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MEDICAL VERSION

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PHASE I TRIALS: HOPE OR HYPE?

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Many patients worry about the prospect of being a “guinea pig” when they participate in clinical trials. It is important to reconcile this notion with the reason why trials are still being performed – cancer treatment is not perfect, and new approaches need to be tested in a rational manner, with the aim of increasing effectiveness and/or reducing side effects. For certain types of cancer, e.g. early stage germ cell tumours, where existing regimens can cure up to 95% of patients, few trials are available since the margin for further improvement is minimal.

WHAT IS A PHASE I TRIAL?

Prior to being introduced into the clinic, any new drug regimen would usually have gone through extensive testing in laboratories as well as toxicology studies. Toxicology studies are directed towards understanding the effects of these compounds on the organs of larger animals such as primates. With this information at hand, the first introduction of a new drug or combination of drugs is typically a dose-finding phase I trial.

The main objective of a phase I trial is to determine an appropriate, safe and tolerable dose for later testing in phase II and III studies. Phase II trials examine drug activity in a specific tumour type, and phase III, compares the new regimen against the standard of care. While phase I trials involve 20-50 patients, phase II and III trials typically involve up to a few hundred to thousands of patients. Hence, trials of each stage have different objectives that need to be attained before a drug can be registered by regulatory bodies (e.g. FDA, HSA).

TOO LITTLE, TOO LATE

In the past, drug development in oncology has been inefficient, with less than 5% of new drugs successfully meeting trial objectives and gaining eventual approval. Majority of chemotherapy and targeted drugs have taken up to 10 years from the first introduction to clinic in phase I, through to final approval by regulatory authorities after completion of a positive phase III trial. Drugs like tamoxifen, paclitaxel and more recently gefitinib, have all undergone such protracted evaluation. Thankfully there are now tremendous efforts to accelerate this process so that the odds for success are higher and promising drugs are made available sooner.

CHASING BETTER LEADS

Leveraging on technological and computational advances from the genetic revolution in 2000, new drugs are increasingly made with even higher precision and applied to enriched patient populations – or matching the “right drug to the right patient”. This has led to a series of phase I trials that have shown dramatic results even in the most treatment resistant cancers – vemurafenibin BRAF+ metastatic melanoma, crizotinib in ALK+ lung cancer.

It is notable that these trials involve molecular profiling of patients prior to enrolment – that is, knowing the exact genetic makeup of an individual’s tumour – so that only a specific subgroup of patients that harbor a specific drug sensitive phenotype are recruited into a trial.

MODERN DRUG DESIGN

It is important to appreciate that drug discovery and development is very different from what it was 20 years ago. While many anticancer agents were discovered serendipitously, for example – from an accidental experiment involving platinum electrodes and worms (cisplatin), or a plant screening program (paclitaxel) – modern drugs that are tested today tend to be purposefully designed. New techniques like fragment-based design and computer based modeling, increase the likelihood of having a pharmacologically active drug in the clinic.

GETTING IT RIGHT IN PHASE I

How does one “get it right” then? If recent trials are anything to go by, it would seem that profiling individual tumour samples (archival and fresh biopsies) in order to obtain genetic readouts may be a way forward. Thorough understanding of how the body handles a drug (pharmacokinetics) or the effect of drugs on the body, are important. This may include studies of immune activation, circulating cancer cells and target modulation assays on white blood cells or in certain trials hair follicles and skin biopsies. Certain high-resolution research scans (MRI, CT or PET) may also be performed. Altogether, such information will allow us to better apply the drug in later phase trials.

PATIENT-DRIVEN RESEARCH

A common concern is that such trials only serve to benefit the pharmaceutical companies. This is a misperception, since one of the challenges in any trials unit is to ensure that only the most promising regimens are offered to patients so that they have the highest possible chance to benefit. Hence, before any trial is launched at NCCS, the rationale and design are thoroughly considered both by clinicians as well as a centralised institutional review board (CIRB). This comprises of a committee that includes professionals and lay people and provides an objective critique of the adequacy of the design of a trial.

Are there any benefits to participating in a clinical I trial? It is important to emphasize that patient safety is the highest priority in a phase I trial. Thus many safety assessments are usually incorporated, such as regular blood tests or heart function scans. Some patients actually prefer being part of a clinical trial since they have additional trial personnel support and regular follow-ups. Additionally it can also allow access to drugs that might not yet be available or registered in Singapore. For instance, at the time of writing, while the latest breakthrough drug in specific subgroup of lung cancer patients (Anaplastic Lymphoma Kinase, or ALK) crizotinib was approved by US FDA in Oct 2011, it has yet to be registered in Singapore, and hence participation in a phase III trial is one of the more expedient way of gaining access to drug. In fact, crizotinib was approved on the basis of impressive phase I data in a trial comprising of approximately 80 patients, where response rates of 57% was seen. A second generation ALK inhibitor is now also available in the clinic in the phase I setting.

In conclusion, phase I trials are experimental treatment approaches that may be suitable for some patients. Patient safety remains the highest priority. And while it is impossible to predict where the next breakthrough will come from, participation in a clinical trial will undoubtedly contribute to the progress of medical science, and just maybe, this leap of faith into the last two decades of cancer research, will be worth the gamble.

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EAT, BREATHE, LIVE RESEARCH

Guo Tiannan is one of the few doctors who have been awarded the Ray Wu Prize this year. **VERONICA LEE** speaks to the Chinese native and discovers what it takes for a foreigner to be successful in research in Singapore.



After graduating with a medical degree from Tongji Medical College in Wuhan, China, Dr Guo Tiannan decided not to practise medicine. Instead, he went on to embark on further studies that allow him to venture into scientific research. His choice was to experience work in flow cytometry in a large hospital in Wuhan before setting his sight on Singapore and joined NCCS as a research officer in the Division of Medical Science

He chose gastric cancer research over others as gastric cancer is prevalent in Asia; yet little research was done on this subject. Dr Tiannan decided to study targeted therapy in the treatment of cancer cells. The therapy used in targeting the membranes of cells saw some responding well while others remained resistant. To understand this outcome, he is now putting his efforts on inner cells to harness the protein used in targeted therapy that is already present in the inner cells. He is conducting a preclinical trial on animal models to ascertain the efficacy of the drug compound.

While doing research, Dr Tiannan also pursued a doctoral programme with the Nanyang Technological University, under the supervision of Assistant Professor of Sze Siu Kwan, NTU's Director of Proteomics Core of Bioscience Research Centre and Professor Kon Oi Lian, Head, Division of Medical Science at NCCS. The good work that Dr Tiannan was doing caught their eyes and they nominated him for the Ray Wu Prize. This prize is awarded to graduate students for excellence in life science research for their innovation, independent thinking and dedication.

In Prof Kon's nomination letter to Peking University, she wrote: 'the quality and intensity of his research work will be very difficult for other graduate students and post-doctoral fellows to replicate'. Describing him as very proficient in bioinformatics and writing programmes that facilitate analysis of large mass spectra datasets, she said: "Tiannan is intellectually well developed and a deep thinker. He has astonished me by his ability to integrate multiple and diverse data sets from proteomic, transcriptomic and genomic experiments.

He has unusual abilities to derive novel insights from his system biology approach and played a part in our recent finding that over-expressed Met Kinase is also located in mitochondria."

Looking back, Dr Tiannan said that he had the privilege of working with Prof Kon and Prof Sze who work very hard. That has made life as a researcher much easier for him. "They work seven days a week and does not take much leave during the year. That has helped pave the way for me as they are contactable for advice and guidance easily."

Like his supervisors, the humble Dr Tiannan's commitment to his work is no less. It was well known among his peers that he spends his weekends writing publications and grant papers. His family knows he is not to be distracted while he works at home.

Indeed, his single-mindedness in research and having such strong work ethics, passion is the overarching reason. On why he chose research over medicine as a career, the soft-spoken man who lived in Hubei China said it is the absence of boundaries in research that excites him. "Research is creative and it presents many opportunities to do anything and there are no boundaries in what we can do."

As he looks forward to graduating early next year, he has already set his sight on furthering his studies, preferring to venture into proteomic and bioinformatics, which he said are two exciting fields that have yet to be explored fully. With a long term ambition to be a leading expert in biomedical science, he already has a plan and is already pursuing a post-doctoral fellowship in Switzerland, intending to deepen his knowledge in mathematics and statistics for about two years.

NEW CALLING FOUND DURING SABBATICAL

Sabbatical leave certainly means different things for different people. For Prof Zelig Tochner, it led to a more meaningful preoccupation as he got to fulfill his dream that looked impossible by others. **VERONICA LEE** catches up with the leading proton therapy expert from University of Pennsylvania.



Today, proton therapy is able to deliver precise treatment, both for disease sites that called for high doses of radiation, or by increasing the precision of the radiation by limiting the dose to normal tissue, unlike conventional therapy. While the same amount of radiation is delivered to normal tissue in conventional therapy, proton therapy is able to minimise its dose to normal tissues by 50-70%. It is especially useful in children when great precautions have to be taken to minimise the long term complications arising from radiation treatment which may affect their physiological development in the long run.

Apart from children, Prof Tochner said that Proton Therapy is also effective for people who have received radiation treatment but have recurrences, where normally, further radiation treatment cannot be given without a high risk of damaging the normal tissues. It may also be beneficial to healthy elderly patients who have tumours in the brain and neck region, where access to these areas are generally difficult.

Prof Tochner met National Cancer Centre Singapore (NCCS) oncologists and administrators at the annual meeting of Particle Therapy Co-Operative Group (PTCOG) in May 2011. The meeting led to more discussions about proton therapy and a visit by a team from NCCS to the University of Pennsylvania to view the facility. In December, he was invited to visit the Radiation Oncology Department and met the officials from the Ministry of Health to study the setting up of proton therapy facility in Singapore.

Prof Tochner's journey with proton therapy took off after meeting a man with "a crazy idea" as he called it then. This was some 15 years ago when he was attending an ASTRO (American Society of Therapeutic Radiology and Oncology) meeting when the man shared his vision about expanding the use of protons in a medical setting. Then, the use had seemed fairly limited with little thought that it would one day be a new treatment modality for many areas in the body. Many in the audience had thought that the man was a dreamer and laughed at him. Instead of agreeing with the majority, Prof Tochner became excited by the idea.

With 15 years of experience in radiation oncology under his belt, Prof Tochner decided to go on a sabbatical at the University of Pennsylvania. During his stint there, he became involved in the visioning, planning of and negotiating of contract for the proton therapy facility, which is now the largest in the world. He returned briefly to Israel, before he was invited to return to the university to continue in the work to build the facility. All in all, it took about 10 years and the facility only began to treat patients in 2009.

Explaining the long time that he took to build the facility, Prof Tochner, who is now the medical director of the Roberts Proton Therapy Center at the Hospital of the University of Pennsylvania said; "It took us many years to sign a contract with the vendor before we were able to start building the facility in 2006. It was three and a half years before we started treating patients. The facility is so massive and the sheer size of the systems is a major consideration when we were designing the building."

When asked if healthcare providers would also take as long to build the facility in Singapore, Prof Tochner said confidently, "Leveraging from the experience of other facilities as well as ours, it is possible to start treating patients three and a half years from the time you seal a contract."

He said in the West, proton therapy is now not a new treatment modality for cancer. The first attempt began in 1950 in nuclear physics research facilities and applications were limited to small tumours in the body in a few parts of the body such as the neck region and the brain. It was only in the 1970s that proton therapy, which uses ionising radiation to target tumours with a beam, became routine for medical applications with the imaging advancements and development of sophisticated computers and improved accelerator and treatment delivery technology.

As precision is critical in proton therapy, more time is needed to position the patient for the most effective treatment. "Although a course of proton therapy is the same as conventional therapy, more time is needed to position the patient so that treatment can be delivered precisely. This means that we are only able to treat two patients in an hour as compared to the three to four patients that are treated with conventional therapy.

Prof Tochner said that with a population of five million people, he thinks that Proton Therapy will be well utilised in Singapore. "I think proton therapy will benefit many Singaporeans, especially children and young adults." He cautioned that many who does not understand the impact proton therapy has on the quality of care will not see its benefits. "You have to place your bet on it and once you build it, you will realise how good such medical technology is for the patients."

When asked to comment on the quality of healthcare at NCCS, Prof Tochner gave the thumbs up. "I am impressed with the modern systems and the integration of the three disciplines. Your staff are asking the right questions and this definitely shows that the centre is heading in the right direction to provide quality patient care. The way ahead for NCCS is to anticipate problems. It is best to assume that nothing is perfect. We should always look for problems in the system to improve so that we can better deliver patient care," he said.