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Oncology Treatments

Rising to the dosing and convenience challenge

Q&A with Elizabeth Shaheen

Advances in oncology mean that in many more situations, therapies are extending life, and many more cancer patients are receiving years – not just months – of therapy. When we think about convenience and compliance, we typically think about chronic conditions, and cancer is now a chronic condition for many patients. So, has the time come for a conversation about dosing and convenience in oncology?

Focusing on that conversation earlier in the drug development process could mean finding not just the most effective dose, but the most convenient dosing and delivery for the patient – resulting in a decreased burden on patients' day-to-day lives as well as reduced cost for both the patient and the healthcare system.

We spoke to oncology biopharma leader, Elizabeth Shaheen to explore this topic further.

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Elizabeth Shaheen is a drug developer with 20 years of biotechnology experience, in senior global commercial, public relations and R&D development roles that span the entire oncology drug life cycle. She has worked in mid-sized and large pharmaceutical companies, including seventeen years with AstraZeneca. Elizabeth's direct pharmaceutical experience spans the US, UK, Japan and China markets. She has a Masters in genomic medicine from the University of Cambridge and an MBA from Shanghai Jiao Tong University.

Roz Lawson has led consultancy projects with companies across the pharma, biotech and medtech sectors for more than 15 years. She helps clients optimize the launch of new products and drive portfolio growth, through opportunity assessment, commercial model design, launch strategy and in-market effectiveness. Roz has broad therapeutic area experience, with particular focus on oncology, rare diseases, diabetes and women's health.

Oncology treatments have come a very long way over the past twenty or so years, but what challenges do patients still face?

It's been an exciting period for drug developers across oncology. We've seen phenomenal improvement in treatments, both in terms of efficacy and lessened adverse events. In the US, the mortality rate has decreased by thirty percent, and this is even more significant when you consider the improvement in early diagnosis and screening programmes.

In parallel, however, treatment durations tend to be longer, which presents a different challenge. If you look at hepatocellular carcinoma twenty years ago, a patient was probably going into hospital once a month for five months of therapy before unfortunately progressing. With the increased survival rates that we see today, patients may be on treatment for twenty-four or forty-eight months, and that's just for one stage of therapy. So having achieved the tremendous feat of extending survival, patient convenience has become a significant challenge for oncology drug developers.

Regulators also realise that convenience while on therapy plays a major role in patient lives and outcomes. This was particularly apparent in the early days of the COVID-19 pandemic, when patients were struggling to get into the hospital setting to receive treatments. So, we have started to see an increase in guidance and approvals – permitting less frequent dosing in certain cases, or updated guidance around drug administration that might require a hospital setting. For example, pembrolizumab was approved for six-weekly dosing and PHESGO, a pertuzumab, trastuzumab, and hyaluronidase triplet combination, was approved for use via subcutaneous prefilled syringe injection, broadening its administration beyond the IV clinic.

There have been a number of these 'patient convenience' approvals globally that have been directly influenced by the COVID-19 pandemic, and potentially have a long-standing benefit for patients.

We need to plan for not only delivering efficacious treatments with limited side effects, but also focus on decreasing the burden of receiving IV once a month for forty-eight months for example. Without this focus on convenience, we jeopardize real-world patient outcomes versus what was achieved in the controlled clinical trial setting.

How much does convenience impact patient adherence on oncology treatments?

A retrospective study showed that only ten percent of patients finished two years of therapy – even with checkpoint inhibitors and their advances for lung cancer treatments, and even in a very aggressive metastatic setting. When you consider what a PDL-1/PD-1 checkpoint inhibitor could do for extending survival, that's quite a shock! Of those that did adhere to two years of therapy, seventy-five percent had a chance of survival at five years.

I would also highlight an element of financial toxicity when we talk about adherence. In the US, it's expensive for the patient to get IV therapy, in terms of the cost of the healthcare professional (HCP) administration and the infusion process. And across all countries, there's the cost of taking time out of work for IV infusions for patients, and potentially caregivers.

Drop-out can be due to side effects and tolerability of course. There are disease areas, perhaps not yet in oncology, but in the immunoglobulin space for example – whereby if you move to subcutaneous delivery instead of IV, there are fewer side effects. So, by making dosing more convenient, there may be clinical benefits. Ultimately, I think the earlier a drug developer can explore these aspects, the more potential for the drug, the more benefit for the patient; and then we will see more patients continue their therapy.

There's clearly something not working correctly, when you see so many patients dropping off and not completing their full duration of therapy. Efficacy advances might be enough for the physician to decide which therapy to use, but when it comes to the real-world setting, efficacy might not be enough for every patient to stay on therapy and conclude their treatment.

With improved cancer survival rates, we've seen that the whole area of immuno-oncology and particularly the PD-1/PDL-1 checkpoint inhibitors are often credited as playing a big role over the last decade or so. What's next for the checkpoint inhibitors?

We are going to see impressive data coming through over the next couple of years in the early disease setting for multiple tumor types. Checkpoint inhibitors across the board – whether it's atezolizumab, pembrolizumab, durvalumab, or nivolumab – have all invested in the early disease setting. There have been questions about trial length and whether regulators would approve some of them, but there's new hope based on BMS's recent neoadjuvant lung approval. Given the rapid agency approval, even using an event-free survival (EFS) endpoint where there was some uncertainty in lung cancer, these trials may be reading out sooner than expected. With these read-outs in an early setting, there could be a disruption in the PD-1/PDL-1 class influencing which companies are able to gain the greatest share of the market.

I think what will continue to be of interest with the checkpoint inhibitors, is what resistance mechanisms may develop. We have ten years of real-world data – how will the tumor respond and then how do you treat any drug-related resistance, which will likely develop? I think there's more around the science that we're waiting to see.

There has also been a burst of excitement towards some of the early CD47 data that was shown at American Society of Haematology (ASH), and there are more than 21 anti-CD47 inhibitors in development right now. This said, the FDA recently put a partial clinical hold on that same Gilead study that was shown at ASH for anti-CD47 inhibitor magrolimab in combination with azacytidine. Industry and analysts are holding their breath to see what happens next in this space.

Looking at different data readouts and focus across conferences, what would you say was the theme of the last year or so, both in solid tumors and hematological conditions?

I would certainly say dosing. It's not just the dose volume, but also when to dose, and the importance of dosing appropriately depending on the type of tumor.

Ipilimumab (Yervoy) is a good example with very different dosing regimen for lung cancer versus melanoma. The tremelimumab data combined with durvalumab (Imfinzi) in non-small-cell lung cancer has been really interesting.

AstraZeneca took a disease-area, science-led approach, giving a priming loading dose of tremelimumab and stopping there. What you see is a flood of cytokines to the cancer which directs the checkpoint inhibitor, in this case, PDL-1.

Without that focus on dosing for both ipilimumab and tremelimumab, we may not have seen the overall survival benefits that we've seen across the clinical trials.

Then if you look at the CD47 agents, magrolimab's trial almost failed in Phase I by focusing on the dosing, Gilead were able to understand resistance mechanisms, and exploit that to get an efficacious dose without the toxicity traditionally seen in anti-CD47 drugs. They had a 1mg/kg starter dose to limit dose-related toxicity, and then moved to a 30mg/kg maintenance dose.

What are going to be some of the major milestones or pivotal points in this field over the next five to ten years?

Again, I really believe that in the near term, oncology dosing must become more convenient. We talked already about the early disease setting and how long those durations of therapy are going to be, and then we talked about potentially receiving years of therapy even in the metastatic setting. With the advancements drug developers are making, if a cancer is diagnosed early, most patients will live to be on at least five years of therapy – we already see that in the breast cancer space.

Dosing beyond dose-finding has probably been an under-appreciated aspect of drug development, at least in oncology. But now that drug developers and scientists have done such a great job extending life with oncology products, and we know the drugs of the future are only going to be better – how do we create a dosing conversation earlier in the drug development process in terms of not just finding your right dose, but finding a convenient dose and delivery? This could be an on-body device with a subcutaneous formulation, or something else that removes the need to come into a hospital and sit in an IV chair.

At this year's ASCO, Sanofi presented data on high-volume subcutaneous isatuximab administered via an on-body device. The small Phase I showed bioequivelence but also a potential for reduced injection-related adverse events. So, in some cases, there may clinical benefits associated with convenience that we can measure.

The other element to highlight in the context of drug delivery devices is the opportunity for smarter collaboration between the mechanical engineering of devices and the scientific development of the drug itself.

I also see scope for developing additional guidance around aspects a device company should be measuring in terms of drug absorption, which could accelerate bringing these tools to the market. Saline solution is traditionally used in device proof-of-concept studies, which will not illustrate how a drug is going to be absorbed into the body. This seems like a great opportunity for stronger industry collaboration.

You wouldn't expect a device engineer to understand a drug beyond the physical properties of flowing into the body, and most pharma companies don't advise on how to engineer a device's pressure rate. But clearer and stronger collaboration potentially presents a sweet spot, that ultimately improves a drug's therapeutic index, convenience, and patient adherence.

Is 'big data' something you see as having significant impact over the next five to ten years?

I very much hope so. The late José Baselga often used to say that there are rules for cancer, we just need to understand them. So, how do we use big data across all the clinical trials that drug developers have, that healthcare systems like the NHS have, to understand the rules of cancer, so we are able to deliver personalised treatments at a cost-effective and widespread scale?

I use the analogy that any one of us can go to a store and buy a small, medium, or large piece of clothing and it may or may not fit as expected, but there's always the option of a tailored piece of clothing. Both do the job, but there are benefits with having something super-tailored, although it can be much more time consuming and costly to do so. With big data, can we get to a place where we're able to provide to patients en-masse, a treatment that's tailored just enough?

Are some of those data being collected and analyzed today, or is that still some time away?

Some of that is happening. The UK has done a tremendous job in terms of a nationalized healthcare system that has data, as well as leading scientists – whether it was the 100,000 Genomes Project, or some of the library data that are being collected on proteomics. I think the UK is leading here due to its openness and data accessibly.

There are also leading global researchers that are focused on data. The Francis Crick Institute comes to mind; they are using computational biology, so understanding resistance mechanisms and then applying mathematics to see what could be predicted in the future. In the US system however, one health institute is not easily or legally able to share data with another without patient sign-off. This is one of the reasons why they UK has been able to make important strides across many cancers in this area.

There is still reticence across the industry to collaborate on big data potential due to competitive considerations. Imagine the potential however from all checkpoint inhibitor trials being compiled and analysed. Perhaps with confidential computing there could be near-term solutions for this.

There are still barriers within a single organization in terms of how data are being kept and used for future drug development efforts – a randomized controlled trial can be 1,500 to 3,000 patients, but are those data being used to inform future research or only in the context of that particular clinical trial? I hope things evolve whereby we're able to better use already-available data to benefit patients.

What else should pharma and biotech be focusing on to help drive great patient outcomes?

The best drug development teams I've worked on are genuinely thinking about the patient every step of the way, whether it's the commercial forecast, the design and dosing of a drug, or the toxicity.

Imagine the scenario where a patient is offered a five-minute administration time versus thirty minutes – they'd naturally prefer the five-minute procedure.

But if it's five minutes with a nurse injecting a pre-filled syringe into their thigh versus thirty minutes with a small on-body device they can largely manage themselves, you are likely to receive a different answer. That's what I mean when I say it's beyond the TPP, and that it is the entire drug experience rather than a single characteristic.

Pharma companies are well-intentioned and are starting to include the patient lens in development and commercialization decisions, but there's undoubtedly more to be done in terms of putting themselves in the shoes of a patient to deliver a total offering.

There's a lot of pressure on drug development to get a dose. And being able to advocate for both getting a dose and exploring what might be other convenient doses is a careful balancing act given the pressure on early clinical development teams.

I think it's too easy when you're developing a drug to just look at the specifications and say, "Okay, I need this amount of volume," or "I need this amount of overall response rate" as specified in the TPP. The best individuals and teams always understand and are focused on that, but also continually consider what that total package means to a patient.

Looking forward

Product development and brand strategy

There is no question that there have been real and meaningful advances in oncology in the past twenty years. Our ability to treat more tumor types, at both earlier and later stages, has resulted in improved survival rates, delaying disease progression, and extending lives by months and years. Immuno-oncology therapies and particularly the PD-1/PDL-1 checkpoint inhibitors have played a big role, and we have seen that there is more to come from these therapies, as well as exciting innovations in other areas.

Big data and AI promise to unlock innovative approaches in many therapy areas – and especially in oncology. First, this is in tailoring the treatment – getting all those Rs aligned: right patient, right drug, at the right time, at the right dose, with the right delivery for the right tumor setting. Second, finding ways to share data has enormous benefits in developing therapies for patients with rare cancers, many of which have previously been considered untreatable. Cell and gene therapies have an exciting role to play here.

Where we have achieved the incredible and have lengthened survival, we now need to help patients to achieve clinical trial outcomes in a real-world setting. Dosing and drug delivery are key here. If we can make treatment convenient for the patient, we decrease the burden on their day-to-day lives as well as reducing costs for patients, their families, and carers, as well as the healthcare system.

All of this underlines the need to put the patient at the heart of product development and brand strategy, throughout the product life cycle. This means truly understanding the patient experience, and then providing support and removing barriers every step of the way.

Lumanity applies incisive thinking and decisive action to cut through complex situations and deliver transformative outcomes to accelerate and optimize access to medical advances. With deep experience in medical, commercial, and regulatory affairs, Lumanity transforms data and information into real-world insights and evidence that powers successful commercialization and empowers patients, providers, payers, and regulators to take timely and decisive action.

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