

INVITED REVIEW

Current small cell lung cancer treatment in China

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Keywords

Chemotherapy; Chinese population; epidemiology; radiotherapy; small cell lung cancer.

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Received: 24 October 2014;

Accepted: 21 November 2014.

doi: 10.1111/1759-7714.12218

Thoracic Cancer 6 (2015) 233–238

Abstract

Background: The treatment status of small cell lung cancer (SCLC) in Mainland China has never been reported; therefore, this study is the first multicenter survey investigating the status of epidemiology and treatment options of SCLC in Mainland China.

Methods: Two questionnaires were designed to obtain information in 12 medical centers in five major Chinese cities. The hospital information questionnaire was designed to outline SCLC patients' characteristics and treatment preferences in each medical institution, and the patient information questionnaire collected detailed treatment information of 298 SCLC cases in these hospitals.

Results: SCLC represented 13.7% and 18.3% of all lung cancer patients in 2005 and 2010, respectively. Clinical management of SCLC follows mainstream clinical guidelines in general. The most widely applied first-line treatment mode for limited-stage patients was combined chemoradiotherapy (66.2%), while 77.0% of the extensive-stage patients received chemotherapy alone as initial treatment. Etoposide with cisplatin or carboplatin were the most accepted first-line chemotherapy regimens. The objective response rate was 58.3% after first-line chemotherapy and 23% of the patients who responded well to first-line treatment received prophylactic cranial irradiation. As for second-line chemotherapy, single regimen topotecan or a combined regimen containing topotecan were preferred (53.0%).

Conclusions: The treatment options indicated in our study are in accordance with the international clinical guidelines, which is valuable for the improvement of future guidelines, health care standard, and even the better distribution of health care resources in China.

Introduction

Lung cancer has become the most common cancer and the leading cause of cancer-related death in the world.¹ In 2010, both the incidence and mortality rates of lung cancer in China ranked first among all malignancies.² As a distinct histological subtype of lung cancer, small cell lung cancer (SCLC) accounts for 14% of all newly diagnosed cases of lung cancer worldwide. The relatively poor prognosis, in part because of its aggressive clinical course and widespread metastases at diagnosis, makes the disease a serious public health issue.³

Evidence-based guidelines are essential in today's clinical practice. Currently, treatment guidelines on SCLC are available in the United States and Europe, as well as in China.⁴⁻⁶ However, clinical practice patterns may deviate from guidelines because of a variety of factors in the diverse health care settings in China. Because the real treatment situations of SCLC in China have never been reported, adherence to clinical guidelines is beyond our knowledge.

Therefore, we implemented a survey to probe the current status of SCLC treatment patterns in China. The data revealed in this study may help provide references for the refinement of future clinical guidelines and health care policies.

Methods

The survey was conducted between 2011 and 2012 in five major cities in Mainland China, including Beijing, Shanghai, Hangzhou, Jinan, and Changsha. Twelve hospitals including comprehensive cancer centers, chest hospitals, and general

hospitals were involved in the study. Two questionnaires were designed to obtain information. The hospital information questionnaire was designed to outline SCLC patients' characteristics and treatment preferences in each hospital, and the patient information questionnaire collected both diagnoses and regimens of each patient (Table 1).

Results

Twelve medical centers submitted the hospital information questionnaire and the treatment options of 298 SCLC cases were collected.

Results of the hospital information questionnaire

Epidemiology and patients' characteristics

In 2005 and 2010, the number of lung cancer cases was 8748 and 11 671, respectively, while the number of SCLC cases was 1197 and 2139, respectively. SCLC represented 13.7% and 18.3% of all lung cancer patients in 2005 and 2010, respectively (Fig 1).

SCLC patients' characteristics including age, gender, stage, and brain metastasis status are shown in Table 2.

Overview of therapeutic options

Among 12 hospitals, seven preferred concurrent chemoradiotherapy and five preferred sequential chemoradiotherapy as first-line treatments for limited stage (LS)-SCLC patients. All centers preferred etoposide with cisplatin or

Table 1 Essential questionnaire items

Hospital information questionnaire	<ol style="list-style-type: none"> 1. Number of lung cancer/SCLC patients for primary treatment in 2005 and 2010, respectively 2. Age, gender, stage, with or without brain metastasis at diagnosis of SCLC patients for primary treatment 3. First-line treatment options for LS-SCLC 4. Second-line chemotherapy regimens for patients who responded to first-line treatment and progressed 5. Ranking of several factors including effectiveness, cost, and toxicity in regimen selection 6. Ranking of efficacy evaluation including response rate, time to progression, progression-free survival, overall survival, quality of life
Patient information questionnaire	<ol style="list-style-type: none"> 1. Gender, age, smoking history, and family history 2. Diagnosis, stage, with or without brain metastasis 3. First-line treatment information, including therapeutic modalities (chemotherapy alone, concurrent chemoradiotherapy or sequential chemoradiotherapy), regimen and cycles of chemotherapy, efficacy, and prophylactic cranial irradiation 4. Second-line treatment information, including therapeutic modalities, chemotherapy regimen and cycles, efficacy 5. Time to progression, loss of follow-up or death

LS, limited stage; SCLC, small cell lung cancer.

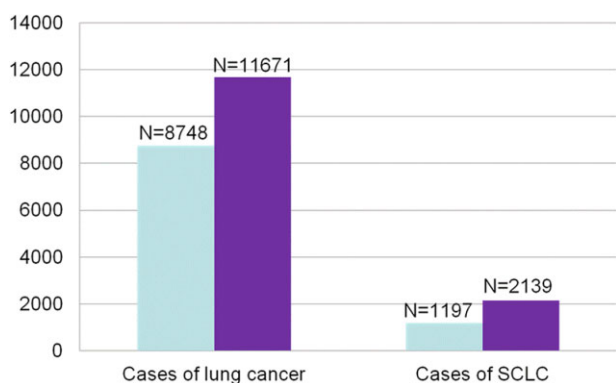


Figure 1 Numbers of lung cancer and small cell lung cancer (SCLC) patients in 2005 and 2010. ■, 2005; ■, 2010.

carboplatin (EP/CE) as a first-line chemotherapy regimen. The preferred second-line chemotherapy regimen was single-agent topotecan in eight centers, and topotecan-based combined therapy in four centers. Other options for second-line chemotherapy provided in the questionnaire include single-agent irinotecan, irinotecan-based combined chemotherapy, and chemotherapy regimens for treating non-small cell lung cancer (NSCLC).

A number of essential factors that should be considered in chemotherapy regimen selection were listed in the questionnaire. The ranking of these factors is summarized as follows (from the most significant to the least): effectiveness; hematological toxicity; gastrointestinal adverse reaction; hepatic and renal toxicity; cost of the drug; and neurotoxicity and passage through the blood-brain barrier (BBB). In addition, the ranking of common indicators in the evaluation of the efficacy of treatment is (from the most significant to the least): time to progression (TTP)/progression-free survival (PFS); response rate (RR); overall survival (OS); and quality of life (QOL). We also inquired into the reason behind the uniform choice of topotecan as a second-line regimen. Efficacy was of

first concern, followed by lower hematological toxicity, better passage through BBB, and less non-hematologic toxicity.

Results of the patient information questionnaire

Patients' characteristics

Of the 298 SCLC patients that participated in this survey, 235 were male (78.9%), and 215 (72.1%) were younger than 65 at the time of diagnosis. As for their clinical characteristics, 208 patients (69.8%) had a smoking history, and 41 (13.8%) reported a family history of cancer. Pathology revealed that 277 cases (93.0%) were pure SCLC, 18 (6%) had an NSCLC component, and the information of three patients was not provided. One hundred and thirty cases (43.6%) were clinically staged as LS-SCLC and 166 (55.7%) as extensive stage (ES). Staging details were not available for two patients. Four of the 130 LS-SCLC patients (3.0%) and 26 of the 166 (15.7%) ES-SCLC patients had brain metastasis at the time of diagnosis.

First-line treatment modalities

Eighty-six of the 130 LS-SCLC patients (66.2%) began their treatment with combined chemoradiotherapy, including 34 cases (26.2%) with sequential chemoradiotherapy, 33 (25.4%) with concurrent chemoradiotherapy, and 19 (14.6%) with chemo-radio-chemo "sandwich" therapy. Thirty patients (23.1%) were treated with chemotherapy alone. Other treatment methods used were as follows: four cases (3.1%) received surgery alone, six (4.6%) received surgery with chemotherapy, three (2.3%) received surgery with chemoradiotherapy, and one case (0.7%) radiotherapy alone.

One hundred and twenty-seven of the 165 evaluable ES-SCLC patients (77.0%) received chemotherapy alone as first-line treatment (6 patients were enrolled in clinical trials). Thirty-eight patients (23.0%) received combined therapy, including 25 cases (15.2%) with sequential chemoradiotherapy, seven (4.2%) with concurrent chemoradiotherapy, five (3.0%) with chemo-radio-chemo "sandwich" therapy, and one (0.6%) with surgery. First-line treatment information was not available for one patient (Table 3).

First-line chemotherapy regimens

The details of chemotherapy regimens were collected in 149 of the 151 patients who received chemotherapy alone as their first-line treatment (patients who participated in clinical trials were excluded). In 138 out of 149 (92.6%) cases, patients received an etoposide and platinum regimen, including an EP regimen in 113 (75.8%) cases and CE in 25 (16.8%). Other regimens used were as follows: four cases (2.7%) with

Table 2 SCLC patients' characteristics

Year	2005	2010
Age		
<65 y/o cases (%)	755 (63.1)	1431 (66.9)
≥65 y/o cases (%)	442 (36.9)	708 (33.1)
Gender		
Male cases (%)	984 (82.2)	1753 (82.0)
Female cases (%)	213 (17.8)	386 (18.0)
M/F	4.6	4.5
Limited stage cases† (%)	465 (41.7)	857 (40.1)
Cases with brain metastasis at diagnosis‡ (%)	222 (20.1)	445 (20.8)

†Data was provided from 10 hospitals in 2005. ‡Data was provided from nine hospitals in 2005. SCLC, small cell lung cancer.

Table 3 First-line treatment modalities†

	Treatment modalities	
	LS	ES
	Cases (%)	Cases (%)
Chemotherapy alone	30 (23.1)	127 (77.0)
Clinical trials	0 (0)	6 (3.6)
Combined chemoradiotherapy	86 (66.2)	37 (22.4)
Sequential chemo-radiation therapy	34 (26.2)	25 (15.2)
Concurrent chemoradiotherapy	33 (25.4)	7 (4.2)
Chemo-radio-chemo "sandwich" therapy	19 (14.6)	5 (3.0)
Surgery alone	4 (3.1)	1 (0.6)
Surgery with chemotherapy	6 (4.6)	0
Surgery with chemoradiotherapy	3 (2.3)	0
Radiotherapy alone	1 (0.7)	0
Total	130	165

†Staging data was not available for two patients and first-line treatment information was not available for one patient. ES, extensive stage; LS, limited stage.

amrubicin/cisplatin (AP), two (1.3%) with etoposide/cisplatin/cyclophosphamide (EPI), one (0.7%) with topotecan/cisplatin regimen, and four (2.7%) with other regimens.

There were 123 patients treated initially with combined chemoradiotherapy and the first-line chemotherapy regimen was recorded in 121 cases. An EP regimen was adopted in 85 out of 121 cases (70.2%), and CE in 34 of 121 cases (28.1%). The other two patients received EPI and venorelbine/ifosfamide/cisplatin (NIP) regimens.

We also analyzed the chemotherapy regimen of 40 patients during the course of concurrent chemoradiotherapy. Twenty-nine were treated with EP and nine with a CE regimen. The treatment regimens of two cases were not available.

The number of chemotherapy cycles in first-line treatment

The total cycles of first-line chemotherapy were reflected in the questionnaire for 274 patients and the median number of first-line chemotherapy cycles was four. Fifty-three patients (19.3%) received fewer than four cycles of chemotherapy. Reasons for discontinuation included 21 cases (39.6%) with disease progression, 14 with poor tolerance (26.4%), 16 patients (30.2%) refused further therapy, and two (3.8%) had incomplete concurrent chemoradiotherapy (Table 4).

The efficacy evaluation of first-line treatment

The efficacy of first-line treatment was evaluated for 286 patients, including 25 (8.7%) cases with complete response (CR), 142 (49.6%) with partial response (PR), 62 (21.7%)

Table 4 The number of cycles in first-line chemotherapy ($n = 274$)

Cycles	Cases (%)
1	5 (1.8)
2	22 (8.0)
3	26 (9.5)
4	85 (31.0)
5	122 (44.5)
6	14 (5.2)

with stable disease (SD), and 57 (20.0%) with progressive disease (PD). The median time to progression (TTP) was 6.8 (0.7–21) months.

Second-line treatment

Second-line treatment for 157 patients was recorded in the questionnaire. Of 134 evaluable cases, 90 (67.2%) received chemotherapy alone, 32 (23.9%) received chemoradiotherapy, and 12 (8.9%) received radiotherapy alone.

Of the 122 patients whose second-line treatment contained chemotherapy, the regimen of 102 cases was provided (Table 5). The total cycles of second-line chemotherapy were recorded in 115 patients: including 30 cases (26.1%) who completed one cycle, 47 cases (40.9%) with two cycles, and 38 (33%) who received more than two cycles of chemotherapy. Efficacy to second-line treatment was evaluated in 106 patients, including 14 PR (13.2%), 30 SD (28.3%), and 62 PD (58.5%). The median TTP of second-line treatment in 78 patients was 2.1 (1–9) months.

Prophylaxis and treatment of brain metastasis

After first line treatment in patients who had a good response to initial therapy (CR and PR), 148 cases were free of brain metastasis at diagnosis, and were potential candidates for prophylactic cranial irradiation (PCI). According to ques-

Table 5 Second-line chemotherapy regimens ($n = 102$)

Regimen	Cases (%)
Single agent topotecan	38 (37.3)
Combined regimen containing topotecan	16 (15.7)
EP	17 (16.7)
CE	6 (5.9)
IP	9 (8.8)
CAV	2 (1.9)
Single agent etoposide or teniposide	2 (1.9)
Other regimens	12 (11.8)

EP, etoposide with cisplatin; CAV, cyclophosphamide/adriamycin/irinotecan/cisplatin; CE, etoposide with carboplatin; IP, irinotecan/cisplatin.

tionnaire results, 34 of 148 cases (23.0%) were eventually administered PCI, 109 (73.6%) were not, and five patients' (3.4%) data was not available.

Thirty of 298 patients (10.1%) developed brain metastasis at the time of diagnosis (13 of them had clinical symptoms). Twenty-two of 30 cases (73.3%) received radiotherapy, including 19 cases (63.3%) with whole brain radiation therapy (WBRT) and three (10%) with stereotactic radiotherapy (SRT). Chemotherapy drugs that may pass the BBB, such as temozolomide, lomustine, topotecan and irinotecan, were not used.

Discussion

This is the first multicenter survey investigating the status of epidemiology and treatment options of SCLC in Mainland China. Our survey reveals a drastic increase in the number of both lung cancer and SCLC patients in 2010 compared to 2005, a vivid reflection of the soaring incidence of lung cancer in recent years. The percentage of SCLC patients of all lung cancer patients is noteworthy as it is relatively constant over the years, meaning that the incidence of SCLC has increased simultaneously with NSCLC in China in the past five years. The majority SCLC patients were male in both 2005 and 2010. As has been reported in the US and Europe, the incidence of SCLC is decreasing; however, incidence in women is increasing.^{7,8} Because a large number of SCLC cases are attributable to cigarette smoking,⁹ the decreasing incidence of SCLC in developed countries reflects the reduction in both smoking prevalence and in the tar-concentration in cigarettes.^{7,8} However, a smoking prevalence remains high in the Chinese population and the consumption of tobacco continues to rise,^{10,11} which may imply a potential increase in the incidence of SCLC in China.

Lüchtenborg *et al.* reported that approximately 1% of SCLC patients were treated surgically;¹² however, the results of our survey (4.7%, 14/298) were significantly higher, probably a result of the growing popularity of low-dose computed tomography screening for lung cancer; therefore solitary pulmonary nodules can be detected earlier. Surgeons are more likely to take active treatment when they find solitary pulmonary nodules. For LS-SCLC patients, the combined treatment of chemotherapy and concurrent chemoradiotherapy has gained worldwide acceptance and is recommended in several guidelines.⁴⁻⁶ In our study, the results of the hospital information questionnaire also revealed that chemoradiotherapy was the most accepted treatment mode for LS-SCLC patients, further verified in the analysis of the patient information questionnaire in our study. Concurrent chemoradiotherapy is the most recommended in guidelines.^{4,5} In our survey, however, sequential chemoradiotherapy, chemo-radio-chemo "sandwich"

therapy, and chemotherapy alone were all represented. Potential factors that might influence the choice of treatment mode include performance status and the tolerability of the patient; most SCLC patients are elderly with basic diseases and poor heart and lung function, which influence the implementation of concurrent chemoradiotherapy. For patients with ES-SCLC, chemotherapy alone is the standard treatment.⁴⁻⁶ In our survey, radiotherapy was used in a proportion of patients with extensive stage (22.4%). These patients received palliative radiotherapy in addition to chemotherapy in order to ease local symptoms, which was still in accordance with the principles addressed in guidelines.

EP/CE are the most recommended first-line chemotherapy regimens for SCLC.⁴⁻⁶ In our survey, 92.6% of the patients were treated with an EP/CE regimen as first-line therapy, reflecting strict adherence to guidelines. PCI is recommended in patients who respond well to first-line treatment.⁴⁻⁶ The relatively low percentage (23%) of patients who eventually received PCI in our survey was mainly ascribed to the poor performance status of these patients. Single-agent topotecan and CAV are recommended in second-line chemotherapy.^{4,5} The results shown in our survey are primarily in line with these suggestions.

The medical centers that participated in our survey are located in major cities with large populations and health care resources, and generally reflect the real world situation of epidemiology and the treatment of SCLC in Mainland China. The basic health care situation provided in small cities and rural areas was not included in our survey, the limitation of which should not be overlooked. Considering that a majority of cancer patients generally pursue medical service in local or national medical centers, our study is still of great significance in reporting SCLC treatment status. This survey was not a standard cross-sectional study and had a relatively small sample size. Considering that all centers involved in our survey are normalized cancer-treating hospitals with large numbers of cancer patients from all over China, the results shown in our survey are representative of the status of SCLC treatment, in accordance with international clinical guidelines, and can serve as a reference for guiding further clinical practice in China.

Conclusions

Guidelines direct clinical practice, but the limited knowledge of the present situation of clinical practice for SCLC patients in Mainland China serves as invaluable feedback for further clinical study. Our survey is the first study providing a revealing insight into the epidemiology and treatment status of SCLC in Mainland China, which is valuable for the improvement of future guidelines, health care standards, and the better distribution of health care resources.

Acknowledgments

We thank all of the doctors and patients who participated in the study. This study was supported by Beijing Municipal Science and Technology Project (D141100000214005) and GlaxoSmithKline (GSK) China.

Disclosure

No authors report any conflict of interest.

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