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Five new therapies or just one new treatment? A critical look at immune checkpoint inhibition in urothelial cancer

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“It is clear that we are just at the beginning of the new immune era in the treatment of cancer. The field is ripe for progress in studying further combinations that enhance the activity of the immune system and overcome pathways of resistance”

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Physicians have been enlivened by the first major breakthrough in over 30 years in metastatic urothelial cancer (UC) with the approval of five new therapeutics involved in immune checkpoint blockade. These newly approved agents in UC are monoclonal antibodies blocking PD-L1 including atezolizumab, durvalumab and avelumab, or monoclonal antibodies against PD-1 including nivolumab and pembrolizumab. PD-1, a checkpoint protein present on activated T cells, interferes with T-cell antigen receptor mediated signaling to act as an ‘off-switch’ and thus avoid immune attack on self-cells [1]. PD-L1 protein is present on normal cells and binds PD-1, which allows this downregulation of T-cell response. However, many cancer cells also express PD-L1, allowing them to masquerade as normal cells and avoid immune-mediated attack. By interfering with the PD-1/PD-L1 interaction, these drugs allow for a heightened immune attack on cancer cells.

The concept of immune-mediated therapy is not new in UC. Bacillus Calmette-Guérin (BCG), a live attenuated strain of *Mycobacterium bovis*, has been used for four decades in superficial bladder cancer and is thought to allow a more robust local inflammatory response via intravesicular treatment [2,3]. IFN- α has also been used as an immune modulatory approach, given both intravesically in combination with BCG [4,5], and systemically in combination with chemotherapy, with variable activity reported [6]. A more recent gene therapy approach using an IFN- α -expressing adenovirus has resulted in more sustained levels of IFN- α in the bladder [7]. Ipilimumab, an anti-CTLA antibody, has been explored in localized bladder cancer and resulted in tumor immune infiltrates and pathological clinical responses in 3 of 12 patients treated with neoadjuvant ipilimumab [8].

Atezolizumab was first granted accelerated US FDA approval in May 2016 following front line platinum-based therapy with an observed response rate of 15%, which was an improvement over the 10% historic control [9]. Activity was observed in both PD-L1 positive and negative tumors, resulting in approval regardless of PD-L1 status [9]. Of the 45 responders, 38 patients had ongoing durable responses at 11.7 months. Subsequently, nivolumab, durvalumab, avelumab and pembrolizumab were approved with similar response rates around 15–21% and trend toward durable responses in each trial [10–12]. Pembrolizumab is currently the only immune checkpoint inhibitor with Level I evidence from a Phase III trial showing improved survival compared with single agent taxanes. A recent update on a Phase III study suggests atezolizumab as a second-line therapy has not achieved its survival end point [13]. Further data from this trial are needed to determine whether this was due to trial design, due to crossover of the taxane group or if this truly suggests a lack of benefit with atezolizumab. Atezolizumab and pembrolizumab have been approved for first-line treatment in metastatic UC in cisplatin-ineligible patients. A front-line single-arm Phase II study showed that the overall response rate (ORR) to atezolizumab was 23% and complete response rate was 9%; another front-line single-arm Phase II study showed ORR to pembrolizumab was 29% and complete response rate was 7% [14,15].

These agents have been well tolerated for the most part with a side effect profile quite different than that of traditional cytotoxic chemotherapies. Grade 3–4 adverse events have been similar in the 15–18% range in each of the five agents. True immune-mediated adverse events have been lower, in approximately 2–5% range, and include pneumonitis, transaminitis, rash, thyroid abnormalities and colitis. In the first-line setting, 8% of patients had to discontinue atezolizumab due to treatment-related toxicity [14]. One notable difference is that 20.5% of patients had an infusion-related reaction (Grade 1–2) with avelumab [12]. The CheckMate 275 study indicated that the quality of life for patients improved on nivolumab therapy from baseline and remained stable with treatment [10]. In the Phase III randomized pembrolizumab data, rate of adverse events was significantly lower in the pembrolizumab group compared with the chemotherapy group (60.9 vs 90.2%, respectively) [16].

Multiple strategies have been explored to determine which patients respond best to these treatments. Efforts have been made to stratify responders by PD-L1 expression, TCGA (The Cancer Genome Atlas) subtype and IFN- γ signatures. Currently, all five drugs are approved regardless of PD-L1 expression. Interestingly, data in atezolizumab showed that a higher frequency of PD-L1 tumor cell expression was seen in the TCGA basal subtype compared with luminal subtype (60 vs 23%); however, responses were seen across all TCGA subtypes [9]. Later data suggested higher mutational load was associated with improved response and overall survival (OS), again across all TCGA subtypes and PD-L1 subgroups [14]. The CheckMate 275 study with nivolumab showed an ORR for the whole cohort of 19.6% [10]. For those with PD-L1 expression >1%, ORR was 23.8% and median overall survival (mOS) was 11.3 months. For those with PD-L1 expression <1%, ORR was 16.1% and mOS was 5.9 months. Basal molecular subtype tumors had highest IFN- γ signature which also correlated with higher PD-L1 expression and higher proportion of responders. Durvalumab was evaluated in Phase I/II study and selected for 40 patients with PD-L1 positive and 21 patients with PD-L1-negative tumors [11]. The ORR was 46.4% in the PD-L1-positive subgroup and 0% in the PD-L1-negative subgroup. An expanded cohort of 182 patients showed an ORR of 17%, where PD-L1 positive patients had ORR of 26.3%. A companion diagnostic VENTANA (SP263, AZ, USA) assay was approved in conjunction for assessment of PD-L1 expression in tumor tissue. Overall, it appears that clinical responses of the anti-PD-L1 agents may correlate more with PD-L1 expression status than those of the anti-PD1 agents. However, this may not be relevant to clinical decision on patient selection for therapy as patients with both PD-L1-positive and PD-L1-negative tumors respond to immune checkpoint agents.

Our inability to use PD-L1 expression for selection of appropriate patients has been attributed to many factors. There is heterogeneity of these assays, and while there is a trend toward better response in higher PD-L1 expression, there are not clearly defined cutoffs and standards for these individual antibodies. Furthermore, there is clear plasticity in PD-L1 expression. Several studies across several tumor types have shown changes in PD-L1 expression on tumor cells after treatment with chemotherapy, begging the question of how to best pair or sequence chemotherapies to upregulate PD-L1 expression and enhance efficacy of checkpoint inhibition [17].

Much work is ongoing to understand molecular characteristics to predict benefit with chemotherapy [18] and immunotherapy [9,10] in UC. Treatment with atezolizumab resulted in more responses in luminal 2 tumors, while treatment with nivolumab suggested basal 1 tumors had the most benefit. However, both datasets suggested low levels of activity in luminal 1 tumors. Luminal 1 tumors appear more immunoquiescent, lacking the immune markers expressed in luminal 2 and at even higher levels in basal tumors [19]. The enrichment for FGFR3 mutations in the luminal 1 subtype [19], suggests the potential for FGFR3 inhibitors as a therapeutic in these immunologically cold tumors. Clinical activity also appeared lower in the basal 2 tumors, a group with the highest levels of expression of immune markers. These basal 2 tumors also have a claudin-low signature associated with epithelial–mesenchymal transition (EMT) [19]. The presence of myeloid-derived suppressor cells associated with these EMT tumors suggest a potential pairing of checkpoint inhibitors with therapies that deplete or control immune regulatory cells [20].

Objective responses with immune checkpoint monotherapy remains in approximately 15–20% range, suggesting many still do not benefit from these therapies. Although some might consider transitioning from a PD-L1 to a PD-1 inhibitor or vice versa upon progression, it seems unlikely that the immune stimulatory effects observed with these single agents will overcome resistance observed with prior PD-1/PD-L1 blockade. Pairing CTLA-4 blockade along with PD-1/PD-L1 blockade has been effective in other tumor types to enhance the immune response and is being further explored in UCs in multiple ongoing clinical trials. There are also novel agents that affect immune response such as IDO inhibitors and OX40 agonists that are being developed to enhance efficacy in combination with checkpoint inhibitors. These agents are also being studied in earlier stage disease to see if they can have an impact on patients treated in the neoadjuvant setting, or even in patients who are hoping to avoid cystectomy with high-risk nonmuscle invasive UC. As we build more immune enhancing combinations and move into earlier stage

disease, we will need to become even more adept at managing toxicity from checkpoint inhibition. While these drugs are generally well-tolerated, it is critical to keep a close eye for insidious immune-related complications for early intervention.

Although we now have five new therapies to choose from, considering that they target the same signaling pathway with the similar clinical response and toxicity, it seems likely that we have only one new therapy for our patients. It is clear that we are just at the beginning of the new immune era in the treatment of cancer. The field is ripe for progress in studying further combinations that enhance the activity of the immune system and overcome pathways of resistance with the hopes of enhancing future efficacy for a larger population of UC patients.

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