



Benefits of precision medicine in lung cancer: experience from a single institution

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Received 13 July 2022, Accepted 16 September 2022, Published online 21 October 2022

Abstract – Lung cancer remains the leading cause of cancer death worldwide and in China. Over the past two decades, targeted therapy and immunotherapy have improved the five-year survival rate of lung cancer, and precision medicine has played a great part in this progress. However, owing to the heterogeneity, complexity, and economic disparity, the usage of precision medicine is still low, which generally results in a poor prognosis. In view of the current bottlenecks, such as low early diagnosis rates and the poor prognosis of lung cancer patients, our team predicted and identified early diagnosis markers of lung cancer. We have described the genetic characteristics of lung cancer patients, identified potential treatment targets, and explored accurate treatment schemes for the disease. We have also promoted their application by conducting bioinformatic analysis, high-throughput sequencing, liquid biopsy, and improved FISH and other technologies. This has formed an integrated system for the precise diagnosis, treatment, and transformation of lung cancer research, obtaining good social benefits after their application.

Key words: Precision medicine, Lung cancer, Integrated system.

Background

According to the latest data from the GLOBOCAN 2020 Statistics and National Cancer Center, lung cancer is still cancer with the highest mortality rate in the world and China, especially among males and in urban areas. According to the data, the number of new lung cancer cases in China is about 820,000, and the mortality rate is 47.51/100,000 [1–3].

Lung cancer is a very heterogeneous group of cancers, from cellular and histological to molecular and genetic levels. This has an important impact not only on lung cancer classification but also when defining prognosis and therapy decisions [4]. With the development of next-generation sequencing (NGS) and liquid biopsy, heterogeneity at the molecular and genetic levels indicate the complexity of decision-making in the process of diagnosis and treatment.

As for traditional therapy, the first-line treatment for advanced lung cancer depends on the histological classification. In recent years, the NCCN guideline updates are frequently based on positive data from clinical trials, especially for non-small cell lung cancers (NSCLCs), for which the therapy regime varies according to genetic mutation and PD-L1 expression. For small cell lung cancers (SCLCs), chemotherapy containing platinum would be the preferred recommendation for most patients in China even though the PD-L1 inhibitor,

Atezolizumab or Durvalumab, combined with chemotherapy has been recommended as the first line treatment because of the cost implications. For squamous-cell carcinoma, immunotherapy plus chemotherapy is recommended as a substantial number of patients consider chemotherapy alone. Even for adenocarcinoma, patients from less developed areas still accept chemotherapy as their only option.

Precision medicine in lung cancer

Since 2015, precision medicine has entered an era of rapid development, which applies modern genetic technology, molecular imaging technology, and diagnosis, biological information, and big data technology, combined with the patient's clinical and individual information, to implement accurate risk prediction and accurate disease diagnosis and treatment. Precision medicine was first applied to lung cancer and has been continuously promoted, especially in NSCLC. In the past two decades, tremendous advances have been made in understanding the biological and genetic drivers of NSCLC. As a result, many targeted and immunotherapy drugs represented by tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors are now being used to manage advanced NSCLC and adjuvant therapy of early-stage lung cancer, with the hope of improving outcomes and curative rates [5]. Many umbrella and basket trials are designed based on molecular classifications and

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histopathological types. Although most of the studies are common alterations in the epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) oncogenes, rapid advances in molecular characterization have led to the development of novel therapeutics in advanced NSCLC, such as ROS1-rearranged, BRAF V600E-mutant, NTRK-rearranged, MET-altered, uncommon EGFR-mutant, RET-rearranged, HER2-positive, KRAS G12C-mutant, and NRG1-rearranged, leading to a host of new treatment options for advanced NSCLC. These findings have advanced our ultimate goal; to improve outcomes for patients with lung cancer [6].

To improve the level of regional clinical, precise diagnosis, and treatment, Qingdao Precision Medicine Center of Oncology was established in 2016 as one of the earliest precision medicine centers in China. In the past five years, Professor Zhang and her team have explored and established an integrated system for the precise diagnosis and treatment, and transformation research of lung cancer. There have been good social benefits after popularization and application. At this point, we will introduce our research experience about precision medicine for lung cancer at our institution.

Experience about precision medicine

Precise diagnosis

For people at high risk of lung cancer, we developed early screening technology using non-invasive FISH with high sensitivity, which was approved as a major innovation project in Shandong Province and obtained a national invention patent. Based on the data from NGS, we performed extensive analysis aimed at exploring the genetic profile of Chinese lung cancer patients. Firstly, the frequencies of targetable genetic alterations in 177 patients with lung adenocarcinoma were analyzed by defined age categories, showing a distinctive molecular profile in the younger group, those younger than 45 years old. Notably, higher frequencies of ALK and HER2 genetic alterations were associated with younger age. However, a reverse trend was observed for KRAS, STK11, and EGFR exon 20 mutations, which were more frequently identified in the older group aged more than 46 years old. Furthermore, concurrent EGFR/TP53 mutations were much more prevalent in the younger patients (81.6% vs. 46.8%), who might have had a poorer response to treatment with the epidermal growth factor receptor tyrosine kinase inhibitor [7]. To find highly efficient biomarkers for clinical diagnosis of NSCLC patients, we used gene differential expression and gene ontology to define a set of 26 tumor suppressor genes, which were down-expressed at stages II and III in lung cancer samples, and 15 of the tumor suppressor genes were significantly down-expressed in stage I tumor samples [8].

Precise therapy

All the guidelines for clinical therapy have been issued based on clinical trial data. In the past five years, thirty-five international and domestic multi-center clinical trials for lung cancer have been carried out at our center. Patients could accept cutting-edge therapy by participating in clinical trials, especially

phase I clinical trials of new anti-tumor drugs with a new molecular structure, which we first carried out as the team leader in Shandong Province. Moreover, we also designed and launched some innovative phase II clinical trials based on clinical discovery and literature reviews [9, 10].

In addition to standard precise therapy and clinical trials, we are still conducting research to explore therapy-related biomarkers. We demonstrated that TP53 mutations are an independent predictor of poor outcomes in advanced NSCLC patients treated with first-generation TKI therapy [11]. Another study showed that alternative splicing may play an important role in tumorigenesis and deserves further study as molecular diagnostic biomarkers and therapeutic targets [12]. The other major development was to do with lung cavitations, which is common with apatinib therapy and is a potential prognostic marker [13]. We also identified AURKA, KIAA0101, CDC20, MKI67, CHEK1, HJURP, and OIP5, which were correlated with the worst overall survival (OS) rates in NSCLC and may be critical genes to focus on in the development and prognosis of NSCLC [14].

Artificial intelligence and big data are important tools for advancing precision medicine. By studying the published medical literature, clinical trials, and clinical guidelines, artificial intelligence systems could provide an individualized therapeutic regimen. Since April 2017, IBM Watson for Oncology (WFO) has been used in our institution, and the concordance was examined between the treatment recommendation proposed by WFO and clinical decisions recommended for 113 lung cancer patients, whose concordance was slightly above 80% [15].

Tumor resistance to radiation or chemotherapy has been a difficult problem for disease therapeutics. Our group constructed oncolytic adenovirus targeting cancer stem cells (CSC), which showed an enhanced radiotherapeutic response. Proton therapy may be more effective than photons in eliminating recurrent or persistent NSCLC, which could be attributed to the effective response of chemo-resistant CSCs to proton therapy. In addition, the Coxsackie- and adenovirus receptor (CAR) could be a marker of CSCs in models of treatment-resistant NSCLC [16].

Achievements and social benefits

Depending on the construction of the integrated medical, teaching, and research system for precision medicine of lung cancer led by Professor Zhang, local lung cancer patients could obtain the most standardized, advanced, and individualized treatment available. With the continuous popularization and application of research results, the early diagnosis rate of lung cancer has increased by 30%, significantly prolonging the OS of patients with a high quality of life, this has achieved remarkable social benefits and promoted the improvement of precision medicine in Shandong Province (example in [Video 1](#)).

At our institution, five National Natural Science Foundations of China, six Chinese Postdoctoral Science Foundations, and a major scientific and technological innovation project for Shandong province have been conducted by our team. This has been done with the support of 40 research papers and two publications about “Precision Diagnosis and the Treatment of Malignant Tumors” which have been published to better guide

Initial CT scans



Video 1. A case report about precision diagnosis and therapy of advanced lung cancer with rare mutations. The patient has been treated with two kinds of 3rd EGFR-TKI targeted to EGFR mutation plus with Bevacizumab according to the disease progression. The PFS is up to 21 months, and the patient is still with stable disease now. <https://vcm.edpsciences.org/10.1051/vcm/2022005#V1>.

precision therapy. Meanwhile, Professor Zhang participated in compiling *China's Lung Cancer Clinical Diagnosis and Treatment Guidelines* for three consecutive years over the period 2018–2021. The institution has also been granted many awards, including the Science and Technology Award of the China Anti-Cancer Association, the Medical Science and Technology Award of Shandong province, and the Qingdao Science and Technology Progress Award.

The challenges for precision medicine in lung cancer treatment

Although the development of precision medicine has been rapidly improving, it is facing both opportunities and challenges. The inconsistency between basic research, clinical

practice, and the low implementation rate have become the main obstacles for precision medicine therapy in China. In addition, the uneven development of regions and medical institutions in China and the genomic characteristics of lung cancer are important reasons as well for this low implementation rate. At present, few patients with small cell lung cancer and squamous-cell carcinoma can benefit from precision therapy based on NGS. However, individualized pharmacokinetics, organoids, and the Patient Derived Xenograft (PDX) model may be useful tools for expanding the range of precision therapy.

With targeted therapy and immunotherapy application, the treatment response evaluation criteria have also changed accordingly. The effective criteria no longer only depend on the degree of tumor shrinkage, but the overall well-being of patients and the immune-related reactions are also taken into account.

Another reason for the low implementation rate is the high cost of genomic testing and precision therapy. Compared with no tumor profiling in patients with metastatic lung adenocarcinoma, tumor profiling improves quality-adjusted survival, but it is not cost-effective, especially in the wild type and where there is a rare mutation [17]. This situation could be improved by expanding the coverage of medical insurance and supplementary commercial insurance for targeted drugs and immunotherapy [18].

Conclusion

Precision medicine has made great progress in the treatment of lung cancer. The integrated system for the precise diagnosis, treatment, and transformation research of lung cancer established in our institution has elevated the early diagnosis rate of lung cancer and improved the prognosis of lung cancer patients. This has benefited local lung cancer patients due to a much higher success rate. However, due to the complexity and heterogeneity of lung cancer development, we have found that it is “just the tip of the iceberg” in terms of the work that still needs to be done. The development and popularization of precision medicine still have a long way to go.

Conflict of interest

The authors declare no conflict of interest.

Funding

This work was supported by a grant obtained from the Qilu leader training project (Na Zhou) and major innovation projects in Shandong Province (2018CXGC1204 to Xiaochun Zhang).

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Cite this article as: Zhou N, Jiang M & Zhang X. Benefits of precision medicine in lung cancer: experience from a single institution. *Visualized Cancer Medicine*. 2022. 3, 4.