ASSOCIATION OF COMMUNITY CANCER CENTERS

IMMUNO-ONCOLOGY INSTITUTE

Predictive Modeling to Inform IO Regimen Choice

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Immune-related adverse events (irAEs) are extremely common in patients being treated with checkpoint inhibitors for advanced melanoma. The type, quality, and severity of these adverse events, however, varies by treatment regimen and by patient. For example, in patients receiving the combination of the CTLA-4 inhibitor ipilimumab and the PD-1 inhibitor nivolumab for metastatic melanoma, up to 50% experience a severe irAE, leading to trips to the emergency room, hospitalizations, discontinuation of therapy, and sometimes life-threatening or fatal sequelae. While the rate of irAEs is lower in patients receiving PD-1 agents alone, patients with pre-existing autoimmune disease, such as rheumatoid arthritis or lupus, have higher toxicity rates with potentially lower response rates to IO agents.

How might cross-specialty collaboration accelerate development of predictive modeling to inform IO regimen choice?

Efficacy of these agents is also dependent on multiple factors. Patients with advanced melanoma who express PD-L1 appear more likely to have a response to single-agent PD-1 inhibitors than those whose tumors do not. But patients who develop an autoimmune toxicity to checkpoint inhibitors requiring discontinuation of therapy (e.g., colitis or hepatitis) have similar efficacy rates to those who continue on therapy, leading some to speculate that autoimmune toxicity may be an on-target effect of these agents.

Beyond the above general principles, we do not yet have the tools to predict which patients will achieve efficacy and which will develop toxicity on checkpoint inhibitors. For example, age does not appear to predict toxicity type or severity. BRAF mutational status may be associated with poorer response, but the data are unclear. As such, therapeutic decision-making is compromised. In the first line treatment of advanced melanoma, choices include single-agent PD-1 inhibitors, combination PD-1 and CTLA-4 inhibitors, and, in those with BRAF mutations, BRAF and MEK inhibitors. If we are able to develop better predictive models for who will achieve efficacy and who will develop toxicity to these agents, then we could potentially tailor a personalized, individualized regimen for each patient.

These predictive models should include models that can be best provided by large databases and various modeling techniques. They should take into account not only disease characteristics, such as stage, but also genomic and histologic features. Extensive exploration of retrospective data in patients treated with these agents might also allow pattern development based on clinical characteristics. A robust system of patient-reported outcomes (PROs), concomitant medications, and patient demographics could allow for retrospective analysis among patients who have received IO for melanoma, and could suggest associations that predict efficacy and toxicity. Combining these clinical data, often available retrospectively in patient charts or through well-designed prospective observational trials, with known genomic and histologic data could help create a signature that might predict for efficacy and toxicity. Similarly, real-time PROs might predict real-time impending toxicity or failure of efficacy.

Only now, with newly available large-scale clinical genomic data at our fingertips, can we begin to explore the possibility of predictive modeling.

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The ACCC Immuno-Oncology Institute is supported by Bristol-Myers Squibb (charitable donation); EMD Serono; Kite, a Gilead Company; and Merck & Co, Inc. (educational grant).