

Prof. Yun Fan: persistence guarantees expertise, patience conquers difficulties

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Introduction

The ancient Greek aphorism “*know thyself*” engraved on the forecourt of the Temple of Apollo epitomizes the human desire for the exploration into the unknown. In fact, never has mankind dragged their feet in understanding themselves, as in the achievements scientists have made all these years in the studies of disease and pathology.

Ere the 2017 WCLC journey, AME Editors were sent across China to conduct in-depth interviews with an army of distinguished experts in the field of lung cancer. Together we learned how these soldiers fought for the nation that has the largest number of patients, and how they dedicated their lives to inventing the most-advanced weapons and probing into the enemy camp. From the past, they reflect and learn from mistakes; at present, they work hard and make changes; for the future, they make plans and improvements.

May this issue take you to the innermost world of these Chinese scholars, where you can delve into their wealth of knowledge and be inspired.

“I have been working in the same hospital and the field for many years, I think that it is toilsome being a doctor. It requires a strong sense of responsibility, but meanwhile you feel bittersweet because it challenges you and you are always learning.”

Prof. Yun Fan, Chief Physician, Director of Thoracic Tumor Center, Zhejiang Cancer Hospital, executive member of China Society of Clinical Oncology (CSCO), vice chairman of Professional Committee of Small Cell Lung Cancer (SCLC) of CSCO, vice chairman-designate of Medical Oncology Committee, Zhejiang Provincial Anti-cancer Association, vice chairman of Anti-Cancer Drugs Committee, Zhejiang Provincial Anti-Cancer Association, vice chairman of esophageal cancer specialty committee of Zhejiang Province Anti-cancer Association, member of the standing committee of Oncology Branch, Zhejiang Medical Association, editorial board member of *Journal of Clinical Oncology* and other journals.

“Focus on one thing at a time and do it remarkably well”, the Chinese saying from an ancient book *Rites* can be a



Figure 1 Professor Yun Fan.

true reflection of Prof. Fan (*Figure 1*). She was born in a family that had no doctors, but encouraged by his father, she formed a strong tie with medicine. Since Prof. Fan's graduation from the Wenzhou Medical College (now Wenzhou Medical University) in 1989, she has been working in the Department of Oncology of Zhejiang Cancer Hospital and this field for about 28 years.

As the saying goes “*Determination gives you the resolve to keep going in spite of the roadblocks that lay before you.*” Brain metastases are a common occurrence in patients with non-small cell lung cancer (NSCLC) and affect many people. Prof. Fan challenges herself to study in this field; she conducted a research on the mechanism of meningeal metastasis in patients with NSCLC with EGFR mutations, which was selected for an oral presentation at the 17th



Figure 2 Professor Yun Fan (right) was a visiting scholar at MD. Anderson Cancer Center.



Figure 3 Professor Fan during her oral presentation at the 17th WCLC, 2016.

World Conference on Lung Cancer (WCLC) in 2016. We are aware that TKI is very effective for brain metastases in patients with NSCLC with EGFR mutation, the unresolved problem is: why do some patients have brain metastases and others do not?”

Accepting challenges, striving for excellence persistently

AME: You have been working in the Department of Oncology of Zhejiang Cancer Hospital for about 28 years, what makes you to work so persistently?

Prof. Fan: Looking back, I realize that I have been already

working here for so many years. Sometimes when I see young students I can't help but exclaim, “where has the time gone?”

My father encouraged and inspired me to become a doctor, he thought highly of doctors in treating the wounded and rescue the dying. I started doing clinical work in Department of Oncology and never changed it, I guess you could say it's a kind of loyalty. It is extremely hard being a doctor, it requires a strong sense of responsibility, but meanwhile you feel bittersweet because it challenges you and you are always learning (Figure 2).

This is a multifaceted challenge. For example, the first challenge may be finding out how to treat difficult cases, and the other challenge could be how to deal with a patient that was well-treated, but now suffers from metastases and a relapse, and another challenge is in the fact that there is no end to academic and skills improvement. I think if you like a challenging job you can try to be a medical oncologist, as it challenges you constantly.

Overcome difficulties, fight against brain metastases in lung cancer

AME : You were selected to do an oral presentation at WCLC in 2016 (Figure 3), is it also challenging that to research on mechanism of meningeal metastasis in patients with NSCLC with EGFR mutations?

Prof. Fan: In general, the incidence of brain metastases in patients with NSCLC is about 30% to 40%, however reaches 50% in patients with EGFR mutations, this incidence rate is very high, and therefore has drawn great attention to the fact that brain metastasis is a major issue in the management of lung cancer. As we are all aware tyrosine kinase inhibitor (TKI) is very effective in NSCLC patients with EGFR, but the unsolved problem is: why do some patients have brain metastases and the others do not?

Meningeal metastasis is a very dangerous complication of lung cancer, it develops rapidly and is more difficult to treat as compared to brain metastasis. Once patients suffer from meningeal metastases, their remaining survival time will be calculated by month if they do not receive effective treatments, most of whom may die within 3 months. Therefore, we focused our research on the mechanism of meningeal metastasis. We wanted to find out the reasons behind why patients with EGFR mutations who had TKI therapy but still suffered from meningeal metastases. We stored both cerebrospinal fluid specimens from patients who have meningeal metastases, and their tissue samples

before treatment. We chose second-generation sequencing technology to discover genomic differences between the two specimens. The results showed that when comparing cerebrospinal fluid specimens and primary tissues, there were significant differences in the cell cycle and DDR related genes, which may be related to meningeal metastasis.

We will dig deeper into this field in the next step, whether it be basic research or clinical research, we will be implementing further study. For instance, we will explore whether there are genetic differences between patients have brain metastasis and those that do not, and what kinds of biomarkers may predict patients who potentially will develop brain metastases.

AME: *We look forward to your further study. What is the current progress for treating patients with NSCLC and brain metastases?*

Prof. Fan: The current progress for treating NSCLC and brain metastases mainly include two methods, drug treatments and local treatments. For drug treatments, there was previously no effective drug treatment for patients with NSCLC and brain metastases, and the standard treatment was whole brain radiotherapy. Professor Yilong Wu led the BRAIN study which found out that targeted therapy is better than radiotherapy in terms of both the rate of remission and PFS, which underpins TKI therapy's position as a primary treatment method for patients with EGFR mutation and brain metastases (1). Secondly, if patients suffer from brain metastases during TKI therapy, that involves the research of drug resistance mechanisms.

In terms of EGFR signal pathway, the latest AURA study found that osimertinib had significant curative effect in patients with T790M-positive NSCLC and brain metastases (2). Crizotinib therapy is a common treatment for ALK-positive patients, however it has limitations in treating brain metastases due to its low blood-brain barrier transmission rate. The most prominent drug at the moment is Alectinib, and the J-ALEX research has proven its positive curative effects on patients with brain metastases (3). Apart from TKI, there are other effective drugs for treating brain metastases, particularly immune drugs, such as PD-1/PD-L1 monoclonal antibody. Some subgroup analysis and phase II clinical studies confirmed that these drugs have a certain effect on brain metastases and they appear to be promising.

When it comes to local treatments, we use whole brain radiotherapy to treat brain metastases, but this method has side effects such as cognitive disorders after treatment. It

is a basic consensus for us to classify patients into either oligometastases or multiple diffuse metastases. Patients with oligometastases can be treated with stereotactic radiosurgery (Gamma Knife treatment), and if they can be treated with Gamma Knife, there is no need to add whole brain radiotherapy. However, patients with multiple diffuse metastases will still require whole brain radiotherapy. Another research is on the optimal timing for asymptomatic brain metastases in patients with EGFR mutation. Currently, there are only retrospective studies in this area but no randomized controlled Phase III trials. It is still controversial whether to add whole brain radiotherapy in the beginning of the treatment or not, and even though some results from retrospective studies agree that this method will increase the patients' survival, I think it needs to be proven by future randomized controlled Phase III trials.

Teamwork makes the dream work

AME: *You have been doing clinical work and research for many years, what part of this experience has left the deepest impression on you?*

Prof. Fan: During the brain metastasis research, I had a profound experience that was multi-team cooperation. We received great support from Peking Union Medical College Hospital. The team shared the same interest, so we co-conducted some research on brain metastasis in lung cancer, communicated specimens, and collaborated on other topics. I think multi-team cooperation is definitely very important, in particular co-research on rare molecular subtypes. Another collaboration is that between the clinical research team and the basic research team; everyone has different expertise, and without teamwork it is difficult to continue in-depth research, especially if the subject is seeing rapid progress, such as lung cancer study, many mechanisms need to be explored. Prof. Yilong Wu's team has made an extraordinary achievement in this field (*Figure 4*).

Speaking of cooperation, if we were to look at it from a clinical point of view, we may consider the method everyone is talking about: multidisciplinary team (MDT). MDT is now gaining popularity and benefits both clinic and patients. In our hospital, the MDT has regular discussions every Wednesday morning in order to solve clinical problems. For example, we could not decide on an effective way to treat a patient with Stage III NSCC, then the team discussed about it together. We also have online

MDT meetings, which connect many Thoracic Oncology MDTs from different hospitals in the Zhejiang province; we gather and discuss various cases and provide patients with an optimal treatment plan. Now we have 8 centres that have joined our online MDT meetings, and we communicate and exchange ideas regularly. Regardless of what form it comes in, cooperation and communication is very important. We participate in meetings at home and abroad, host seminars (Figure 5), just so as to carry out further cooperation.

AME: *These are great cooperation methods both clinically and academically, but how do you integrate and transfer them?*

Prof. Fan: In the early beginning, our team focused on



Figure 4 Professor Fan (left) with Professor Yilong Wu (middle), and Professor Conghua Xie (right) at WCLC 2016.

solving clinical problems, we hoped that we could solve them through scientific research. Now we put more efforts into transformational research, we explore the nature of clinical problems and then return to clinic to seek validation.

We completed a study which I think is rather meaningful. As gemcitabine is commonly used to treat NSCLC during chemotherapy, the standard gemcitabine administration is on days 1 and 8. Many patients that live far away would rather stay in the hospital between consecutive treatments instead of going home. Therefore, they end up occupying hospital beds for about one week, which is a waste of clinic medical resources.

We thought about changing gemcitabine administration to days 1 and 5 instead, as this method has been used to treat patients with other tumors. In order to use this method, we had to confirm that the efficacy will not be affected after the change of the administration time, also, the drug's toxicity cannot be increased. We performed a Phase II study to observe whether gemcitabine disappeared completely on day 5 from a perspective of drug metabolism. If it disappeared completely then its toxicity will not be superimposed. From clinical observation, we use gemcitabine on days 1 and 5 combined with cisplatin primary treatment to treat advanced NSCLC, and then compared efficacy, toxicity and historical data. From the results of our Phase II study, we could not detect any trace of gemcitabine and its metabolite in the patients' plasma. There was no significant statistical difference when comparing the reported data of the method that combined gemcitabine administration on days 1 and 5 and cisplatin to



Figure 5 Professor Yun Fan (front row, sixth from the right) led “The 1st Qianjiang Summit Form of Precision Treatment for Lung Cancer” in 2015.

treat advanced NSCLC in terms of efficacy and toxicity.

Never-ending personal development

AME *Apart from clinical work and academic research, what do you enjoy doing in your spare time?*

Prof. Fan: I enjoy reading books, listening to music, sometimes I go out as well.

AME *What kinds of books do you enjoy?*

Prof. Fan: I feel relaxed when I am reading. I enjoy reading essays, and sometimes novels. I read three well-written books last year, *The Best Farewell*, *Complications: A Surgeon's Notes on An Imperfect Science*; and *Better: A Surgeon's Notes on Performance*, they are all related to medicine and written by Atul Gawande. My favourite one is *The Best Farewell*.

AME *The three books are also relevant to your work.*

Prof. Fan: That's right. These three books are particularly suitable for budding medical practitioners. The author shares his experience and opinion about being a surgeon, and many quotes in the books have become well-written "mottos". Besides experience, techniques, he writes: "*But, as the field grows ever more complex and technological, the real task isn't to banish paternalism; the real task is to preserve kindness.*"

It is indeed important for us to we have a responsible attitude and to remain committed to providing comfortable services.

To comfort always, to be responsible, to build trust

AME *You are conscientious and responsible, I think patients respect you and trust you.*

Prof. Fan: A lot of patients come and tell me, "*I am here because of you,*" or they may say, "*someone in our village introduced you to me.*" I think if we are conscientious, responsible doctors that treat patients well, they can also feel it and will recommend you to others. This reflects patients' trust.

AME *We know that patients trust you, but in oncology there are still some situations where the curative effects are still unsatisfactory. How do you deal with this and communicate with patients?*

Prof. Fan: In order to bring better treatments for patients,

we have to improve our professional skills continuously, which can also be a process of self-discipline. Many times, we also need to "enlighten" patients and their families.

My principle is to provide treatments actively when patients can be treated and cured, so as to give them an opportunity to improve the condition. For other conditions, if there is no strong indication that they should undergo treatment, I will communicate with their families and recommend palliative care to relieve their pain. If you communicate with them patiently, most patients and families will accept it. We need to think about death rationally. In China, it is a lack of death education, many people think that it is not auspicious to talk about death. Most Chinese people seem to not have religious beliefs, therefore, it is quite scary for them to face "death". As famous American doctor E. L. Trudeau would have it, "*To cure sometimes, to relieve often, to comfort always.*" Doctors need to "comfort" patients often.

Looking into the future, targeting immunization and tobacco control

AME *What are your expectations on the future development of WCLC 2017 and NSCLC?*

Prof. Fan: We have 6 articles were selected for poster presentations, mainly in 4 areas: NSCLC brain metastases treatment, EGFR TKI resistance mechanism, rare EGFR mutation treatment and the combination of single agent anti-PD-1/PD-L1 treatment.

The current study of lung cancer mainly focuses on two areas: targeted therapy and immune therapy. We really hope that we will see more recent news in these two areas at WCLC this year.

In addition, I would like to use AME as a platform to appeal to the public on the enhancement of tobacco control, as well as the prevention against environmental pollution prevention. In terms of lung cancer, one of the biggest differences between the East and West is incidence. In the United States and other Western countries, the incidence has been significantly reduced, but it continues to rise in China. The two major reasons are smoking and air pollution. Therefore, the government and individuals should pay a great attention to tobacco control and management of air pollution.

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Footnote

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