A journey searching for a cure for leukemia

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Jorge E Cortes speaks to Natasha Galukande, Assistant Commissioning Editor. Dr Cortes received his medical degree from the Universidad Nacional Autonoma de Mexico (Mexico City, Mexico). Cortes has worked at the MD Anderson Cancer Centre (TX, USA) since 1991 where he is the Director of the Leukemia Fellowship Program, Deputy Department Chair, Chief of the sections of Acute Myeloid Leukemia and Chronic Myeloid Leukemia, DB Lane Cancer Research Distinguished Professor for Leukemia Research and Professor in the Department of Leukemia. He has been the principal investigator or coprincipal investigator for more than 100 funded research projects and has authored more than 600 peer-reviewed articles, 33 book chapters and four books. He has been honored several times over his career for his research and educational contributions. Cortes has spoken at, given presentations at, and appeared as a featured guest at or chaired more than 575 international, national, state and local conferences.

What initially drew you towards research in leukemia?

Leukemia is a field involving diseases that are aggressive and affect patients' lives, although it has seen a lot of progress in recent years. There has been enough progress for you to see that these outcomes can be changed. This progress is perhaps best represented in childhood leukemia where, with proper management, it has turned into a highly curable disease. These reasons made leukemia research sound like a very interesting field to get involved in, where if you develop a good strategy and use the tools you have properly then you can impact the lives of many patients. It is the right combination of a field where you are able to make an impact and gain benefit for patients. Additionally, the biology of these diseases is very interesting and something that you are able to effectively study because of the tools that are available. Leukemia for me is the right combination.

How did you then become involved in clinical trials for improving treatment for leukemia patients?

A lot of what happens to us in our lives depends on the circumstances and the people you meet and your mentors. I have had wonderful mentors who I started working and getting involved with: Kantarjian, O'Brien, Keating, Freireich (MD Anderson Cancer Center, TX, USA), Estey (Fred Hutchinson, Cancer Center, WA, USA) and many others. They then gave me projects as a fellow in leukemia. Between my previously discussed interest and passion in this field, with the availability of resources to progress I started getting involved in clinical trials early in my career and I was fortunate enough to see results. Some of the steps and results I saw were small but, ultimately, every little helps.

Throughout my career I have become increasingly involved. Early in my career as a trainee I had more of a peripheral involvement, working with senior people and trying to follow their steps. As my career progressed I became more directly involved in developing concepts, designing trials and strategies, and mentoring people. I followed the journey of people in research.

What do you feel is the biggest challenge facing the field today?

We have made a lot of progress, but there is still a lot of progress to be made. I think nowadays we have the tools and the technology to dissect the biology of the disease. We have the technology to then translate this into treatment options for patients.

Some of the challenges that I see, however, involve culture, for example, the general perception of clinical trials is frequently not positive. Some people, both patients and physicians, often feel that being in a clinical trial is like being a 'guinea pig' – one of many expressions that are frequently used. The way that I view it is that patients that

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have been in clinical trials have benefited greatly and made progress for themselves.

Another big challenge facing the field today concerns the administration level. It is very frustrating to see how many patients are denied care by third-party payors because their insurance does not cover clinical trials. I think that it is a huge challenge because it impedes progress and limits treatment access to patients. I think that this should almost be illegal to prevent the patient from having the option to participate. The only way that this is going to change is through changes in regulation. In clinical trials all care is frequently standard and the same as you would expect from an approved drug, therefore, it should be covered. The difference with clinical trials is that they help you to understand additional aspects of the disease as you offer new treatment options to patients in need and provide excellent care. The insurance companies, however, often deny coverage even when the drug on the clinical trial is free.

■ **As the program director of the Leukemia Fellowship Program, you are involved in educating & training others in the field. How did you become involved in this & what do you think the benefits are?**

As previously mentioned, my own mentors really made a difference to my career; not only in teaching me but also by directing my life towards something that I really enjoy. Therefore, I felt like it was almost an obligation to give back and start doing the same thing for people coming after me. I find it very enjoyable. You see young guys that were just starting their careers and are now my colleagues in the department. Sooner or later these people are going to go ahead of me. I find this really great and think that, if you are a good mentor, you take enjoyment from people's success and seeing them advance their careers.

■ **You have presented & featured as a guest or chair at over 575 conferences. What do you think is the importance of these meetings?**

The most attractive part is when you have the opportunity to discuss and interact with your colleagues. The more you can trigger questions, and even have people challenge what you are saying, the more you advance. If people express their opinions during discussions and they differ from your own opinions then it helps you to think in different ways. The meetings are a very enjoyable method of teaching.

A conference that I particularly enjoy is the International Chronic Myeloid Leukemia Foundation annual meeting. It is a great conference organized yearly, a bit smaller then the other conferences but full of people with the same focus, which makes for rewarding and stimulating discussions.

■ **You have been the recipient of many awards. What do you feel is the biggest achievement of your career so far?**

I think your achievements are what you can do for patients. When a patient does well and improves then that is your biggest achievement. This Christmas I received a card from a patient I saw 12 years ago. The Christmas card had a picture of the patient with two young children of their own and her husband. She is now having a great life, but 12 years ago she was dying from leukemia. I think that is your biggest achievement when you help a patient's life like that. You can look back and think about it, the position that the patient was in and how they are now.

■ **You recently led a Phase II trial involving the drug quizartinib in acute myeloid leukemia. What led to the development of this drug?**

Acute myeloid leukemia (AML) generally has a dreadful prognosis. We started recognizing a few years ago that there are abnormalities in the mutations in *FLT3* in approximately a third of patients. These abnormalities appeared to be a very good candidate for developing drugs against this particular molecule. So the need for better treatment for AML and the discovery of potential targets made it attractive to study and, ultimately develop drugs such as quizartinib, which is a very potent inhibitor of FLT3.

■ **What are the benefits of quizartinib?**

The drug definitely works; from laboratory data you can see that it is effective. It has clinical activity and gives you good responses in a number of patients, many of whom have failed on other therapies. Treatment for AML is challenging though. It is not as simple as 'one drug is going to cure patients'. We need to focus on combinations, the best ways to approach these drugs and then incorporate this into therapy. There are many things that we need to do and learn about the drug.

■ **Should the drug meet approval, how do you feel it will affect the clinic & future research?**

The drug will definitely help in the clinic, I am convinced that patients will benefit and have

increased survival. The important thing that I would say in regards to future research is a lot of important research on a drug comes after the drug is approved. After the drug is approved you have more freedom to carry out studies that are more challenging and innovative. I think in the future we will start to look at different ways and forms of using this drug as we will not be as limited. Also, when you have a drug that affects a particular pathway, like this one, it helps you to better understand the specific pathway and to learn things that you did not know before you had the ability to specifically affect that pathway. So I think it will also impact positively on future research for that reason.

■ **What other research are you currently involved in?**

I am involved in the identification and development of many new drugs; particularly for chronic myelogenous leukemia and AML. For the past 3 years I have worked on three drugs for chronic myeloid leukemia that were approved last year, which was very rewarding. AML is a lot more challenging but I am working with a number of drugs that I think will have great potential for helping patients. Some of them are in very early stages of development. While some of these drugs target different pathways, others focus on the immune mechanism that I am very interested in. Improvements in the outcome of patients by new drug developments are what I chose to focus most on.

There are a few drugs that I am particularly excited by, one is an inhibitor of Wnt-1. The drug is in its very early stages of development but I am positive about its future potential. The pathway appears to be an important one for the survival of the earliest cells, called the stem cells, and conceptually it is a very attractive drug. The early data we are starting to see is looking very interesting so it is a drug that I like a lot.

I am working on another drug that is an inhibitor of the molecule called GRB2, which is a linker molecule. When something is activated inside the cell it is similar to a chain with one thing leading to the next. One of the linkers in this chain leads to the eventual activation of different pathways. Therefore, when you block or break one of these linkers in the chain that the activation can be disrupted. This is the task that the drug aims to do. Its very early days but I think that the concept is attractive. With the early data appearing interesting we will continue working on it.

■ **Are there any current 'hot topics' in leukemia research?**

One of the things that we are trying to do is work on discovering more precisely the molecular events that happen because the more we understand it, the better we are going to be at developing new drugs. One of the important things will be to understand how one molecular abnormality works with another molecular abnormality to give us leukemia. We understand that these are very complex diseases – it is not possible to block one thing and stop leukemia. Due to the complexity you will have to combine more than one drug, perhaps several drugs, to have an impact. Therefore, understanding this molecular complexity is very important.

■ **Finally, where do you think leukemia medicine will be in the next 5 years?**

I think that the expectations for cure are going to be much greater in 5 years than they are now. I am convinced within my professional career we will be curing the great majority of patients with leukemia. In 5 years time I do not think that there will be big improvements, although there will be a few more drugs approved that will lead to a much better outcome for the majority of patients. In 10 years time I think that AML will be highly curable. The cure rates for AML are already getting very close to what we have for childhood leukemia. This pattern will continue.

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