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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

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Kathy Pritchard-Jones, Professor of Paediatric Oncology at University College London (UCL) and President of the

International Society of Paediatric Oncology (SIOP) discusses the latest advancements in childhood cancer treatment, the importance of clinical research studies run based on mechanism of action, the excitement and concerns around CAR T therapies, and how sponsors can better serve patients by listening and involving them to address clinical unmet needs.

Could you please introduce yourself and the organization you represent?

I am the current president of the International Society of Paediatric Oncology (SIOP), a global organization that has been in existence for over 53 years. It brings together multidisciplinary professionals from around the world in a common purpose: cure more children with cancer, cure them better to have fewer side effects, and improve equality of access to care and effective medicines.

We have a strong focus on education, training. advocacy and research. However, the society itself does not conduct clinical research, but rather convenes and promotes multinational collaboration with a focus on cancer in children and young people.

With the right combination of therapies, workforce, knowledge, and infrastructure, childhood cancer is highly curable. However, childhood cancer survival rates vary dramatically around the world, and unfortunately, not all children have equitable access to the safest and most effective therapies. One of SIOPâ??s main goals is to help improve the clinical research capacity for paediatric cancer around the world, as it is the best way to raise the level and quality of survival for children globally.

What are some of the main differences between childhood and adult cancers?

The biology of childhood cancer is very different to adult cancer. The mutations are in developmental control genes. There are commonalities: some of the pathways that are known to be dysregulated in adult cancer and which have been effectively targeted in adult cancer are also operative in childhood cancer but in a different environment. Most childhood cancers have a much lower mutational burden than adult cancers, and often the spectrum of mutation types is different, even if the gene is the same.

On the other hand, one of the main issues when testing a new agent is that for an adult cancer the trial might be done in a year, but in childrenâ??s cancer it takes up to two years, sometimes longer, due to the small number of eligible patients. Since we are dealing with a completely different set of diseases compared to the commoner adult epithelial cancers, a very skilled and experienced multidisciplinary team is needed to get the correct diagnostic tests for risk stratification, and then to direct the child to an appropriate treatment regimen. As a paediatric oncologist, it is in my DNA to want to offer patients enrolment in clinical trials at first diagnosis â?? the childhood cancer community understands that one of the best ways to access current best practice is to go into a frontline clinical study, whereas the mentality when dealing with adult cancer is often to seek clinical trials only at relapse.

How would you assess the current environment in terms of innovation and medical treatments for childhood cancer?

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 worldâ??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 â?? 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 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.

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 childâ??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.

What is your take on CAR-T therapies, and do you foresee them eventually becoming frontline treatments?

The concept that one can use the bodyâ??s own immune system to recognize its own cancer and eliminate it is fascinating. Right now, it is about being able to understand and predict who will benefit the most from it, because these therapies are complex and very expensive for health systems. If money is spent in one area on a small group of patients, then it is being taking away from a budget for another group. Also, it is important to understand more about the side effects because evidence is starting to emerge that they can be quite severe. Understanding the long-term effects that CAR-T therapies can have on some patients is crucial, especially when it comes to bringing the therapy to

the frontline.

It does seem that most childhood cancers are not going to respond to these immunotherapies if they are used in the same way as with adult cancers because the mutational burden is much lower and the biology is different. Trials are needed to see where they have their place, but it is also necessary to engage with the parents and survivors to obtain long-term outcome data. This can be done indirectly through getting their permission to access their healthcare records on an ongoing basis; something parents and survivors are generally overwhelmingly positive about when their data can contribute to advancing knowledge. However, it does mean that they need to be involved in the design of studies and how they will capture the long term follow up from the very beginning of when the therapies are introduced.

Do you think sponsor companies are doing a good job when it comes to listening and involving patients in addressing clinical unmet needs?

The pharmaceutical industry has not performed well on this front in the past. When they have stepped forward to support an individual patient disease group, they have sometimes put these groups in a compromising situation where they can be seen as advocating for the company rather than the disease and the clinical need in their patient population. I believe an interesting solution lies in the way the ACCELERATE program is doing it â?? bringing together multiple pharma stakeholders, with multiple childhood and cancer survivors and parentsâ?? organizations â?? and it is in that collective voice where the patient organization retain their independence.

Pharma companies can then listen to what the clinical unmet need is thanks to a community that has been galvanized into working with them. This will help get the best drugs in each category into clinical studies as well as support current patients and survivors to sign up for studies and contribute with their long-term data, understanding that sharing depersonalized data in a format that industry can access is essential for learning how to use these new treatments and potentially move them to the frontline.

A possible next step is using CAR-T cell therapy in solid tumours, what needs to happen for this to become a reality?

It is still early days, but we need to keep going with the studies. If CAR-T works in leukaemia, then there is a clear rationale as to why it should also work in solid tumours. With neuroblastoma for example â?? a cancer type that when it presents with metastases at diagnosis is very challenging to cure â?? children have very intensive treatments, including high dose therapy and radiotherapy. Here at Great Ormond Street Hospital, the application of CAR-T cells to neuroblastoma is being explored in early phase studies right now.

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