Novel Embolotherapy and Combination Therapy for Interventional Oncology

A discussion on the landscape of IO combination therapies, the future of radiogenomics, and the effect of center and operator volume on IO procedures.

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With immunotherapy garnering increased prominence over the past several years, what are the primary ways in which interventional oncology (IO) can augment the exciting potential of this field?

This is where IO can have a pivotal, very empowering role. One of the things we've discovered about immunotherapy is that it often needs an adjunct therapy for greater benefit. In fact, several trials are now combining multiple immunotherapies or immunotherapy with targeted therapies. Most locoregional therapies are associated with a weak immune response that may be synergistic and/or amplified when combined with immunotherapy. Therefore, the combination is theoretically appealing. Our procedures can almost act like vaccines.

What is IO's potential role in the Cancer Moonshot Initiative? What would need to happen politically to get the global oncology community together?

In Cancer Moonshot, IO would have to be used in combination with a systemic therapy or with another combination. To succeed, we need multiple specialties coming together. In my microcosm, we're very in line with our surgeons, oncologists, and radiation oncologists. We have great relationships, and we collaborate on several projects involving systemic, surgical, and locoregional therapies—with the surgeon, oncologist, or me serving as principal investigator on various trials. When collaborations increasingly occur on the ground, societies often then follow suit. However, we need the literature to support the combined approach. When the literature shows that this works, people will want to listen.

How would you characterize the current literature base for IO combination therapies?

It's in its fetal stages, but there is a lot of excitement. There are several preclinical trials and a few clinical trials, but it's minimal on clinicaltrials.gov. That being said, the clinical rigor is high, partly because a lot of oncologists are involved in those trials. Prospective randomized trials are the benchmark, but registries do have a very important role. Starting with a registry can help hone in on which populations to include in a prospective randomized trial. The trial success rate can increase if it is tailored to the appropriate patient population. However, there are lot of things we don't understand in this field, and thus further studies are needed. For example, some patients initially respond to immunotherapy but then stop responding over a period of time. What other factors are coming into play that cause that new onset of resistance, and how do we prevent that? And what is it, in addition to certain biomarkers, that makes some people respond fabulously and some not respond? There are so many questions and so many opportunities.

Which novel combination therapies do you believe are closest to prime time, and how close are they?

I think locoregional therapy plus anti–programmed death-1 (anti-PD-1) or anti–cytotoxic T-lymphocyte–associated protein (anti-CTLA) for liver cancer is the closest. We have a combination trial at University of California, Irvine and another trial in Europe currently recruiting patients evaluating the combination of locoregional therapy and immunotherapy with anti-PD-1 on clinicaltrials.gov. In my previous life at the National Institutes of Health, Dr. Wood and I were coauthors on an article published by Drs. Duffy

and Greten on the combination of anti-CTLA-4 and ablation (NCT01853618).[1]

Especially in newer fields, clinical trial experiences can teach us not only the degree to which novel therapies are successful but also how to better study future therapies in the same setting. How have the endpoints of modern IO trials evolved in recent years, and for what reasons? How do you predict endpoints will change, if at all?

That's a very controversial question. Recently, IO trials are less about overall survival (OS) and more about progression-free survival (PFS) and softer endpoints such as response and time to progression. The FDA and the oncology community still want to examine OS as the main endpoint, but they have been more open toward significant patient-centric endpoints such as PFS. That being said, other endpoints will not fly. We tried to get a phase 2 trial with response rates as the primary endpoint, and the FDA did not agree, so instead we chose PFS. However, depending on the patient population, I do not think that OS is realistically feasible, such as with intermediate hepatocellular carcinoma. We can look at OS if it's end-stage hepatocellular carcinoma or end-stage colorectal cancer, but when there is the potential for 5-year survival and several lines of systemic therapies can be given, things will get muddied and it's hard to evaluate OS. The theme of this year's Society of Interventional Radiology (SIR) annual meeting was joining the big leagues, and part of this is upping our game and our research. The quality of our research must improve to the level of our oncology colleagues, and I do believe that it is.

What do we currently know about how volume of the center or operator skill set affects outcomes in IO procedures?

Several surgical studies have demonstrated that the more experience an operator has, the better patients will do in general. Interventional radiology (IR) is similar in that sense. However, more and more, the small community hospitals want to start offering more advanced procedures, but they do less than a handful per year. This is very common to the United States. In Canada, European countries, and Asia, there are large academic centers where these services are centralized. This may create a patient access issue, but these centers are very experienced. In an article we published, a large-volume center performed 13 ablations in a 10-year time span, which is very low. Although 95% of hospitals were considered as low volume with that definition, that is not how I would define high volume. My definition of a high-volume center would be ≥ 25 procedures per year.

What's more, a lot of hospitals don't have IR or it is not a focus. Interventional radiologists may only do procedures 1 or 2 days a week, and the rest of the week is diagnostic work, or they are told they can do IR, but they have to read 25 CTs per day. It's hard to juggle more advanced procedures, and they just don't have the bandwidth. I do believe that the landscape will change with the new residency.

You've recently published on the intersection of radiogenomics and IR.[2] Where are we most likely to see the results of applying genetic profiles to therapy selection and approach in the near future?

I think "near future" is the key phrase. There's still a lot of work that needs to be done before radiogenomics can be routinely applied. Artificial intelligence and neural networks are the key component. Rather than having biopsies and images tell you the profile of the patient, genetic profiling can help evaluate which biomarkers are present and may help triage patients. The problem with biopsies is that you get a very focal piece of the tumor; you're just taking where your needle went.

An article published in *The New England Journal of Medicine* described intratumoral heterogeneity with numerous mutations within a single tumor.[3] Currently, we look for certain mutations and give patients targeted therapies that kill cells with that mutation, which naturally selects the cells without that mutation to start growing. As a result, we see patients with partial or temporary responses. The concept of multiple biopsies is becoming more mainstream. So, we perform another biopsy, and then we start a different drug, and the patient may respond for a little while, and the cycle continues. However, if we had the ability to analyze the whole tumor rather than what is at the tip of the needle, we may be able to improve the regimen for maximal effect from the start. Moreover, rather than having to perform a series of biopsies in a particular patient, we could obtain the information during routine, completely noninvasive imaging.

Let's say we're talking in 10 years at SIR 2029, and every case is done with a radiogenomic profile. What will have happened between today and then for that to be true?

A lot of technology-savvy experts (way smarter than me) will have analyzed a lot of images. A huge amount of data will need to be studied so that genetics can be correlated with an appearance on imaging while eliminating a lot of noise. At the end of the decade, a computer will analyze the images and determine which three or four mutations are present in that sample or provide a percentage likelihood that the patient carries a specific mutation. To do that, you need thousands and thousands of data.

To an outsider, it might seem as though the barrier to entry in researching IO combination therapies is rather high. What is your advice

for physicians interested in participating in the next phases of research?

I would advise physicians to forge associations within their own hospital. Proposing research ideas and getting buy-in and input from oncologists are key. Second, we need a more pronounced foothold within pharmaceutical companies. Learn about how to do research. More advanced cutting-edge research is associated with a lot of regulations for human protection, but if you do not know the rules, you can get in serious trouble including losing your license to practice medicine. Also, reach out to mentors and make sure that you have the proper infrastructure.

Do you predict increased subspecialization of IO within IR practices, such that a small portion of interventional radiologists will focus entirely on IO, or do you believe that a larger number of interventional radiologists will add certain oncologic procedures to a multifaceted practice?

I think that subspecialization will occur, but currently, we are far from it. A lot of interventional radiologists practice in small community hospitals or private settings where they still have significant amount of diagnostic radiology coverage. Therefore, the first step is getting all interventional radiologists to be 100% IR. That would be a major battle. I am confident that as procedures become less and less invasive, IR will be more in demand and we will obtain 100% IR duties for all practice settings, after which, subspecialization will probably start to happen. The same way we have surgical oncology and vascular surgery, I think we will have vascular IR, oncology IR…we're far from that—we will get there. ■

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Disclosures: Sponsored research with UCI, SillaJen, Sirtex; research collaboration with UCI, Philips Medical Systems Inc., Teclison/Cheery Pharma; shareholder in Bruin Biosciences Inc.