Interview with Professor Pamela Kearns

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Pamela Kearns is a Professor in clinical pediatric oncology in the School of Cancer Sciences at the University of Birmingham. She is the Director of the Cancer Research UK Clinical Trials Unit and is responsible for the Children’s Cancer Trials Team, who are the designated lead for the UK's National Portfolio of clinical trials for pediatric cancer and leukemia. The focus of her work is preclinical laboratory-based studies through to early-phase clinical trials. In 2009, Pamela Kearns was elected a Fellow of the Royal College of Paediatrics and Child Health.

Interview conducted by Alexandra Hemsley, Commissioning Editor.

Q What led to you pursuing a career in oncology?

My background is actually quite complicated. I initially started out as a physiologist; I completed a science degree in physiology before going into medicine. At the time, I wanted to do what is now called translational medicine. I just wanted to do more applied science and saw medicine as a route to my goal. After I graduated from medical school, I went through the usual training scheme for pediatrics, which was my preferred specialty. One of the very first jobs I did was in pediatric oncology – it just combined everything I wanted to do; oncology is just so fascinating in terms of the science behind it, plus it is a challenging clinical specialty. The rest is history – I completed my training as a pediatrician and then specialized in oncology. I went back to laboratory-base research and was awarded my PhD before competing my training in clinical pediatric oncology.

Q What do you consider to be the most significant developments in the field of childhood cancer treatment over the last decade?

This is a really hard question – it is hard to pin it down to one single thing. I think probably one of the most important things that has evolved, rather than being a discovery, is the way we work in national and international networks. Childhood cancer is rare, so the only way to make progress is through effective collaborations. Over the last decade, excellent national and international networks have been set up that are able to collaborate through sharing resources, sharing ideas and thereby deliver high quality basic science research. Importantly, these networks are also delivering clinical trials across Europe and now increasingly in collaboration with North America. This high level of collaboration is probably one of the most important things to be have been achieved over the last decade. In terms of what has been delivered, we understand so much more about the biology of certain pediatric cancers that our treatments are increasingly based on stratifying an individual’s treatment according to what we know about disease biology and response to treatment. This has been one of the biggest changes in the approach to treatment over the last decade.

*School of Cancer Sciences, University of Birmingham, Edgbaston, Birmingham, UK
Tel.: +44 121 414 7845
E-mail: p.r.kearns@bham.ac.uk
Q Are there any unique challenges associated with conducting pediatric clinical trials?

This comes back to the rarity of the disease; childhood cancer is a rare disease overall and then divides into many different types of cancer. In order to deliver a clinical trial in pediatric oncology, we need to do multisite, multi-country studies. The constraints of the EU Clinical Trial Directive, which regulates clinical trials in Europe, have been very challenging, particularly when delivering trials in multiple member states where the interpretation of the EU Clinical Trial Directive is not uniform. The Directive has meant that, even though the majority of our trials do not introduce any new drugs, the level of governance imposed mirrors that for ‘first-in-man’ studies. Our standard treatments are based on licensed drugs that are routinely not used in their licensed indication. In pediatric cancer trials, we rarely introduce new unlicensed drugs, but are making incremental improvements in treatment protocols based on familiar drugs – drugs with which pediatric oncologists have several decades of experience, as well as an extensive knowledge of their side-effect profiles. In spite of this, the regulatory requirements to deliver these trials are no different from first-in-man new drug development trials, making it resource intensive and difficult to deliver.

Q What led to you founding the Early Clinical Trials Committee of the International BFM study group?

The International BFM Study Group is a global clinical study group for hematological malignancies. One of its major themes is late-stage Phase III treatment improvement trials, such as taking standard treatments and improving the way they are delivered. There is a huge need for bringing in new drugs for children with leukemia, and so along with my colleague Dr Michael Zwann, we started talking to the different International BFM Disease Specific Committees about the work we were doing in the Innovative Therapies for Children with Cancer Consortium. There was so much interest in new drug development within the International BFM that the Board approved establishment of the Early Clinical Trials Committee to discuss delivering early-phase clinical trials for leukemias and lymphomas and their integration into late-phase trials.

Q Have the results of the CLOUD trial been surprising?

Two things were good about the CLOUD trial. One of those was that we were able to complete the trial in a timely fashion, which can be quite challenging for early-phase trials regarding children. The second was the overall response rate, which was over 40% that was surprisingly high in this very heavily pretreated group of patients. The primary objective of the trial was to look at the safety of combining clofarabine with DaunoXome® in the pediatric age group. It proved to be a very tolerable combination. What we really need to do now is see whether we can get even better patient response rates if we take it to a patient population that has not had so much previous treatment. That is for the future. So, although the results of the CLOUD trial were promising in that there was a good patient response rate, we should not over-interpret the results, as it was quite a selected patient group.

Q Have there been any particular challenges associated with the international pharma Phase I study of nilotinib in childhood Philadelphia-positive leukemias?

This is a Phase I study for patients with Philadelphia positive leukemias, who have failed the current first-line treatment, which is imatinib. This is a very, very rare group of patients. Novartis, who are sponsoring this trial, have been fantastic in recognizing that this was going to be a challenge and still persevering with the study. Novartis opened this as an international study and were prepared to open a lot of sites across Europe, knowing that each of these sites might sometimes recruit only one or sometimes no patients. This is a huge investment to get access to the numbers of pediatric patients that we actually need to be able to answer the question about a drug that is already in use in adult practice. However, the study is important because we need the pharmacokinetics data in children to know that the dose is correct for the pediatric population, and similar activity can be achieved in the pediatric population, compared with that seen in adults.

Q How is research investigating the use of epigenetic modulators as therapeutic agents in acute leukemia progressing?

This is progressing well. We are looking at DNA demethylating agents to see if they have a role in mostly acute myeloid leukemia, but also lymphoblastic leukemia, and the short answer is they are certainly active and you can get good cell kill at very low doses. What is challenging is determining the mechanism of action and translating that into the clinic. We really want to know what the target or targets are. That may sound a bit strange when I have already said they are DNA demethylating agents; however, it is more likely that the drugs will have multiple targets and yet we are not sure if we can identify a particular biomarker that would predict
a response to any particular DNA methylating agent. The data so far suggest it is not going to be one single or even multiple biomarkers – it is going to be much more complex. Our preclinical data on the activity of these drugs are so far looking very promising and it is time to take it into the clinic. We will continue to look for the biomarkers once we take the drugs into the clinic so that we can come back into the laboratory afterwards and further investigate the elusive mechanism.

Q Can you tell us more about the Innovative Therapeutics for Children with Cancer Consortium?

The Innovative Therapeutics for Children with Cancer is a consortium that was established over 5 years ago now. It is an academic consortium that started out in five and has now expanded to seven European countries. It comprises a network of academic institutions and tertiary referral centers for children with cancer, with expertise and interest in running Phase I trials. We have established the network so that we could effectively deliver early Phase I trials for children with cancer using centers that had the right level of expertise to do it. When the consortium started, there was very little interest from the pharmaceutical industry to develop drugs for children’s cancers, and the principal reason comes back to rarity. For the pharmaceutical industry, there was no huge economic advantage to conducting early-phase trials in childhood cancers. At around the same time that the consortium was established, a change in the EU law occurred, called the Paediatric Regulation, which mandates the pharmaceutical industry to consider pediatrics in their drug development plans. We have now developed good partnerships with the pharmaceutical industry and are starting to deliver the trials that may lead to cancer drugs obtaining market authorization in pediatric indications. It is far from perfect yet, and I do think we have a long way to go before every big pharmaceutical company considers childhood cancer, but we have certainly made a lot of progress.

Q Are there any particular challenges associated with liaising with a network of 21 UK tertiary referral centers for children with malignant diseases?

The main challenge are resources. Having a stable network of 21 centers is an advantage because we know the centers well, we know the investigators and we know how they work. From that point of view, each time we have a new trial that opens, we can deliver it well across the 21 centers, because they know us and we know them. There is a high demand from sites to participate in all clinical trials. For children with cancer, there is a strong ethos that treatment is best delivered within a clinical trial. At the moment, the scope of our clinical trial portfolio means that, for around two-thirds of children at the time of diagnosis, there will be a clinical trial for which they would be eligible and most eligible diagnosed patients will be recruited into a trial. We are trying to close the gap so that one day every child diagnosed with cancer will have the opportunity to go into a clinical trial, but to do that, we need a lot of small trials each addressing small disease groups. We aim to open trials quickly but our resources and the resources the sites have are obviously limited, and so our main challenge is to do what we want to do, constrained by the resources that we have.

Q How do you see the field progressing over the next 10 years?

In the next decade, I think we will be moving towards much more personalized medicine trials, trials with even smaller sub-groups, introducing targeted treatment. In order to do this, we are going to have to further increase our international collaboration, widening the net to be able to deliver personalized medicine trials and this will require considerable rationalization of the rules that govern clinical trials.

The other area we need to address is that, whilst we are very successful at curing childhood cancer – 75% of childhood cancers are cured with what we are doing now – it is not without a considerable cost to the children. There are unacceptable long-term side-effects for many of the drugs that we are using now. Over the next decade, trials are going to need to look at how we can reduce the burden of treatment for children by reducing the long-term side effects, for example, the effects on fertility or the risk of secondary cancers when they are older; realistically, this is only going to come with new drugs that work through different mechanisms and with improved side-effect profiles.

Disclosure

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