COMMENTARY

Staying on Course

Obtaining the highest level of evidence in interventional oncology requires that we stay on course and strive for positive prospective randomized trials.

BY NADINE ABI-JAOUDEH, MD

Between 2008 and 2016, most oncology prospective randomized trials pertaining to hepatocellular carcinoma (HCC) failed. None of the many trials demonstrated improvement in overall survival (OS) or progression-free survival (PFS). Oncologists kept trying different strategies and different molecules until, lo and behold, they succeeded with regorafenib, nivolumab, and lenvatinib.[1-3] Several other therapeutic strategies are also expected to yield positive results. In fact, some trials are now aiming to compete with transarterial chemoembolization (TACE). During the decade of negative results, the oncology community did not decide that registries were the best option nor did they move away from patient-centered significant endpoints such as OS or PFS. In an investigational device exemption application in which I was involved, the FDA requested that we choose patient-centric endpoints (ie, OS, PFS). During our application, the FDA rejected time to embolization failure and time to progression as primary endpoints, and they are generally not accepted in the oncology community.

Several arguments have been leveled against performing prospective randomized trials, let alone with a survival endpoint, including the fact that several surgical practices were integrated/approved without level I evidence. Indeed, transplantation was approved with level IIA evidence and metastectomy of lung tumors was integrated based on surgical registry data. However, the latter remains controversial, and in both cases, any trial with level I evidence will supplant these therapies. In the end, the group with the level I evidence will get the patients.

Prospective randomized trials are hard and expensive to conduct; however, nothing of value is easily obtained. It may not be possible to obtain level I evidence, but that should always be the goal. Registries reflect population data and are more realistic than the artificial environment of a prospective trial. Registry data should be used to choose the appropriate target population for prospective randomized trials but cannot be the ultimate level of evidence of our specialty. The National Cancer Institute and Oxford Centre for Evidence-Based Medicine developed the level of evidence to define evidence-based medicine.

Finally, one additional argument against prospective trials with a survival endpoint is that patients with intermediate HCC have a prolonged life expectancy. Indeed, the results from studies by Llovet et al[4] and Lo et al[5] cannot be replicated. A prospective randomized trial with OS for intermediate HCC may not be logical, but PFS is an excellent surrogate.

Oncologists learned from their failed trials, and we must learn from their experience. A positive trial requires an effective agent and an appropriate target population. In the regorafenib trial, patients had to have tolerated sorafenib to be enrolled.[1] The appropriate target population is key. For instance, if the yttrium-90 (Y-90) studies were performed in patients with right-sided colorectal cancer, the outcome may have been very different. Registries are an excellent way to narrow down the target population.

We also need to understand the pathophysiologic effects of our procedures. Why is it that certain patients respond to TACE or Y-90, while others do not? When we understand the elements affecting the response, we can choose the right patients and also work on countering the factors preventing the desired response. A focus on basic science research is pivotal, even if it does not profit one particular entity, as it will benefit all of us.

TACE has demonstrated survival benefit for HCC, but several systemic therapies may dethrone TACE with prospective randomized data on PFS and OS.

In the "Tumor Boards in Interventional Oncology" article in this issue of *Endovascular Today*, we involved surgeons, oncologists, and radiation oncologists to raise awareness about novel surgical and radiation oncology therapeutic options (ie, aggressive surgeries for colorectal carcinoma that may limit the role of locoregional therapies). Our specialty should be aware of upcoming oncology and surgical therapeutic options so that we know where we stand.

Finally, prospective randomized trials were chosen to be the best level of evidence for a reason. Ultimately, lowering our standards will only hurt our specialty. We must stay our course, and if it takes 20 years to get another positive trial, 2022 is just around the corner. ■

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