European Journal of Cancer 84 (2017) 168–172

Available online at www.sciencedirect.com

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journal homepage: www.ejcancer.com

Review

The changing diagnostic pathway for lung cancer patients in Shanghai, China

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Received 9 April 2017; received in revised form 17 July 2017; accepted 22 July 2017
Available online 17 August 2017

KEYWORDS
Lung cancer;
Rapid diagnosis;
Treatment decision

Abstract Accumulating evidence suggest that patients with advanced non–small-cell lung cancer (NSCLC) and specific genomic alterations including epidermal growth factor receptor and microtubule-associated protein-like 4 anaplastic lymphoma kinase could significantly benefit from molecular-targeted therapies compared with chemotherapy. Recently, immunotherapy based on programmed cell death 1 (PD-1) and its ligand (PD-L1) blockade prolong survival in patients with advanced NSCLC, especially in those patients with positive expression of PD-L1 and when used in the first-line setting. Therefore, the diagnosis, clinical staging and molecular genotyping must be quick and efficient so that we can make a timely and precise decision for treatment strategy. In our department, it takes a median 4 working days (range 3–6) for a new patient from initial respiratory consultation to treatment decision, whereas in many countries, 14 workdays is considered a reasonable timeline. In this article, we will provide detailed information on the diagnostic pathway for a new patient suspected of having lung cancer to the final treatment decisions in our department.

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http://dx.doi.org/10.1016/j.ejca.2017.07.036
0959-8049/

1. Introduction

Lung cancer is one of the leading causes of cancer-related death both in China and worldwide. More than 70% of lung cancers are diagnosed at an advanced stage [1,2]. In China, ~50% of patients diagnosed with non–small-cell lung cancer (NSCLC) would harbour epidermal growth factor receptor (EGFR)–activating mutations and 5–7% of the patients would harbour anaplastic lymphoma kinase (ALK) translocation [3,4]. With the accumulation of molecular knowledge, patients with NSCLC and specific genomic alterations could benefit from molecular-targeted therapies [5]. To date, nine clinical trials have consistently demonstrated that EGFR-tyrosine kinase inhibitors (TKIs) including gefitinib, erlotinib, and afatinib can result in better progression-free survival (PFS), objective response rate (ORR), and quality of life than standard platinum-based chemotherapy in patients with EGFR-mutant NSCLC for first-line treatment, but no overall survival (OS) benefit, because crossover was allowed between treatment arms [5]. However, a pooled analysis of the LUX-Lung 3 and LUX-Lung 6 trials did show a better OS with afatinib compared with standard chemotherapy in patients harbouring an exon 19 deletion [6].

Two randomised trials demonstrated that first-generation ALK-TKI, crizotinib, showed longer PFS and higher ORR than chemotherapy in patients with advanced *ALK*-positive NSCLC in the first- or second-line setting [7,8]. Second- or third-generation ALK-TKI (ceritinib, alectinib) have shown more promising antitumour effect than crizotinib and may replace this first-generation ALK-TKI [9,10]. In addition, crizotinib showed good PFS and response rate in patients with NSCLC and ROS1 fusion [11]. Therefore, it is necessary to know the oncogenic driver mutation (e.g. EGFR, ALK, and ROS1) status at initial diagnosis.

Recently, a phase III randomised trial, KEYNOTE-024, demonstrated that pembrolizumab was associated with significantly longer PFS and OS and fewer adverse events than platinum-based chemotherapy in patients with advanced NSCLC and PD-L1 expression on at least 50% of tumour cells despite crossover treatment being allowed [12]. As yet, pembrolizumab has not been approved by the China Food and Drug Administration. The addition of a PD-L1 immunohistochemistry (IHC) test is reasonable even now for planning future therapies and for the ongoing clinical trials (KEYNOTE-042; NCT02220894) on the efficacy of anti-PD-1 (pembrolizumab) in patients with PD-L1-positive advanced or metastatic NSCLC.

Collectively, it means that the diagnosis, clinical staging, and molecular genotyping must be quick and efficient so that we can make a timely and accurate decision for first-line treatment.

2. How fast can that treatment pathway be?

Rapid and accurate diagnosis and genotyping workflow is needed due to the developments of precision medicine and desire of patients and clinicians to minimise the delay of treatment. In our department, it would take a median 4 working days (range 3–6) for a new patient from initial oncology consultation to treatment decision (Fig. 1)—whereas in many countries, 14 working days is considered a reasonable timeline. The median number of nights for a patient in hospital or hostels was 3 with a range of 1–5 (Fig. 2). We base this on an audit of approximately 4000 patients in our department from September 2011 to December 2015. More than 80% of them were diagnosed with advanced stage (IIIB-IV). Our institution is a specialised hospital focused on thoracic and respiratory disease and has 14 clinical departments including thoracic surgery, medical oncology, respiratory, tuberculosis, radiotherapy, occupational medicine, radiation with over 1000 beds. We serve a population of 3 million from all over the country with expertise still kept in the big cities (e.g. Beijing, Shanghai and Guangzhou). More than 80% of the patients could have obtained a proportion (40–75%) of reimbursement from the distinct healthcare policy in their region. Over 90% of patients had symptoms and abnormal radiological records including chest X-ray (~30%), chest CT scan (~50%) or whole body PET-CT (~10%), whereas 10% of the patients were incidental findings on physical examination at outpatient clinic. The following context is the conventional clinical pathway for a new patient suspected of having lung cancer to the final treatment decisions. The patient will stay in hospital or local hotel for 2 nights if not able to go home.

2.1. Day 1: Medical history collection

When a patient with probable advanced lung cancer comes to our department, the resident doctor would take a medical history check, routine bloods, blood coagulation test, electrocardiogram, tumour markers test and perform a contrast chest CT scan and make a preliminary diagnosis in the morning clinic. In the afternoon, the resident would report results to the attending physician.

2.2. Day 2: Pathological diagnosis and further staging

In the morning, the attending physician performs or guides the resident to perform a CT-guided fine needle aspiration, core biopsy or EBUS-TBNA. Half of the samples would be sent to the Department of Pathology for diagnosis and the other half would be stored at −80 °C for molecular analysis. The whole process of sample collection and storage would be supervised by a medical coordinator. At the same time, the peripheral blood would also be collected. We would extract the