THE CHANGING ONCOLOGY LANDSCAPE: An Interview with Medpace's Franklin O. Smith

Dr. Franklin Smith, Medpace's vice president of medical affairs and specialist in hematology oncology, reflects on advances in oncology drug development.

Q How has the landscape for oncology treatment changed, given the breakthroughs in cancer immunotherapy and precision medicine?

It is important to understand where we have been and how we got to this point because that lays the foundation for current to future cancer therapy. Over the past one hundred years, cancer therapy has evolved so that it's based upon four modalities: surgery, radiation therapy, chemotherapy, and hematopoietic cell transplantation. These modalities are not going to go away anytime in the foreseeable future, but there are likely very few opportunities for big, significant improvements in each of these four areas.

We are now at an exciting time in medicine where we can harness the full power of science and biology, finding ways to take advantage of science, to develop new therapies for patients, such as immunotherapy or immuno-oncology.

Franklin O. Smith, MD, FAAP, FACP

One of the questions that has intrigued scientists and oncologists for decades has been, 'With this very powerful immune system, why does cancer exist? Why doesn't our immune system just take care of it?' What scientists have found is that cancer has found ways to evade the immune system, so these new immunotherapies are based upon ways to now target those evasive maneuvers to make the cancer "visible" to the immune system.

There are two broad categories of immuno-oncology. One is based upon monoclonal antibodies, which block these signals that hide the cancer cells from the immune system. These are called checkpoint inhibitors. The other are cellular therapies, such as CAR-T (chimeric antigen receptor T-cells), which can be genetically engineered to make them into "angry" T-cells, that can specifically target cancer cells.

Immuno-oncology is not going to necessarily replace chemotherapy, surgery, radiation and hematopoietic cell transplantation, but it is increasingly finding its role in cancer therapy. It is probably now starting to replace some chemotherapy, and I think that for the next 10 years, much of the work we are going to see in cancer research and clinical trials is going to be based upon immuno-oncology approaches.

In addition to an increasingly large number of CAR-T cell and similar immune effector cell therapies, we are going to see different combinations of checkpoint inhibitors and checkpoint inhibitors paired with other types of drugs, such as epigenetic modifiers. The next decade of cancer research will likely be based on combination therapies that are largely based on these exciting checkpoint inhibitors.

In terms of precision medicine, I prefer the term 'increasingly precise medicine' because I think physicians have always used personalized therapy for their patients. As we learn more and more about the biology of cancer, medicine and approaches to the treatment of patients gets increasingly sophisticated, and the treatment of patients becomes increasingly precise.

What we are learning now is that there is great heterogeneity in human beings; there is great heterogeneity in cancers. A lot

of these cancers are driven by a relatively small number of driver mutations. If we can understand what is driving a cancer—what is making it resistant to known forms of therapy—we can offer that patient a treatment that is directed specifically to what's driving the cancer. Understanding more about the patient and his/her cancer's biology, we can now start to identify specific treatments that are targeted to specific abnormalities.

Tying these concepts together, we still have the foundation of cancer therapy with chemotherapy, surgery, radiation, and hematopoietic cell transplant, but importantly, we now are adding onto that foundation better knowledge of cancers and drugs that may be more targeted to specific abnormalities in that patient's cancer. We are now learning how to harness the incredible power of the immune system to seek out and kill cancer cells, where these cancers previously had been "hiding in plain sight" from the immune system.

Q What are the key challenges in designing protocols for oncology studies?

We are moving away from assigning treatment based upon the tissue from which the cancer arose. What we are finding is that by using this approach, we have more drugs to test than we have patients available. In terms of designing protocols, we still must assess safety, efficacy and how a new approach to treatment compares to standard approaches. How do we test the large number of drugs and therapies that are becoming available to us when we have an increasingly small number of patients defined by molecular characteristics? This is a great problem to have, but it is a problem, as the competition for patients to enroll on these exciting clinical trials is becoming increasingly challenging.

In terms of our work at Medpace, this challenge can be overcome by outstanding feasibility work and our ongoing work with dedicated and enthusiastic investigators.

Q How do you think master protocols will impact advances in oncology drug development?

Given the paradigm shift to base treatment on identified molecular targets, master protocols are the wave of the future. These study designs are an efficient and effective way to test numerous targeted agents in the context of a single protocol. I have the honor to serve on the Board of Directors for the Leukemia & Lymphoma Society (LLS), which has a master protocol for acute myeloid leukemia (AML). The LLS serves as an "honest broker" to negotiate with numerous pharmaceutical and biotech companies to have their drugs brought into a common master protocol.

A single protocol testing numerous agents also decreases the burden of scientific review, institutional review board and ethics committee review because everything is embedded within a single protocol.

Given the increasing number of drugs and potential molecular targets, remarkable advances in our understanding of the biology of cancer, and the complexity and expense of executing clinical trials, I think we are going to see an increase in the number of these master protocols over the next decade.