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Review Article

# Current Status of Small Cell Lung Cancer in China

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**Abstract**

In China, Small Cell Lung Cancer (SCLC) accounts for over 15% of lung cancers. Until now, the morbidity of SCLC has been increasing due to the ineffective smoking cession in China. Following the Chinese Guidelines of SCLC, the treatment of SCLC in China has been getting more and more standardized, which leads to the mortality of Chinese SCLC reaching the worldwide average. Although the outcomes of patients with SCLC has been limited improved, the Chinese scholars have made many attempts for the treatment of SCLC including emphasizing lung screening, accurate disease staging, multidisciplinary team-work, as well as actively translational medical research. Multi-center clinical studies regarding to amrubicin hydrochloride, lobaplatin, endostar and ipilimumab have been launched, as well as controversial problems for radiotherapy and surgery on SCLC. In addition, translational medicine researches on Circulating Tumor Cells (CTCs), Myeloid Suppression Cells (MDSCs) and next generation sequencing have been conducted to explored novel drive genes and prognostic markers of SCLC, which will provide more evidence to guide the diagnosis and treatment of SCLC.

## ABBREVIATIONS

SCLC: Small Cell Lung Cancer; NSCLC: Non-Small Cell Lung Cancer; LS-SCLC: Limited-Stage Small Cell Lung Cancer; ES-SCLC: Extensive-Stage Small Cell Lung Cancer; DNA: Deoxyribonucleic Acid; AP: Amrubicin in Combination with Cisplatin; EP: Etoposide in Combination with Cisplatin; OS: Overall Survival; PFS: Progression-Free Survival; ORR: Overall Response Rate; EL: Lobaplatin Combined Etoposide; TTP: Time To Progression; ASCO: American Society of Clinical Oncology; CR: Complete Response; PR: Partial Response; SD: Stable Disease; PCI: Prophylactic Cranial Irradiation; IFRT: Involved-Field Radiotherapy; CT: Computed Tomography; INF: Isolated Nodal Failure; MST: Median Survival Time; CTCs: Circulating Tumor Cells; MDSCs: Myeloid Suppression Cells; UGT1A1: UDP-Glucuronosyltransferase 1A1; CSCLC: Combined Small Cell Lung Cancer.

## INTRODUCTION

Lung cancer is the most common malignancy worldwide. In 2012, the reported morbidity and mortality rates are as high as 13% (1.8 million) and 19.4% (1.6 million), respectively [1]. Approximately 15% of lung cancer cases are Small Cell Lung Cancers (SCLCs), which are highly related to smoking [2,3]. SCLC is a very invasive, fast-growing cancer that distinctly differs from other cancers in its histological and clinical features, response to treatment and therapeutic strategy. SCLC often spreads rapidly; approximately 70% of cases present with metastases at diagnosis, and the median overall survival rate is only 8–11 months with a 5-year survival rate of less than 5% [4-6]. Although being sensitive to chemotherapy and radiotherapy, SCLC patients are liable to relapse and often present with drug resistance.

In Europe and America, SCLC incidence has decreased through the implementation of tobacco control, but the number of female patients is increasing, leaving the current prevalence of males to females as 1:1 [7]. There has been little progress in the development of therapeutic approaches for SCLC in the past 30 years [7], and overall survival has not been significantly improved for the past 15 years [8].

Lung cancer incidence has been increased in China due to huge Chinese populous in the world and a large number of smokers. 2012 Chinese Cancer Registry Annual Report identified that in 2009 the incidence rate was 53.57/10 million and ranks top one in all malignant diseases, top one in male patients, and top two in female ones; the mortality rates was 45.57/10 million and top one among in overall malignant diseases [9]. According to GLOBOCAN, there are 3,065,000 newly diagnosed lung cancer cases in China in 2012, accounting for 22% of worldwide cases. Recently, the proportion of newly SCLC cases in China has been changed due to aid of newly advanced technologies in diagnosis regarding to cytological and pathological detection, as well as the changes of lung cancer patients' number. Different from Western countries, there are not very effective policies in China to reduce tobacco consumption, thus the incidence of SCLC, especially in the north, is still increasing in line with the increasing number of smokers. Considering the sex ratio, SCLC is slightly more common in men than in women.

Although translational researches on diagnosis and treatment

for SCLC have not been developed as fast as that for Non-Small Cell Lung Cancer (NSCLC), Chinese scholars have made great progress in the diagnosis and treatment of SCLC in pace with the increasing social and public attention. Here we present the treatment progress made in Chinese patients with SCLC.

## Medical treatment of SCLC in China

Because SCLC is rarely operable, chemotherapy is the priority for treatment. Combinational chemotherapy is effective in 85–95% in limited-stage SCLC (LS-SCLC) with 50–60% patients showing a complete response and 60–80% in Extensive-Stage SCLC (ES-SCLC) [10]. For decades, chemotherapeutic drug development for SCLC has been slowly, leaving etoposide and cisplatin as the standard chemotherapy for a long time [11,12] Besides, only irinotecan is recommended by the National Comprehensive Cancer Network (NCCN) guidelines as a standard first-line therapy for ES-SCLC [13]. Chinese researchers have been attempting some new drugs for SCLC, including topotecan, teniposide, nedaplatin, oxaliplatin etc, however most of them are single-center and small-size studies.

Numerous clinical studies on new drugs have been conducted in recent years relying on very rich resource of Chinese patients, which also gradually improve Chinese clinical study, NSCLC is the main target in clinical researches and achieved more than SCLC did. Amrubicin has shown promising for the treatment of SCLC. Amrubicin, a synthetic anthracycline, can inhibit topoisomerase II and relax supercoils of deoxyribonucleic acid (DNA) for replication. Data from Japanese researchers showed amrubicin has good efficacy and tolerance [14,15]. It was first approved in Japan in 2002 and is applicable for treatment of lung cancer including SCLC and NSCLC. Clinical trials of amrubicin in Western patients showed that it is not inferior to standard regimen in the first-line and second-line treatment. From June 2008 to July 2010, Sun et al. organized a phase III clinical trial to compare the effects of amrubicin in combination with cisplatin (AP) and etoposide in combination with cisplatin (EP) in patients with previously untreated ES-SCLC. The aim of this study is to evaluate the efficacy and safety of AP therapy in Chinese patients with ES-SCLC. A total of 300 patients from 24 cancer centers were enrolled, of whom 299 were randomized at a 1:1 ratio to the AP group (n=149) or EP group (n=150). The primary endpoint was overall survival (OS), the secondary endpoints were progression-free survival (PFS), overall response rate (ORR) and general safety. With respect to OS, AP group was 11.79 months and EP groups was 10.28 months (P=0.0787). For AP and EP groups, ORR was 69.8% and 57.3%, and the median PFS was 7.13 months and 6.37 months (P=0.3548), respectively. The incidence of adverse events in AP group were slightly higher than EP group, and the most common adverse events (grade 3 or 4) were bone marrow failure (23.5% and 21.3%, respectively), neutropenia (54.4% and 44.0%, respectively), and leucopenia (34.9% and 19.3%, respectively). No obvious cardiotoxicity was observed. The phase III trial demonstrated AP therapy was not inferior to EP therapy for previously untreated ES-SCLC patients in terms of OS and toxicities, which were predictable and manageable [16]. It's worth mentioning that this study is the first multicenter phase clinical trial for SCLC in China, and the results of this study were reported at the American Society of Clinical Oncology annual meeting in 2013 and the Chinese Society of Clinical Oncology annual meeting in 2012, respectively.

As cisplatin has distinct dose-limiting toxicity on renal, ear, neuron and gastrointestine, drug resistance induced by treatment and other side-effects, its long-term and wide clinical application is restricted. Chinese researchers have been actively exploring new platinum drugs and various regimens for more efficient, lower toxicity, and no cross-resistance. Lobaplatin, a third-generation platinum-based anticancer drug first marketed in China in 2005, is currently in the research stage, showing similar toxicity to carboplatin and no cross-resistance to cisplatin.. The results of clinical study showed that the ORR of Lobaplatin combined Etoposide (EL) for advanced SCLC can be up to 92% [17]. There was no significant difference between EP and EL with respect to median Time To Progression (TTP) and one-year survival rate. Base on the good prospect of lobaplatin in the treatment of SCLC, from September 2010, Cheng, as main principle investigator, started a prospective, randomized, positively controlled, multi-center clinical trial (HNCA002) in China (registration number: ChiCTR-TRC-10001047). This study aims to compare the effective, safety and tolerance profile of EL regimen (etoposide-lobaplatin) with EP regimen (etoposide-cisplatin) for ES-SCLC. A total of 14 research centers participated in this study. This study has been completed with a total of 240 cases enrollment and the results are processed at present.

Besides chemotherapeutic drugs, the Chinese scholars have also explored targeted drugs. Endostar is a new kind of biological products under the category of angiostatins, which has broad-spectrum antimicrobial and anti-angiogenesis effects. Endostar inhibits angiogenesis in tumor by inhibiting the migration of endothelial cells to form blood vessels and cutting off the nutrition supply to tumor, as well as inhibiting tumor proliferation and transfer. As Endostar shows good effects on NSCLC treatment, Chinese scholars also hope it would show great effects on SCLC. Zhou et al reported the results of a pahse study using cisplatin/etoposide and endostar for ES-SCLC [18]. Thirty-three patients were enrolled and the ORR, median PFS and 6-month PFS was 69.7%, 5.0 months, and 33.3%, respectively. The median OS was 11.5 months, and the 1-year OS was 38.1% (95% CI, 26-50.1%). This study suggests that the addition of endostain to cisplatin and etoposide in patients with ES-SCLC results in slightly improved PFS and OS compared with historical controls who received only cisplatin and etoposide. Endostar plus cisplatin /etoposide appears to be well tolerated. At 2012 American Society of Clinical Oncology (ASCO) Annual Meeting, Lu et al reported the results of a randomized phase II study of recombinant human endostatin in combination with chemotherapy in previously untreated ES-SCLC (NCT00912392). 140 patients were enrolled, and 137 patients were qualified to be analyzed. Patients were randomly assigned to the endostar treatment (n=68) and control group (n=69). Patients in endostar group with Complete Response (CR), Partial Response (PR) or Stable Disease (SD) were treated with single-agent endostar until disease progresses or unacceptable toxicity occured. The primary end point was PFS, and the secondary end points were OS and ORR. Median PFS was similar between the two groups, 6.2 months in endostar and 5.9 months in control group (P=0.163, HR 0.762; 95%CI 0.519-1.119), respectively. Median OS and ORR

were 12.4 months versus 12.3 months (P=0.475, HR 0.835; 95%CI 0.508-1.371), and 76.5% versus 68.1% in endostar group and control group (P=0.275). The rates of ≥ 3 grade adverse events were similar in both groups and no new or unexpected safety events related to endostar were observed. The study showed that the addition of endostar to carboplatin plus etoposide for treatment of ES-SCLC didn't improve the PFS and OS significantly, but toxicity profile was acceptable [19].

In recent years, Chinese researchers also participate in many international multi-centric clinical studies. A randomized, multicenter, double-blind, phase trial comparing the efficacy of ipilimumab plus etoposide/platinum versus etoposide/platinum in subjects with newly diagnosed ES-SCLC (CA 184156) is recruiting in China, this study will provide more data about ipilimumab in Chinese SCLC patients.

## Radiotherapy of SCLC in China

SCLC is classified into limited stage and extensive stage according to whether lesions are in the same visual field of radiotherapy, in line with the Veterans Administration Lung Study Group staging system, which can highlight the importance of radiotherapy in the treatment of SCLC. Radiotherapy is an indispensable part of comprehensive treatment for LS-SCLC.LS-SCLC standard treatment includes chemotherapy and early-stage thoracic radiotherapy. Prophylactic cranial radiation therapy is also crucial for patients and presents good efficacy. For some patients, surgical resection, adjuvant chemotherapy and adjuvant chemoradiotherapy are also necessary.

In recent years, evidence-based data from clinical studies performed in China playes guiding roles in the clinical diagnosis and treatment of SCLC. Thoracic radiotherapy has long been controversial in its target range. Particularly after induction chemotherapy, there has been a lack of forthcoming and reliable data as to the target range of radiotherapy is determined by tumor size of prior to chemotherapy or that of post-chemotherapy, as well as whether prophylactic irradiation targeting mediastinal lymphatic drainage area is necessary. Chen et al reported that 85 LS-SCLC patients enrolled in a prospective randomized non-inferiority trial [20] and all patients received EP regimen. After 2 cycles of EP, patients were randomly assigned to two groups: one group received thoracic radiotherapy according to the post-chemotherapeutic tumor area (study arm, n=43) or pre-chemotherapeutic tumor area (control group, n=42). Prophylactic irradiation at mediastinal lymphatic drainage area was omitted for both arms. 45 Gy/30Fx/19 days thoracic radiotherapy was administered concurrently with cycle 3 chemotherapy. Prophylactic Cranial Irradiation (PCI) was administered to patients who achieved complete response. The results of interim analysis showed the local recurrence rate of experimental group and control one was 31.6% and 28.6%, respectively (P = 0.81). The failure rate for isolated nodal were 2.6% and 2.4%, respectively (P = 1.00). Mediastinal N3 was the only factor to predict failure of isolated nodal (P = 0.004; odds ratio [OR], 29.33; 95% CI, 2.94-292.38). One-year and 3-year overall survival rates between the experimental group and the control were 80.6% versus 36.2%, and 78.9% versus 36.4%, respectively (P =0.54). However, ideal methods guiding how to choose appropriately radiotherapeutic area for LS-SCLC remains to be elucidated as there is no highly solid clinical evidence. Fu *et al* reported that IFRT based on CT scan is safe and applicable in a retrospective study in 2011 [21] evaluating the safety in patients with LS-SCLC treated with involved-field radiotherapy (IFRT). In their center, two consecutive phase II clinical trials for patients with LS-SCLC were reviewed retrospectively. 108 patients received combination of chemotherapy and thoracic radiotherapy and the irradiation area only covered primary tumor and involved lymphatic regions based on Computed Tomography (CT) scan. Median follow-up time was 21 months, and 78 patients experienced treatment failures. Out of 28 patients with local-regional recurrences, in-field recurrence, out-of-field recurrence or both-field recurrence were found in 16, 10 and 2 patients. 5 patients (4.6%) were observed Isolated Nodal Failure (INF), which all happened in the ipsilateral supraclavicular area. There are 4 patients who developed simultaneously supraclavicular nodal failure and distant metastases. The median overall survival and the median progression-free survival were 27 months (95% confidence interval, 24-30 months) and 16 months (95% confidence interval, 12-21 months), respectively.

The two findings described above were cited by *NCCN Clinical Practice Guidelines in Oncology: Small Cell Lung Cancer* (V2.2013) for it provides favorable evidence-based medicine data for LS-SCLC radiotherapy. This fully reflects that clinical achievements derived from China have been recognized throughout worldwide.

## Surgical treatment of SCLC in China

Surgical resection as the main therapeutic option for SCLC has been negated since 1960s when Fox's findings showed poorly long-term outcomes of SCLC after surgery [22]. Following the TNM staging emerging for SCLC and new data publishing, the surgical treatment for SCLC again becomes an issue. In China, studies addressing surgical resection for SCLC are rarely reported and most of them are retrospective analyses. Wang et al retrospectively analyzed the efficacy of different therapy styles in 845 cases with SCLC [23]. 272 of limited-stage patients were classified into three groups: 48 cases were treated by surgery followed by chemo/radio therapy, 174 by chemotherapy followed by surgery then chemo/radiotherapy and 50 for control by chemo/radio therapy only. There was a significant difference between the chemo/radiotherapy group and surgery followed by chemotherapy group with respect to 3- and 5- year survival rates but not the 1- year survival rate. In 174 cases with the limited-stage lesion treated by surgery combining with pre- and postoperative chemo/radiotherapy, the 1- , 3- , 5- , and 10- year survival rates were 88.4%, 58.9%, 46.5% and 11.5%, which were significantly different from the other two regimens. The patients with the LS-SCLC might be benefited from a rational surgical treatment with pre- and post-operative adjuvant chemo-radiotherapy. Another study analyzed retrospective data from 45 cases with LS-SCLC treated with surgery. The 1-, 3- and 5- year survival rates of patients were 74%, 37% and 30%, respectively. The median overall survival was 29 months. This study concluded that through integrated therapy, surgery can achieve good outcomes for patients with LS- SCLC [24]. Lu et al reported that in a retrospective study performed in 154 patients with SCLC [25], the overall median survival time (MST) was 16.1months and 1-year survival rate was 60. 3%.The MST was 18. 3 months

for the 30 patients (19.5%) who received surgery and 14. 7 months for the other 124 patients (80.5%) who received only chemotherapy (P > 0.05). The 1-year survival rates were 62.8% and 63.3%, respectively (P > 0.05). For the patients with LS-SCLC, there was no significant difference in the MST and survival rate between the patients who received surgery than those who didn't receive surgery (24.4 vs 19.8 months, 70.0% vs 68.6%, P > 0. 05). According to TNM staging system, the 1-year survival rate was 100.0% for the patients with stage. For the 13 patients with stage, the MST was 30.2 months for the 6 patients in surgery group and 26.6 months for those in non-surgery group (P > 0. 05). The 1-year survival rates were 66.7% and 85.7%, respectively (P > 0.05). Surgery had certain value in the treatment of early-stage (stage) SCLC. Surgery combined with chemotherapy and radiotherapy was recommended for patients with early-stage (stage) SCLC. Consistent with international guidelines, surgical treatment is available for SCLC patients at T1–2, N0–1 in China. Currently, there are also a number of multi-center collaborative studies.

### Translational medicine concerning SCLC in China

To date, Chinese researchers have mainly focused on studies concerning SCLC pathogenesis, heterogeneity and molecular targets. Compared with other tumors, SCLC samples are more difficult to obtain. Circulating Tumor Cells (CTCs) provide an alternative sample to primary tumors and are regarded as "liquid biopsy specimens", which may help to detect micrometastases and recurrence. As reported in HNCA002 study, CTCs in the peripheral blood are detected to investigate the correlation of CTCs to SCLC prognosis and therapeutic efficacy. However, the data from this study is still being analyzed at present. Furthermore, researchers also explored the correlation of Myeloid Suppression Cells (MDSCs) and clinical features for SCLC in order to define the clinical value of MDSCs in diagnosis and treatment. For the first time, Chinese scholars identified the existence of MDSCs in SCLC patients and characterized their histology and unique cell surface markers. The level of MDSCs was associated with SCLC stage, metastasis and treatments, implying MDSCs might be a novel biomarker for early diagnosis and prognosis for SCLC patients. DNA sequencing was used to detect the gene polymorphism of UDP-glucuronosyltransferase 1A1 (UGT1A1) in the peripheral blood of patients with SCLC, and to explore the significance of different types of mutations in the efficacy of Irinotecan and toxicity prediction. Mao et al [26] analyzed diverse gene mutation status (EGFR KRAS, PIK3CA, BRAF and PTEN) in combined small cell lung cancer (CSCLC). Wang et al discovered that both loss of miR-886-3p expression and hypermethylation of the miR-886 promoter are the promising indicators for poor outcomes, as well as new therapeutic targets for SCLC. Up to now, SCLC studies remain limited, thus further researches, expecially translational investigations, are urgently needed to define novel driven genes and biomarkers to guide diagnosis and treatment of SCLC.

### Standardized strategies for SCLC in China

Comparing to NSCLC, SCLC gaines less attention. To improve the diagnosis and treatment of SCLC in various regions of China and broadcast the concept of comprehensive treatment to clinicians, in 2010 the Chinese Society of Clinical Oncology founded SCLC committee, which consists a lot of domestic experts. This Committee has done a lot of works on both basic and clinical research for SCLC, such as developing multi-center clinical trials, constructing information platform for SCLC patients, and holding SCLC workshop at the annual conference of Chinese Society of Clinical Oncology. All of these activities not only strengthen the domestic inter-regional cooperation, but also establish domestic norms and consensus that greatly benefit SCLC patients. In addition, Chinese Thoracic Oncology Group also participates in developing standardized treatment and clinical research strategies in SCLC, which effectively promotes to standardize treatment of SCLC and actively facilitate SCLC clinical researches in China.

For a long time, China had no authorized guidelines for SCLC diagnosis and treatment, which causes huge discrepansy betwen different regions. In 2011, the Ministry of Health of China promulgated the Chinese Guidelines on the Diagnosis and Treatment of Primary Lung Cancer (2011 Version) in order to guarantee the quality of medical care and medical safety, regulate and improve lung cancer diagnosis and treatment, and eventually improve patient prognosis [27]. These guidelines were compiled jointly by experts engaged in surgery, internal medicine, radiotherapy, imaging and pathology in lung cancer major in China, taking into consideration the lung cancer evidence-based guidelines formulated by NCCN, the International Association for the Study of Lung Cancer and the Chinese Society of Lung Cancer. The national conditions, current health care system and truly medical consumption levels, as well as the limitation of doctors who work in low rank hospitals, such as Levels 2 or Level 3 are all well considered when the guideline was drafted. Requirements for SCLC diagnosis and treatment are detailed in these recommendations, which successfully guide the clinical acticities for SCLC in China. The guidelines are constantly updated with improvement of evidence-based medicine. In the end of 2013, it were revised again at an expert group meeting so that the 2014 edition is able to meet the needs of the current clinical practice.

In recent years, the cancer treatment in China has continually evolved. However, some of SCLC patients often fail to receive timely and standardized treatment for various reasons including uneven economic development or lack of proper public awareness etc. To raise the awareness of cancer patients, Chinese lung cancer experts issued "Lung Cancer Patient Education Handbook", which covers medical knowledge about SCLC, information of screening and diagnosis, choice of treatment and so on. The aim of this introduction is to provide help for patients and their families to face SCLC and choose timely treatment.

## CONCLUSION

In China, smoking and environmental pollution result in increasing lung cancer patients, therefore SCLC prevention and treatment is an important healthy issue in China. With the efforts of government and academic organizations on the standardization of SCLC treatment, achievements with respect to early diagnosis, clinical modes etc have been obtained. However there are still certain unkown left for SCLC, such as surgical treatment is suitable for some SCLC patients, but only few clinical studies of SCLC surgery in China are ongoing; whole genome sequencing of SCLC in Chinese race has been performed registry network system about Chines tumor patiens is insufficient and not able

to provide authoritative data for the national onset of SCLC; SCLC survey system is not well established etc. In the future, more attention and investment needs to be focused on SCLC so that it will provide more detailed data for SCLC population in China, and actually improve survival outcomes of patients.

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