Immune Checkpoint Inhibitor–Based Therapy as a Backbone in Cancer Treatment

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Abstract

At JADPRO Live 2019, Krista M. Rubin, MS, FNP-BC, and Anthony J. Olszanski, MD, RPh, reviewed the basic concepts of immunotherapy and the current treatment landscape, and discussed emerging data for immune checkpoint inhibitor–based combinations that are being explored in late-stage clinical trials.

The armamentarium of oncology health-care providers was restricted to chemotherapy for decades, but today's treatment landscape is dominated by a host of novel agents, including immunotherapies, which have significantly improved outcomes for many patients, even cure for some patients with diseases once considered to be untreatable only recently. With these new agents, however, comes a steep learning curve for health-care providers who are grappling with unfamiliar terminology and a need to understand concepts once reserved for scientists. At JADPRO Live 2019, Krista M. Rubin, MS, FNP-BC, and Anthony J. Olszanski, MD, RPh, discussed the use of agents with novel mechanisms of action and toxicity profiles.

"Advanced practitioners are in a strategic position to influence treatment outcomes, but the contemporary oncology care environment poses new challenges," said Ms. Rubin, a nurse practitioner in the Center for Melanoma at Massachusetts General Hospital in Boston. "Vigilance, knowledge, willingness for ongoing learning, and the ability to navigate a rapidly changing landscape are now requirements for the job."

As Dr. Olszanski explained, oncologists now have access to numerous agents, such as targeted therapy, and the introduction of synthetic biology to augment or hone natural mechanisms of disease control. What's more, a plethora of approved agents that enhance the natural immune system has opened up new opportunities for treatment.

"The field of immuno-oncology has exploded since 2011, extending from melanoma to treat a stunning breadth of diseases, and patients are now surviving well beyond historical

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metrics," said Dr. Olszanski, Director of the Phase I Developmental Therapeutics Program, the Director of the Medical Oncology Melanoma Program, and Vice Chair of the Department of Hematology-Oncology at Fox Chase Cancer Center. "This success, in turn, has impacted drug development, which is now flooded with a multitude of investigational agents, some of which appear to border on scientific fantasy."

IMMUNOTHERAPY

Of all the immunotherapeutic agents available, checkpoint inhibitors have perhaps received the most attention. As Dr. Olszanski reported, there are currently seven immune checkpoint inhibitors approved by the FDA. These agents fall into three categories: anti–CTLA-4 (ipilimumab); anti–PD-1 antibodies (pembrolizumab, nivolumab, and cemiplimab); and anti–PD-L1 antibodies (atezolizumab, avelumab, and durvalumab). At the time of the session, combination ipilimumab and nivolumab was also approved in metastatic melanoma and advanced renal cell carcinoma.

"Melanoma is a great example of a cancer once thought to be incurable that had no effective treatments available—nothing that prolonged survival," said Dr. Olszanski. "Even in the world of interleukin-2, there was only a 6% complete response rate, and only those patients appeared to have a survival advantage."

As Figure 1 shows, cancer treatment regimens that include immunotherapy have dramatically raised the tail of the curve, increasing overall survival relative to standard cancer therapies.

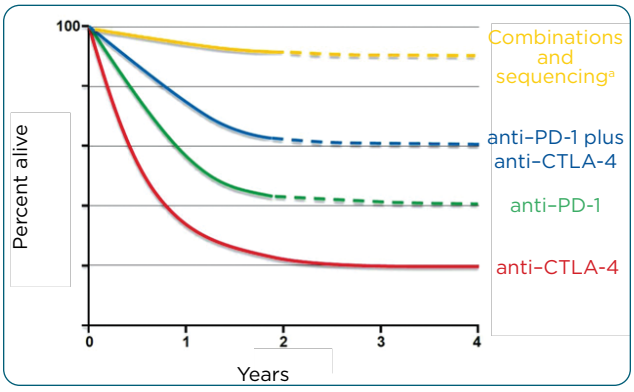

Figure 1. Duration of effect of single agent and combination cancer immunotherapies on survival. This graph does not represent exact data. Adapted from Emens et al. (2017).
[a]Ongoing investigations.

PREDICTING PATIENT RESPONSE

As researchers attempt to determine the best treatment approaches, it's up to clinicians to keep patients on treatment and healthy as long as possible by guiding proper management. This starts with patient selection. As Ms. Rubin reported, pembrolizumab was approved in the first-line setting of mNSCLC in patients with greater than 50% PD-L1 expression.

"We have recognized that there is clearly a relationship between PD-L1 expression and responses, but in truth, there is much variability among responders. While best responses tend to be seen in patients with higher PD-L1 expression, responses have also been seen in patients whose tumors express little or no PD-L1," said Ms. Rubin.

PD-L1 is still being investigated and is an important marker of drug discovery, but is not necessary for every disease. In metastatic melanoma, for example, PD-L1 status is not used as a clinical decision-maker. There are other areas of research being explored to predict patient response. As Ms. Rubin explained, the tumor microenvironment has received a lot of attention recently as researchers search for clues within the immune system, including T-cell activation and T-cell infiltration.

"The pathology report contains quantitative analysis of T-cell infiltrates," said Ms. Rubin. "The goal is for the immune system to recognize the melanoma in the skin, so if T cells have been identified within the tumor, which usually happens quickly, then we are very reassured."

Although the tumor microenvironment has become a hot topic of research, Ms. Rubin also emphasized the need for caution with respect to recommendations for patients.

"We really want to be thoughtful about the influence we have on the gut microbiome," said Ms. Rubin. "The big concern is affecting a patient's chance of responding to treatment by inadvertently manipulating their gut bacteria."

In potential candidates for immunotherapy, for example, said Dr. Olszanski, the use of antibiotics should be reserved for more serious diagnoses than sinusitis, i.e., nasal congestion, which is a common side effect associated with checkpoint inhibitors.

"We have to treat patients using evidence-based medicine," Dr. Olszanski added. "Sinus congestion is one of the most underreported side effects observed with chronic use of checkpoint

inhibitors. Patients can lose their sense of taste and smell, and their primary care provider may want to prescribe antibiotics."

According to Ms. Rubin, part of being an advanced practitioner involves education of not only patients but other health-care providers whose specialty is not oncology. Mindfulness of all the medications patients are on and the potential interactions is also critical for success, she said.

BIOMARKERS OF TOXICITY

Radical advancements in cancer therapies have also brought a host of challenging toxicities. Research into biomarkers is not only aimed at predicting patient outcomes, said Ms. Rubin, but also the likelihood of associated toxicity.

"The last thing we want is for patients to have serious and potentially permanent or life-threatening toxicity when they may not have needed the drug, so we really need to focus on these biomarkers that may help us determine best responders," said Ms. Rubin. "A lot of attention is now being directed at assessing risk for toxicity and identifying biomarkers that suggest how long patients should be treated."

Several immunotherapeutic agents were approved for indefinite use, meaning that patients would remain on treatment until intolerable side effects or relapse, which could be a very long time. Moreover, with dual checkpoint inhibitor therapy, indefinite treatment duration poses even greater challenges, as more than half of patients experience grade 3 or higher toxicity (Weber et al., 2016).

"Patients on dual checkpoint inhibitors have the potential to be very sick, which makes it especially important for providers to have a solid understanding of potential toxicities associated with these agents," said Ms. Rubin.

Nevertheless, said Dr. Olszanski, while toxicity is an expectation, it's one that providers are expected to be able to manage properly. It's important to remember that the enemy is cancer, he observed.

"We have seen many patients who were taken off therapy because they were mismanaged, when in reality, they could do well with proper management," said Ms. Rubin.

ENHANCING TREATMENT EFFECTS

Finally, in addition to combining modalities, other approaches are being explored to enhance treatment effects. As Ms. Rubin reported, clinicians have observed abscopal effects in many patients following radiation therapy, whereby shrinkage of untreated tumors occurs concurrently with shrinkage of tumors within the scope of the localized treatment (Weichselbaum, Liang, Deng, & Fu, 2017).

"The hypothesis is that radiotherapy is exerting a direct cytotoxic effect on tumor cells while also reprogramming the tumor microenvironment to exert a potent antitumor immune response and enhances antitumor immunity," Ms. Rubin explained.

According to the presenters, oncolytic viruses are another exciting area of research (Marelli, Howells, Lemoine, & Wang, 2018). In melanoma, for example, the FDA has approved an oncolytic herpes virus, talimogene laherparepvec (TVEC), as a direct intratumoral injection.

"With melanoma, we see a lot of local disease, presenting as bulky tumors in the area of the primary, and it can be quite terrible and morbid for many of our patients," said Ms. Rubin. "The goal with an oncolytic virus is have a local effect on the area of the tumors and then possibly a systemic effect, as well. I think we'll see much more of this approach in the future." ●

Disclosure

Ms. Rubin has served as a consultant for Merck. Dr. Olszanski has received research support and acted as a consultant for Alkermes, Array, Merck, Merck-EMD Serono, Novartis, and Pfizer.

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