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Targeted Immunotherapy Breakthroughs in Renal Cell Carcinoma: Ushering in Another New Era

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Greater understanding of the biological mechanisms that drive the development and proliferation of renal cell carcinoma (RCC) has led to the development of several targeted therapies over the last decade, specifically oral VEGF-targeted tyrosine kinase inhibitors (TKIs) and mTOR inhibitors. These new drugs have completely changed the treatment paradigm of metastatic RCC and improved survival and quality of life for patients.

Despite the enormous strides forward brought by the targeted therapy era, just two or three years ago many thought-leaders warned that we were reaching a plateau in how much progress could be made by simply optimizing current targeted therapy usage or developing new VEGF-targeted TKIs and mTOR inhibitors (so called "me-too drugs"). Now, in come the targeted immunotherapies to change all that!

By 2013, the first early clinical studies were suggesting efficacy of immune checkpoint inhibitors in patients with advanced or metastatic RCC and other malignancies. By blocking inhibitory checkpoint signalling pathways involving the programmed death 1 (PD-1) receptor and/or its ligands (PD-L1/2), a targeted immune response can be achieved against malignant cells leading to cell death with relatively minimal effects on normal tissues.

In November 2015, the New England Journal of Medicine published results of the pivotal CheckMate 25 trial comparing nivolumab to standard of care everolimus for patients with advanced clear-cell RCC who had received previous treatment with one or two regimens of antiangiogenic therapy. A total of 821 patients were randomized (1:1) to receive 3 mg/kg of nivolumab intravenously every 2 weeks or a 10-mg everolimus orally once daily. The median overall survival was 25.0 months with nivolumab vs 19.6 months with everolimus. The hazard ratio for death with nivolumab versus everolimus was 0.73 (98.5% CI, 0.57 to 0.93; P=0.002), which met the prespecified criteria for superiority (P≤0.0148). The objective response rate was 25% with nivolumab and 5% with everolimus (P<0.001). Grade 3 or 4 treatment-related adverse events occurred in 19% of the patients receiving nivolumab and in 37% of the patients receiving everolimus. The most common event with nivolumab was fatigue (in 2% of the patients), and the most common event with everolimus was anemia (in 8% of the patients) [1].

The United States Food and Drug Administration approved nivolumab for the treatment of patients with advanced renal cell carcinoma who have received prior anti-angiogenic therapy. Studies of other targeted immunotherapies in RCC are on-going and most experts agree that the approval of nivolumab opens a new and promising chapter in the treatment of advanced RCC. This approval is anticipated to precede the approval of other similar drugs and will hopefully lead to further breakthroughs in the treatment of RCC and other genitourinary malignancies.

Despite great hope for these new drugs, enormous clinical questions remain and years of clinical research will be necessary to optimize the use of targeted immunotherapies in renal cell and other genitourinary cancers. For example: How will these therapies work in real-world patients that can't qualify for clinical trials due to co-morbidities, poor performance status, or excluded sites of metastases? Might these new therapies be useful in neoadjuvant or adjuvant setting for borderline resectable or resectable RCCs? Should they be combined with VEGF-targeted TKIs or mTOR inhibitors or CTLA4-inhibitors as in melanoma? What is the optimal sequence of therapies for differing clinical scenarios? What is the role of PD-1 expression in RCC tumor tissues and can this function as a biomarker of response? Do outcomes with these agents vary across RCC prognostic categories, histological grades, or RCC subtypes?

Many of these questions and more are already being explored in clinical trials. For example, an international multicentre phase III trial in which patients with previously untreated unresectable or metastatic RCC were randomly assigned to the combination of nivolumab plus ipilimumab or to sunitinib has already completed accrual (NCT02231749).

Although it is yet to be proven through clinical research, theoretically anti-PD-1/PD-L1 blockade may provide especially needed treatment options for metastatic non-clear cell RCCs and other histological variants of kidney cancer, which are driven by different molecular mechanisms than clear cell RCC and have poorer response to available VEGF-targeted TKIs and mTOR inhibitors.

The approval of VEGF-targeted tyrosine kinase inhibitors (TKIs) and mTOR inhibitors ushered in a great new era in the treatment of metastatic RCC. The approval of nivolumab for progressive metastatic RCC ushers in another new era in the treatment of metastatic genitourinary cancers. Although many questions remain, it appears that we may be entering into a new world of immunomodulation to fight genitourinary and other cancers. As research in this area continues to progress in the basic science and clinical arenas, great optimization of these new treatments is anticipated and even more powerful and efficacious options for patients are surely on the horizon.

Reference

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