PHARMA BOARDROOM

InFocus

Patient Engagement in the Era of CAR-T

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In collaboration with: NOVARTIS

Contents

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Preface

In recent years, the much-discussed concept of "patient centricity" has been top-of-mind across all corners of the pharma industry. This is especially pertinent now that many innovative drug makers are seeking to become much more than just purveyors of pills and expand along the life science continuum, providing positive healthcare outcomes and wellness solutions in place of mere units of product. Perhaps nowhere, though, has real patient centricity been more in evidence than with the new generation of cell and gene-based therapies.

This is largely because with state-of-the-art, biology-based, personalised medicines — such as cell gene and neoantigen therapies — the traditional boundaries separating the patient, the process, and the product are very much blurred. "What really distinguishes treatments such as chimeric antigen receptor T cell therapies is the patient is not just the recipient of a drug product. The patient is the product," explains Marc Boutin, global head patient engagement at Novartis and former CEO of the US National Health Council. "Patients are truly central to each and every activity as the patient's own cells are the starting material for all manufacturing processed and, after genetic modification, form the essence of the final material," he emphasizes.

This exclusive new report builds on insights from patient advocacy groups, patient engagement experts from within the pharma industry, regulators, HTA bodies, as well as the physicians at the forefront of CAR-T treatment to paint a picture of what patient engagement looks like in the era of CAR-T therapies, the progress that has been made so far, and the long road left to travel towards truly patient centric therapy development and treatment pathways.

REGULATORY & HTA PERSPECTIVES

Representatives from medicine regulators and health technology assessment (HTA) bodies from across Europe, APAC, and MEA weigh in on some of the regulatory and HTA issues that cell and gene therapies such as CAR-T throw up, the importance of integrating insights from a greater variety of stakeholders earlier in the medicine approval process, and how new kinds of evidence can be generated and assessed.

A Broader Spectrum of Insights

"With advanced therapies we realized that we needed to engage and work with academics a lot more because many of the ideas and initial research actually come from that community, who have not traditionally been commercial drug developers. Therefore, they are less familiar with the regulatory and clinical development processes, the post-authorization requirements, large-scale clinical trials, etc. At the same time, because patients are more involved in the development, there is a seminal role for them to play as well. Even before the formation of the Office for Advanced Therapies, EMA's Committee for Advanced Therapies (CAT) included patient and healthcare professional representatives as full members, with full voting rights."

Ethical Conundrums

"One of the main issues is how to deal with out-of-specification therapies, i.e. when an advanced therapy presents one or more parameters that fall outside the authorized specifications. This is not an uncommon occurrence. The ethical dilemma is that you have a product that falls outside established parameters, but has been produced using the patient's own material, and sometimes the patient's condition is so severe that they are running out of time. The argument is whether the product should be used on the patient anyway? This is a very difficult choice, and it requires a dialogue between the patient and their doctor, certainly. From our side, we are always trying to avoid this scenario, and we work with sponsors closely to ensure that we define the best product specifications. We cannot have specifications so tight that products fall out of them frequently and materials are wasted but we also need to ensure that we have efficacious and safe therapies. At the end of the day, we need to set some parameters – and to do that well, we have to work very, very closely with all the stakeholders."

Ana Hidalgo-Simon
EMA

Earlier Engagement

"Cell, tissue and gene therapy, precision medicine and pharmacogenomics are a few emerging areas to watch closely in the next few years. Rapid advancements in these areas have led to the development of more novel and innovative health products in the market. To support these innovations, we engage the companies at the product development stage to provide early scientific and regulatory advice. We also developed guidance to provide clarity to the developers on what is necessary to meet the regulatory requirements of the final products."

New Frameworks

"In the area of cell, tissue and gene therapy, we recently implemented the regulations for Cell, Tissue and Gene Therapy products (CTGTP) in Singapore. This significant milestone was years in the making – from the early days of policy conceptualisation and design, to public consultation of all relevant stakeholders, including researchers, industry, and healthcare professionals, and eventual refinement and drafting of the regulations. This new class of health products comprises stem cells, tissues and genetically modified organisms, which can be engineered to grow healthy and functional tissues to reconstruct, regenerate or repair damaged tissues or organs; or new genes introduced into the body to treat or cure diseases. It is an area of therapy that is developing rapidly and has the potential to transform the current practice of medicine and offer potential cures for chronic and debilitating diseases."

Choong May Ling, Mimi
HSA

Data & Assessing Long-Term Efficacy & Safety

"Our decisions are often challenged – and our discussions prolonged – by the lack of long-term data on both effect and possible side effects. And in the mix, we see very high prices that will weigh heavily into the hospital budgets.

In collaboration with Amgros, we are beginning to strike new, innovative agreements with the industry and are exploring the possibilities of creating different models. While we have certainly not reached our destination, we are trying to find solutions to challenging questions. For example, how do we evaluate new drugs which are given once but which are potentially effective for life? Which stakeholder carries the risk of a drug not working five years into the future? Could we make a payment model so that the risk is shared? Also, given the nature of some of the new drugs coming to market, if a company wants to make a deal for a large group of patients in different areas, could we make a bigger basket of agreements?

I would like to mention that Denmark has the best collection of healthcare data in the world. The Danish Regions have built a health data authority to which we deliver a lot of data from the hospitals as well as some from GPs. Currently, we and the health data authority are co-chairing a National Hospital Medicine Registry which receives data from the hospitals on the use of expensive drugs. We are currently only using part of this data, but it is a highly promising project, and we hope to see the results of it in one or two years.

In terms of the industry, I would love to discuss the possibility of making agreements based on post-treatment data and real-world evidence with industry associations like Lif and EFPIA. Perhaps we can find ways to collect data in new collaborative ways that will enable us to evaluate treatments and make innovative agreements."

Jørgen Schøler Kristensen
Danish Medicines Council

Supporting the Development of CAR-T

"CAR-T therapies have already been approved in Saudi Arabia. We have very advanced hospitals that are working with these therapies and we have the regulation in place. For instance, we are working with King Faisal Specialist Hospital & Research Center to use these treatments,

There are also plans for Riyadh to become a center for healthcare and health tourism within the region. The availability and safety of medications, as well as the robustness of the regulatory process, are very important enablers for these plans to succeed so we have an important role to play.

We also want to support companies to manufacture CAR-T therapies locally, so we are investing in the regulation and talent ecosystem around this."

Hisham Bin Saad Al-Jadhey
SFDA

A Refreshed HTA Playbook

"We have had to relate to new kinds of evidence which are structured in new ways. For example, there has been a need to handle umbrella, basket, and single-arm trials as grounds for medical approval; meaning that the clinical trial paradigm has been turned upside down.

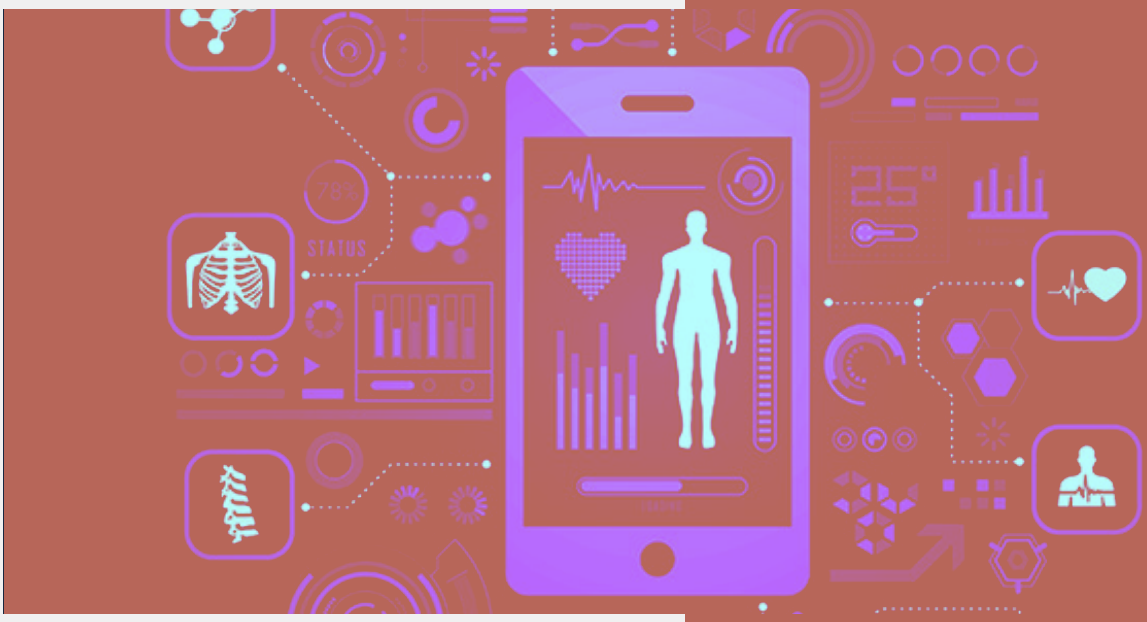
Over the past five to ten years, we are, on national and regional level, increasingly being asked to grant reimbursement for products where the data is based on Phase I studies, even though, traditionally these studies only included healthy volunteers. This is especially true of new products in oncology, orphan drugs and precision medicine.

This is of course challenging but we must not forget the basic tools with which we start every assessment. In the national setting at TLV we had our first experiences with CAR-T about two years ago. Then we realised that many of the challenges we were facing were also those facing us in assessing traditional products. The difference is that these uncertainties were multiplied by a larger number for cell and gene therapies.

After that, since medical approval had already been granted, we had to focus on follow-up data and evidence generation and how we were able to make wise decisions now that are still meaningful for the downstream decision maker. We must maintain the triangle of relevance, predictability, and flexibility.

If the HTA always says that more research is needed and that the data is too weak to draw any conclusions, then downstream stakeholders like regions, individual clinics, and clinicians will have to meet the patient and make decisions without us. Therefore, TLV has preferred to say that an assessment result is very uncertain and that it is of utmost importance to follow-up and generate further data. Clinicians should know that they have a responsibility, if they want to use an expensive new drug, to make sure that we can follow up the results."

Niklas Hedberg
EUnetHTA



A 'BOLD VISION' OF CAR-T PATIENT ENGAGEMENT

This thought leadership piece was written by Marc Boutin, global head of patient engagement at Novartis

Marc Boutin
Global Head Patient Engagement, Novartis

"How are you today?"

For patients, this question may be a challenge. Honest answers can stop a conversation straight away. I know what I am talking about. 25 years ago, a series of tragic diagnoses hit my family. Over a short period, all diagnosed loved ones passed from cancer, HIV and other diseases. A decade later I became a patient myself, suffering from cancer and an autoimmune disease. I could feel the pain of giving a polite answer to the conversational "how are you today?" question myself.

Conversational questions have a role in daily life. But they become obsolete in building deeper relationships. When I started my career as a patient advocate, I often felt that regulators and sponsors reached out to me with such conversational questions, usually shortly before – or around – a drug's approval. I had the impression that they were rather seeking confirmation for their assumptions than real input.

It took a lot of effort, but gradually, groups like the National Health Council, succeeded in changing the ecosystem. Today, the FDA recognizes that patients are as much experts in their diseases as researchers and physicians. When I joined Novartis in 2020, my commitment was to bring the spirit of this patient-centric movement to the private sector.

Together with the leadership of Novartis and my team, we have created a bold vision towards patient engagement.

Our vision puts a holistic and consistent engagement of patients across the whole lifecycle of medicines at the center of who we are and what we do. We will co-create patient relevant endpoints and co-design our clinical trial protocols with the community. And we aim to generate meaningful patient insights prior to defining our brand strategies.

This vision is of special value when we look at CAR-T therapies. In this area, patients are truly central to all activities as a patient's own cells are the starting material for every manufacturing process and – after genetic modification – the essence of the final product.

CAR-T therapies are uniquely complex given their mode of action, their circular manufacturing model and the treatment modality as one-time therapies with a long-time therapeutic effect that is even considered potentially curative by some. Each of these aspects has a profound impact on how we engage with patients and while some require immediate action, others demand endurance and long-term engagement.

CAR-T – the need for immediate, short- medium- and long-term engagement with the community

Immediate: Counter the pandemic impact:

The most immediate need for patients around the globe is to counter the detrimental effects of the pandemic. COVID19 prevented many patients from seeking prevention and therapy. In the CAR-T space, there was a drop in referrals of CAR-T eligible patients to the specialized CAR-T treatment centers. This is worrying, as most CAR-T eligible patients have no other viable treatment option. We even heard stories of patients who decided against CAR-T treatment to avoid blocking ICU beds that could potentially be used for COVID patients. However, most CAR-T patients will never need an ICU bed as treatment of side-effects (such as the infamous cytokine-release-syndrome) has improved enormously since the early days. As the world returns to a "new normal", it will be paramount to ensure that the level of cancer prevention and appropriate treatment also returns to "normal. For many patient advocacy groups, the pandemic also had severe consequences, including a loss of fundraising opportunities that are often vital. Given the fundamental role these groups play in the healthcare ecosystem, these challenges need to be addressed jointly by the public and private sector.

Short term: Build awareness and understanding of rapidly changing treatment paradigms:

In the short term, building awareness and understanding of the rapidly changing treatment paradigms in blood cancers is a priority. CAR-T therapies are a very powerful tool in treating advanced, aggressive blood cancers. For the individual patient, their full therapeutic benefit depends on many factors that need to be understood and put in context with other treatment options. One example is the overall fitness of a patient's T-cells – a key success factor in CAR-T therapies. As the science and medicine is complex, patient advocacy groups play a central role in this area. For Novartis and other sponsors, this space is a sensitive area and requires utmost responsibility. Our country teams received requests from patients and caregivers who asked for access to CAR-T therapies, in approved as well as in non-approved indications. Often, such requests were triggered by highly visible TV or newspaper reports. We need to strike a balance between providing accurate information on a transformative therapy and the responsibility to manage expectations for patients whose cancer cannot be treated with CAR-T therapies. The role of the patient engagement function in Novartis is to be a critical voice in all our internal discussions and decision-making processes, ensuring that this balance is well kept.

Medium-term:

Expand access and build the real-world dataset, complemented with meaningful

PROs:

As the sector continues to commercialize CAR-T therapies around the globe and in earlier lines of treatment, there is an ever growing demand from patients, healthcare providers and payers to understand the true long-term benefit of the therapy through real-world evidence. For one-time therapies such as CAR-T and gene-therapies, this space holds some new challenges for us as well as for scientists and patient advocacy groups. How can patients, who may feel "cured" after a successful CAR-T therapy be encouraged to share their long-term health data for such longitudinal studies? How will the situation evolve for young patients, who may be treated while being a teenager before leaving their homes to work or study abroad? These questions can only be tackled in true collaboration with the patient community and again, patient advocacy groups do play a vital role.

Additionally, there is a need to build a set of meaningful patient-reported outcomes (PROs) which complement the "hard", medical data. As CAR-T therapies may increasingly be used in earlier lines of therapy, the quality of life before, during and after therapy will be an important parameter. Complete remission (CR), progression-free survival (PFS) and event-free-survival (EFS) are key – but for patients it will be paramount, "how" these outcomes are achieved. Compared to some standard-of-care interventions (e.g. stem cell transplants), CAR-T therapies do not require long hospitalization periods. We all assume that this is of real patient benefit (especially for children and young adults who may miss on education during treatment) but there is a lack of validated evidence. Organizations such as the Global Lymphoma Coalition are already deeply involved in this area. Contributing to building this evidence will be a key objective of our patient engagement teams in Novartis and we are supporting the collection of such insights, for example through educational grants given to patient advocacy groups.

Long-term:

Co-create research and clinical trials for CAR-T therapies: As the field matures, we need to ensure that clinical trial set-ups and protocols are co-created with the community. In Novartis, our objective is to do this for all newly starting trials and potentially even earlier, as we define our research and development strategy. This is the core of our big picture vision for patient engagement – to be the first pharmaceutical company to consistently and systematically engage patients across the medicine's lifecycle.

I firmly believe that the potential of CAR-T therapies will continue to grow in indications outside of hematology, potentially even outside of oncology. This will require a constant, open, transparent, and responsible collaboration with patient communities. Only together can we ensure that research programs target the right indications with appropriate trials and harvest the full benefit of patient insights.

As the pandemic will hopefully come to an end soon, I truly look forward to meeting many representatives of the patient community in real life again. I hope, they will give me honest answers to the non-conversational question "What's your opinion on Novartis' collaboration with the patient community?"

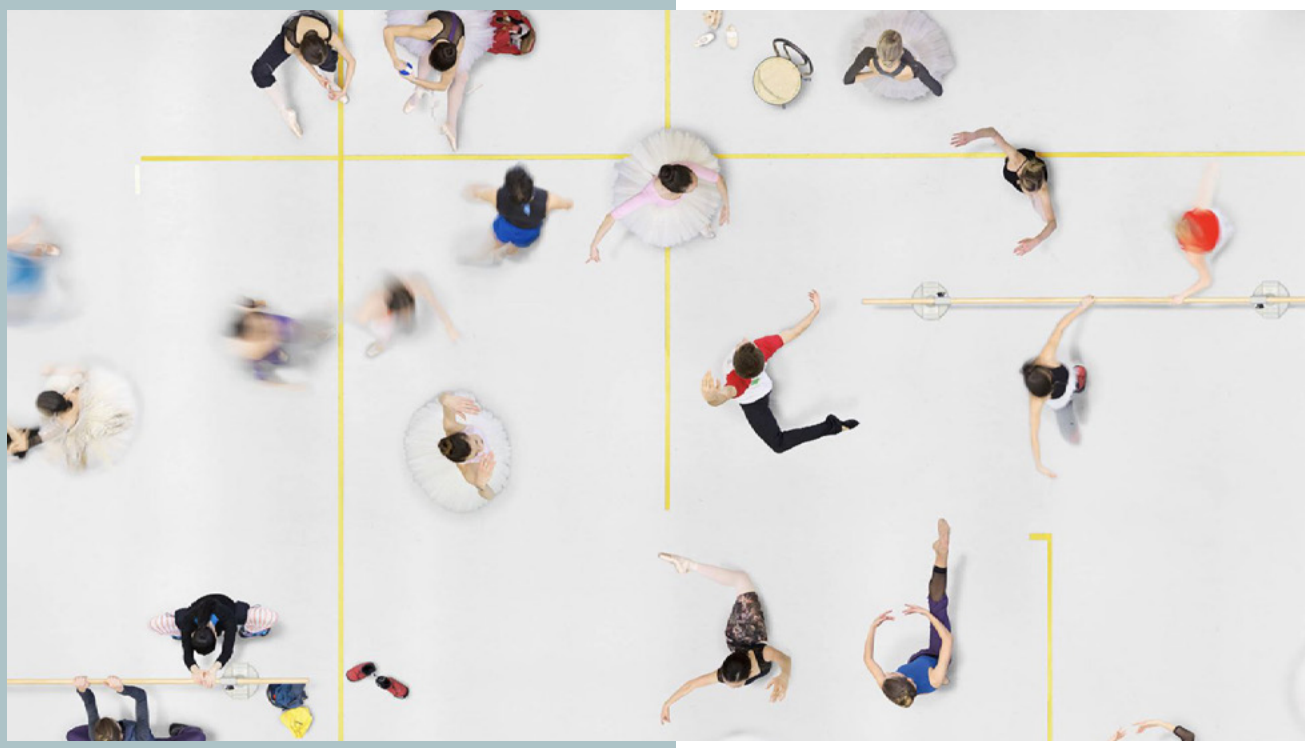
IMPROVING THE CAR-T PATIENT JOURNEY

Claire Saxton and Lauren Kriegel of Cancer Support Community, the largest professionally led non-profit network of cancer support worldwide, discuss how cancer patient and caregiver perspectives need to be better integrated into the treatment process. This is an especially prescient issue for next-generation cell and gene therapies such as CAR-T which, as Saxton and Kreigel outline, require greater levels of patient access and associated support programs.

On the CAR-T patient journey today...

CLAIRE SAXTON (CS): On CAR-T one of the first things that we did was a needs assessment, talking to KOLs and members of CAR-T healthcare teams across the US as well as patients and caregivers. Some very clear themes emerged, highlighting a communication gap. In many other oncology treatments, the big gap in communication is ensuring comprehensive biomarker testing, but CAR-T required a step-by-step guide. Much like bone marrow transplants, CAR-T does not involve multiple rounds of the same therapy. Each step of the process is different. Reaching step one does not mean that the patient knows what step two looks like.

A lot has been done by cancer centres and their nurse navigators, but patients need more help, especially in a big country like the US where a lot of CAR-T happens at a distance from where the patients actually live. The idea of somebody having to move for their treatment for four to 10 weeks along with their caregiver means that lots



of logistical and practical information and resources are needed. Because of the overwhelming amount of information to communicate, it can be really hard for patients and their caregivers to retain it.

Additionally, CAR-T generally comes as a third-line therapy, meaning that lot of these patients are very ill or medically fragile and have already been through a lot. So many here in the US are dealing with issues of financial toxicity, because of the cost of all the lines of treatment they have had up until that point.

On managing patient/caregiver expectations...

CS: People always invest hope in new technologies, which has pros and cons. When you talk to patients, if they have had severe neurotoxicities, they often do not remember that period at all. However, this same period can be traumatic for caregivers seeing their loved ones in the ICU, perhaps failing to recognise their own family members.

Therefore, our needs assessment concluded that we had to set expectations for very different perceptions of what those side effects look like, because in general, they are short term. The long-term side effects that most people have after coming out of CAR-T cell therapy are in fact from their earlier lines of therapy.

LAUREN KRIEGEL (LK): There is a good level of education within the medical community but sometimes that level of education is not there for the average everyday person. In my previous position, when we started our CAR-T program, we had to have a contingency plan for an extremely high level of patient requests. It is not widely known that CAR-T is only for certain diagnoses and only to be used once frontline therapies have failed.

CS: Through telling patient success stories, it cans seem like CAR-T is a miracle cure for all. However, it will only work with a specific set of patients and probably only have long-term positive impact for a third of that cohort. Therefore, while it is incredible to those patients where it succeeds, there are also those patients who relapse or who do not get a good response. We do not tend to tell those stories. Therefore, when we have worked with pharma companies on CAR-T awareness campaigns we have been very clear on the need to manage expectations.

On game changers they would like to see in the patient journey...

The first is more access. CAR-T will not move out to every cancer centre out there, but a greater number of centres offering CAR-T will help in terms of fewer patient having to relocate. That is still always going to be an

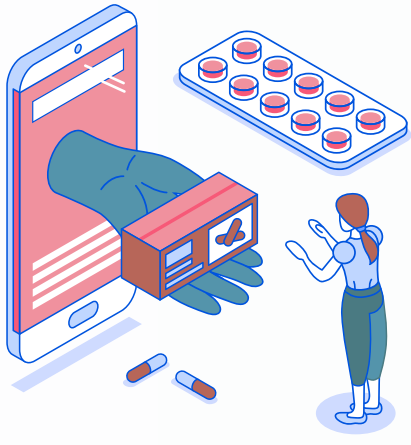
Lauren Kriegel
Helpline Community Navigator, Cancer Support Community

Claire Saxton
Vice President, Patient Experience, Cancer Support Community

issue unless the process changes to a point where it could be administered in the community setting.

Moreover, the more support that is available to patients and caregivers the better. This is especially true for patients without a readily accessible caregiver, those whose insurance will not cover the treatment, and those who simply cannot afford to take 10 weeks off to receive it. Additionally, the possibility of CAR-T being offered as an earlier line of treatment would also be game changing.

LK: As a big advocate for mental health parity, I would love to see increased access to mental health services for people going through CAR-T. Speaking with a mental health professional before undergoing such a procedure would be enormously helpful to ensure that patients are as prepared as possible for the emotional impact.



Advice for pharma on engaging with advocacy groups...

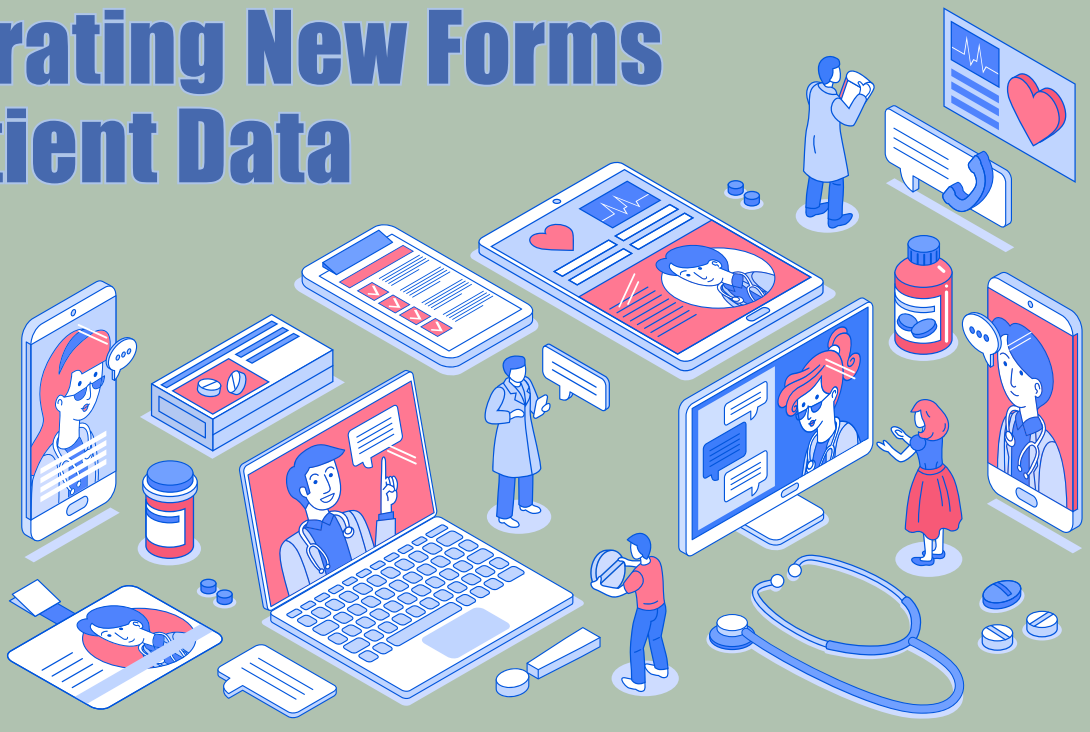
LK: Given my background as a social worker, I would love to see pharma companies opening up funds for assistance with things related to the treatment. In my experience, pharma companies have patient assistance programs that usually help solely with the cost of the medication. However, sometimes they need lodging, transportation, and help with other items.

CS: I have worked with some pharma companies who are ahead of the game and really involve the patient point of view from the beginning of their projects. However, there are also companies that do not think about that until they are about to go to market or launch an awareness campaign. Additionally, many start-up companies do not begin to think about patient-centricity until they are acquired by a larger firm with the infrastructure and resources to invest in it.

If companies bring in the patient perspective from the beginning, the insights they gain could make their clinical trial process go quicker and create a better understanding of how patients make decisions between different treatment options. Having patient advocacy groups and patients and caregivers themselves represented on advisory boards can help ensure that the therapy is designed for the whole patient and not just for the cancer cell.

> “If companies bring in the patient perspective from the beginning, the insights they gain could make their clinical trial process go quicker and create a better understanding of how patients make decisions between different treatment options”

Integrating New Forms of Patient Data



The Lymphoma Coalition has been collecting data via global patient surveys since 2008, initially with only a limited impact on the scientific community. Lorna Warwick, who was brought in as CEO to increase the reach and impact of the Coalition's reporting, explains what this data shows and how it can be better integrated in the medicine development and approval processes.

What has CAR-T's impact been on the lymphoma patient community?

LORNA WARWICK (LW): CAR-T, which was touted as a game-changing curative treatment, has been the answer for some patients, but not all. We still see a significant number of patients that are either not responsive or relapsing, usually within the two-year mark. The question is therefore how we do a better job of figuring out which treatment is best for which patient and what order we should be progressing through these treatments to take the best advantage of what is currently available. There is work to be done around how the state of a patient's T cells impacts their response to a CAR-T therapy and whether we should be harvesting T cells earlier in the treatment paradigm in case of a relapse later. I know there are clinical trials investigating these things, but we are learning a lot from the real world.

There are many relapsed/refractory patients wondering whether there are any treatments left for them; we need to do more research to figure out how to cure them. Data is key. We are asking what we can learn from the data and how quickly it gets pushed back into a mechanism whereby researchers can use it to start looking at that next step. So far, we have not been very good at this. Data needs to be gathered and fed back into the system within realistic timeframes so that scientists can learn more and move forward. There are still gaps. For example, many CAR-T patients did not feel prepared for what happened to them. We prepare patients well for high-intensity side effects like CRS and neurotoxicity, but often the greater patient concerns are around smaller, lesser-known, things like weight issues, muscle cramping, and persistent ongoing fatigue. In total, we are seeing a lot of conversation among patients where they feel unprepared about how to cope.

Lorna Warwick
CEO, Lymphoma Coalition

Industry sponsors argue that CAR-T should be moved up into a first-line therapy. If such a move is to happen, the use of patient and scientific data will be crucial. Is the Lymphoma Coalition working with that data, if so how, and which stakeholders will need to ensure that patients share their data?

LW: We now see more analysis of the data, a lot of which comes from the willingness of pharmaceutical companies to share both clinical trial and real-world data. I am hoping that these companies remain willing to share data, at least with the doctors participating in their clinical trials, so that we can incorporate that data and then make better choices about trials in the future.

As we are looking at earlier lines of therapy, are we learning something about the patients that have responded well? Have they all had similar prior therapies? Do they have some other common characteristics? Would the therapy work better in a particular group if given earlier, or would it perhaps never work for that group? It is about figuring out what makes a particular patient a great candidate compared to others. The sharing of data – which pharma companies have traditionally been somewhat reticent to do – will have a giant impact.

The mission of drug companies tends to be to find cures for specific diseases, whereas patient groups look to improve quality of life. What are your thoughts on the compatibility of these two missions?

LW: Our surveys show that the number one thing that patients and caregivers look for is a cure. Number two is quality of life. If we are not curing patients, then we really need to focus on that quality of life. At the end of the day, if a drug extends a patient's life for a certain number of years but has made them so sick that they are unable to enjoy that life, then there was no benefit.

INSIGHTS FROM THE LYMPHOMA COALITION'S 2020 GLOBAL PATIENT SURVEY ON LYMPHOMAS & CLL

Patient information, guidance and support

70% of patients were told their lymphoma subtype at diagnosis

Only 32% agree strongly that they have good conversation with their doctor about care and treatment

Only 40% were informed and completely understood how to manage side effects of treatment.

52% are definitely involved as much as they want to be in decisions about their care and treatment

35% of patients got a second opinion about their most recent treatmen, but just 6% changed their doctor as a result.

70% of patients were told their lymphoma subtype at diagnosis

Effects of diagnosis and treatment

Fatigue was the most commonly reported symptom of lymphoma/CLL (64%)

Fatigue was the most commonly reported side effect of treatment (69%)

40% of patients indicated they had experienced fear of cancer relapse as a result of their lymphoma diagnosis.

35% of patients use exercise programs to help them with their fear of cancer relapse.

60% report that their treatment side effects have negatively impacted on everyday activities that people their age usually do.

32% of patients who discussed their fear of cancer relapse with their doctor reported that the doctor did not folllow up about it.

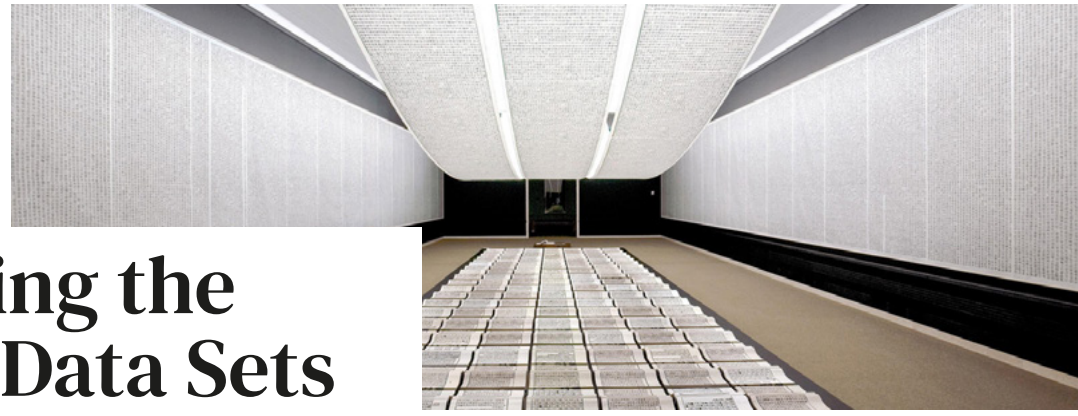
Barriers to treatment

70% of patients reported that there were no barriers preventing them from receiving treatment.

50% of patients reported that they were not presented with an opportunity to take part in a clinical tiral

80% of patients in India and 44% in China reported that financial difficulties were barriers preventing them from receiving treatment

13% of patients are currently, or have been, in a clincial trial for their lymphoma or CLL.



Creating the Right Data Sets

The Lymphoma Coalition's Natacha Bolaños outlines why the collection of more real-world evidence is crucial to moving CAR-T therapies to earlier treatment lines and pinpoints the stakeholders who should assume responsibility for the collection of this data.

Natacha Bolaños
global alliances manager and regional manager Europe, Lymphoma Coalition

We need more real-world evidence. Clinical trials are relevant of course, but real-world evidence is even more relevant considering that patients out there are not necessarily the ones with the inclusion/exclusion criteria that were mapped for the clinical trial. On top of that, in the context of CAR-T (at least with the first clinical trials) a big effort to capture clinical data was done, but they were not so efficient when it came to capturing the quality of life data or patient-reported outcomes.

If we think about moving CAR-T to earlier lines of treatment we should have a transparent discussion on sustainability, pricing, and reimbursement strategies, including associated costs of pre- and post-care for CAR T-cell therapies as these costs are reimbursed insufficiently. because health systems, in general, won't be sustainable with the current prices of innovative therapies. Combined with the expected expansion of indications, the financial burden on healthcare systems will increase substantially with a direct impact on patient access to these treatment options. We also need more hospitals with the experience and the availability to deliver the therapy.

In the context of CAR-T, I think that the EMA has done a good job in making data collection mandatory. Every patient needs to have a follow up of at least 15 years. My hope would be to expand that data collection window, because 15 years (depending on the age of the patient) may not be enough if you consider children for example. After 15 years of collecting their data, we would need to continue the follow-up.

I would also hope for a collection of data not only in terms of clinical outcomes, but also in the quality of life and patient-reported outcomes and other parameters as, for instance, associated cost of care, resources allocation, or variability in clinical practice. That is why the GoCART Coalition came to be. It is a strategic partnership between the European Haematology Association and the European Society for Blood and Marrow Transplantation (EBMT) to advance in the field of cell and gene therapies. The idea behind it is to be a pre and post-authorization registry, to monitor product manufacturing, safety, efficacy, harmonize data collection and support patient access to these novel gene and cell therapies and overcome barriers in regulation.

Patients are also part of the GoCART Coalition; the idea is to gather data sets, different cohorts from all over Europe with everybody reporting in the same format in order to build a big platform. GoCART is working not only to ensure that these data sets are built correctly, but also that the analysis of the data is done correctly. This will create a better understanding of where the gaps are and ensure that patient outcomes are not overlooked.

Defining Patient-Centricity in Therapy Assessment

Zack Pemberton-Whiteley
CEO, Leukaemia Care UK

Zack Pemberton-Whiteley, CEO of UK-based blood cancer charity Leukaemia Care, discusses the importance of patient and patient organizations' involvement in the decision-making process for therapy appraisals, the use of HTA, and his take on moving CAR-T cells to an earlier line of therapy.

Do you think pharmaceutical companies are making the effort to truly incorporate the patient perspective into the drug development process?

ZACK PEMBERTON-WHITELEY (ZPW): I think it would be unfair to put all of this on HTA. All stakeholders have a huge role to play in this, and if we are talking purely in the context of access, one important consideration is the evidence that is put in front of HTA bodies. The predominant stakeholder responsible for producing that information is the pharmaceutical industry, or individual pharmaceutical companies, in a single appraisal. The industry has come a long way recently in terms of trying to be more patient centric, but we are still a long way from where we want to go. It is very easy to talk about patient centricity without really walking the talk. While we are seeing lots of interesting initiatives and pilots on incorporating the patient perspective into drug development, I am yet to see any companies doing it well systematically.

The healthcare professional perspective has been incorporated for many years; we need to think about incorporating the patient perspective in a similar manner at each stage, genuinely listening to and acting on the feedback we are receiving from individual patients and from the patient community as a whole. There is a clear tension between what regulators are asking for and what patients are asking for, and fundamentally, we are doing this for patients. Therefore, if the regulators are asking for something different from the patients, then the industry but also the regulators need to think differently about what they are asking for and what it is that truly matters to patients with that particular indication.

What is your take on the potential and limitations of CAR-T therapy?

ZPW: Cell and gene therapies in the context of cancer are fascinating. One of the things that is quite unusual when it comes to CAR-T therapy is the awareness of it as a class of treatments. When CAR-T was first being approved by the EMA and was being talked about in the context of reimbursement in the UK, there was widespread media coverage, which was quite unusual, and we were constantly getting queries about it. Normally, the queries we get around treatment are from people who want to understand what their treatment options are. However, those asking us questions about CAR-T were mostly ineligible for the indication. Phrases in the media like "a potential cure for leukaemia" led to people with a different form of leukaemia than the ones for which CAR-T was indicated were asking us questions about something which was not a viable treatment option for them at the

time they were asking these questions. There was a great deal of hype around CAR-T, and much of that hype understandably still exists today as these are treatment options that offer a great potential for the future.

However, looking at CAR-T is only an option for a very small proportion of leukaemia patients as a whole and is only currently approved for patients who have exhausted numerous treatment options. Therefore, while therapies like CAR-T hold great promise for the future, they are for most people only a hypothetical treatment option.

> "The industry has come a long way recently in terms of trying to be more patient centric, but we are still a long way from where we want to go"

As a patient advocate, what is your main concern with CAR-T therapy? Are you comfortable with accepting CAR-T as an earlier line of therapy for diseases against which it has proven effective?

ZPW: The results that we are seeing with CAR-T therapy are incredibly promising. However, no treatment is without its side effects. We are aware of the severity of the side effects of CAR-T therapy, particularly in the early days after infusion.

However, we have not yet received all the long-term data we would like. It is also early days for this treatment, we have had patients who have been treated with them for several years now, but the EMA requires 15 years of data collection, and even after 15 years we might still want to know more about the long-term effects of CAR-T therapies.

We hope to see new treatments coming through for leukaemia. We hope they will be available to the broadest possible group of patients. But there is a reason why we conduct clinical trials, and that is to make sure that treatments are safe and effective for patients. And we must wait for further clinical trial data. Talking from the NHS perspective, NICE alongside other stakeholders – including patient organizations – need to see the data in the same way we would do with any new treatment option, and assess whether it is appropriate, safe, and effective.

CAR-T therapies really highlight uncertainty and the role that plays in the process when we were looking at these new treatments. We are talking about many years of potential benefits for which we do not yet have the data. Many of the benefits are hypothetical or modelled for the future. We obviously have to make decisions in the short term and ask if this is safe and in the interests of patients. But knowing how clinically effective they are going to be for the long term is uncertain right now.

CAR-T therapies really stress how we have to deal with managing this uncertainty as a society and how HTA bodies and the industry has to find ways to ensure patients can still access those treatments. The further data that is needed must be collected on an ongoing basis to make sure that patients can access treatments in the meantime. We cannot wait 15 or 20 years for that data to read out. Patients need access to treatment options now.

Should patient advocacy groups have a role in helping to gather that data?

ZPW: Patient advocacy groups have a huge role to play in HTA. One of the areas where their capacity in many cases is currently underused is in looking at the data gaps, and how we can get patients and healthcare professionals involved in the collection of further data to address uncertainties.

Clearly there is a role to play in data collection, but also in interpreting that data. I have said a few times when we are determining the value of treatments that we should be doing it from the perspective of patients, what matters to them, what outcomes are important to them, and seeing if the new treatments that we are assessing are improving those outcomes. At the end of the day, we should be measuring the things that matter to patients, not the things we think we can change with new treatments, because if they are not the same thing, it is the ones that matter to patients that are important.

PATIENT ENGAGEMENT ROUNDTABLE: A VARIED GLOBAL PICTURE

As complex cutting-edge therapies come online, industry sponsors are increasingly looking to engage with patients, caregivers, and advocacy groups earlier and more broadly in the medicine development process to better understand their needs. However, as the below insights from four of Novartis Oncology's patient engagement leads show, successfully integrating patient voices means different things in different geographies, where language, education, culture, healthcare systems, and economic factors must all be taken into consideration.

CANCER PATIENTS: DIFFERING CHALLENGES

KARIN BLUMER
DIRECTOR GLOBAL PATIENT ENGAGEMENT, NOVARTIS ONCOLOGY

There are four geographic levels to patient issues. The first is a patient's local treatment and the impact it has on them individually. The second are national-level issues such as pricing and reimbursement decisions and treatment guidelines. Third are regional-level issues such as the EMA's approval processes or research policies in Europe. Fourthly, there are issues of a global scope such as scientific trends and global clinical trials. We interact with patient groups according to these metrics, but the real impact for an individual patient always happens locally. This means that, ultimately, my work is meaningless if it does not support my colleagues working on a national or local level and helping the real patients.

We are at a very interesting historical phase for two reasons. Firstly, the digital natives – those who have grown up with self-empowerment and Dr Google – are becoming adults and parents. The generation of non-digitally savvy patients is reaching the end phase of their lives. My generation, now in our 50s, may not be native but we have the internet and digital skills in in our daily toolkit, which is very different from the generation of my parents who are now in their 80s. The inability of patients like my mother to access information autonomously, at least in the developed world, is gradually phasing out.

Secondly, we have had the biggest ever learning and training experience on research and clinical development over the last two years through the global discussion around the development of COVID vaccines. As a positive result of the pandemic, most patients and caregivers – in fact most citizens – now have at least a basic understanding of what drug development and what a clinical trial is.

In addition to this time argument, there is a geographic question about patient empowerment where we still see a very scattered image. In my opinion – one year into my global role – a lot of this has to do with language. The most empowered patients tend to be in countries that are either native English speaking or in those, such as Germany, where school education prioritizes English as foreign language so access to English language content is not difficult.

In countries without high levels of English, not only can patients not access medical information through Google as easily, but they also encounter more challenges in connecting with other patients. The patient empowerment movement has its strong cultural roots in the Anglo-Saxon world.

On a deeper level, another issue may be the paternalistic nature of certain healthcare systems. Within such systems, patients tend not to speak up or challenge their doctors. However, I firmly believe that the maturity of the digitally native generation will challenge this paternalism and encourage greater patient empowerment, no doubt spurred on by the COVID pandemic.

ANGELINE HO
COMMUNICATION & PATIENT ADVOCACY LEAD, ONCOLOGY CELL & GENE THERAPY, ASIA PACIFIC CLUSTER, NOVARTIS

Asia-Pacific is a very large region, holding approximately one third of the global patient population, and it is still growing. The cancer burden in Asia-Pacific is also large, but there are significant disparities between the region's wealthiest and poorest economies in terms of public healthcare expenditure, infrastructure, and levels of training among healthcare professionals. This makes working in APAC challenging but at the same time very exciting, dynamic and rewarding with many opportunities that can make a difference in the lives of patients.

Increasingly, cancer patients in APAC are becoming more well-informed with the prevalence of the internet and social media, often using these online resources to get more information about possible treatment options. In some cases, patients travel to other regions or countries where there are more medical expertise and treatment options.

For many patients today, the focus of the treatment outcome has shifted from survival alone to also include quality of life. Doctors and patients may have different treament end goals so it is always im-

portant for patients to let their voices be heard. What is an issue for the doctor may not necessarily be an issue for the patient, vice versa.

Additionally, in many Asian cultures, being sick is still a sensitive topic. In some cultures, even shameful. Patients in this region may be reluctant to let others know that they had cancer because this may affect their chances at employment, marriage, and how they are perceived as an individual. Therefore, sometimes it is difficult to get patients to share their stories and lived experience.

MELANIE CROCE-GALIS
DIRECTOR, US PATIENT ENGAGEMENT, ONCOLOGY, NOVARTIS

The US is a big country with robust patient advocacy groups. However, because of this size, there are still many pockets without the necessary information and resources. Our large and diverse population is very divided in terms of education and economic levels, and unfortunately, our own healthcare system drives some of that inequity. There are also significant divides – geographic, racial, economic, etc. – that lead to great disparities in health care across the country and that is one of our major challenges. I'm committed to addressing these disparities to ensure all Americans have access to the information and resources to improve their health and possibly save their life. When patients better understand their treatment options, they can be advocates for themselves and take back a measure of control over their lives that a cancer diagnosis can take away.

There is an added level of financial stress in the US for people with cancer as well. On top of the trauma of finding out that they have cancer, many have to worry about whether or not they will be able to make the necessary copayments, or if treatment will be approved by their insurance company. It is a big job for both caregivers and patients, especially for patients who do not have much in the way of caregiver support. This is something that I am very attuned to and we work hard at Novartis to make sure our patient support services address as many needs as we can so that patients can focus on the most important thing – beating cancer.

CHRISTIAN CONRAD
SENIOR PATIENT ENGAGEMENT MANAGER, NOVARTIS ONCOLOGY GERMANY

Germany is very developed in terms of medical knowledge, science, and health insurance. Almost everybody has some form of health insurance, either public or private. As soon as a therapy is approved here it should be reimbursed.

Although there are many advantages, the issue is that they are not always distributed evenly. Regional problems are common, as the healthcare system is decentralized, therefore a lot of bureaucracy is involved. CAR-T centres are a perfect example; with the many referrals and costly treatments that are needed the process does not flow as smoothly as it should and that is something that we still need to work on. This relates not only to CAR-T but to all innovative therapies.

NEW MODELS OF INDUSTRY/PATIENT INTERACTION

KARIM BLUMER

There is a lot of room for improvement in the way we talk to, and about, patients. This will allow not only our actions, but also our language, to become more patient-centric. We need to speak to patients in a language that is understandable, as far as it complies with laws and regulations, because we must carefully strike a balance between legitimate simplification and accuracy.

Additionally, many of the professional patient organisations nowadays are extremely well versed in the science. When we invite patient organisations to review our clinical trial protocols to ensure that they are sufficiently patient-centric, for example, they understand the science perfectly. However, the ultimate recipient of our messages is not only the patient advocacy groups but the actual patients and we need to

become better at communicating with them. Moreover, we need to seek dialogue with the authorities on jointly working on regulations that allow for more patient-centric language.

Again, paediatric oncology is a good example. A child will not understand a 40-page informed consent sheet, but – as we agree that children, depending on their age, should be able to grasp what is happening to them – we need to work with patients and caregivers to develop material that is understandable to children.

MELANIE CROCE-GALIS

There must be more conversations between advocacy groups and pharma, and between patients and pharma. Novartis is recognizing this in our new strategy towards patient engagement. Patient engagement is a two-way street. I spend a lot of time trying to learn about what patients want to know and what kind of gaps there are with patient needs. We are listening to patients, answering questions, and soliciting feedback that we can internalize to help make their journey better.

Advocacy groups are critical partners in this journey. I have the utmost respect for our US advocacy partners. They take on a huge role in patient and provider education, as well as patient support. We work very closely with our partners to understand and support their priorities, as they talk to patients every day and know best how to help.

At the same time, we can't forget that there are many, many patients who aren't connected to advocacy groups. The inequity in the US plays into this question. As the COVID-19 lockdowns showed, many people are isolated and without sufficient internet access, bandwidth, or other resources to take advantage of webinars or other telehealth opportunities. From an equity perspective, it is very important for us to be diverse in who we work with and make sure we are reaching all patients and helping our advocacy partners do the same.

ANGELINE HO

It is important to use a different model of patient engagement that is more suited to the needs and unique values of patients in Asia. Key topics to consider include the multi-racial, multi-lingual and multi-cultural context in Asia, understanding the impact of culture on health-seeking behavior, considering values like filial piety, modesty in attire, respect for seniors, respect for authority and the issue of "face". For example, in western cultures, more emphasis may be placed on a patient's autonomy. In contrast, in Asia, seniors with cancer may not even know the diagnosis, as their family members may have requested the doctor not to reveal the diagnosis to their loved ones. Patient engagement models should be based on local patient insights from their respective cultures. It is not a one-size-fits-all approach.

CHRISTIAN CONRAD

In essence patient engagement and patient advocacy is about talking and listening to the patients and getting their insights. These insights are not limited to the collection of data but are more about trying to understand the patient's perspective. This is really important for Novartis and our commitment to patients and caregivers; the company tries to include the patient community's perspective in all of its work and be very transparent. In my role, I talk to patient organizations and patient advocacy groups to get their perspectives, learn what moves them, and figure out what could help them in their journey.

When I talk to individual patients that are not a part of any patient organization, they are always happy to receive information and have a guide during the process they are going through. On the other hand, patient organizations generally have a stronger awareness of the political landscape, so they bring initiatives and have physicians or medical experts on their side, as community consultants. It does change how they interact with me.

For example, a patient with a haematological disease like lymphoma or leukaemia has an acute need and is supported by their caregivers or relatives, which is something we must always take into consideration. Therefore, we make sure to include the caregivers and the relatives in the discussion, and not only the patients or physicians. However, when we talk about the same subject with a patient organization the focus is more on strategy and the overarching goal.

A COALITION FOR EUROPE

GoCART is a European multistakeholder coalition of patient representatives, healthcare professionals, pharmaceutical companies, regulators, Health Technology Assessment (HTA) bodies and reimbursement agencies, and medical organisations founded by the European Society for Blood and Marrow Transplantation (EBMT) and the European Haematology Association (EHA). EBMT President Nicolaus Kröger explains why such a coalition was necessary in Europe, how the patient voice is being integrated into its registry, and the overall progress that has been made in its two years of existence.

What are the origins of the GoCART Coalition?

NICOLAUS KRÖGER (NK): Cell therapies are very interesting because they are a type of living drugs, since the cells are alive within the patient, unlike conventional medicines, which are metabolized by the body. As a result, they are also potentially curative in nature, so they are a great treatment option.

But we also recognize there is a big hype surrounding them, so we thought it would be great to advance the field by establishing a CAR-T registry across Europe. This was also important because there are so many stakeholders involved in cell and gene therapy. We have disease-specific groups, medical groups, industry groups, regulatory authorities, payers, hospitals and so on. A CAR-T registry could be of interest to all of them, so we decided to establish the GoCART Coalition.

How has the Coalition progressed since its foundation?

NK: Over the past two years, we have stepped up our efforts to bring more CAR-T clinical studies to Europe. However, regulation presents a challenge, with different national requirements leading to a lack of harmonisation. The GoCART Coalition aims to create more awareness on the EU level of the need for greater harmonisation across Europe on approval processes, ethical terms, contracts, and data protection, thereby facilitating increased numbers of clinical trials in Europe. Having seen the potential for CAR-T cells in the lymphoma field at an earlier stage of the disease, for example, as well as other new indications coming up, more clinical studies are crucial.

There is a big debate surrounding the longer-term sustainability of CAR-T therapies and other cell and gene therapies. Currently they are being used for rare diseases and usually in patients with end-stage disease where all other options have been exhausted. Do you see CAR-T therapies achieving wider adoption – in terms of patient numbers and also the types of disease indications – in the future?

NK: I would say cell and gene therapies will not become mainstream like, say, medication for hypertension or antibiotics, for instance. I suspect it will be for specific groups of patients, perhaps mainly for haematological malignancies. But I do think they will be used for earlier disease stages, where they might not only be more effective but would also reach larger patient populations.

Nicolaus Kröger
president, EBMT

For the moment, the focus has really been on autologous CAR-T therapies, where the patient's own T-cells are extracted and manipulated, which is complicated. The manufacturing time was also an issue because sometimes patients at the end stage of cancer cannot wait that long. Allogeneic CAR-T therapies are more what we call 'off-the-shelf' therapies, they can be manufactured ahead of time but it is more complex to engineer because genome editing needs to be done to avoid host rejection. In addition, it is theorized that because the T-cells come from healthy donors, they might be less depleted than the T-cells extracted from cancer patients. Currently, only autologous CAR-T therapies have been approved by regulators.

What is exciting for autologous CAR-T therapies is the development of on-site or Point-Of-Care (POC) manufacturing. Companies are developing very small manufacturing plants that could engineer the patient's T-cells directly at the hospital or even by the patient's bedside, which would be a gamechanger. Some centres in Germany have already received approval from the regulators to trial this, and the government in Spain is also supporting such efforts, I believe.

How significant is the integration of patient reported outcomes into the registry and what are some of the challenges around collecting and integrating them?

NK: One of my ambitious goals is to include patient reported outcomes in the registry, which we are now working on. However, regulatory and data protection issues can complicate this because we want to avoid having the names of the patients in the registries. Another challenge is collecting the data itself. Currently, quality-of-life questionnaires are handed out by physicians to patients, but many forget to do so. One idea would be to allow patients to upload their insights digitally direct to the registry and cut out the physician in the middle.

Data will presumably play a major role in advancing CAR-T therapies to earlier lines of treatment. Sponsors support a move from fifth/sixth line of treatment to second/third so that the patients' cells are not exhausted but patient groups do not necessarily agree, asserting that we need to follow the science and that insufficient data current exists. What is your point of view?

NK: I completely agree with the reservations of patient groups. Patients need to first be treated with medicine for which a strong evidence base has already been established before moving onto newer products for which less data exists such as CAR-T cells. More clinical studies on CAR-T as an earlier line of therapy are therefore needed for things to change; we should foster an environment where more trials are held and encourage patients to participate in them.

We should focus on evidence-based medicine and not be swayed by the hype. Patients are in a very delicate position if they are ill and if they read about something that could save their life, they will naturally want it. However, we should be honest and counsel our patients around what is based on evidence and what on hope. This is only fair.

Some patient groups have told us that the CAR-T patient journey is not particularly smooth and that there is a lack of clarity around which stakeholders are responsible for which elements. What are your thoughts?

NK: It must be remembered that CAR-T cell therapy is still very new and that the progress that has been made on this front is, therefore, quite positive. Cell therapy with stem cells was developed by academia and represents a big change for the pharmaceutical industry. For drug companies, dealing with cells rather than drugs is a novelty; drugs have very clear specifications whereas with CAR-T we are talking about living organisms, where the dose of cells is never the same. It all depends on how many cells you can collect, how many can be successfully transduced with genetic procedures, how many expand in the patient, and how many stay active in the patient over time.

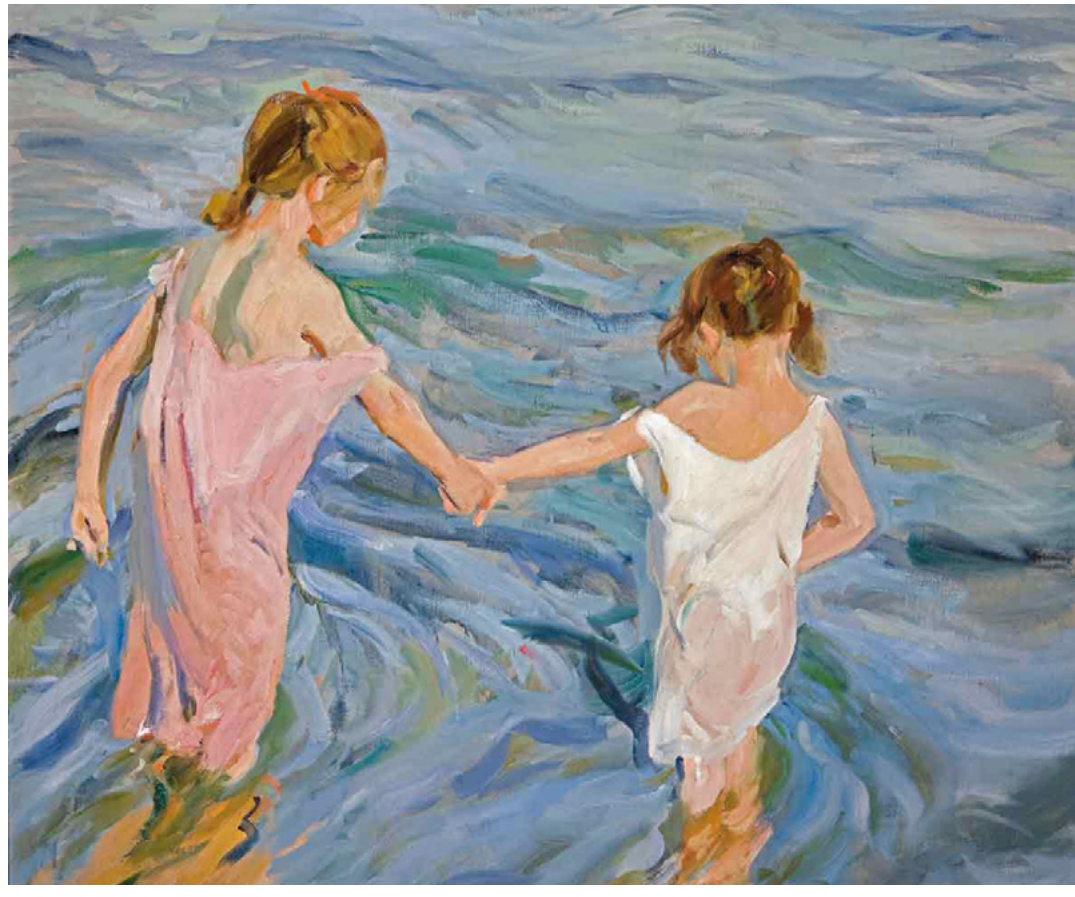
> "More clinical studies on CAR-T as an earlier line of therapy are needed for things to change"

Paediatric-Specific Studies: A Real Need

Kathy Pritchard-Jones, Professor of Paediatric Oncology at University College London (UCL) and President of the International Society of Paediatric Oncology (SIOP) assesses the current environment in terms of innovation and medical treatments for childhood cancer, calling for greater numbers of child-focused clinical trials.

There is a real need for paediatric-specific studies, which is a challenge in terms of numbers and access. In high-income countries, over 80 percent of childhood cancer patients are now long-term survivors with a relatively small number of children with relapses. In fact, sometimes there are more drug products on the market than there are children eligible to go into the study. However, only 10 percent of the world's children live in a high-income country, the other 90 percent are in low- and middle-income countries, and that is where the greatest clinical need is.

Many upper-middle-income countries – particularly in Latin America and Asia -are organizing themselves and can run multicentre clinical trials. If we can upskill them and give them more clinical research capacity, they will be in a good position to contribute patients to early phase clinical studies at specified centres. It has



Kathy Pritchard-Jones
professor of paediatric oncology, UCL & president, SIOP

been estimated this could increase enrolment into early phase trials by 450 percent. These patients need the opportunity to be able to take part in studies, for which industry needs to show a willingness to work with centres in these countries and accept their data into the approval portfolio.

Programs such as ACCELERATE are looking to achieve this by bringing the voices of regulators, pharma manufacturers, researchers, academia, parents, and survivors together and finding the best way to conduct studies. For targeted therapies against particular cancers, we need to look for the compound that has the best evidence in adults but that can also be given in a child-friendly formulation. Safety is one of the main concerns because hopefully some of these targeted therapies will be able to move quite rapidly to frontline therapy. Therefore, it is important to make sure that new treatments do not alter the side effect profile in an adverse way, particularly with long term consequences.

> **“One of the key messages in terms of new therapies for childhood cancer is that clinical studies should be both demanded of industry and expected to be run based on mechanism of action”**

Conventional treatment with normal chemotherapy or radiotherapy is very burdensome and can have long term side effects on fertility, neurocognition, growth, heart function and so on. There is a real need to identify new agents that could replace some of this effective chemotherapy, but it is a challenging process and requires equivalence studies. If a treatment has a 90 percent overall survival rate, changing it to something new requires data from many patients and data points in order to ensure that it is safe and equally efficacious. The aim of doing it is not just to reduce acute short-term toxicity, but also to make sure that the child grows up to be a healthy adult survivor.

However, securing a 20 to 50 year follow up in a clinical study taking place today is complicated. The childhood cancer community is working very hard on linking clinical trial data into national cancer registries and using real-world data. That has its own challenges, requiring hospitals to have information systems that accurately capture the types of therapies that patients are receiving and a regulatory information governance process within which data at a sufficient level of population can be brought together to interpret the results. This can mean data sharing between countries.

On the other hand, since childhood cancer is relatively rare, in most countries care is generally delivered through specialist centres, not in ordinary hospitals. The treatments are complex, meaning that getting the right diagnosis and sub-classification of a child's tumour and which risk-stratified treatment arm they need, is also challenging. It is only possible to assemble the necessary collection of expertise in a larger institution; therefore, the role of academic clinical centres for the treatment of childhood cancer is fundamental.

One of the key messages in terms of new therapies for childhood cancer is that clinical studies should be both demanded of industry and expected to be run based on mechanism of action. The FDA has already changed its position on this issue significantly, and the EMA is also considering doing so, but it is a travesty that when innovations such as ALK inhibitors were developed for adult lung cancer, the industry was not obliged to do studies in children. The industry argument was that lung cancer does not occur in children, even though the same gene is mutated in childhood neuroblastoma. This move towards mechanism of action requirements for clinical studies should make access to innovative therapies more equitable for children with cancer.

REFINING THE RESEARCH PARADIGM

Dr Maria T. Millan, president and CEO of the California Institute for Regenerative Medicine (CIRM), which aims to advance basic and translational research in regenerative medicine in the State of California, shares her perspective on the critical importance of investment in basic science and research and how accessibility and affordability are being integrated into the Institute's research programs.

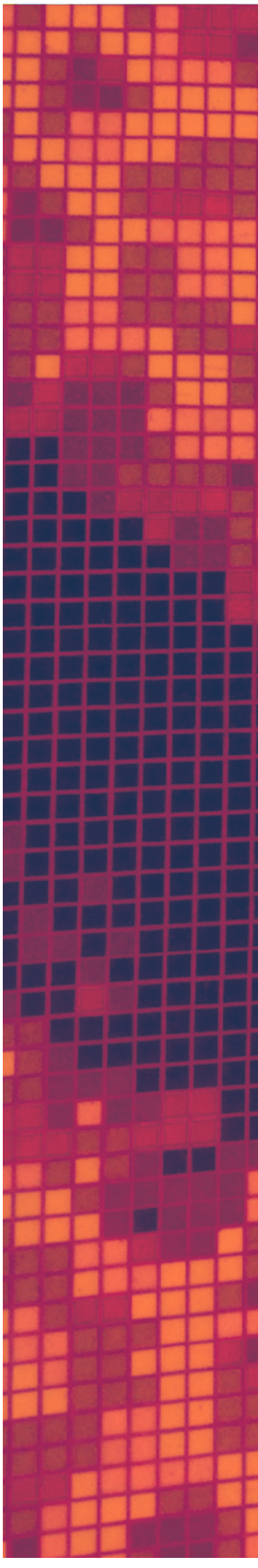
Maria T. Millan
president and CEO, CIRM

Regenerative medicine like CAR-T therapies and gene therapies have been game changers for the sector and certainly for patients. But they have typically come with extremely high price tags that have generated significant debate amongst payers and other stakeholders. Is CIRM adopting the access & affordability topic in the way it approaches its mission?

MARIA T MILLAN (MTM): Firstly, I think we are still at the beginning of the journey. It took a long time before the first CAR-T therapy was approved and we still only have three CAR-T products approved by the US FDA, the third just approved recently. They are being reimbursed through different models so the whole sector is still in the process of learning.

In terms of CIRM, we do recognize this challenge, so Proposition 14 [in 2020, Californian citizens voted to approve USD 5.5 billion to continue CIRM's research – Ed.] actually includes funding provisions for us to work on ways to make these treatments more accessible and affordable. An Accessibility and Affordability Working Group (AAWG) has been formed, which is chaired by CIRM's Vice-Chairman Senator Arthur Torres, who has extensive health policy experience. We are still in the initial stages but we have made a commitment to this and we will figure it out. For instance, will we also fund studies to look at how we can increase access and affordability? Will we look at post-marketing studies and Real World Evidence (RWE)? We have always been an evidence-based, data-generating, science-driven organization but increasingly we also understand that there is science that goes beyond the lab or the clinic that relates to how patients can access the therapies they need. We need to ask the right questions so that we can provide policymakers and other stakeholders with the answers they need to make pricing and reimbursement decisions.

Relatedly, we have also incorporated aspects of diversity, equity and inclusion into our operations, strongly supported by our board. For instance, when we launched our emergency COVID funding last year, we made it a requirement for all funding applications to outline a plan for addressing diversity, equity and inclusion in their research programs, both in clinical trials and in basic research, for example, in terms of the types of cell lines used. We have now incorporated the same principle into our current call for funding applications, and we expect to continue refining this as we go along. We will also be tracking our progress on this.



When we interviewed Dr Peter Marks, director of the US FDA Center for Biologics Research and Evaluation (CBER), he highlighted that regenerative medicine was a priority for them and that CBER was actively working on growing the US's leadership position in gene therapy, particularly. How do you assess the agency's efforts in this space so far?

MTM: They have a great vision and I am very impressed with what the FDA has done with the 21st Century Cures Act and the creation of the Regenerative Medicine Advanced Therapies (RMAT) designation, in particular. CIRM programs have benefited from this RMAT program as it provides an opportunity for real time and frequent interactions with the FDA that account for the unique aspects of regenerative medicine programs in efforts to accelerate development while ensuring safety and an evidence-based approach. They are understaffed – especially with COVID these days – but they have been building expertise in this area and have provided both a lot of guidance as well as many opportunities for industry to work in partnership as the field of regenerative medicine grows.

The industry at large struggles with knowing when and how to invest in early-stage programs. What are some learnings you can share?

MTM: The CIRM model has been a great demonstration of how regenerative medicine technologies could be evaluated. We have managed to bring in over USD 13 billion in industry funding because we de-risked promising programs in a very methodical and structured manner, with inputs from industry experts and external evaluators.

To me, one of the most attractive aspects of regenerative medicine is that even early-stage clinical trials give you positive or negative signals, even with the smaller clinical trial sizes, purely because of their mechanisms of action. Another attractive aspect is that it lends itself to platform technologies really well, which allows companies to potentially develop therapies for many different indications.

At the same time, there are challenges because it is still a young field. Consistency in therapeutic development and manufacturing is a major issue but I think this will resolve itself as the sector matures and becomes less siloed. It is widely recognized that we need specialized manufacturing infrastructure to build this new field and we believe this is best accomplished through public-private partnerships.

I would also like to emphasize again the critical importance of investment in basic science. Science is not a linear path to the clinic. The path is meandering and many things often converge serendipitously along the way of drug development. But there needs to be investment and a structure that facilitates such serendipities. I will close with this example. One of the first programs CIRM started when we were established was an education program to fund scientists so that they could explore what was then a brand-new area of research. One of the participants of that program was Derrick Rossi, co-founder of Moderna, a molecular biologist by training originally from Canada. With our funding, he went to work at the lab of Stanford's Dr. Irv Weissman (a pioneer in stem cell biology) and later on, at Harvard where he actually developed mRNA technology for use in his stem cell research. Subsequently, he spun out Moderna and of course, Moderna has been able to develop a COVID-19 vaccine in less than a year as a result of this mRNA technology. This mRNA technology, initially a stem cell project, has now revolutionized vaccine development.

The Physician's View

Paediatric oncologist Navin Pinto, MD outlines the patient journey for children receiving CAR-T therapies and how the work of his CAR-T team at the University of Washington School of Medicine could provide proof of principle for pharma to take forward and make available more widely or expand to different indications.

Can you give us some insights into the patient experience and journey in CAR-T?

NAVIN PINTO (NP): It is a very frightening prospect for patients. This is not like other therapies where a patient meets the eligibility criteria for a treatment, has a few tests and a meeting with a doctor to describe the therapy, and the next day begins. CAR-T often involves traveling to another centre far away from the patient's home to collect their T cells. For very young children, that often involves surgical placement of a catheter into a large vein, to have enough blood flow to allow for a large collection of T cells, and then the process of manufacturing takes anywhere from two to four weeks. Many of these cancer patients have multiple relapsed aggressive cancers, and for them, that is a very long period of time.

Many patients that come in are eligible for CAR-T, and one month later, when their cells are ready, they are too sick to receive treatment. That is often the scariest prospect and probably where pharma will have some role in shortening the manufacturing time. We need to think about how to provide off the shelf therapies so that we do not have to collect the cells from everybody and can make a more feasible and widely applicable therapy for patients.

Do you present CAR-T to patients as the preferred solution when the eligibility criteria is met?

NP: It varies. For my own patients, this may be one of several options that are discussed. We do not have a track record of this CAR-T therapy being the solution for the solid tumours that I treat. I usually present this to families as one of many options that could be tried; these are just a novel therapy that has a chance of having an effect, but the issues around time to manufacture and the procedures that need to be undergone to collect the T cells often lead families to choose another route.

> "We need to think about how to provide off the shelf therapies so that we do not have to collect the cells from everybody and can make a more feasible and widely applicable therapy for patients."

Then there is a second group of families and parents who have sought us out from another centre or even country and who have decided that CAR-T is the way to go.

Is there any message that you would like to share with other CAR-T stakeholders around what can be done better?

NP: Academic partners working in this space must look for wider applications. As an example, I am working on a CAR-T for a paediatric cancer called high-risk neuroblastoma. That affects about 300 children a year in the United States, so it is a very rare cancer but with a very high rate of relapse. However, the same target is expressed in adult prostate cancer, which affects 100 times more patients. These kinds of connections could be better picked up on by industry to assess the wider applications for CAR-T.

Navin Pinto
paediatric oncologist, Seattle Children's Hospital & University of Washington School of Medicine

Childhood Cancer: More Focus Needed

Nicole Scobie is president of Zoé4life and a European board member at Childhood Cancer International, the largest parent-led international organisation supporting children with cancer. Scobie explains why research into childhood cancer therapies has plateaued in the past 15 years and the work that remains for CAR-T therapies to be as transformative for children with cancer as first hoped.

Nicole Scobie
president, Zoé4life; & European board member, Childhood Cancer International

Oncology is a huge area of focus for pharmaceutical companies today, but to what extent are the new therapies being brought forward really addressing the needs of paediatric patients?

NICOLE SCOBIE (NS): Pharmaceutical companies are very slow in developing new drugs for childhood cancers. Solutions to this issue include the European Medicines Agency (EMA)'s Paediatric Regulation, which ensures that whenever a pharmaceutical company wants to put a new drug for adults onto the market, it must also develop and test it on children.

Without this legislation, many pharmaceutical companies would not test their drugs on children, as it is very expensive to do so. While the Paediatric Regulation has been of benefit for many childhood diseases, it has failed in cancer, with pharmaceutical companies allowed to apply for a waiver when a disease is not considered the same in children as in adults.

For example, a waiver from having to test an Alzheimer's drug in children makes sense. However, this is not the case in cancer. For example, a pharmaceutical company developing an ALK inhibitor – a target present in adult lung cancer but also in neuroblastoma and other cancers in children – was able to successfully apply for a waiver and not develop the drug for children, even though it has been shown to work in children by academic researchers.

Pharmaceutical companies' lack of engagement is a big issue, although it is understandable given the high costs of developing new drugs for cancer in children, as well as the rarity of indications like neuroblastoma.

However, we at CCI feel that children should be a priority and have lobbied pharma companies to develop their drugs in children, even though they probably could have received a waiver from the EMA. We have also been working with the EMA so that they do not accept waivers for drugs when they can see that there is a target in children.

What is your perspective, as a parent of a child with cancer, on cell and gene therapies' potential as cures for cancer?

NS: Historically, there have been three main tools for cancer treatment – surgery, radiotherapy, and chemotherapy – which help cure around 80 percent of children with cancer in high-income countries. While this ratio may seem positive, it still means that one in five children living with cancer will die. Cancer is the leading cause of death by non-communicable disease in children globally, an issue not restricted to developing countries alone. Indeed, even in Switzerland where we sit, cancer is the leading cause of death by dis-

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ease and one child every week dies of cancer; something that we feel is unacceptable.

Oncology research has plateaued in the last 15 years, with some childhood cancers now constantly relapsing and others still lacking any treatment. For instance, diffuse intrinsic pontine glioma, a type of brain tumour, has a zero percent cure rate today and most patients only survive for nine months.

Therefore, there is an urgent need for ground-breaking new approaches such as cell and gene therapies. Phenomenal accomplishments have already been made with CAR-T therapies, for example, which is extremely exciting.

However, we see several issues around CAR-T. The first is access and cost, even in countries like Switzerland where specialised CAR-T centres exist. There are very strict limitations on which patients qualify for trials for these treatments and access is almost impossible in geographies like Eastern Europe. For even the most developed economies, financing a treatment for a single patient that costs hundreds of thousands of dollars is a challenge.

Secondly, although CAR-T is currently in vogue and has worked well in leukaemia and lymphomas, there is still a long way to go before it becomes a viable option for solid tumours.

How comfortable are you with accepting CAR-T as an earlier line of therapy for diseases against which it has proven effective?

NS: It is difficult to make a new therapy a frontline therapy when current frontline therapies already work, even if they have high levels of toxicity and long-term side effects. In leukaemia for example, stem cell transplants often work and have a more than 60 percent survival rate, but CAR-T therapies' efficacy in the long term is not yet proven. The ideal scenario scientifically would be to have a randomised trial to compare stem cell transplants with CAR-T therapy at first relapse; we could even compare the long-term side effects. But this scenario comes with complicated ethical considerations: a highly toxic treatment that has a good chance of working, versus what appears to be a less toxic treatment with many unknowns. As a parent, which would you choose?

Today, CAR-T is generally only used following several relapses and when there is no alternative treatment. Moving CAR-T up to at least the first relapse would have to be done via a collaboration between academia, pharmaceutical companies and patient advocates. Such a coalition could help design clinical trials that make sense so that parents of children with cancer are willing to collaborate.

As opposed to adults, where there are already proven therapies, most children with cancer are treated via clinical trials, which is what has to happen to get the data we need. We do not have to protect children from research, but rather protect children with research, otherwise many children will be out of options when it comes to treatment. There is currently insufficient scientific evidence; and pharmaceutical companies need to do a better job of evaluating their medications in children so that doctors are not left using off label medication for children to gather data and evaluate if they work, which is mostly the case today.

> "We do not have to protect children from research, but rather protect children with research"

The most important thing when developing clinical trials is to engage the patient community early in the development process. The industry should not be afraid to contact patient organizations and have them be part of designing clinical trials; in fact, it would help to ensure that they are developing trials that work and that are going to be successful.

Paediatric Oncology & Data Standardisation

Dr Sam Volchenboum outlines the important role that data will play in the new era of targeted and personalised therapies and the impact of the work that his research group at the University of Chicago is doing to collect and standardise the data of children with cancer across the world.

One of the biggest problems so far is that the deluge of genomic data coming in tends not to be collected with relevant clinical data, much of which sits languishing in the electronic health records. Therefore, the data that come with the genomic data are either that which the investigator collects on basic indicators like age and diagnosis, often presented on a spreadsheet, or clinical trial data, which can be very selective.

We are interested in, firstly, getting all the clinical trial data and linking it up to the genomic data to enrich it, something we have been successfully doing. Now we are talking about initiatives to go back to the electronic health record, get out the actual data on these kids, and try to centralize it so that it can be studied more effectively. That represents an enormous opportunity.

One of the problems we have is that most clinical trials themselves are still written in a word processor when we should be building our trials in a more structured format so that the data contained within them can be formatted automatically. There is a problem all the way back to the source that needs to be solved. Until then, we are just going to keep playing catch-up to transform our data into the preferred format. I foresee a move over the next five years back towards creating trials in a structured format, facilitating better data collection.

The idea is that, with larger, more standardised data sets, questions can be asked that could not with smaller data sets. Many paediatric cancer subsets are so rare that thousands of patients are needed just to just get to the 100 or 200 patients that are relevant for a study. Paediatric cancer treatments and diagnostics have moved forward with better stratification of patients through molecular and other types of testing, with patients divided into increasingly granular groups for treatments and outcomes. The more data we have, the more people can look at the different groups, their outcomes, and how they were treated to try to come up with better stratification schemes.

For instance, the neuroblastoma group has taken the data in our flagship project the Pediatric Cancer Data Commons (PCDC) and come up with increasingly better ways to stratify patients into risk treatment groups, so that patients who do not need as much therapy are given less, and those who do are given more. That has only been made possible by the large number of patients – currently over 22,000 – that we have put together. Therefore, we are hoping to power these studies that could not be powered sufficiently by a small cohort of patients, once we get patients from all over the world on board.

Additionally, using only patients from one country in studies means that the data will often be very localized to a restricted set of racial and ethnic groups. By collecting data from all over the world, we will be able to better develop models and algorithms that can take into account the global diversity around disease.

Sam Volchenboum
associate professor of pediatrics, dean of master's education, associate chief, research informatics officer associate director, Institute for Translational Medicine, University of Chicago

THE EMERGING MARKETS PERSPECTIVE

Chillermo Chantada
president-elect, International Society of Paediatric Oncology (SIOP)

Dr Guillermo Chantada, incoming president-elect of the International Society of Paediatric Oncology (SIOP) highlights the progress of paediatric oncology in Latin America and gives a call to arms to the global pharmaceutical industry to situate more research in this field in his continent.

It is no secret that big pharma companies do not conduct a significant amount of R&D in Latin America. What do you see as the role of clinicians in paediatric oncology when it comes to R&D?

GUILLERMO CHANTADA (GC): We have a history here in Latin America of clinicians working in clinical trials, but we do not have enough access to new experimental drugs despite the fact that there are many children with cancer living here and many centres with the requisite capabilities. For instance, I am personally involved in two or three protocols in Latin America for new drug filing.

One of the reasons for this lack of access is that 80 percent of our children are treated in public hospitals sponsored by the government, and it is not a priority for any government to develop new drugs. While governments are not willing to invest in this, they are still interested in improving their results on evidence-based treatments or randomized treatments with therapy intensification or therapy reduction, and that is what is being done for the most part in Latin America.

Do you believe Latin America can bring competitiveness and diversity to paediatric oncology?

GC: Absolutely, that is something we are trying to achieve with SIOP; there is a great opportunity for Latin American countries. Interestingly, most patients are treated in a small number of institutions, so we have centralized care, good access, and many children.

One of the problems is funding, but SIOP has a great role as a catalyst to bring the attention of several stakeholders that are going to accelerate knowledge growth not only in the countries in which we are doing the studies but in many countries in the region and worldwide.

What is your take on CAR-T compared to typically used oncology treatments? What was your first impression when the therapy came to the market?

GC: The introduction of CAR-T was like a dream come true to me. The results, not just in ALL – the disease that has FDA has approved for use in children – but also with second-generation CAR-T cells for other tumours, have been striking. We are even trying injecting CAR-T cells intraocularly for retinoblastoma, so it is a great way forward.

Still, there are some pieces missing, I strongly believe that medical evidence is very context-sensitive. If something has proven to be cost-effective, or it has improved results in one setting, that will not necessarily be the case in other settings. In Latin American countries we do not have the same favourable access conditions as in Europe or the US. Without the labs or clinical facilities to support the children, results are not going to be the same. Under these circumstances, other treatments could be more effective.

I am convinced that in our countries we do not have to apply the regulations or the approvals exactly as in the high-income countries; we must do those studies here and check how well they perform. CAR-T is a perfect example of a therapy that has to be studied here. My dream is that the pharma industry starts supporting research initiatives in our region just as they do it in high-income countries, and then adapt that treatment to our reality comparing it to the standard treatments and see how well CAR-T performs. We might get information that otherwise would not be available.

It seems like the position of patient advocacy groups is that because the real-world evidence from 15 years down the line does not exist, they struggle to support CAR-T as a first line of treatment. What is your take on that?

GC: I can give you the example of immunotherapy for neuroblastoma. We have an FDA approved treatment for patients that have undergone a transplant procedure that improves results. However, we have many centres here that are not equipped to do transplants but could access the drug. It might be that the drug itself can give good results even if a patient did not have a transplant, but we do not know that yet, so what should we do? Should we use the drug the same way it is used in the US or Europe even when our reality is different? Or should we generate our own evidence to see how the drug can benefit children here?

That is where these partnerships between pharma and different groups should take place as they do in high-income countries. It would be easier to assume that any result would be the same as in Europe or the US, but that is not necessarily the case.

What message would you like to send from Latin America and as the upcoming president-elect of SIOP?

GC: We need our voices to be heard. It is starting to happen, but we still need to generate data. Pharma should consider that, especially in paediatric cancer, supporting research in the region is vital. What we constantly get is a treatment being approved in the US and Europe and two years later being brought here with the intention of using it the same way it is being used in these other countries. But what ends up happening is that only a small number of patients get the drug, we do not get any results, do not know if the drug is useful or not, and lose the opportunity of saving more children.

We could accelerate knowledge, save more children, and position drugs for more indications if we were able to conduct research here as well.

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