

Immuno-Oncology: Breaking Barriers, Exploring Solutions, Improving Patient Care

ACCC Immuno-Oncology Institute Virtual Visiting Experts Recap

Breaking Barriers

For many patients with cancer, immune checkpoint inhibitors represent a game-changing innovation. Each year approximately 270,000 cancer patients are treated with immuno-oncology (IO) agents, and today a majority of community oncologists are using IO agents in clinical practice. Since the first United States (U.S.) Food and Drug Administration (FDA) approval for ipilimumab in 2011, six checkpoint inhibitor agents are now approved for a range of indications, and two chimeric antigen receptor T-cell (CART-cell) therapies are approved for hematological malignancies. As these exciting advances move into mainstream clinical practice, the Association of Community Cancer Centers (ACCC) member survey data show that it remains complex for cancer care teams to integrate biomarkers into practice, select patients for IO therapy, and monitor treatment response and the emergence of immune-related adverse effects (irAEs).

Although IO therapies produce durable benefit for many patients, immunotherapy response entails a multi-step process that includes initial immunotherapy administration, immune cell activation and proliferation, and the effect of treatment on the tumor.^{1,2} Response patterns pose monitoring challenges for clinicians, especially since patients can respond weeks to months following initial treatment and even modest response is often associated with overall survival benefit. At the same time, IO agents have unique immune-related toxicities. While these are

relatively infrequent, irAEs can be potentially fatal and can occur up to two years after the last IO treatment dose. Many irAEs are challenging to recognize, in part because they were under-reported in clinical trials (e.g., musculoskeletal and cardiac adverse effects),³ and in part because the presentation of some autoimmune irAEs (e.g., nephritis or diabetes) is often distinct from how these conditions present outside of the immunotherapy setting. Adding to the complexity, new indications are emerging and combination therapy continues to expand, bringing fresh challenges for identifying patients that would benefit from combination approaches over single agent therapy. Combination approaches also increase the potential for irAEs and reinforce the importance of developing sound monitoring strategies, as well as the need for biomarkers to determine irAE risk.

As immuno-oncology is increasingly integrated into community practice, experience with and knowledge of effective management of patients receiving IO therapies continue to grow. Thus, there is a clear need for ongoing education for clinicians and the entire multidisciplinary oncology care team. In response, the ACCC Immuno-Oncology Institute developed a multidisciplinary curriculum workshop bringing together faculty experienced in delivery of immunotherapy with cancer program staff in the earlier stages of IO integration. Over the past two years, these IO Visiting Experts Programs were hosted by ACCC Cancer Program Members nationwide. Faculty and participants engaged in discussions on the

WEBINAR FEATURED FACULTY:
Immuno-Oncology: Breaking Barriers, Exploring Solutions, Improving Patient Care

- Tanguy Seiwert, MD, Assistant Professor of Medicine, University of Chicago, Illinois
- Una Hopkins, RN, FNP-BC, DNP, Administrative Director, Cancer Program, White Plains Hospital, Center for Cancer Care White Plains, New York
- Vamsidhar Velcheti, MD, FACP, FCCP, Director of Thoracic Oncology, NYU Langone Perlmutter Cancer Center, New York
- Ali McBride, PharmD, MS, BCOP, Clinical Coordinator, Hematology/Oncology, University of Arizona Cancer Center, Department of Pharmacy, Arizona

Dr. Velcheti was formerly with Cleveland Clinic, Ohio

nuances and complexities of IO delivery, with a focus on advancements, operations, and effective practices.

To expand the reach of this highly successful IO Visiting Experts Program, key discussion points were distilled into a virtual interactive webinar presented in July 2018 by a multidisciplinary oncology faculty—comprised of an oncologist, administrator, nurse, and pharmacist. This article summarizes top-line takeaways from the webinar along with frequently asked questions on integrating immunotherapy into practice from Visiting Expert Program participating sites. Access the full webinar on demand at acc-cancer.org/io-breaking-barriers

Exploring Solutions

Effective Strategies for Monitoring and Managing irAEs

Monitoring patients' irAEs demands clinical vigilance by a broad multidisciplinary team that includes an expanded range of specialists with experience in the unique characteristics and management of irAEs. During his presentation, Dr. Vamsidhar Velcheti emphasized the value of identifying champions in each relevant specialty who can provide oversight, ensure staff and patient education, and implement locally relevant strategies that have potential to prevent adverse event escalation and reduce hospital admissions, which is ultimately key to reducing costs of care (Figure 1).⁴

Patients with emergent irAEs may seek care in a variety of

settings [e.g., primary care, emergency room (ER), urgent care]; therefore, it is crucial to educate a wide range of staff about IO treatment and recognition of adverse events, including not only infusion nurses and internists or hospitalists, but also primary care physicians and ER providers, through tried and tested education strategies such as:

- “Lunch and Learn” sessions that partner with pharmaceutical companies or grand rounds and nursing rounds;
- Biweekly institutional tumor boards that encourage participation from regional oncologists and encourage active discussion of complex cases—this can be especially relevant for treating patients with IO who have pre-existing conditions for which there may be no data as yet; and
- IO sessions targeting ER fellows to provide an overview of irAE signs and symptoms in the first-line emergency setting.

ACCC has also developed resources to support community cancer programs in developing multi-specialty toxicity teams focused on irAEs. Additionally, patients need to be engaged participants in their care, educated on and aware of immediate, as well as, late-emerging or chronic side effects. Patients and caregivers need consistent education and reinforcement on the importance of reporting irAEs to their oncology care team and of having a contingency plan for managing adverse effects.

Figure 1. Effective Strategies for Monitoring and Managing irAEs



Finally, published guidelines on irAE management from the National Comprehensive Cancer Network (NCCN), the American Society of Clinical Oncology (ASCO), and the Society for Immunotherapy in Cancer (SITC), and information from pharmaceutical companies are available in downloadable formats for phones and tablets.

Clinical Trials and Biomarkers

Several biomarkers currently exist to identify response to checkpoint inhibitors including expression of programmed death ligand-1 (PD-L1), microsatellite instability (MSI), and tumor mutational burden (TMB). Currently, clinicians have little capacity to predict the onset of serious irAEs and autoimmune events. Thus, new classes of biomarkers and biomarker combinations to determine patients at high risk for irAEs are an active area of research. Among these biomarkers are targets such as auto-antibodies and canonical disease auto-antibodies, T-cell epitope spreading and auto-reactive T-cells, and the effects of microbiome diversity on immune repertoire and tolerance. Until these and other biomarkers are approved, the toxicity profiles of checkpoint inhibitors provide a useful decision-making resource to guide individualized therapy selection.

Improving Patient Outcomes

Financial Access, Reimbursement Processes, and Budgeting

Financial toxicity remains a significant operational barrier to IO treatment. For Una Hopkins, RN, FNP-BC, DNP, overcoming this hurdle means that individualized care must include allocating resources to support financial navigation for patients. While employing financial advocates or medication assistance coordinators is a significant investment for community cancer

programs—as these services are not reimbursable—establishing this role within a cancer program mitigates the patient’s distress, expands awareness of financial resources, and helps to ensure the sustainability of treatment. Dr. Hopkins also recommends identifying a point person from the financial or reimbursement staff to focus on IO agents and build expertise on the nuances of the various patient support programs, including manufacturer replacement programs, co-pay support programs, co-pay foundations, and patient assistance programs, in order to identify and liaise effectively with pharmaceutical partners.

These new agents are costly, so careful attention to reimbursement is an imperative operational concern. For example, new-to-market IO agents often lack a specific J Code (or in the case of drugs paid under the Hospital Outpatient Prospective Payment System, a C Code). To ensure accurate reimbursement, the financial team should establish clear approval, reimbursement, and billing processes (Figure 2), and designate a reimbursement specialist to liaise with pharmacy and regularly review approvals and denials (Figure 3).

The Role of the Oncology Pharmacy in Integrating IO Therapies to Clinical Practice

As more combination therapies emerge and sequencing options expand, and as payer approval becomes increasingly dependent on the results of PD-L1 and other forms of testing, it will be important for pharmacists, whose role extends across clinical care (Figure 4), to work hand-in-hand with oncologists and other members of the oncology team to select treatment, determine dosing, incorporate testing panels into the workflow, and secure access to treatment with immunotherapy.

Figure 2. Recommendations for Approval and Reimbursement Processes

APPROVAL PROCESS		PAYER APPROVAL PROCESS	
High Dollar Medication Approval Process	Robust Off-Label Policy and Procedure	Physician/Advanced Practice Provider	Pharmacist Role
<ul style="list-style-type: none"> • Full benefits investigation • Utilize pharma services if allowed per program policy • Prioritize staff resources to enroll every viable patient into a support program, regardless of on or off-label use 	<ul style="list-style-type: none"> • Predetermine all off-label requests • Make patients aware of risks/benefits, including financial risk • Require patients to sign an Advance Beneficiary Notice or Notice of Non-Coverage • Use peer review process for appeal if needed 	<ul style="list-style-type: none"> • Identify patient who may benefit from IO therapy • Participate in peer-to-peer conversations if needed • Discuss rationale for off-label use if applicable • Provide additional primary literature support if necessary 	<ul style="list-style-type: none"> • Retrieve supporting literature • Monitor and review CMS approved compendia and national/local coverage • Track off-label use • Entry should trigger alerts to pharmacy director, P&T Committee chair, and reimbursement specialist team

Figure 3. Features of the Reimbursement Specialist Role

<ul style="list-style-type: none">• Verify medical insurance
<ul style="list-style-type: none">• Obtain copies of pertinent information from patient medical record (treatment plan, diagnostic studies, etc.)
<ul style="list-style-type: none">• Retrieve supporting literature (if not already provided by team)
<ul style="list-style-type: none">• Verify compendia and NCD/LCD support
<ul style="list-style-type: none">• Identify appropriate ICD-10 code(s) and HCPCS code(s) for medications
<ul style="list-style-type: none">• Draft letter of medical necessity (prescriber to sign)
<ul style="list-style-type: none">• Fax letter and supporting evidence to payer
<ul style="list-style-type: none">• Confirm payer has received information
<ul style="list-style-type: none">• Continue to follow up until approval/denial received, have process in place to track these

While such access in many other countries is highly regulated and determined by technology assessments and other mechanisms, in the U.S., institutional formulary review plays a larger role. In the U.S. hospital Pharmacy and Therapeutics (P&T) Committees are another crucial mechanism for weighing institutional costs against putative clinical benefits, especially if there are small efficacy differences between therapies but there are other differences that might be important to consider (e.g., dosing schedules, route of administration). Care pathways also are another mechanism that can be used to optimize decisions on which therapies to carry on formulary.

When integrating IO into practice, the oncology pharmacy is a key resource for other critical operational concerns, such as inventory management, medication preparation, dispensing and distribution, and managing drug waste (e.g., through rounding or flat-dosing). Oncology pharmacists also provide oversight for medication safety, electronic medical record use, and compliance with risk and mitigation strategies. Finally, the oncology pharmacy plays a key role in managing off-label IO use in circumstances where there are no other treatment options for patients or where therapies are supported by NCCN guidelines but not yet FDA-approved, through, for instance, drug replacement programs. The recently enacted Right to Try legislation also enables terminally ill patients who have exhausted all other treatment options to seek access to Phase 1 investigational therapies, including immunotherapies.

Conclusion

Novel IO agents with differing mechanisms of action and combination immunotherapies will continue to improve overall outcomes for patients with cancer. As Dr. Tanguy Siewert observed: *survivorship is a good problem to have*. We didn't have people in lung cancer who survived 3-5 years and now we see patients with dramatic benefit and so we need to start thinking about survivorship.

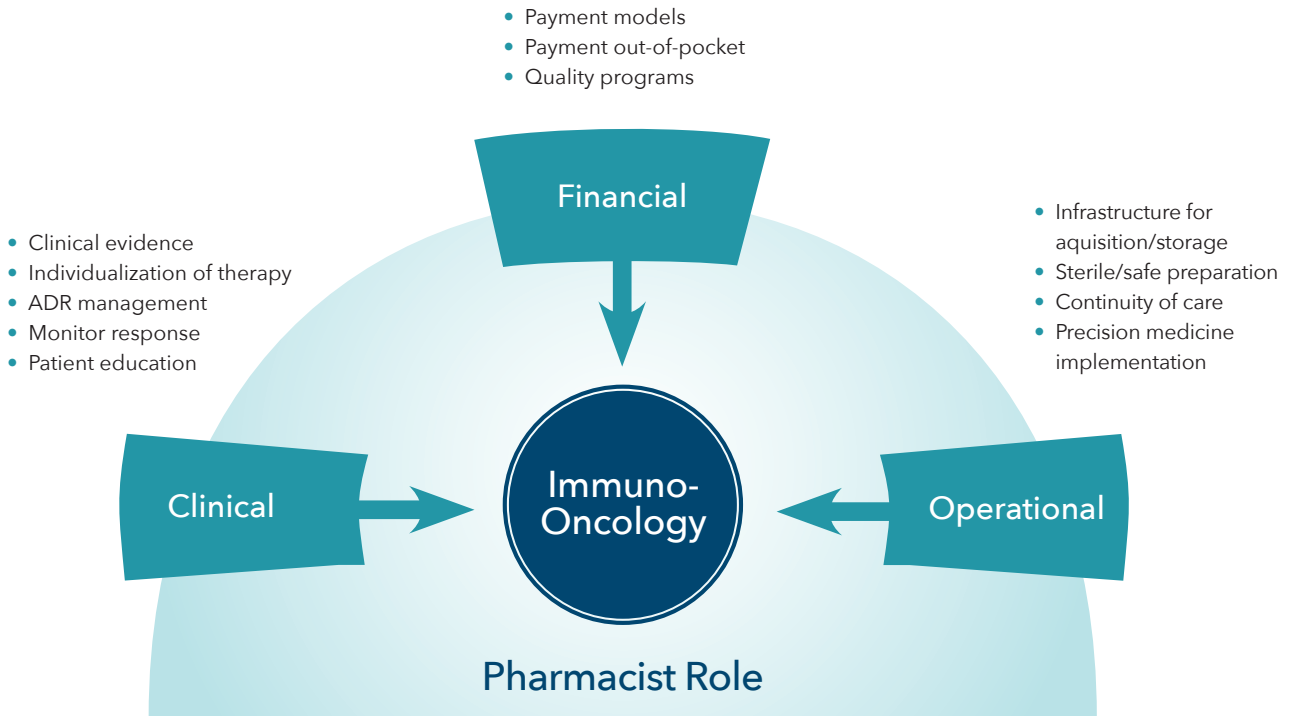
Yet the rapid pace of advancement and the volume of information in the IO arena remains challenging for cancer care teams to absorb. Ongoing education will continue to be critical for the entire cancer care team, including non-oncology specialists, patients and caregivers. And the "good problem to have," survivorship, is also becoming an increasingly important issue in IO. As the number of survivors treated with IO grows, it is imperative to educate patients and their families not only about the potential benefits, but also the limitations of treatment. Finally, although the publication of evidence-based guidelines is a welcome development in irAE management, many questions remain about differences in irAEs among IO agents, the potential for prolonged duration of irAEs, and whether and how to re-challenge patients with immunotherapy following the development of irAEs. Therefore, toxicity teams and other strategies to manage irAEs are critical approaches to effectively managing irAEs and optimizing patient outcomes.

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Figure 4. Pharmacist Role in Immuno-Oncology



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Educational Grant

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