

Prof. Jianhua Chang: gaining a foothold in China, launching Chinese-style clinical trials

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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.

Expert's introduction

Prof. Jianhua Chang, MD, chief physician, Department of Medical Oncology, Fudan University Shanghai Cancer Centre Fudan University Attached Tumor Hospital. Graduating in 1988, he obtained the Master and PhD degrees in Xiangya Hospital of Central-South University. In 2002, he started the researches in lymphoma and lung cancer at Sun Yat-sen Cancer Center as a postdoctoral researcher. He is now the Vice Chairman of Molecular Tumor and Immunotherapy Committee, Chinese Research Hospital Association, Permanent Member of Lung Tumor Committee, Chinese Medical Education Association, Member of Clinical Oncology Committee, China Anti-Cancer Association, Member of Small Cell Lung Cancer Committee, CSCO, Vice Chairman of Molecularly Targeted Therapy and Immunotherapy Committee, Shanghai Anti-Cancer Association, Chairman of

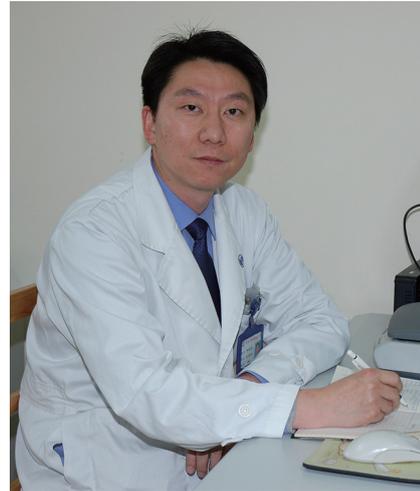


Figure 1 Prof. Jianhua Chang.

Chemotherapy Committee and Member of Breast Cancer Committee, Shanghai Anti-Cancer Association, Member of the American Society of Clinical Oncology (ASCO) and the International Association for the Study of Lung Cancer (IASLC). He has been engaging in the diagnosis, education and research in chemotherapy and anti-cancer drugs for many years. He serves as the main investigator in a wide range of national and international multicenter randomized controlled trials. His research interests consist of the individualized treatments for advanced lung cancer, oesophageal cancer and mediastinal cancer.

At 4 pm of 12th September, we made a visit to the Oncology Ward of Fudan University Shanghai Cancer Center. There were patients in patient clothing and patients awaiting consultation with their relatives at every corner of the hospital. They looked either contemplative or worried about their own conditions or their relatives. “*These patients come from all over China with faith in our hospital,*” said a doctor in the hospital.

As an oncologist, Prof. Chang (Figure 1) meets a great



Figure 2 Prof. Chang was making a presentation at the conference.

deal of cancer patients in middle or advanced stage every day. When he was asked about how to avoid the catastrophe brought by cancer and how to prevent the tragedy from happening, he answered, “*This is why we need to do the three-grade prevention.*” Firstly, from the national and social perspectives, the government should play a leading role in improving the environment, minimizing pollution and raising the awareness about the concept of anti-cancer. Moreover, through early screening, we would be able to provide early diagnosis and treatment that would enable a higher cure rate through radical treatment at the early stage of cancer. Thirdly, for the middle and advanced-stage patients, we should provide them with standardized treatment if possible so as to prolong their life. For the incurable cancer patients, we would attempt to cure and manage cancer as a chronic disease, minimizing the pain and enhancing their living quality. As Prof. Chang said, “*Only if the whole society work together would there be a chance for mankind to beat cancer.*”

A deep look into Xinjiang

In December 2013, Prof. Jianhua Chang, as a member of the first cadre engaging in the 10-year project of aiding the Department of Oncology, Kashgar Prefeitura No.2 Hospital, had successfully accomplished the a-year-and-a-half mission and returned with glory. China has been making a great effort in aiding Xinjiang since new China was founded. Many mentors have chosen to leave for Xinjiang to give a helping hand to its establishment. Prof. Chang speaks unobtrusively, “*We are just carrying forward the spirits of industriousness and selflessness from our mentors. We still have a lot more to do.*”

Kashgar Prefeitura, where Prof. Chang stayed at that period of time, is located at the southern part of Xinjiang.

90% of the local people were Uygur. Language was thus a great barrier to his team. There was a great deal of medical staff, but the level of medical technology was rather backward and not standardized. Meanwhile, there often was shortage of medicine due to its special geographical location. Worse still, the short-term vocational trainings held can hardly make medical staff fully master the latest technologies. Therefore, Prof. Chang and his colleagues decided to help Xinjiang comprehensively—stationed in Xinjiang and going deep into their daily routines. The local hospital also put faith in their team, allowing them to manage the academic and research works of different departments, getting involved in the whole medical process, helping to delineate and improve the shortcomings of their medical services, and standardizing each operation of the hospital.

The development of Xinjiang in general still lags behind in comparison to the eastern developed regions. Thus, there is room for development. For instance, some conventional practices adopted in the eastern regions are not yet seen in Xinjiang. As the saying goes, it is better to teach someone how to fish than to feed him with a fish. Nowadays, many hospitals in developed regions have established long-term connections with Xinjiang and have been referring talents to assist in its development. Concurrently, medical staff in Xinjiang are even invited to their hospitals to further study or helped to cultivate their own postgraduates. Prof. Chang told us that the first batch of postgraduates cultivated by Fudan University has already graduated and they are still keeping in close connection.

Shanghai has an annual fund for supporting the development of Xinjiang, Tibet, Yunnan and Africa. It is with this fund that more and more learning sessions and academic conferences can be held and have the new knowledge widely spread. “*My colleagues and I will probably go to the Xinjiang regions, where, on the one hand, we can take a look at the spectacular sceneries. On the other hand, we can pass on our knowledge to them, which I believe the local medical staff would warmly welcome.*” (Figure 2).

Individualized approach to manage cancer

“*The patients in South Xinjiang are simple-minded. They are lacking in basic medical knowledge and thus have great trust in doctors. The only limitation is their economic condition—they do not have money.*” Coming to this point, Prof. Chang felt deeply sorry for them, “*Many patients come here for one single treatment only when they have money, which they make by, for*

instance, selling a goat. Seldom do they have the chance to have a systematic treatment. I still remember there was an early breast cancer patient who could have undergone radical resection. Yet, as she did not see any major issue with her body, she decided to return home to live her usual life. Unfortunately, her tumor had a metastasis the next year. It is really pitiful. She is meant to have a higher chance of recovery.”

From the perspective of ethnology, the gene expression of Uygur is different from that of the Han. We should fully understand their clinical features to select the optimum treatment for their own good. “Taking lung cancer as an example, oncogene driver especially EGFR mutation is very high among Asians. It can be 50% or even 60%. Yet, the rate in Uygur is relatively low. The options of treatment can thus differ greatly,” explained Prof. Chang. In comparison to the Han, the lifestyle of Uygur is different as well. For example, they like to barbecue food and smoke the local cigarettes. Although there is no air pollution in Xinjiang, the incidence of lung cancer is noticeable due to the consequences of smoking.

The launch of Chinese-style clinical trials

Prof. Chang has taken part in several national and international multicenter randomized controlled trials as the main investigator. He thinks the vital key to a successful multicenter randomized controlled trial is standardized execution, which, in other words, means whether the trials are under the strict guidance of Good Clinical Practice (GCP). “New medicine would be used in patients when it enters the market. If the trials were not standardized, the generated data would be problematic, and we would not be able to obtain an accurate result,” indicated Prof. Chang.

It is delightful to see China putting more and more emphasis on standards nowadays. In the past, there were not many doctors participating in this kind of trials, while the GCP training was not standardized enough and the experimental results were far from flawless. Prof. Chang mentioned that, in these days, not only the pharmacy and therapeutics departments but also some independent factories have already changed their mindsets and catch up with the international standards. Each detail is getting more and more standardized in terms of management, operation and clinical practice. The incidence of lung cancer in China is very high in comparison to foreign countries and other Asian countries. It is not a good thing of course, but it does facilitate clinical trials by a large sample size. Therefore, often can data be generated and obtained in China faster

than other countries. Given time, China will be ahead of other countries in this aspect. “We may soon be able to develop our own medicine with better performance instead of importing from foreign countries. Taking lung cancer as an example, the curative effect for Asians is better than that for Europeans, and is with longer survival period. It is something we are all eager to see. We aim not only to take part in global clinical trials, but launch our own trials. I hope we can further optimize the principles and rationales of our clinical work,” Prof. Chang said seriously. We are also looking forward to seeing the success of Prof. Chang’s team in bringing good news to all patients in need.

Conversation with Jianhua Chang

AME: *What are the therapeutic approaches to the late lung cancer patients with brain metastases?*

Prof. Chang: Nowadays, the incidence of brain metastases remains high in lung cancer, especially small cell lung cancer (SCLC). The longer the survival period is the higher ratio of the occurrence of brain metastases is. Taking SCLC as an example, there would only be 10% of incidence at the beginning stage. If the patients could live more than 3 years, the ratio would jump drastically to 60% to 80%. With the prolongation of the survival period, the ratio of metastases in vital organs will be further increased. With regard to non-small cell lung cancer (NSCLC), the remedy used to be rather limited with dependence on radiotherapy and topical remedy. Today, many drugs can pass through the blood-brain barriers. For example, targeted drugs have very good performance with 60% to 70% of effectiveness to extracerebral lesions and 70% to intracranial lesions. The 3rd generation TKI medicine launched earlier this year not only has high effectiveness (60% to 70%), but leads to few side effects. It certainly is a better alternative for both doctors and patients.

AME: *What kind of patients is prone to late-stage brain metastases? Can they prevent it and how?*

Prof. Chang: Late-stage brain metastases occur in certain group of people, such as SCLC patients. In fact, the metastasis is preventable. We are now doing the preventive work for limited-stage patients. What limited stage means is that the tumor has not yet metastasized to other organs, but only in one side of the lungs or on the mediastinum. The patient would have the radiotherapy indications. By

using chemotherapy and radiotherapy at the same time, we can relieve and control the tumors. If there is no brain metastasis, prophylactic cranial irradiation (PCI) can intervene at this time. These procedures are indexed in our guideline. In other words, it is already the standardized treatment approach for our clinical practice.

It is shown that after ten times of PCI, there is apparently a decline in the ratio of brain metastasis. For patients without PCI, the ratio of brain metastasis remains very high with lower survival period. However, for NSCLC patients, the result of PCI is not obvious. Recent findings of large-scale clinical trials have indicated that the occurrence of brain metastasis has no direct relationship with PCI. Thus, for these patients who have a positive result in the generic test and receive treatment with targeted drugs, this can be considered as a way for prevention. For patients with no history of brain metastasis, after medication, the medicine will stay in the brain. Any tumor cell entering the brain will be killed immediately. Even it is not a preventive measures, it does achieve the effect of prevention.

AME: The toxicity management in molecular targeted therapies is of utmost importance. Can you share your clinical experience in toxicity management of the NSCLC targeted therapies?

Prof. Chang: I think it is a very crucial matter. In the past, some said the targeted drugs were simple. Patients could get the prescription from doctors and take the medicine at home. Even though targeted drugs have a different toxicity spectrum from that of the traditional chemotherapy drugs, it does not mean they are lower in toxicity. Chemotherapy may lead to alopecia, damage of liver and kidneys, killing of blood cells, infection and anemia, whereas the side effects of targeted drugs include skin rash, diarrhea, hypertension, non-healing wounds and some serious toxic hepatitis. If doctors do not fully understand the drugs and have them prescribed to patients without informing them about the side effects, it can be very dangerous. Continuing education is thus important not only to patients but also to the doctors as a whole. Albeit most of the toxicity of the molecularly targeted drugs is predictable and controllable, we must be fully aware of the serious or fatal adverse reactions caused by these drugs. Doctors should make good use of their “weapons” to provide anti-cancer treatment with low toxicity and high effectiveness, to which toxicity management is the prerequisite.

AME: Compared with NSCLC, what are the main challenges for the rare late-stage lung cancer such as squamous-cell carcinoma, small cell lung cancer? How to conquer them?

Prof. Chang: The reason we think squamous-cell carcinoma and SCLC are more difficult to be cured than NSCLC is that there is no suitable target spot for them. Without a target spot, the existing targeted drugs cannot function, and we have no choice but to rely on the traditional chemotherapy. In other words, the approach to the management of this sort of cancers remains stagnant. For example, chemotherapy is kind of effective for SCLC. The only problem is that its effect lasts only a short period of time and so it does not guarantee long-term survival. The tumor often regrows after half a year or even 3 months. When the tumor recurs, the curative efficacy thereafter will be even lower. There are a variety of lung cancers and they will be divided into different sub-types in the future. We may use different medicine or drugs based on their sub-types. Individualized treatment will be carried out based on different kinds of tumors, genetic driver and target spot to select the appropriate medication. There are instances without accurate target spot that can be treated with immunotherapy like squamous-cell carcinoma and small cell lung cancer. They are also our hurdles. How do we get over them? This is something worth our exploration.

AME: As we know you excel at the clinical diagnosis of pulmonary and bronchial neuroendocrine tumors, can you briefly introduce the background and the difficulties in treatment?

Prof. Chang: There are different types of neuroendocrine tumors, including those in pancreas and liver. The pulmonary and bronchial neuroendocrine tumors are the relatively special one, which can be divided into 4 sub-types. Carcinoid tumors grow slowly and are relatively inert. It would not affect the living quality of patients even without treatment, which is simply surgical resection. Large and small cell neuroendocrine carcinoma will have hyperplasia. The speedy cell division would bring short tumor doubling time. Radiotherapy and chemotherapy can have a great impact on this kind of patients. However, it is prone to recurrence. Until now, there is no ideal clinical method and it would bring the cancer-related symptoms like hyponatremia. The tumor having the endocrine functions is why the cancer is named

as neuroendocrine tumor. It would release toxins to disturb the endocrine system and it may induce complications. The incidence of the pulmonary neuroendocrine tumor is relatively low but basically the SCLC would contain neuroendocrine tumors. The incidence of SCLC is about 20% to 25% among all types of lung cancers.

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Footnote

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