Could PD-L1 prove to be an effective therapeutic target for bladder cancer?

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Keywords: immune checkpoint inhibition • urothelial bladder cancer

Highlighting this year's American Society for Clinical Oncology (ASCO) conference were presentations focusing on T-cell immune checkpoint blockade as a therapeutic target in solid tumors. Promising results in melanoma, lung and renal cancers have led to further disease-specific Phase I and II trials of immune checkpoint blockade in other solid tumors refractory to treatment.

Metastatic urothelial bladder cancer (UBC) is one such tumor; this disease is associated with limited treatment options and a poor prognosis. The last significant advance in metastatic bladder cancer treatment came with the application of cisplatin-based chemotherapies over two decades ago. Despite the widespread use of cisplatin-based combination regimens and improved supportive care, 5 year survival rates for metastatic UBC remain around 15%. The response rates with second-line chemotherapies continue to be dismal, generally around 20% or less, with median survivals of 6–9 months. Thus, the identification of new therapeutic targets for UBC is crucial to improving outcomes in this disease. There is already precedent for use of immune therapy in UBC; treatment of superficial bladder cancer with intravesicular BCG remains the standard of care for non-muscle invasive carcinoma. BCG stimulates a plethora of immune responses, including the activation and recruitment of CD4⁺ and CD8⁺ T lymphocytes.

The programmed death-1 receptor is an inhibitory transmembrane receptor expressed by CD4⁺ and CD8⁺ T lymphocytes that plays a crucial role in the regulation of T-cell response. It is a member of the CD28/CTLA-4 family of T-cell regulators that, when engaged by its ligands, PD-L1 (B7-H1) or PD-L2 (B7-DC), leads to dephosphorylation of proximal signaling molecules downstream of the TCR complex via src homology region 2 domain-containing phosphatase (SHP)-1 and -2, as well as augmentation of PTEN, leading to decreased T-cell proliferation, survival and protein synthesis. Ligand expression in the form of PD-L1 and PD-L2 is, thus, necessary in the development and maintenance of immune tolerance and the prevention of autoimmunity. The upregulation of PD-L1 expression by tumor cells, however, is thought to be a mechanism by which solid tumors evade or develop tolerance to immune regulation. Urothelial bladder tumors have been shown to have levels of PD-L1 expression similar to other solid tumors [1]. Interestingly, higher levels of PD-L1 expression are seen in more advanced and metastatic tumors compared with early-stage tumors [2], both supporting the notion that higher PD-L1 expression can help tumors evade immune regulation, as well as highlighting the promise of PD-L1 blockade.

At ASCO, updated results of an ongoing Phase I study of the human anti-PD-L1 monoclonal antibody MPDL3290A in meta-

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static UBC were presented [3]. An overall response rate of 52% was observed in 65 patients treated at 15 mg/kg intravenous every 3 weeks. Nearly all (97%) of these patient were previously treated with cisplatin-based chemotherapy, the vast majority of which (71%) had one or more prior regimens. Of the 30 patients who had strong (2+ to 3+) PD-L1 expression by immunohistochemistry (IHC), 43% demonstrated an objective response. In the 25 patients with weak IHC (0 to 1+) to PDL-1, 11% demonstrated an objective response. The median time to first response was 42 days (range 38–85 days). At the time of the data analysis, 16 of the 17 responds were ongoing. The predominant toxicity of patients treated with MPDL3290A was fatigue.

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These results identify immune checkpoint regulation via PD-1/PD-L1 blockade as a promising therapeutic lead in metastatic urothelial cancer. In fact, MPDL3290A

was given Breakthrough Therapy Designation by the US FDA on 31 May 2014. A recently opened Phase II trial of 300 platinum refractory UBC patients will further define the response rate of MPDL3290A in the population of patients with platinum refractory UBC. Upfront treatment with MPDL3290A will also be examined in patients who are platinum ineligible. That 11% of patients who had weak or no expression of PDL-1 by IHC responded demonstrates that further studies are needed to correlate biological markers with response and progression.

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