Thoracic Cancer ISSN 1759-7706

INVITED REVIEW

# Medical management of lung cancer: Experience in China

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**Keywords**
Chemotherapy; non-small cell lung cancer; small cell lung cancer.

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Received: 16 August 2014;
Accepted: 19 August 2014.

doi: 10.1111/1759-7714.12168

Thoracic Cancer **6** (2015) 10–16

## Abstract

Lung cancer is the leading cause of death from cancer worldwide, as well as in China. A multidisciplinary treatment strategy for lung cancer, which includes medical and radiation oncology, surgery, and pathology is used in clinical practice in China. Chinese lung cancer patients are treated according to different pathologic and genetic types of the disease. For those with active epidermal growth factor receptor (EGFR) mutation, EGFR tyrosine kinase inhibitors (EGFR-TKIs) are used in first-, second- or third-line and maintenance treatment of non-small cell lung cancer (NSCLC). For patients with anaplastic lymphoma kinase (ALK) gene rearrangement, Crizotinib is a promising treatment in advanced NSCLC patients. A platinum-based regimen remains the mainstay of first-line systemic therapy for advanced NSCLC patients who are negative for EGFR mutation or ALK gene rearrangement. For patients with non-squamous NSCLC, Pemetrexed plus Cisplatin is recommended in first-line systemic therapy. An Endostatin combination with chemotherapy is used in first- and second-line advanced NSCLC patients. S-1 presents a new option of chemotherapy in advanced NSCLC cases. Cisplatin-based doublet chemotherapy is commonly used in NSCLC patients after surgery as adjuvant therapy. EGFR-TKIs are now being assessed in the adjuvant setting. The standard first-line chemotherapy regimen of small cell lung cancer (SCLC) is platinum with Etoposide (PE). Amrubicin provides similar survival compared with the PE regimen with an acceptable toxicity profile in extensive stage SCLC patients. Supportive care, such as traditional Chinese medicine and pegylated filgrastim, play an important role in improving patients' quality of life.

## Introduction

Lung cancer is the most common cause of cancer death worldwide, as well as in China. In 2012, 652 842 new cases of lung cancer occurred in China, accounting for 35.8% of all cases worldwide. Mortality from lung cancer in China was 597 182, which also represented one third of deaths from lung cancer worldwide.[1] Of lung cancer patients, 22% have regional disease that spread to regional lymph nodes, and 57% have metastasized cancer, both may benefit from chemotherapy.[2] In 2013, lung cancer clinical trials held in China accounted for nearly 15% of the total number in the world.[3] China is predicted to become the third largest pharmaceutical market in the world in 2014.[4]

Most Chinese lung cancer patients receive treatment according to Chinese guidelines, such as the "Chinese guidelines on the diagnosis and treatment of primary lung cancer (2011)," an evidence-based clinical practice guideline subject to the guidelines developed by the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO).[5] After a patient visits the hospital, the top priority is to make a comprehensive and definitive diagnosis. Pathological evaluation is performed to classify the histologic type of lung cancer. Molecular targeted drugs have been extensively evaluated in lung cancer. Following the Chinese guidelines, detections of therapeutic targets, such as epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK), have found widespread use in optimizing our therapeutic strategy in non-small cell lung cancer (NSCLC).[6,7] The low-dose computed tomographic screen has become an essential technique for early detection of lung cancer in China.[5] Positron emission tomography-computed tomography (PET-CT) improves the sensitivity and specificity for diagnosis and treatment decisions in lung cancer.[8,9] The American Joint Committee on Cancer (7th edition) staging system is used. Surgical approaches provide the best

chance of cure for early-stage NSCLC patients. Compared with open thoracotomy, video-assisted thoracoscopic surgery has been extensively used for stage I or II lung cancer patients in China, with reduced hospitalization and similar short-term outcomes.[10,11] Postoperative radiotherapy has significantly reduced local relapses and improved the survival of IIIA-N2 NSCLC patients.[12,13] The following are medical management methods for lung cancer patients in China, according to different pathologic and genetic types of the disease.

## Patients with active epidermal growth factor receptor (EGFR) mutation

The primary focus of gene types in Chinese NSCLC patients is the EGFR mutation. Using direct DNA sequencing and the amplification refractory mutation system (ARMS), relative EGFR mutation abundance could predict a benefit from EGFR tyrosine kinase inhibitors (EGFR-TKIs) treatment for advanced NSCLC.[14] Significant ethnic variation has been found between the Chinese and Caucasian population. In routine testing in academic medical centers in developed cities, such as Beijing, Shanghai, and Guangzhou, EGFR mutation was confirmed in 50.2% of Chinese patients with advanced lung adenocarcinoma, which was significantly higher than that in Indians or Caucasians.[15] Because of the higher incidence of drug-sensitive mutation, Chinese patients derived a significant benefit from EGFR-TKIs therapy. Progression-free survival (PFS) was 14 months and overall survival (OS) was 39 months in Chinese mutation-positive NSCLC patients given Gefitinib, similar to results from Japan and Korea.[16–18] Chinese researchers have also conducted and published a series of related studies on issues including first-, second-, third-line, maintenance and adjuvant treatment. The China Food and Drug Administration (CFDA) approved gefitinib in 2005, Erlotinib in 2007 and Icotinib in 2011, for patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen, regardless of their EGFR mutation status. Gefitinib has also been approved as first-line therapy in NSCLC patients with EGFR active mutations in 2012.

With almost 50% of patients recruited from China, the IPASS study has confirmed that gefitinib represents the best first-line treatment option for East Asian NSCLC patients with EGFR sensitizing mutations.[19] In patients who had advanced pulmonary adenocarcinoma and who were non-smokers or former light smokers, 250 mg per day of gefitinib resulted in a one-year PFS of 24.9%, compared with 6.7% in the carboplatin-paclitaxel cohort.[19] Rash and diarrhea were the most common adverse events, which were recorded in 66.2% and 46.6% patients in the gefitinib group, respectively.[19] The INFORM study has proven that PFS was significantly longer with gefitinib compared with the placebo as maintenance therapy in Chinese patients with locally advanced NSCLC.[20] Compared with standard chemotherapy, the OPTIMAL study suggested that erlotinib conferred a significant PFS benefit and more favorable tolerability in advanced NSCLC patients with sensitizing EGFR mutations.[21] The IMPRESS study has just completed recruitment and is in the stage of follow-up to assess the efficacy and safety of continuing gefitinib in addition to chemotherapy in EGFR mutation-positive NSCLC patients, who have progressed on first line gefitinib (NCT01544179).

Icotinib, a non-mutation specific EGFR-TKIs, is China's first homegrown anticancer drug. Compared with those given gefitinib, the ICOGEN study has found that patients given icotinib had less drug-related adverse events and similar PFS in previously treated advanced NSCLC.[22] Icotinib is now being tested in the CONVINCE study compared with Pemetrexed-based chemotherapy as first-line induction and maintenance treatment in advanced lung adenocarcinoma with EGFR-mutation (NCT01719536). The efficacy of icotinib as adjuvant therapy is also evaluated in two ongoing studies in China (NCT01929200, NCT01996098).

## Patients with anaplastic lymphoma kinase (ALK) gene rearrangement

Compared with EGFR mutations, ALK gene rearrangement was detected in a low percentage of NSCLC patients. Chinese researchers have reported positive ALK gene rearrangement in 4.9%~11.6% of Chinese NSCLC patients.[23,24] Notably, ALK gene rearrangement was mutually exclusive with EGFR mutations.[25] Apart from real-time reverse transcription-polymerase chain reaction and direct sequencing, a novel fully automated immunohistochemistry (IHC) assay has been a reliable screening tool in routine pathologic laboratories for identification of patients with ALK rearrangement.[26]

Crizotinib, a targeted inhibitor of ALK, is a promising treatment in advanced NSCLC patients.[27] Based on the results of the PROFILE 1005 study, which included 190 patients recruited from China, crizotinib was approved by the CFDA in 2013 for locally advanced or metastatic NSCLC patients with positive ALK gene rearrangement. The PROFILE 1007 study confirmed that crizotinib was superior to standard chemotherapy in previously treated, advanced NSCLC patients with ALK rearrangement.[28] An interim analysis showed that the crizotinib group had a median PFS of 7.7 months and a response rate of 65%, both significantly higher than patients treated with chemotherapy alone.[28] Elevated aminotransferase levels were the most common adverse event associated with crizotinib, found in 16% of patients.[28] A phase III, randomized, open-label, efficacy and safety study is currently recruiting participants to demonstrate the superiority of crizotinib compared to first-line chemotherapy in East Asian

  

NSCLC patients with advanced disease and ALK rearrangement, including Chinese patients (NCT01639001).

## Patients who are negative for EGFR mutation or ALK fusions

Platinum-based regimens remain the mainstay of first-line systemic therapy for advanced NSCLC in patients who are negative for EGFR mutation or ALK gene rearrangement. In China, gemcitabine (27.4%), docetaxel (16.2%), paclitaxel (13.5%), and pemetrexed (9.2%) were the most common choices in platinum-based two-drug regimens for first-line chemotherapy.[29] Scagliotti *et al*. found that in patients with adenocarcinoma or large-cell carcinoma histology, OS was statistically superior with pemetrexed plus cisplatin compared to gemcitabine plus cisplatin, with lower rates of grade 3 or 4 myelosuppression.[30] In patients with squamous cell histology, there was a significant improvement in survival with gemcitabine plus cisplatin.[30] In advanced non-squamous NSCLC patients who had not progressed during first-line treatment of pemetrexed plus cisplatin, maintenance of pemetrexed every three weeks resulted in a statistically significant 22% reduction in the risk of death.[31] Thus, for patients with non-squamous NSCLC, NCCN guidelines recommend pemetrexed plus cisplatin. According to a 2010 national survey of medical treatment status in Chinese NSCLC patients, only 16.4% of Chinese adenocarcinoma patients were treated with pemetrexed.[29] In 2011, pemetrexed was approved by the CFDA in combination with cisplatin therapy for the initial treatment of patients with locally advanced or metastatic non-squamous NSCLC.

As a second-line systemic therapy regimen in patients with advanced NSCLC who had previously failed platinum-based chemotherapy, treatment with docetaxel resulted in better OS than that of best supportive care,[32] and better PFS than that of Vinorelbine or Ifosfamide.[33] Compared with docetaxel in the second-line treatment of patients with advanced NSCLC, treatment with pemetrexed resulted in equivalent PFS and OS, with less neutropenia and related hospitalization.[34,35] Although previously treated advanced NSCLC patients with EGFR wild type tumors have a better prognosis from erlotinib than from best supportive care, median PFS was significantly longer in patients treated with docetaxel than with erlotinib as second- or third-line therapy.[36]

Nab-paclitaxel, an albumin-bound formulation of paclitaxel, has greater antitumor efficacy and higher intratumor paclitaxel concentration than that of solvent-based paclitaxel.[37] A phase III trial compared the efficacy and safety of albumin-bound paclitaxel with solvent-based paclitaxel in advanced NSCLC patients as first-line carboplatin-based chemotherapy. In patients with squamous cell histology, albumin-bound paclitaxel plus carboplatin demonstrated a significantly higher overall response rate (ORR), 41% *versus* 24%.[38] In patients with non-squamous histology, the albumin-bound paclitaxel plus carboplatin and the solvent-based paclitaxel groups had similar ORR.[38] Patients over 70 years old in the albumin-bound paclitaxel group showed significantly increased OS *versus* those in the solvent-based paclitaxel group.[38] Albumin-bound paclitaxel resulted in significantly less sensory neuropathy and neutropenia, but more thrombocytopenia and anemia compared with solvent-based paclitaxel.[38] Nab-paclitaxel plus carboplatin was approved for advanced NSCLC treatment in 2012 by the United States Food and Drug Administration, but has not yet been approved by the CFDA.

S-1, an oral fluoropyrimidine agent, yielded a response rate of 22% and a median OS of 10.2 months in advanced NSCLC patients without prior chemotherapy.[39] Japanese researchers conducted a randomized phase III trial and found that the PFS and OS rates were similar between S-1 plus cisplatin and docetaxel plus cisplatin groups.[40] A significantly lower rate of neutropenia and infection were observed in the S-1 plus cisplatin group.[40] Compared with 10.55 months of carboplatin plus paclitaxel, carboplatin plus oral S-1 resulted in a median OS of 14.0 months and better tolerance in chemotherapy-naive patients with advanced squamous cell lung cancer.[41] The results of an efficacy and safety analysis from a phase III, multi-center, parallel controlled clinical trial of docetaxel plus cisplatin versus S-1 plus cisplatin as first-line therapy in Chinese advanced NSCLC patients (SC-103 study; JapicCTI-111479) will be published soon. The EAST study (JapicCTI-101155) is now recruiting participants with advanced NSCLC after failure of at least one prior platinum-based regiment. This randomized, controlled, multicenter, open-labeled, phase III clinical trial is aimed at establishing the non-inferiority of S-1 to docetaxel monotherapy in OS.

Angiogenesis inhibitors have definite therapeutic effects on NSCLC; however, there is a need for biomarkers that could prospectively identify the patients who would benefit most. Recombinant human endostatin (Endostar) was developed by the Chinese pharmaceutical industry with promising antiangiogenic and antitumor effects. Results of clinical trials have confirmed the improvement of survival in Chinese advanced NSCLC patients after treatment of Endostar.[42] Note that these studies did not consider EGFR mutation or ALK rearrangement status as exclusion criteria. In 2005, the CFDA approved endostar combined with cisplatin and vinorelbine as a regimen for stage III-IV NSCLC patients. Bevacizumab, a recombinant monoclonal antibody that blocks the vascular endothelial growth factor, is one of the treatment options for NSCLC in combination with chemotherapy. However, the CFDA have not yet approved bevacizumab for lung cancer treatment.

 

## Adjuvant therapy in non-small cell lung cancer (NSCLC) patients

Most clinical guidelines recommend adjuvant chemotherapy for NSCLC patients with stage II-III disease. Cisplatin-based doublet chemotherapy is commonly used in NSCLC patients after surgery, but its impact on survival is limited and it has severe adverse reactions, such as myelosuppression. Recently, the TREAT trial found that, compared with cisplatin plus vinorelbine, adjuvant chemotherapy with four cycles of cisplatin plus pemetrexed had significantly less hematological toxic effects and superior dose delivery.[43] Targeted therapies, especially EGFR-TKIs, are now being assessed in the adjuvant setting. As a randomized phase III clinical trial, the BR19 study demonstrated no disease-free survival (DFS) or OS benefit from gefitinib in completely resected stage IB-IIIA NSCLC patients, and even in patients with sensitive EGFR mutations.[44] However, because of the small number of patients with sensitive EGFR mutations in the cohort, the results do not adequately reveal the effects for mutation-positive patients.

Ongoing adjuvant studies of EGFR-TKIs all focus on EGFR mutation-positive patients. The SELECT study reported the efficacy of adjuvant erlotinib in NSCLC patients with sensitive EGFR mutations. After two years of Erlotinib, the two-year DFS from enrollment is 94% (95% confidence interval [CI], 80%–99%), with 10 recurrent patients.[45] The RADIANT study is a phase III trial comparing daily erlotinib versus placebo in resected stage IB-IIIA NSCLC patients with EGFR mutations. This study was completed in 2010 and will provide results in three to four years. Wang *et al.* conducted a randomized phase II study to assess pemetrexed plus carboplatin as adjuvant chemotherapy with or without gefitinib in resected T3N2M0 NSCLC patients with EGFR mutation.[46] The administration of gefitinib following pemetrexed plus carboplatin adjuvant therapy showed significant improvement in DFS, as reported at the 2013 American Society of Clinical Oncology (ASCO) Annual Meeting. Another ongoing randomized phase III trial is studying gefitinib compared to cisplatin-based chemotherapy in adjuvant settings for Chinese patients with EGFR sensitizing mutation (NCT01405079).

## New agents in small-cell lung cancer (SCLC) chemotherapy

The standard regimen of small cell lung cancer (SCLC) is a platinum doublet with etoposide, which benefits survival in patients with both limited and extensive stage. In SCLC patients treated with etoposide plus cisplatin regimens, the median OS was 14.5 months in limited and 8.4 months in extensive disease.[47] The efficacy of carboplatin-based and cisplatin-based regimens have been compared in meta-analyses. As the first-line treatment of SCLC, these two regimens resulted in similar OS and PFS, with significantly differently toxicity profiles: higher myelosuppression with carboplatin, and higher neurotoxicity and renal toxicity with cisplatin.[48] Compared with etoposide-platinum doublets, irinotecan plus carboplatin prolongs survival in extensive-stage SCLC patients, with significant improvements in OS and PFS, more diarrhea, and less hematological toxicities.[49]

Unfortunately, the median OS is only 14–20 months for patients with limited-stage disease and 9–11 months for patients with extensive-stage disease, even after treatment with etoposide-platinum doublets and thoracic radiotherapy.[50] Better treatment options are necessary to improve prognosis. Dose-intense chemotherapy with a third drug, such as ifosfamide or paclitaxel yielded no significant survival improvement, but carried a greater risk of unacceptable toxicity.[51,52] Maintenance chemotherapy of Topotecan after four cycles of standard regimens failed to improve OS or quality of life in extensive-stage SCLC. To evaluate the benefits of a new generation of chemotherapy agents, several clinical trials are under way.

Amrubicin is an anthracycline that could inhibit topoisomerase II. A randomized phase III clinical trial compared the efficacy and safety of amrubicin plus cisplatin versus etoposide plus cisplatin as first-line treatment for extensive SCLC (NCT00660504).[53] In amrubicin plus cisplatin and etoposide plus cisplatin groups, the median OS was 11.79 and 10.28 months, the median PFS was 7.13 and 6.37 months, and ORR was 69.8% and 57.3%, respectively. The amrubicin regimen was also well tolerated, but yielded a slightly higher incidence of adverse events, such as bone marrow failure, neutropenia, and leukopenia. However, in the JCOG0509 study, a phase III randomized trial, amrubicin plus cisplatin (AP) proved inferior to irinotecan plus cisplatin (IP). Jotte *et al.* found that SCLC patients treated with second-line amrubicin had similar median OS, and a lower incidence of hematologic events, but more febrile neutropenia observed with amrubicin *versus* topotecan.[54] With a similar survival rate and an acceptable toxicity profile compared to the current standard treatment for SCLC, ambrubicin plus cisplatin would be a new option in SCLC patients with extensive disease.

## Supportive care in lung cancer patients

Traditional Chinese medicine has become an important part of the supportive treatment of lung cancer. Gensing Rg3, an active component of ginseng, attenuates tumor angiogenesis via inhibiting endothelial progenitor cell differentiation.[55] In mouse models of lung cancer, gensing Rg3 plus gemcitabine yielded significantly more tumor necrosis and anti-angiogenic effects when compared with gemcitabine

  

monotherapy, resulting in the suppression of tumor growth.[56] Sun *et al*. conducted a randomized clinical trial to confirm the clinical effect of gensing Rg3 in combination with vinorelbine plus cisplatin in advanced NSCLC patients. They found that oral gensing Rg3 led to a better response rate (33.3% vs. 14.5%) and median OS (10.0 vs. 8.0 months).[57]

Most chemotherapeutic agents exert various side effects that hamper the efficacy and safety of treated patients. Neutropenia is one of the most common dose-limiting toxicities of many chemotherapy regimens. Recombinant human granulocyte colony-stimulating factors (rHuG-CSFs), such as filgrastim and pegfilgrastim are widely used in clinical practice. They stimulate the production of neutrophils and can be used as a prophylaxis for chemotherapy-induced bone marrow suppression. A randomized crossover phase 3 study confirmed the safety and efficacy of pegylated filgrastim (JINYOULI) in patients with chemotherapy-induced neutropenia.[58] A single dose of 100 μg/kg pegylated filgrastim provided similar neutrophil support with daily injections of 5 μg/kg/day unmodified filgrastim. In 2011, pegylated filgrastim (JINYOULI) was approved by the CFDA for patients with non-myeloid malignancies receiving myelosuppressive treatment associated with a clinically significant incidence of febrile neutropenia.

## Conclusions

Lung cancer is the most common cancer with the most common cause of cancer death in China. Our genes are the clues that can tell us what our differences and similarities actually are. Lung cancer treatment needs cross-specialty collaboration in medical and radiation oncology, surgery, and pathology. The way of the future in lung cancer may be in the use of molecular targeted medicines, as almost 80% of lung adenocarcinoma patients harbor oncogenic drivers.[59] Chemotherapy remains the basis of lung cancer treatment. The challenge for clinical investigators is to identify specific markers for groups of patients who may benefit from chemotherapy. With more and more reliable research and clinical studies on lung cancer treatment, we will improve the outcome and survival for Chinese patients with lung cancer.

## Acknowledgments

This review was supported in part by grants from the Research Special Fund for Public Welfare Industry of Health (200902002-1), the Chinese National Major Project for New Drug Innovation (2008ZX09312, 2012ZX 09303012), the Chinese National High Technology Research and Development Program of China (863 Program) (2011AA02A110), the Beijing Municipal Science and Technology Commission Major Project for New Drug Innovation (Z111102071011001), and the Beijing Municipal Science and Technology Commission Project for Beijing Key Laboratory (Z121102009212055).

## Disclosure

No authors report any conflict of interest.

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