Res. 2007; 13: 1757-61.
21. Brahmer JR, Drake CG, Wollner I, et al: Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. J Clin Oncol. 2010; 28: 3167-75.

22. Sznol M, Powderly JD, Smith DC, et al: Safety and antitumor activity of biweekly MDX-1106 (Anti-PD-1, BMS-936558/ONO-4538) in patients with advanced refractory malignancies. J Clin Oncol. 2010; 28: Abstract 2506.
23. Curran MA, Montalvo W, Yagita H, Allison JP. PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors. Proc Natl Acad Sci USA. 2010; 107: 4275-80.