João de Bragança & Nicole Scobie, Childhood Cancer International



Putting the childhood cancer agenda under the spotlight is especially relevant today, as the world's focus has shifted almost exclusively to COVID. We must continue to speak up

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Cancer is one of the most frightening words in any language but is especially heart-wrenching when it comes to children. João de Bragança, President of Childhood Cancer International (CCI) and Nicole Scobie, President of Zoé4life and CCI European Board Member, share CCI's aims as the largest parent-led international organisation supporting children with cancer. de Bragança and Scobie also explain why research into childhood cancer therapies has plateaued in the past 15 years and highlight why much work still remains in order for CAR-T therapies to be as transformative for children with cancer as first hoped.

Can you begin by explaining CCI's purpose and what it advocates for?

Nicole Scobie (NS): Childhood Cancer International has existed for almost 30 years and is the largest parent-led international organization supporting children with cancer. In essence, we are an organisation of organisations, with country level member organisations across the world. Most of these organisations are led by the parents of children with cancer, such as myself, Joao, and most of our Board.

Given that CCI is a global organisation representing 176 organisations in 93 countries, we have many ways of working, with a specific focus on capacity building in developing countries.

João de Bragança (JB): We share knowledge with our member organisations. Many of the organisations joining the CCI family want access to networking, and other experiences. CCI is involved in several projects with local governments and is also active at the EU level, which is something that we share with our members. Parent-led organisations want to leverage our global knowledge and network as well as feel like they are part of a larger family which speaks the same language.

How is CCI aiming to improve the lives of children living with cancer across all of the countries in which it works, regardless of economic development levels?

JB: CCI, as a global organization, has two main roles: closing the access gap and putting the childhood cancer agenda under the spotlight. Closing the gap is one of our primary goals because we are still seeing countries where access to even the most basic therapies is extremely difficult. For patients in those counties, access to innovative therapies such as CAR-T seems almost impossible. We want children with cancer in every country to have access to both basic and innovative treatments.

Secondly, putting the childhood cancer agenda under the spotlight is especially relevant today, as the world's focus has shifted almost exclusively to COVID. We must continue to speak up. Since 2018 CCI has been involved with the WHO's Global Initiative for Childhood Cancer, the goal of which is to give all children with cancer the best chance of survival and reduce suffering, achieving a survival rate of at least 60 percent for all children with cancer by 2030.

As the representative voice of children with cancer, which stakeholders are fundamental to ensure continuum progress towards cure for children?

NS: Partnerships within academia, especially with paediatric oncologists, has been crucial because in paediatric oncology many of the oncologists treating children are also the researchers running clinical trials. They see children dying, want to change things, and so historically have tested new drugs themselves. ACCELERATE, an organisation that I belong to and which initially started as a European group but has now become international, has been a game-changer within this paradigm. We work together as a team of four stakeholders: doctors, parents, pharmaceutical company representatives, and regulators, engaging in an open dialogue. Our shared goal is to identify roadblocks and propose solutions to the development of treatments for children and try to

overcome them.

This collaborative approach has borne fruit: in 2017, together with doctors, we successfully put a motion in front of the European Parliament to increase pharmaceutical companies' investments into new drug development for children with cancer.

There has been a significant increase in the overall rate of childhood cancer in recent decades. How worrying is this trend and to what extent can it simply be put down to improvements in diagnosis?

NS: This increase cannot be pinned on better diagnosis alone. Cure rates are, of course, vastly improved, but we still have little understanding of the causes of childhood cancer. In adult cancers, environmental factors such as smoking can be identified, but there are no easy explanations for childhood cancers.

Secondly, most childhood cancers progress very quickly, are diagnosed at a relatively advanced stage, and are therefore hard to treat. A cancer in an adult may take years to progress to an advanced stage whereas a cancer in a child may reach that stage in months, partly because children's bodies are growing so quickly. This means that child-specific treatments need to be developed; children are not just small adults and medicines that work for adults cannot just be taken and given in smaller doses to children.

Thirdly, the cancers typically diagnosed in children are not the same as those diagnosed in adults. Whereas breast, prostate, and colon cancer are some of the most prevalent cancers in adults, children are more prone to Wilms tumour – which is what my son had –, neuroblastomas, brain tumours, leukemias, and lymphomas.

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?

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 parents of children 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 disease 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.

What are the first questions that CCI asks of new therapies when they become available to children with cancer?

NS: When ground-breaking and innovative new treatments come onstream with a lot of hype, our first thoughts are always around costs and access. However, we must also consider future patient monitoring and the treatment of long-term side effects. Receiving powerful cancer therapies as a child or teenager, especially if those therapies are not designed specifically for growing bodies, means that two thirds of childhood cancer survivors have moderate to severe long-term psychosocial, mental, and physical side effects.

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.

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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.

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.

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