Weighing Evidence Quality in Interventional Oncology

The importance of understanding the levels of evidence related to IO therapies and areas for future research.

BY DEREK BIEDERMAN, MD, AND EDWARD KIM, MD

Providing evidence-based medicine is vital to the delivery of premium patient care without exorbitant costs or undue patient harm. If data are the currency of evidence-based medicine, perhaps interventional radiology can be likened to a proverbial technology startup—tremendous upside potential but a little short on cash. Throughout history, innovation has been constant, rapid, and intertwined within the fabric of the specialty. Although the pace of innovation has undoubtedly been an advantage to interventional radiology, it has also created predictable challenges relating to data accrual and clinical trial design.

WEIGHING THE EVIDENCE FOR IO THERAPIES

In an ideal scenario, clinical decisions would be solely based on level IA evidence—randomized controlled trials (RCTs) with mortality as the primary endpoint. If level IA evidence were able to be rapidly obtained at a low cost, then this ideal scenario would likely mimic reality. However, for many important clinical questions, this is not the case. Understanding the levels of evidence is a critical component to providing the best possible patient care and acting as an informed participant in a tumor board. Hickey et al published an informative review on this topic for interventional oncologists.[1,2]

In reviewing the evidence supporting specific therapies in interventional oncology (IO), it is logical to begin with the initial prospective RCTs showing a survival benefit for chemoembolization over supportive therapy.[3,4] These landmark studies provide the foundation for the level IA recommendation for the use of chemoembolization as a first-line therapy in Barcelona Clinic Liver Cancer (BCLC) stage B patients, and these studies changed the paradigm in the newly burgeoning field of IO. As such, in intermediate-stage patients, chemoembolization has been established as the standard of care, and thus trial designs need to have chemoembolization as the control arm. However, using overall survival as the primary endpoint for a phase 3 RCT in this patient population with a median overall survival of 20 months can be difficult, and surrogate endpoints such as objective response, progression-free survival, and duration of response have been more cost-effective in phase 2 studies, such as PRECISION V. It is interesting to note the difference in the level of evidence supporting chemoembolization (level IA) and the level of evidence supporting transplantation as first-line therapy in patients who are not candidates for resection (level IIA).[5] This is by no means to proclaim the superiority of interventional radiology in practicing evidence-based medicine, but to illustrate how level I evidence, the highest level of evidence that can be generated through good clinical trial design, is not the be-all and end-all of decision-making in clinical practice.

The clinical impact of the choice of delivery vector for chemoembolization in the treatment of hepatocellular carcinoma (HCC) was studied in the PRECISION V trial, which provided level ID evidence of improved toxicity of drug-eluting beads over conventional chemoembolization.[6] Level I evidence also exists for radiofrequency ablation in the treatment of HCC < 3 cm, with data showing similar survival rates compared to resection.[7] An informative prospective randomized study comparing chemoembolization combined with ablation versus chemoembolization alone by Peng et al demonstrated a survival benefit for combination therapy compared to monotherapy.[8]

Radioembolization, an increasingly used intra-arterial therapy for primary and metastatic liver tumors, has been the topic of several recent high-profile studies. Compared to standard medical therapy alone, resin-based yttrium-90 (Y-90) therapy in the treatment of colorectal cancer showed the initially encouraging result in the SIRFLOX study of improved progression-free survival in the liver when combined with standard medical therapy.[9] However, this result did not translate into a direct overall survival benefit in the subsequent combined analysis of the FOXFIRE, SIRFLOX, and FOXFIRE Global trials.[10]

A potential topic of further study is the difference in survival seen between patients with right-sided and left-sided colon cancers, with a significant survival benefit for radioembolization seen in the latter group. Recently, the SARAH trial and the SIRveNIb trial, two randomized prospective trials comparing patients with advanced-stage HCC treated with resin-based radioembolization versus sorafenib, did not demonstrate significantly different survival between the two treatment arms.[11,12] Notably, quality-of-life outcomes were more favorable in the radioembolization treatment arms in both studies.[11,12] Outcomes from two prospective studies on glass-based radioembolization in the treatment of HCC, the STOP HCC trial (NCT0155649) and SORAMIC trial (NCT01126645), are eagerly awaited. A recent RCT performed by Salem et al provided level I efficacy data favoring Y-90 therapy over conventional chemoembolization in BCLC stage A/B patients.[13]

AREAS FOR FUTURE RESEARCH

Despite the steady progress in IO research over the past 2 decades, numerous unanswered questions remain. Niche applications of radioembolization, such as radiation segmentectomy, have garnered interest based on several promising retrospective studies.[14-16] Duplicating these results in a prospective fashion can be challenging given the longer median survival of patients with early and intermediate-stage HCC. Prospective studies comparing radiation segmentectomy to ablative therapy or resection using progression-free survival as an endpoint is a more realistic near-term goal, as progression-free survival have a favored endpoint and surrogate of survival in this patient population because these patients are Child-Pugh A with a diminished risk of the confounding variable of death from natural progression of cirrhosis.

Tailoring treatment options and decisions based on tumor biology is another area that is ripe for further exploration in IO, which mirrors a trend across all of medicine and is currently a topic of active study in the field of medical oncology. Knowing which patients stand to benefit most from interventions could be transformative for IO because it could markedly improve patient outcomes, while avoiding the patient risk and financial cost of treatments that are unlikely to provide a significant benefit. An additional possibility is that knowledge of tumor biology could be utilized in a manner to improve study design. As previously mentioned, in the combined analysis of the FOXFIRE, SIRFLOX, and FOXFIRE Global trials, treatment with radioembolization did not appear to have a significant impact on survival across the entire cohort of patients. During subgroup analysis, a subpopulation of patients with right-sided colon tumors treated with radioembolization had a significant survival benefit. Although this study was not powered to analyze this subgroup of patients, this may provide a signal for further investigation and trial design in this patient population, such as potential differences in the tumor biology and responsiveness to radiation therapy. It may be possible to test therapies in vitro on different tumors of varying genetic composition, enabling smaller studies to be conducted with patients who have molecular tumor profiles known to be highly susceptible to the proposed therapy. Even a modest understanding of how genetic differences in tumors may influence the response to therapy could help tailor the design of eventual prospective studies.

Immuno-oncology is a rapidly burgeoning sector of oncologic medicine, which also remains understudied in IO. Unlike surgical oncology, where the tumor is physically removed from the body, IO therapies kill tumor cells, releasing intracellular contents within the body. This intracellular material contains numerous antigens, which could theoretically potentiate a cellular immune response awakening and activate the body's own intrinsic cancer-fighting mechanisms.[17,18]

CONCLUSION

The pace of innovation and growth in IO necessitates that careful attention be paid to making clinical decisions using the highest-quality evidence possible. Having a robust understanding of the levels of evidence is a critical aspect of providing high-quality patient care and is also important when engaging skeptical clinicians from other oncologic-based specialties. Many IO treatments are supported by level I evidence. However, there are important questions that are either incompletely answered or have yet to be studied. A greater understanding of tumor biology and its potential impact on the efficacy of therapies and the potential synergistic interplay of IO and immuno-oncology are exciting topics for further study. ■

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Derek Biederman, MD
Department of Interventional Radiology
Icahn School of Medicine at Mount Sinai
New York, New York
Disclosures: None.

Edward Kim, MD
Department of Interventional Radiology
Icahn School of Medicine at Mount Sinai
New York, New York
edward.kim@mountsinai.org
Disclosures: Advisory board and speaker's bureau for BTG plc, Boston Scientific Corporation; advisory board for Bristol-Meyers Squibb.