Effects of para–toluenesulfonamide intratumoral injection on non-small cell lung carcinoma with severe central airway obstruction: A multi-center, non-randomized, single-arm, open-label trial

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Objective: To determine the efficacy and safety of para-toluenesulfonamide (PTS) intratumoral injection in NSCLC-SMAO.

Methods: Ninety patients with NSCLC-SMAO received repeated courses of PTS intratumoral injection until tumor sizes had reduced by 50% or greater. Primary endpoint was objective alleviation rate, assessed by chest computed tomography (CT) and bronchoscopy, at day 7 and 30 following final dosing. Secondary endpoints included airway obstruction, spirometry, quality-of-life and survival time.

Results: In full-analysis set (N=88), using RECIST criteria, PTS treatment resulted in a significant objective alleviation rate [chest CT: 59.1% (95%CI: 48.1%–69.5%), bronchoscopy: 48.9% (95%CI: 38.1%–59.8%) at day 7; chest CT: 43.2% (95%CI: 32.7%–54.2%), bronchoscopy: 29.6% (95%CI: 20.3%–40.2%) at day 30]. There was a remarkable increase in FVC (mean difference: 0.35 liters, 95%CI: 0.16–0.53 liters), FEV1 (mean difference: 0.27 liters, 95%CI: 0.07–0.48 liters), Baseline Dyspnea Index (mean difference: 64.8%, 95%CI: 53.9–74.7%) and Functional Assessment of Cancer Therapy-Lung Cancer Subscale (mean difference: 6.9, 95%CI: 3.8–9.9) at day 7 post-treatment. We noted significantly reduced prevalence...
of atelectasis (by 42.9%) and Eastern Cooperative Oncology Group physical performance scale (mean difference: 7.2, 95%CI: 3.9–10.5). Median survival time was 394 days in full-analysis set and 460 days in per-protocol set. Adverse events were reported in 64.0% of subjects. Seven severe adverse events (7.9%) were reported, of which three led to death (drug-related in one case).

**Conclusion:** PTS intratumoral injection is effective and well tolerated for palliative therapy of NSCLC-SMAO.

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## 1. Introduction

Lung cancer is the leading cause of morbidity and mortality among malignant tumors [1] with annually increasing prevalence in China [2]. Despite chemotherapy, radiotherapy and surgery, the 5-year survival rate is 5.0–10.0% [3,4]. In America, one-third of lung cancer patients developed symptomatic malignant airway obstruction [5]. Because of limited penetration to airway lumen, conventional therapy had limited efficacy for advanced lung cancer of central airways (trachea, left/right main bronchus), particularly non-small cell lung carcinoma with severe malignant airway obstruction (NSCLC-SMAO) which is life-threatening [6–9].

Treatment with laser, electrocautery, argon plasma coagulation and stent placement via bronchoscopy is promising for malignant tracheobronchial tumors [10]. However, severe adverse events (hemorrhage, tracheoesophageal fistula, pneumothorax) and the sophisticated and costly instruments have restricted their clinical application, particularly in community settings. Intratumoral injection of tumoricidal medications (i.e. ethanol absolute) has been applied for lung cancer [11]. Admittedly, different medications yielded varying outcomes. High-dose ethanol absolute intratumoral injection resulted in extensive tissue injury leading to significant adverse events (hemorrhage, ethanol intoxication, pain and fever) [12–17]. First-line tumoricidal medications (cisplatin, 5-fluorouracil) debulked intratumoral tumors resulting in amelioration of central airway obstruction [18,19]. However, whether these findings could be applied to NSCLC-SMAO (>50% central airway obstruction) remains unclear. Previous observations on intratumoral injection were confounded by intravenous cisplatin [20] or 5-fluorouracil [19]. Furthermore, treatment options of inoperable NSCLC-SMAO were very limited. Even treated with stenting, survival was reportedly low (~25%) and median survival time was 6.2 months only [21].

Para-toluensulfonylamide (PTS), the low-molecular-weight hydrophilic compound, readily dissolves in ethanol [22,23]. PTS significantly inhibited tumor growth, suppressed cellular activities in vitro via increasing membrane permeability [24], but led to minor injury to adjacent normal tissues [24–26]. Recently, phase 2 trials of breast cancer [26], liver cancer [27,28] and early-stage head/neck tumor [29] have consistently verified the efficacy of PTS. We hypothesized that PTS effectively palliate NSCLC-SMAO by debulking intrabronchial tumor, contributing to ameliorated dyspnea and prolonged survival.

Here, we investigated the efficacy and safety of PTS intratumoral injection in NSCLC-SMAO.

## 2. Methods

### 2.1. Study population

Hospitalized patients with NSCLC-SMAO were recruited from 17 participating sites in China (Table E1).

Eligibility criteria included: 1) patients aged 18–83 years of both gender; 2) physician-diagnosed NSCLC-SMAO, defined as the ratio of tumor diameter and trachea diameter being 0.50 or greater, the ratio of tumor diameter and left/right main bronchial diameter being 0.67 or greater, or the longest tumor diameter being greater than 0.5 cm; 3) lesions suitable for bronchoscopic therapy; 4) tumor(s) with measurable sizes being determined by bronchoscopy, computed tomography, magnetic resonance imaging or roentgenography; 5) platelet count 100,000/mm² or greater.

Exclusion criteria were: 1) cerebral metastasis; 2) cardiovascular disease, including congestive heart failure (New York Heart Association grade 2 or greater), unstable or emerging (within 3 months) angina pectoris, myocardial infarction within 6 months; 3) severe infection and metabolic disorders; 4) liver failure, liver cirrhosis, aberrant blood coagulation; 5) poor general condition or cachexia; 6) prior radiotherapy (within 6 months); 7) pregnancy or lactation; 8) anaphylaxis to PTS.

The study protocol was approved by Ethics Committee of individual participating cites and China Food and Drug Administration (No.: 2009L03443; Medical Ethics Year 2009 [the 12th]). Subjects gave written informed consent.

### 2.2. Study medication

PTS (Lot No.: 070109, 070110 and 070111; Guangdong Dari Chemicals Inc., Guangzhou, China) was stored in 5 ml vials and kept in cooled places by designated research nurses. Within 30 min before use, PTS was diluted with 2 ml ethanol anhydride into 10 ml sterile syringe followed by gentle vortex. Ethanol (final concentration: 30%) was added to facilitate intratumoral injection.

### 2.3. PTS intratumoral injection

Subjects were administered 2% lidocaine hydrochloride via nebulization, and midazolam (1–2 mg) plus sufentanil (5 mg) intravenously for general anesthesia. The bronchoscope (BF260, Olympus Inc., Osaka, Japan) was passed transnasally for inspection of tumor and adjacent tissues. PTS/ethanol mixture was, using NA-1C-1 needle (Olympus Inc., Osaka, Japan), intratumorially injected to lower quadrant of tumor’s root (not endothelium), starting from tumor to adjacent tissues. Each injection covered 4–6 sites. Depth and location of injection could be adjusted. For individual sites, the recommended dose of PTS/ethanol mixture was 0.1–1.5 ml (equivalent to 0.07–1.00 ml PTS), with maximal doses of 7.0 ml (5.0 ml PTS), tailored to tumor’s size. Maximal cumulative dose of PTS/ethanol mixture was 14.0 ml (10.0 ml PTS) for any single day. Local PTS injection leads to tumor coagulative necrosis, forming grossly gray/dark debris. To ensure greater penetration to tumor and alleviate airway obstruction, tissue clamps were applied to remove necrotic debris before dosing at visit 2 and thereafter.

### 2.4. Study design

This was a phase 3, multicenter, non-randomized, single-arm, open-label trial. Randomized, double-blind, parallel-group study was not conducted because it was deemed unethical, according to local ethics committee and China Food and Drug Administration.

Eligible patients received PTS intratumoral injection for 2–3 sessions weekly, with 2 weeks regarded as single course. Four doses
were mandatory for initial course, but doses could be adjusted for remaining courses (Fig. 1A). Post-treatment assessments were performed at day 7 and 30 after the final dose.

2.5. Study endpoints

Co-primary endpoints, measured by bronchoscopy and chest CT, included: 1) Objective alleviation rate [OAR, based on Response Evaluation Criteria In Solid Tumor (RECIST), or World Health Organization (WHO) criteria]; 2) Bronchial obstruction alleviation rate. RECIST criteria evaluated pre- and post-treatment changes in the longest tumor diameter using CT and bronchoscope; WHO criteria were assessed: 100% × (baseline obstruction rate–post-treatment obstruction rate)/baseline obstruction rate. Tumor obstruction rate was, by applying irregular curve estimating algorithms, derived from maximal cross-sectional area of tumor divided by the area of airway lumen at an identical plane.

Bronchoscopic assessment was performed with computer software that calculated tumor sizes, via fixation of bronchoscope at 1.0 cm above the tumor, by applying 1.0cm-thick plastic ring at the nostril to secure accurate positioning whilst maintaining imaging focus at the central target trachea/bronchi. CT was evaluated by three members of independent committee, including tumor size, area and luminal area, with discrepancy being resolved following group adjudication.

Clinical beneficial endpoints were pre- and post-treatment differences in FEV1 and lung aeration.

Exploratory endpoints were pre- and post-treatment differences in: 1) FEV1/FVC ratio; 2) Baseline Dyspnea Index (BDI); 3) Eastern Cooperative Oncology Group physical performance (ECOG) scale; 4) Functional Assessment of Cancer Therapy–Lung Cancer Subscale (FACT-LCS); 5) duration of remission (DOR); 6) overall survival (OS).

Adverse events (AE) and severe adverse events (SAE) were recorded and presented as numbers and percentages. Vital signs were recorded prior to and after PTS injection.

2.6. Statistical analysis

Sample size was calculated based on two-sided tests, with the α of 0.05 and β of 0.80, assuming an OAR of 30.0% and target width
for 95% confidence interval (95% CI) of 20.0%, 89 patients would be needed for enrollment.

We analyzed endpoints based on intention-to-treat principle. Full-analysis set included patients who received at least one dose of PTS. Per-protocol set consisted of those who received at least two weeks of PTS treatment (single course).

Statistical analysis was conducted using SPSS 17.0 (SPSS Inc., III). Numeric data were expressed as mean ± standard deviation or median (interquartile range), and compared with t-test or Mann-Whitney test. Treatment effects were summarized as differences in pre- and post-treatment and 95% CI, and compared with matched paired tests. Categorical data were summarized as count (percentage) and compared with chi-square test. Survival was analyzed with log-rank test. Safety set was evaluated for safety. P < 0.05 was deemed statistically significant.

This study was registered with Chinese Clinical Trial Registry (www.chictr.org.cn), number ChiCTR-TNC-12002648.

2.7. Role of funding source

The manufacturer (Guangdong Dari Chemicals Inc., Guangzhou, China) provided study medication but had no role in patient recruitment, data analysis or manuscript drafting.

3. Results

3.1. Subject enrollment

Between August 2009 and January 2012, 101 patients underwent screening, of whom 11 were excluded (Fig. 1B). Reasons of exclusion were: consent withdrawal (n = 1), non-severe airway obstruction (n = 6), treatment-intolerant cachexia (n = 1), intracranial metastasis (n = 1), other malignancy (n = 1) and no observable intratumoral tumor (n = 1). Finally, 88 and 72 patients were included in full-analysis and per-protocol set, respectively.

Patients in safety set (n = 89) received a mean of 5.1 episodes of PTS injection (total dose: 18.2 ml). 92.1%, 40.4% and 5.6% of patients accomplished at least one, two and three courses, respectively.

3.2. Baseline levels

The cohort consisted of mostly middle-aged males with predominantly stage IIIB and IV NSCLC which affected left/right main bronchus. Baseline levels of full-analysis and per-protocol set were comparable. Squamous cell carcinoma was predominant (75.0%), followed by adenocarcinoma (12.5%). Most tumors were of moderate-to-low differentiation (57.4%). (Table 1)

3.3. Primary endpoints

Rates of complete and partial remission were pooled for calculating OARs. Assessment with chest CT yielded consistently higher OARs of complete remission than partial remission at day 7 and 30 post-treatment, based on RECIST or WHO criteria. (Table 2)

In full-analysis set, according to RECIST criteria, OARs were 59.1% (95% CI: 48.1%–69.5%) and 43.2% (95% CI: 32.7%–54.2%) when evaluated with chest CT, and 48.9% (95% CI: 38.1%–59.8%) and 29.6% (95% CI: 20.3%–40.2%) according to bronchoscopy, at day 7 and 30 post-treatment, respectively. For analyses with WHO criteria, at day 7 and 30 post-treatment, OARs were 67.1% (95% CI: 56.2%–76.7%) and 47.7% (95% CI: 37.0%–58.7%) according to chest CT, and 76.1% (95% CI: 65.9%–84.4%) and 37.5% (95% CI: 27.4%–48.5%) based on bronchoscopy.

At day 7 and 30 post-treatment, alleviation of airway obstruction was achieved in 69.4% and 69.1% of patients according to chest CT, and in 72.8% and 68.5% of patients based on bronchoscopy.

Table 1
Baseline demographic and clinical characteristics.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Full-analysis set (n = 88)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Median: 57.5, Range: 22–80</td>
</tr>
<tr>
<td>Males (No., %)</td>
<td>Median: 73 (83.0%)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>Median: 165.0, Range: 147.0–180.0</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>Median: 56.2, Range: 37.0–88.0</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>Median: 1.6, Range: 1.3–2.1</td>
</tr>
<tr>
<td>Clinical staging</td>
<td>IV (No., %): 46 (52.3%), III (No., %): 37 (42.0%), Other (No., %): 5 (5.7%)</td>
</tr>
<tr>
<td>Histologic diagnosis</td>
<td>Squamous cell carcinoma (No., %): 66 (75.0%), Adenocarcinoma (No., %): 11 (12.5%), Giant cell carcinoma (No., %): 1 (1.1%), Squamous cell carcinoma plus adenocarcinoma (No., %): 1 (1.1%), Miscellaneous (No., %): 9 (10.2%)</td>
</tr>
<tr>
<td>Tumor differentiation</td>
<td>High (No., %): 4 (4.6%), Moderate (No., %): 21 (24.1%), Low (No., %): 29 (33.3%), Unknown (No., %): 33 (37.9%)</td>
</tr>
<tr>
<td>Location of tumor</td>
<td>Trachea (No., %): 11 (12.5%), Left main bronchus (No., %): 33 (37.5%), Right main bronchus (No., %): 34 (38.6%), Right middle lobe (No., %): 10 (11.4%)</td>
</tr>
</tbody>
</table>

OARs according to treatment cycles and total doses of PTS administered are shown in Figure E2.

Typical pre- and post-treatment changes in tumor sizes and airway occlusion are displayed in Fig. 2 and E3. Similar findings were found in per-protocol set (Table E2).

Reasons of discrepancy between bronchoscopic and chest CT assessments are given in Table E3.

3.4. Clinical benefit endpoints

Compared with baseline levels (1.56 ± 0.53L), FEV₁ increased at day 7 (mean difference: 0.27L, 95% CI: 0.07–0.48L, P = 0.01) and 30 post-treatment (mean difference: 0.32L, 95% CI: −0.01–0.66L, P = 0.10) in full-analysis set (Table E4). Per-protocol set yielded comparable findings (not shown). Of 49 patients with atelectasis in full-analysis set, lung aeration was observed in 21 patients (42.9%). Most lung aeration occurred in right middle lobe (50.0%), followed by left lower (40.0%), lower left (38.9%), right lower (35.7%), right lingula (33.3%) and right upper lobe (25.0%) in full-analysis set.

3.5. Exploratory endpoints

In full-analysis set, despite non-significant increases in FEV₁/FVC at day 7 (mean difference: −0.40%, 95% CI: −4.52%–3.72%, P = 0.27) and 30 post-treatment (mean difference: 0.27L, 95% CI: 0.07–0.48L, P = 0.01) (Table 3), FEV₁/FVC improvement was observed in 20.5% and 12.5% of patients, respectively, compared with baseline.

BDI score increased significantly at day 7 (mean difference: 2.19, 95% CI: 1.55–2.83, P < 0.01) and 30 post-treatment (mean difference: 2.23, 95% CI: 1.31–3.15, P < 0.01). ECOG score improvement
was achieved in 34.1% and 25.0% of patients at day 7 and 30 post-treatment in full-analysis set.

PTS treatment led to significant improvement in FACT-LCS scores at day 7 (mean difference: 6.86, 95%CI: 3.79–9.93, P < 0.01), but not at day 30 post-treatment (mean difference: 3.98, 95%CI: –0.59–8.55, P = 0.11).

Per-protocol set yielded similar findings (Table E5).

Of patients in full-analysis set, 37 (42.0%) succumbed. Median survival duration was 394.0 days (25th percentile: 185.0 days; 75th percentile: 460.0 days). (Fig. 3) Patients in per-protocol set had longer survival duration than those in full-analysis set.

3.6. Safety

AE was reported in 64.0% of patients (n = 57), of whom 50.9% (n = 29), 31.6% (n = 18) and 17.5% (n = 10) were rated as mild, moderate and severe. Drug-related AEs were reported in 25.8% of patients (n = 23), of whom 43.5% (n = 10), 39.1% (n = 9) and 17.4% (n = 4) were rated as mild, moderate and severe.
Table 3
All adverse events as rated by the severity.

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Total No. (%)</th>
<th>Severity</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any reported adverse event</td>
<td>57 (64.0%)</td>
<td></td>
<td>29 (50.9%)</td>
<td>18 (31.6%)</td>
<td>10 (17.5%)</td>
</tr>
<tr>
<td>Respiratory system</td>
<td>42 (47.2%)</td>
<td></td>
<td>22 (52.4%)</td>
<td>12 (28.6%)</td>
<td>8 (19.0%)</td>
</tr>
<tr>
<td>Coughing</td>
<td>15 (16.9%)</td>
<td></td>
<td>9 (60.0%)</td>
<td>5 (33.3%)</td>
<td>1 (6.7%)</td>
</tr>
<tr>
<td>Bloody sputum</td>
<td>15 (16.9%)</td>
<td></td>
<td>13 (86.7%)</td>
<td>2 (13.3%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Pharyngodynia</td>
<td>7 (7.9%)</td>
<td></td>
<td>6 (85.7%)</td>
<td>1 (14.3%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Tachypnea</td>
<td>6 (6.7%)</td>
<td></td>
<td>5 (83.3%)</td>
<td>1 (16.7%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Chest distress</td>
<td>5 (5.6%)</td>
<td></td>
<td>4 (80.0%)</td>
<td>1 (20.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Pulmonary infections</td>
<td>5 (5.6%)</td>
<td></td>
<td>3 (60.0%)</td>
<td>2 (40.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Expectoration</td>
<td>5 (5.6%)</td>
<td></td>
<td>5 (100.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>4 (4.5%)</td>
<td></td>
<td>3 (75.0%)</td>
<td>1 (25.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>3 (3.4%)</td>
<td></td>
<td>1 (33.3%)</td>
<td>1 (33.3%)</td>
<td>1 (33.3%)</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>3 (3.4%)</td>
<td></td>
<td>0 (0.0%)</td>
<td>1 (33.3%)</td>
<td>2 (66.7%)</td>
</tr>
<tr>
<td>Others</td>
<td>7 (7.7%)</td>
<td></td>
<td>2 (28.6%)</td>
<td>1 (14.3%)</td>
<td>3 (42.9%)</td>
</tr>
<tr>
<td>Systemic and infection site</td>
<td>20 (22.5%)</td>
<td></td>
<td>13 (65.0%)</td>
<td>7 (35.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Injection site hemorrhage</td>
<td>9 (10.1%)</td>
<td></td>
<td>7 (77.8%)</td>
<td>2 (22.2%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Fever</td>
<td>8 (9.0%)</td>
<td></td>
<td>5 (62.5%)</td>
<td>3 (37.5%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Malaise</td>
<td>1 (1.1%)</td>
<td></td>
<td>1 (100.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Progression of cancer</td>
<td>1 (1.1%)</td>
<td></td>
<td>0 (0.0%)</td>
<td>1 (100.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Edema</td>
<td>1 (1.1%)</td>
<td></td>
<td>0 (0.0%)</td>
<td>1 (100.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Other examination abnormality</td>
<td>8 (9.0%)</td>
<td></td>
<td>6 (75.0%)</td>
<td>2 (25.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Electrocardiogram</td>
<td>2 (2.2%)</td>
<td></td>
<td>2 (100.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2 (2.2%)</td>
<td></td>
<td>1 (50.0%)</td>
<td>1 (50.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>1 (1.1%)</td>
<td></td>
<td>1 (100.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Prolonged partial thrombin activation time</td>
<td>1 (1.1%)</td>
<td></td>
<td>1 (100.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Visible urinary leukocytes</td>
<td>1 (1.1%)</td>
<td></td>
<td>1 (100.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Neutrophilia</td>
<td>1 (1.1%)</td>
<td></td>
<td>1 (100.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Elevated aspartate aminotransferrase</td>
<td>1 (1.1%)</td>
<td></td>
<td>1 (100.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Oxygen desaturation</td>
<td>1 (1.1%)</td>
<td></td>
<td>0 (0.0%)</td>
<td>1 (100.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Skin and subcutaneous diseases</td>
<td>4 (4.5%)</td>
<td></td>
<td>4 (100.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Gastrointestinal tract diseases</td>
<td>4 (4.5%)</td>
<td></td>
<td>2 (50.0%)</td>
<td>2 (50.0%)</td>
<td>0 (0.0%)</td>
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<tr>
<td>Cardiopulmonary diseases</td>
<td>4 (4.5%)</td>
<td></td>
<td>2 (50.0%)</td>
<td>2 (50.0%)</td>
<td>2 (50.0%)</td>
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<tr>
<td>Neurologic diseases</td>
<td>3 (3.4%)</td>
<td></td>
<td>1 (33.3%)</td>
<td>1 (33.3%)</td>
<td>1 (33.3%)</td>
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<tr>
<td>Metabolic and nutritional diseases</td>
<td>2 (2.2%)</td>
<td></td>
<td>2 (100.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Psychiatric disease</td>
<td>1 (1.1%)</td>
<td></td>
<td>0 (0.0%)</td>
<td>1 (100.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Vascular diseases</td>
<td>1 (1.1%)</td>
<td></td>
<td>0 (0.0%)</td>
<td>1 (100.0%)</td>
<td>0 (0.0%)</td>
</tr>
</tbody>
</table>

Data were summarized as count (percentage) unless otherwise stated.

Vital AEs were reported in 20.5% of patients (n = 18). Common AEs were thoracic and mediastinal diseases (47.2%, n = 42) according to Systemic Organ Classification, and coughing (16.9%, n = 15), bloody sputum (16.9%, n = 15) and injection site hemorrhage (10.1%, n = 9) according to Preferred Terms classification.

The most common drug-related AE was cough (12.5%, n = 11), followed by fever (4.5%, n = 4).

AEs leading to treatment cessation were reported in eight cases (9.0%), of which two cases were associated with PTS intratumoral injection (online supplement).

Two patients (2.3%) did not complete treatment course due to disease progression prior to efficacy evaluation; however, no additional treatments were needed.

Seven SAEs (7.9%) were reported. Three patients (3.4%) succumbed. Of four drug-related SAEs, one patient developed airway stenosis and respiratory failure (severe obstruction of bilateral main bronchi), one succumbed due to major hemorrhage (at day 26 post-treatment, possibly related to cancer progression), one reported wheezing (10-year’s history of chronic bronchitis; wheezing occurred at initial dose but remitted thereafter), and one developed heart failure (coincident with obstruction-induced pneumonia at day 1 following the third treatment course; remitted following symptom-based therapy and discharged at day 2 post-treatment).

There were no notable abnormalities (including bone marrow inhibition) in laboratory tests. (Table 3 and E6)

4. Discussion

We demonstrated, for the first time, that PTS intrabronchial injection significantly reduced tumor sizes by eliciting coagulative necrosis, ameliorated airway obstruction, improved lung func-
tion and quality-of-life, and prolonged survival in NSCLC-SMAO. Adverse events were overall mild. PTS was well-tolerated.

Our findings were consistent with previous reports. In nude mice, PTS inhibited tumor growth via necrotizing lung cancer tissues in vivo, abrogating cell metabolism and increasing membrane permeability in vitro [22]. PTS increased lysosomal membrane permeability, cathepsin activation, mitochondrial cytochrome C release and inhibition of adenosine triphosphate biosynthesis [30]. Effects of PTS were dose-dependent [29]. PTS conferred efficacy in breast cancer, liver cancer and skin cancer, in phase 2 clinical trials [25–29]. In phase 2 trials of advanced peripheral lung cancer [18,20], PTS local injection plus cisplatin was effective and safe in inhibiting tumor growth. Intratumoral PTS injection yielded marked tumor necrosis associated with minor injury to adjacent tissues, which was also shown in mouse model [23]. Following removal of necrotic debris, PTS could be safely administered for multiple treatment courses. In keeping with literature reports [18–20], intratumoral PTS injection facilitated the penetration to tumor, which significantly ameliorated airway obstruction, improved lung function and quality-of-life, which collectively translated into prolonged survival.

Improvement in clinical benefit parameters supported the therapeutic potential of PTS intratumoral injection. FEV1 was significantly increased post-treatment, indicating alleviated large-airway obstruction. We noted significantly more cases with aeration, which might be related to suppressed tumor growth. Notably, these effects were sustained to follow-up despite relapse potential. Median survival duration (394.0 days in full-analysis set) was considerably longer than that of laser therapy plus brachytherapy (mean: 285.6 days) [30], intravenous pametrexed plus carboplatin (median: 204.4 days), or gemcitabine plus carboplatin (median: 196.0 days) [31,32]. However, caution should be exercised when interpreting these findings because of the lack of comparator group (i.e. stent placement).

Intratumoral PTS injection had significant local penetration and minor normal tissue injury. In a phase IIa clinical trial on early-stage head/neck tumor [28], injury of tumor adjacent tissues and normal tissues was evaluated via biopsy. The area with tissue necrosis and degeneration was defined as major outcome. Results (unpublished data) showed that PTS led to minor injection-site necrosis and degeneration of tumor adjacent tissues (the area with tissue necrosis and degeneration: 13.6%) compared with tumor tissues (95.5%). This trend was more pronounced when comparing normal tissues with tumor tissues.

PTS was well tolerated. Most AEs were mild-to-moderate. The four SAEs were mostly associated with lung cancer progression, despite worsened airway obstruction possibly due to swelling of necrotic debris. This warranted debris removal via clamps prior to subsequent PTS dosing. Admittedly, PTS/ethanol mixture induced minor injury to adjacent tissues. However, no laboratory testing-related AE was reported, which reaffirmed the safety of PTS injection on systemic metabolism and normal cell growth.

PTS harbors significant tumoricidal effects whilst minor adverse impacts on adjacent tissues. Treatment (including chemotherapy and radiotherapy) that effectively and rapidly alleviated SMAO, the life-threatening form of lung cancer, is lacking. Despite the palliative nature, PTS holds promises for prolonging survival and improving quality-of-life in NSCLC-SMAO. With increasing application of bronchoscopy worldwide, our findings would significantly benefit the treatment of advanced lung cancer in community settings where bronchoscopy is available.

Our strengths included multicenter study design, rigorous endpoint evaluation methodology, long-term follow-up in the most severe form of lung cancer. Due to cost-effectiveness (significantly lower anticipated price post-marketing compared with cisplatin and gemcitabine), PTS might be particularly suitable for NSCLC-SMAO in developing countries.

5. Limitations

“The lack of active comparator group suggested that our findings might have been confounded by subject allocation and study endpoints assessment. However, placebo of PTS has not been approved for clinical trial purposes due to ethics concerns. The significant tumor necrosis leading to diminished tumor sizes occurred rapidly following PTS injection, which could not be interpreted by any other known components. Ethanol at concentrations of 30% or less had no significant tumoricidal effects on NSCLC [22].

Because China Food and Drug Administration has only approved single-arm study design, we were unable to compare the effectiveness of PTS and other established approaches (i.e. airway stent placement).

** PTS intratumoral injection might result in tumor necrosis and transient swelling leading to asphyxia in a few cases. Hence, stent placement is warranted prior to dosing in some patients with very severe airway obstruction (particularly tracheal obstruction).

** PTS injection rested on repeated courses of bronchoscopy.

** The primary endpoint was evaluated with two sets of criteria. Although bronchoscopic assessment was more reliable than CT evaluation for measuring reduction in tumor sizes, the lack of standardized criteria has rendered it challenging to determine a more suitable assessment approach. During study design, the expert panel has elected to evaluate treatment responses based on CT plus bronchoscopic assessment.

** Some patients did not accomplish spirometry or quality-of-life assessments. These patients had significant tumor alleviation following single treatment cycle, and had less willingness to complete further treatment.

** Our study primarily recruited patients with NSCLC-SMAO. However, the powerful tumoricidal effects coupled with high selectivity might have rendered PTS more clinically suitable for milder forms of lung cancer.

6. Conclusion

Our findings have highlighted significant therapeutic potential of intratumoral PTS injection for NSCLC-SMAO, particularly in developing countries with limited medical facilities for performing bronchoscopy.

Author’s contributions


Funding

Guangdong Dari Chemicals.

Clinical trial registry

www.chictr.org.cn, No.: ChiCTR-TNC–12002648
Conflict of interest
None declared.

Acknowledgment
We truly appreciate the insightful suggestions from Drs. Eric Tu, Matt Hsiao, Pierre Hsiao, Morrice Lin, William Huang, Joy Chang, and Biran Wang (PTS International Inc., USA). We also thank Chuang-yu Lin and Zhao-hui Wei (Hangzhou Tiger Statistics Inc., Hangzhou, China) for performing statistical analyses, Guangdong Dari Chemicals Inc. (Guangzhou, China) for providing study medications, and the patients who took consent in participation in our study.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.lungcan.2016.05.012.

References