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Seminar article

Making urothelial carcinomas less immune to immunotherapy

Jorge D. Ramos, D.O.[a,b], Evan Y. Yu, M.D.[a,b,*]

[a] *Department of Medicine, University of Washington School of Medicine, Seattle, WA*
[b] *Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA*

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Abstract

The success of immune checkpoint inhibitors in advanced urothelial carcinoma provides patients with the prospect for durable objective responses. However, the majority of patients do not respond to immune checkpoint blockade. Several potential predictive biomarkers of response have been evaluated in hopes of better identifying likely responders, though each has been shown to have limitations. Going forward, development of reliable predictive biomarkers is imperative. Likewise, innovative treatment combination approaches to convert non-responders to responders are essential to continue making progress in the field. © 2016 Elsevier Inc. All rights reserved.

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Metastatic urothelial carcinoma is associated with a poor prognosis, with a median overall survival of 15 months and 5-year survival rates of approximately 5% [1,2]. Cisplatin-based chemotherapy is effective in the first-line metastatic setting, but responses are not long lasting. Additionally, second-line single-agent chemotherapy has resulted in meager response rates [3–6]. However, through the recognition of the importance of the role of T-cell inhibitory pathways in regulating the immune response to tumors, promising cancer immunotherapies have now emerged. The development of novel monoclonal antibodies targeting immune checkpoints, such as cytotoxic T-lymphocyte–associated protein-4 and programmed death-1 (PD-1), have resulted in improved outcomes in a wide range of malignancies [7–13]. Recently, atezolizumab, a programmed death-ligand 1 (PD-L1) inhibitor, was granted regulatory approval for the treatment of locally advanced or metastatic urothelial carcinoma that has progressed on or after platinum-based chemotherapy. The success of atezolizumab has now ushered in a new era in the development of therapeutic agents for the management of urothelial carcinoma, focused on building on the early promise of immune-oncology agents.

It should not come as a surprise that patients with urothelial carcinoma respond to immune checkpoint inhibitors. Intravesicular bacillus Calmette-Guerin (BCG) works, at least in part, for the treatment of non–muscle-invasive bladder cancer (NMIBC) through local immune cell recruitment and stimulation [14]. BCG has been shown to reduce recurrence, delay progression, and improve survival rates in patients with NMIBC [15]. As a result, BCG was FDA-approved in 1990 for the treatment of NMIBC, representing one of the earliest cancer immunotherapies. More recently, Alexandrov et al. [16] demonstrated that urothelial carcinoma had one of the highest somatic mutational burdens when compared with a variety of other malignancies, only superseded by melanoma and non–small cell lung cancer (NSCLC). Increasing evidence suggests that the mechanism for the clinical responses to immune checkpoint inhibitors in malignancies with high mutational burden is through the production of a variety of tumor-specific neoantigens capable of eliciting a T-cell response [8].

As outlined in the accompanying review by Zibelman et al. [17], several studies have now shown meaningful durable responses with limited toxicity to immune checkpoint inhibitors in patients with metastatic urothelial

* Corresponding author. Tel. +1-206-288-6292
E-mail address: evanyu@u.washington.edu (E.Y. Yu).

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carcinoma. These studies have been compelling enough to encourage development of the many checkpoint inhibitors in earlier disease settings, and this will be discussed by the accompanying review by Singh and Black [18]. Nonetheless, it is important to point out that, at best, objective response rates (ORR) are in the 30% range. Therefore, most patients are not having radiographic evidence of response from immune checkpoint inhibition and the development of predictive biomarkers to identify likely responders and nonresponders is critical. Sweis and Galsky [19] will thoroughly discuss this issue in their accompanying review, but below we touch base on some of the key issues.

To date, the expression of PD-L1, based on immunohistochemistry (IHC), in tumor or tumor-infiltrating immune cells has been the most widely studied predictive biomarker of response with conflicting results. In early phase trials, ORRs to atezolizumab were assessed based on PD-L1 expression on IHC of tumor-infiltrating immune cells using the Ventana SP 142 assay. Patients with $\geq$ 5% infiltrating immune cells based on IHC staining were scored an IHC 2/3, those with $<$5% infiltrating immune cells were scored an IHC 0/1. In the phase I study, ORRs to atezolizumab were 43.3% and 11.4% in the IHC 2/3 and IHC 0/1 groups, respectively [20]. In cohort 2 of the IMvigor210 phase II study, where patients had received previous platinum-based chemotherapy, the ORR to atezolizumab was 28% in patients with IHC 2/3 as opposed with 10% in those with IHC 0/1 [21]. However, in the cisplatin-ineligible cohort (cohort 1) of the study, the ORR was only slightly higher in the IHC 2/3 patient compared with IHC 0/1 at 28% and 22%, respectively [22]. In the KEYNOTE-012 study, patients with $\geq$1% PD-L1 staining on tumor cells, had a 33% ORR in contrast with only 9% in $<$1% PD-L1 staining patients treated with pembrolizumab using the 22C3 antibody by IHC [23]. Yet, the CheckMate 032 study did not demonstrate significant difference in ORR (24.0% vs. 26.2%) to nivolumab in PD-L1(+) and PD-L1(−) patients with metastatic urothelial cancer [24]. For this study, PD-L1(+) was defined as $\geq$1% PD-L1 expression on tumor cells using the Dako PD-L1 antibody. Taken together, these studies suggest that although there may be some association with PD-L1+ staining and response, the results have been inconsistent. Currently, the Ventana SP 142 assay is approved for PD-L1 testing on tumor-infiltrating immune cells, but is not required before treatment with atezolizumab. However, further investigation is necessary to identify the best assay, appropriate cutoff value to define PD-L1 positivity, and which cells (tumor vs. immune infiltrating or both) are most consistently associated with response. It may be that PD-L1 staining may not ever be a reliable predictive biomarker, as expression of PD-L1 has been shown to be dynamic and heterogeneous, resulting in potential for sampling error [25–27]. Another important point is that the negative predictive value of these assays may be low, as there was a significant proportion of patients in these studies that had responses to treatment and did not stain positive for PD-L1 in the tumor. Furthermore, these responses are frequently durable with limited toxicity in contrast with cytotoxic chemotherapy where responses are often brief and with substantial toxicity. Therefore, it is only logical that all eligible patients be treated with immune checkpoint inhibitors irrespective of PD-L1 staining status until these assays are improved or better predictive biomarkers are identified.

With the limitations of PD-L1 staining in predicting response, alternative potential biomarkers are currently under investigation. High mutational burden has been found to be associated with response to immune checkpoint blockade in melanoma and NSCLC [8,28]. In advanced urothelial carcinoma, Rosenberg et al. examined the effect of mutational load on response to atezolizumab using the FoundationOne panel of 315 cancer genes. The authors found that the median mutation load was significantly higher in responders compared with nonresponders, 12.4 vs. 6.4 per megabase, respectively [29]. Additionally, when mutational load was split into quartiles, there was an association with overall survival in both cohorts of the IMvigor210 study [30]. Mutational load has some encouraging early data as a potential predictive biomarker, however, these results require validation, and there remain many unanswered questions. For example, there remain many patients with a high mutational load who do not respond and visa versa. Some cancers, like clear cell renal cell carcinoma have a very low mutational load and yet still respond to PD-1 inhibition [11]. A likely answer is that there are specific, recurrent genomic alterations that associate with response to immune-oncology agents, and this has been demonstrated in nonsmall lung cancer [8]. High mutational load may be an imperfect marker that just increases the likelihood that a patient has the right set of mutations and neoantigens that can confer response to immune-oncology agents.

Another potential predictive biomarker of response to immune checkpoint blockade is based on The Cancer Genome Atlas classification of tumor subtypes. In cohort 2 of the IMvigor 210 study, ORR to atezolizumab were highest in the luminal II subtype (34%), with the other subtypes having a combined response rate of 14% [29]. Of note, PD-L1 staining in tumor-infiltrating immune cells and tumor cells was highest in the basal subtype, again indicating that PD-L1 may not be an effective predictive biomarker. Interestingly, luminal II and basal subtypes have high T-effector gene expression; however, the basal tumors also have high stromal gene expression as opposed to low stromal gene expression seen in the luminal II subtype [30]. Therefore, it is possible that the immune response is inhibited in the basal subtype because of the high stromal gene expression in the tumor microenvironment, and thus, may represent a potential target for combination therapy in the future [30]. Additionally, luminal I (papillary) subtypes have both low T-effector and stromal gene expression, but