Gemcitabine plus cisplatin chemotherapy with concurrent para-toluenesulfonamide local injection therapy for peripherally advanced nonsmall cell lung cancer larger than 3 cm in the greatest dimension

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Para-toluenesulfonamide (PTS), active ingredient being PTS, is a new anticancer drug applied through local intratumoral injection. The aim of this phase II clinical trial was to investigate the response and toxicity of standard gemcitabine (GEM) plus cisplatin (CIS) chemotherapy with concurrent intratumoral injection of PTS in peripherally advanced nonsmall cell lung cancer. Patients received 1250 mg/m^2 of GEM on day 1, 8, and 75 mg/m^2 of CIS on day 1, every 21 days for four cycles. PTS was injected intratumorally through percutaneous injection under computed tomography guidance on days 5, 12, 15, and 18 of cycle 1, and repeated on days 5 and 12 of cycle 2 if a less than 50% necrotic area was achieved after the first cycle according to the computed tomography scan. Twelve (46.2%) patients had metastatic disease, whereas 14 (53.8%) patients had stage IIIB disease. All 26 patients were assessable for response. Overall response rate by intention-to-treat was 53.8% (95% confidence interval: 34.6–73.0%). Median progression-free survival and overall survival were 6.5 months (95% confidence interval: 3.8–10.2 months) and 14.5 months (10.0–18.0 months), respectively. One-year and 2-year survivals were 57.7 and 22.4%, respectively. The grade 3–4 hematologic adverse events were neutropenia in six patients (23.1%), anemia in three (11.5%), and thrombocytopenia in four patients (15.4%). Nonhematologic toxicities were generally mild and usually not dose-limiting. Although grade 1–2 emesis occurred in nine patients (34.6%), only one had grade 3 vomiting. Grade 1–2 cough, local pain, and peripheral neurotoxicity developed in 12 (46.2%), three (11.5%), and five (19.2%) patients, respectively. There were no treatment-related deaths. GEM/CIS chemotherapy with concurrent PTS local injection therapy is a well-tolerated modality with potential activity in previously untreated peripheral advanced nonsmall cell lung cancer patients.

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Introduction

Lung cancer is the most common solid tumor in men in China and is the second most common tumor in women in China, after breast cancer [1]. Nonsmall cell lung cancer (NSCLC) represents the vast majority of all lung cancers with approximately one-third of the patients presenting with locally advanced disease at the time of diagnosis. The prognosis for patients with clinical stages IIIB and IV is exceedingly poor, with a 5-year survival rate of less than 3% [2]. Gemcitabine (GEM) plus cisplatin (CIS) is a standard treatment for advanced NSCLC and is used in many countries as the first-line chemotherapy treatment for NSCLC. The combination has a clear synergistic mechanism of action in preclinical studies [3], and has been proven effective in phase III clinical trials [4–7]. However, the response rate (RR) and overall survival (OS) benefits remain limited and unsatisfactory. Current strategies of concurrent chemoradiation therapy show a better OS when compared with sequential chemoradiation or chemotherapy alone in locally advanced NSCLC but toxicity remains a challenge [8]. Clearly, there is a need to develop alternative effective therapies including improvements in local therapy as well as systemic therapy. New therapies should not only improve RRs and survival but should also improve quality of life (QoL).

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Para-toluenesulfonamide (PTS), chemically known as 4-methylbenzenesulfonamide, is a lipophilic fluid and the active ingredient being PTS at 330 mg per milliliter. PTS is often used as adjuvant for anticancer drugs and has shown independent antiproliferative activity against tumor cells and is a tumor necrotizing chemical agent. Furthermore, PTS therapy shows few histological changes to normal tissues. In-vitro studies showed PTS induced inhibition of human lung cancer cells including multidrug resistance cells [9]. Preclinical research has confirmed the relative safety for the coadministration of PTS with other drugs both *in vivo* and *in vitro* [10]. PTS is therapeutically effective by multiple routes of administration including intraperitoneal, intramuscular, subcutaneous, and intratumoral. Tumor inhibition has been observed in the rodent models at doses of 127 to 690 mg/kg. PTS was assessed for safety in preclinical toxicology testing. We have previously evaluated the concept of treating intra-tracheal tumor with direct intratumoral injection of PTS by using a fiber optic bronchoscope. In that study two complete responses and four partial responses were seen amongst nine patients evaluable for response. Toxicities were all mild and included fever, local pain and somnolence. All toxicity resolved spontaneously [11]. Based on these results, we designed this trial to explore the efficacy and toxicity of PTS local injection given concurrently with standard GEM/CIS chemotherapy in patients with locally advanced and metastatic NSCLC.

Patients and methods

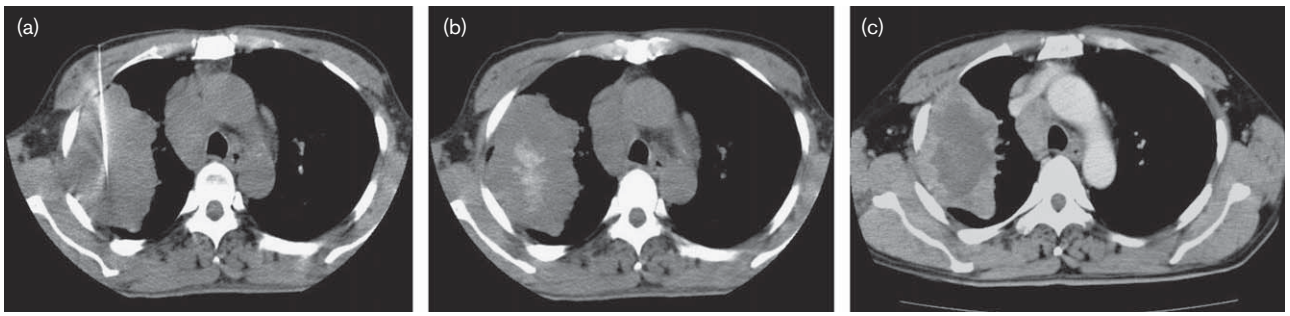
Eligibility criteria

Patients above the age of 18 years with pathologically confirmed stage III or IV peripherally located incurable NSCLC were included into the study. Prior chemotherapy and radiation for local tumor were not allowed. The study required all patients to have either evaluable or measurable disease larger than 3 cm in the greatest dimension. Criteria for inclusion were as follows: Eastern Cooperative Oncology Group performance status scored 0–2, life expectancy of no less than 3 months, adequate hematologic function (white blood cell $> 1.5 \times 10^9$/l and platelets $\geq 75 \times 10^9$/l), renal function (serum creatinine ≤ 2.0 mg/dl or upper normal limit or creatinine clearance 60 ml/min), hepatic function (serum bilirubin ≤ 2.0 mg/dl, serum glutamic oxaloacetic transaminase or serum glutamic pyruvic transaminase $\leq 2.5 \times$ ULN), and human immunodeficiency viruses negative. Patients with vital vessels or nerves proximal to the primary tumor, other malignant tumors, organ transplantation, uncontrolled infection, cardiac dysfunction, or serious concomitant medical conditions were excluded. Pregnant and breast-feeding patients were also excluded. Patients with known or prior allergy to PTS were also excluded. Adequate contraception was required where appropriate. Patients with brain metastasis were not eligible in this study. The protocol was approved by the institutional review board of Guangzhou Institute of Respiratory Diseases, affiliated to Guangzhou Medical College. All patients were fully informed of the investigational nature of the study and provided written informed consent.

Para-toluenesulfonamide local therapy

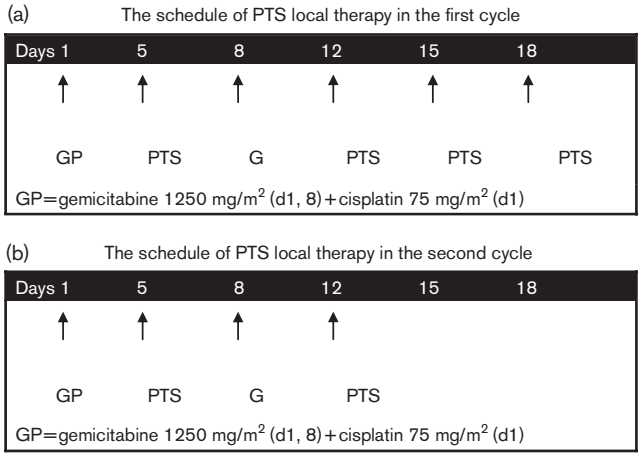
PTS was injected intratumorally through percutaneous injection under computed tomography (CT) guidance (Fig. 1). Methylprednisolone and codeine were preoperatively administered through intravenous infusion and orally, respectively. The schedule of PTS local therapy is shown in Fig. 2. Between 1 and 4 ml of PTS (equivalent to 330–1320 mg) was injected per tumor at each puncture point. Multiple intratumoral injections were performed to adequately diffuse PTS into the tumor masses. Total PTS dosing was determined by tumor size. Injection volumes of 8 and 15 ml of PTS were used for the largest diameter of tumor of 3–5 cm and larger than 5 cm,

Fig. 1



Para-toluenesulfonamide (PTS), active ingredient being para-toluenesulfonamide, was injected intratumorally using percutaneous injection under computed tomography (CT) guidance in patients with nonsmall cell lung caner. (a) CT scan showed the tumor mass (10.5 × 6.0 cm) was lobulated at the right upper lung, the density of uniform boundaries unclear with the adjacent pleural, with mediastinal lymph node metastasis. By the right anterior chest wall puncture, we can see a white high-density needle puncture at the central mass for injecting PTS into mass. (b) CT scan showed a slightly higher central mass density of the drug film sheet after PTS injection immediately. (c) Enhanced CT showed the tumor size was about 9.5 × 5.5 cm after two cycles of treatment, with a large nonenhanced necrotic foci (7.3 × 4.5 cm), the rate of necrosis accounted for 63%, a substantial part of the edge of mass slightly enhanced, mediastinal lymph node shrank compared with before treatment.

Fig. 2



Treatment schedule and para-toluenesulfonamide (PTS) dose. (a) The schedule of PTS local therapy in the first cycle. (b) The schedule of PTS local therapy in the second cycle. G, gemicitabine; GP, gemicitabine 1250 mg/m^2 (day 1, 8) + cisplatin 75 mg/m^2 (day 1).

respectively. A second subsequent PTS intratumoral injection was not administrated if a 70% necrotic area was documented on the CT scan. PTS injection was repeated in the second cycle if a less than 50% necrotic area was achieved after the first cycle according to CT scan.

Chemotherapy and dose modification

GEM was given at a dose of 1250 mg/m^2 over 30 min by intravenous infusion on day 1 and 8, and CIS administrated at a dose of 75 mg/m^2 on day 1. Chemotherapy cycles were repeated every 3 weeks for a maximum of four cycles. All patients received adequate antiemetic therapy before chemotherapy. Granulocyte colony-stimulating factor was administered at the physician's discretion.

Subsequent cycles of treatment were only given when the neutrophil count was $\geq 1.5 \times 10^9$/l, platelet count $\geq 100 \times 10^9$/l and any treatment-related toxicities were less than or equal to grade 1, otherwise treatment was withheld for up to 2 weeks. If adverse events did not resolve to grade 0 or 1 after 2 weeks, the patients were excluded from the study. Treatment was continued at the same dose if patients experienced grade 1 toxicities or other toxicities considered by the investigator unlikely to become serious or life-threatening (e.g. alopecia). For all other treatment-related adverse events with a grade 2 intensity or higher, the dose modification scheme described below was implemented. The GEM and CIS treatment on day 22 was omitted in the presence of a grade ≥ 3 hematological or nonhematological toxicity, and the patient then reevaluated weekly until regressing to less than or equal to grade 1. Missed doses of GEM and CIS were not made up. The subsequent cycle of treatment was reduced by 20% doses of GEM and CIS in the case of a repeated grade 2 or any grade 3 toxicity, and reduced by 40% in the case of a repeated grade 3 or any grade 4 toxicity during the preceding cycle. If a dose reduction of less than 40% was required, the patients were excluded from the study.

Efficacy assessment

The primary endpoint of this study was RR and secondary objectives were toxicity, OS, progression free survival (PFS), and QoL. Before entering the study, all patients received physical examination, full blood count, and serum chemistry analyses. Electrocardiography, chest radiograph, CT scan of the brain, abdomen and thorax, bone scan or skeletal radiograph, urine pregnancy test, and other appropriate procedures were also performed as needed. Patients were given a physical examination, a subjective/objective symptom evaluation, and blood tests twice weekly. Comprehensive biochemistry blood examination was performed every 4 weeks. After every two cycles of treatment, response was evaluated using Response Evaluation Criteria in Solid Tumors. Of the lesions observed before the treatment, a maximum of five measurable lesions from each metastasized organ up to a total of 10 lesions were selected as target lesions. In cases of partial or complete response, a confirmative CT scan was performed 4 weeks later and this was followed by a CT scan after every two treatment cycles. Toxicity was graded according to version 2.0 of the National Cancer Institute-Common Toxicity Criteria. Patients' QoL was assessed at baseline and every cycle, using Lung Cancer Symptom Scale (LCSS) [12]. The LCSS patient scale consists of nine items: six subscales related to major lung cancer symptoms (appetite, cough, dyspnea, fatigue, haemoptysis, and pain), all using 100 mm visual analog measurements, and three summation items (activity status, symptomatic distress, and overall QoL). Tumor-related symptoms were assessed at baseline and before each cycle, with higher scores representing a higher level of functioning or a higher level of symptoms. Patients with a mean change in scores of 5–10 points (in the 0–100 range) reported 'a little' change in QoL. A 'moderate change' in QoL was reflected in scores changing by 10–20 points, and patients who reported 'very much' change in QoL had mean scores that changed by ≥ 20.

Statistical analysis

The trial was designed as a two-stage study according to Gehan [13]. Assuming a RR of 30%, this resulted in a sample size of seven patients for the first stage with a power of 90%. There were four responders during the first stage of the study allowing the second stage sample size for the whole study to be extended to at least 23 patients. Allowing for a follow-up loss rate of 10%, the total sample size was 26 patients with measurable disease. All enrolled patients were included in the intention-to-treat analysis of efficacy. PFS was defined

as the time between the initiation of therapy and either tumor progression or death. OS was defined as the interval from the initiation of therapy to the date of death. OS and PFS were calculated using the Kaplan–Meier method.

Results

Patient characteristics

From June 2005 to December 2006, 26 patients were included into the study. Patient characteristics are listed in Table 1. The median age was 61 years (range, 37–78), with 17 males and nine females. The majority of the patients (84.6%) had either Eastern Cooperative Oncology Group performance status 0 or 1. Twelve patients (46.2%) had metastatic disease, whereas 14 patients (53.8%) had stage IIIB disease. Distal lymph nodes and bone were the most common sites of the metastases. No patients had received prior chemotherapy or radiotherapy. The median primary tumor size was 4.85 cm (range, 3–8 cm).

Clinical response

Twenty-four (92.3%) of the 26 patients were assessable for response; of the two patients not assessable both were lost to follow-up after two cycles of the treatment. All efficacy data are reported using the intention-to-treat principle (Table 2). Fourteen cases of partial response were confirmed, giving an overall RR of 53.8% (95% confidence interval: 34.6–73.0%). All patients completed intratumoral PTS local therapy. The median dose of intratumoral PTS injected was 27 ml (range, 14–80 ml) and the median number of injections performed was four (range, 4–6). Nineteen of 26 patients (73.1%) received four injections and seven patients received more than four injections of PTS. The planned four cycles of chemotherapy with GEM and CIS were administered in 18 of 26 patients (69.2%) without delay or dose reduction, six patients received three cycles and two patients received two cycles. Three patients refused to undergo chemotherapy after three cycles, and one patient refused to further undergo chemotherapy only after two cycles despite medical conditions suitable to receive chemotherapy. At the time of analysis, 20 patients (76.9%) had died, and the median follow-up for all patients was 26 months (range, 18–33 months). The median PFS and OS were 8 months (95% confidence interval: 3.8–10.2 months) and 14.5 months (range, 10.0–18.0 months), respectively (Fig. 3). 1-year and 2-year survival was 57.7 and 22.4%, respectively.

Table 1 Patients characteristics ($n=26$)

Characteristic	All patients (%)
Age (years)	
Median (range)	61 (37–78)
Sex	
Male	17 (65.4)
Female	9 (34.6)
Pathology	
SC	10 (38.5)
AD	14 (53.8)
Others	2 (7.7)
Stage of disease at entry	
Stage IIIB	14 (53.8)
Stage IV	12 (46.2)
ECOG performance status	
0	2 (7.7)
1	20 (76.9)
2	4 (15.4)
Metastatic site(s)[a]	
Lung	11 (42.3)
Liver	4 (15.4)
Pleura	3 (11.5)
Bone	9 (34.6)
Lymph nodes	10 (38.5)
Adrenal	3 (11.5)

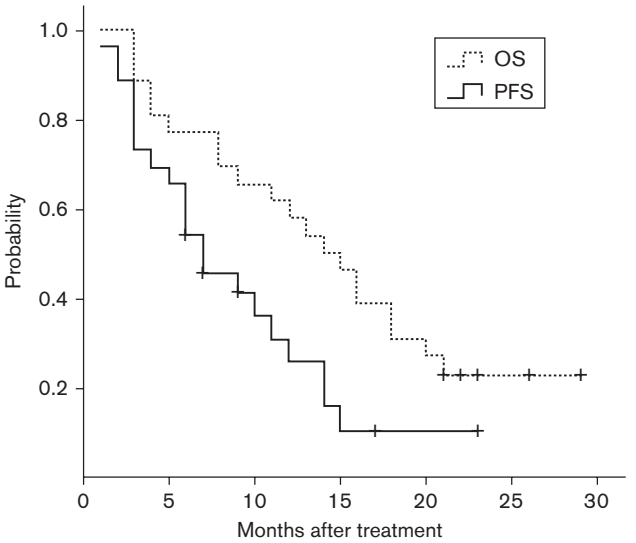
AD, adenocarcinoma; ECOG, Eastern Cooperative Oncology Group; SC, squamous carcinoma.
[a]Because patients could have metastases at multiple sites, the total numbers of metastases are greater than the number of patients.

Table 2 Tumor response (intention-to-treat analysis, $n=26$)

Response	*N* (%)
Complete response	–
Partial response	14 (53.8)[a]
Stable disease	5 (19.2)
Progressive disease	5 (19.2)
Not assessable	2 (7.7)

[a]95% confidence interval = 34.6–73.0%.

Fig. 3



Progression-free survival (PFS) and overall survival (OS) for all patients.

Toxicity

All patients were evaluable for toxicity. The toxicity profile is displayed in Table 3. National Cancer Institute Common Toxicity Criteria grade 3–4 myelotoxicities were as follows: neutropenia in six patients (23.1%), anemia in three (11.5%), and thrombocytopenia in four patients (15.4%). Nonhematologic toxicities were generally mild and usually not dose-limiting. Grade 1–2 anorexia

developed in 15 patients (57.7%). Although grade 1–2 emesis occurred in nine patients (34.6%), only one had grade 3 vomiting. Grade 1–2 cough, local pain, and peripheral neuropathy developed in 12 (46.2%), three (11.5%), and five patients (19.2%), respectively. Three patients (11.5%) developed grade 1 skin rash after chemotherapy. No grade 3–4 hepatic, renal or pulmonary toxicities were observed. There were no treatment-related deaths. No clear toxicity was attributable to the addition of intratumoral PTS and the toxicity profile was consistent with prior studies of GEM plus CIS chemotherapy.

Quality of life

According to LCSS assessment after the fourth cycle of GEM-CIS, 12 patients (46%) and seven patients (27%) reported a greater than 20 points improvement in cough and dyspnea, respectively. Eight (31%), four (15%), nine (35%) and 10 patients (38%) reported a 10–20 points improvement in cough, dyspnea, pain, and overall QoL, respectively. Two patients experienced pneumothorax with PTS injection and one patient experienced bleeding after PTS injection. All the three cases recovered spontaneously within 3 days without requiring medical or surgical intervention.

Table 3 Adverse reactions (by patients, $n=26$)

	Grade[a], *n* (%)			
	1	2	3	4
Hematologic				
Anemia	7 (26.9)	5 (19.2)	3 (11.5)	0
Neutropenia	8 (30.8)	4 (15.4)	4 (15.4)	2 (7.7)
Thrombocytopenia	7 (26.9)	6 (23.1)	3 (11.5)	1 (3.8)
Nonhematologic				
Nausea/vomiting	7 (26.9)	2(7.7)	1 (3.8)	0
Anorexia	11 (42.3)	4 (15.4)	0	0
Cough	10 (38.5)	2 (7.7)	0	0
Local pain	2 (7.7)	1 (3.8)	0	0
Neuropathy	4 (15.4)	1 (3.8)	0	0
Nephrotoxcity	2 (7.7)	1 (3.8)	0	0
Skin rash	3 (11.5)	0	0	0

[a]NCI-CTC version 2.0.

Second-line treatment

Second-line therapy was not specified in the protocol. Palliative radiotherapy was given to three patients with symptomatic progression in lung, bone, or brain. Second-line chemotherapy was offered to 18 patients after progression. The majority of patients went on to receive nonplatinum based therapy as follows: six patients received docetaxel-based therapy, two patients received irinotecan, and 10 patients were treated with gefitinib or erlotinib. Of note, six patients went on to receive third-line treatment.

Discussion

This phase II study evaluated intratumoral injection of PTS combined with concurrent GEM–CIS cytotoxic treatment in patients with advanced NSCLC. After PTS intratumoral injection, varying degrees of necrosis were seen in most local tumors and in some mediastinal lymph nodes. PTS is an effective local injection because it induces tumor necrosis directly; this was documented with anatomic pathology in the patient who underwent resection after PTS therapy in our previous study [11]. The therapeutic effect of PTS therapy is related with the injecting dose [14], so it is suggested to increase the doses as much as possible after the first injection with regard to tumor size and patients response.

We observed an overall RR of 53.8% on intent-to-treat basis, which was consistent with published results of phase II studies employing GEM/CIS. The median PFS and OS were 6.5 and 14.5 months, respectively, with a 1-year survival rate of 57.7%, which is also consistent with current phase II study of GEM/CIS therapy for advanced NSCLC [15–22], as listed in Table 4. Of note, in this study we only enrolled patients with NSCLC larger than 3 cm in the greatest dimension, whereas in other trials patients with one unidimensionally measurable lesion (i.e. a diameter ≥ 1 cm as assessed by spiral CT or ≥ 2 cm as assessed by CT) may be enrolled. Regrettably we cannot compare the primary tumor size in our study with results from other published studies. However, it is conceivable

Table 4 Studies of gemcitabine and cisplatin chemotherapy in patients with nonsmall cell lung cancer

Study	Treatment	No. of patients	RR (%) (95% CI)	PFS, months (95% CI)	OS, months (95% CI)	1-year (%)
Schiller *et al.* [7]	G: 1000 mg/m^2, day 1,8, 15; P:100 mg/m^2, day 1; q4w	301	22	4.2 (3.7–4.8)	8.1 (7.2–9.4)	36
Mok *et al.* [15]	G: 1000 mg/m^2, day 1,8, 15; P: 75 mg/m^2, day 15; q4w	44	46.5 (31–62%)	9.4 (8.2–11.5)	14.5 (8.4–17.6)	56
Moscetti *et al.* [16]	G: 1250 mg/m^2, day 1,8; P:75 mg/m^2, day 2; q3w	46	45.6 (31.3–60.0%)	8 (6–10)	15 (10–20)	75
Kim *et al.* [17]	G:1250 mg/m^2, day 1,8; P: 75 mg/m^2, day 1; q3w	40	52.6 (35.8–69.0%)	4.3 (3.7–7.0)	18.3 (14.2–21.8)	68.9
Kim *et al.* [18]	G: 1250 mg/m^2, day 1,8; P: 35 mg/m^2, day 1,8; q3w	45	51 (37–65%)	6	13.1	–
Gridelli *et al.* [19]	G: 1000 mg/m^2, day 1,8; P: 50 mg/m^2, day 1; q3w	60	43.3 (30.6–56.8%)	6.3 (5.7–8.0)	10.9 (8.8–14.1)	–
Pereira *et al.* [20]	G: 1000 mg/m^2, day 1,8; P: 75 mg/m^2, day 1; q3w	33	27	–	7.5	35
Hussain *et al.* [21]	G: 1250 mg/m^2, day 1,8; P: 40 mg/m^2, day 1,8; q3w	42	43	–	12.5 (6.7–16.5)	51
Liao *et al.* [22]	G: 1250 mg/m^2, day 1, 8; P: 75 mg/m^2, day 1; q3w	51	24 (12.8–37.5%)	4.9	12.1	–
	G: 1000 mg/m^2, day 1,8, 15; P:75 mg/m^2, day 1; q4w	49	27 (15.0–41.1%)	6.9	13.8	–
This study	G: 1250 mg/m^2, day 1,8; P: 75 mg/m^2, day 1; q3w + PTS	26	53.8 (60.8–93.2%)	8.0 (3.8–10.2)	14.5 (10.0–18.0)	57.7

CI, confidence interval; G, gemcitabine; OS, median overall survival; P, cisplatin; PFS, median progression free survival; PTS, para-toluenensulfonamide; q3w, every 3 weeks; q4w, every 4 weeks; RR, response rate; 1-year, 1-year survival rate.

that the larger average primary tumor size of 4.85 cm (range, 3–8 cm) in this study may have negatively influenced the outcome of the therapy. Historically, tumor size is known to affect prognosis for both small tumors (stage I, < 3 cm) [23,24], as well as larger tumors. Large tumor size has a direct influence on survival, with a significantly worse prognosis for tumors larger than 5 cm than for those ranging from 3 to 5 cm [25,26]. In this study, patients with a mild-to-moderate improvement of overall QoL, such as most of the patients (77%) with a large or moderate improvement in cough after the treatment according to LCSS. As this is a small phase II study we cannot come to any significant conclusion regarding any potential benefit for the addition of PTS local therapy to GEM/CIS. However, based on our experience we believe PTS local therapy warrants further evaluation in a prospective randomized setting.

The PTS and chemotherapy combined modality program was well tolerated in our patient population. Importantly, the toxicities do not appear exaggerated compared with GEM/CIS chemotherapy alone [15–22]. Although stereotactic body radiation therapy is commonly used for local tumor control in lung cancer, patients with peripheral tumors can have a more severe course compared with those patients whose tumors are more centrally located [27]. Current strategies of concurrent chemoradiation therapy show a better OS when compared with sequential chemoradiation or chemotherapy alone in locally advanced NSCLC but toxicity remains a challenge [8]. A study by the Vanderbilt Cancer Center Network reported that locally advanced inoperable NSCLC patients reported a 78.6% OR, a 14.3 months OS, and a 61.6% in 1-year survival rate after the therapy with contemporary concurrent chemoradiation. However, grade 3–4 esophagitis was seen in 26% of patients and grade 3–4 pulmonary toxicity was seen in 16.5% of patients [28]. The results in our trial show a similar OR and survival benefit compared with concurrent trials [8,27–29], but have fewer serious grade 3–4 toxicities.

Our current study is certainly limited by the small number of patients and some of the patient characteristics may have contributed to our favorable results. Specifically, many patients went on to receive second-line and third-line treatment programs, a high rate of adenocarcinomas (53.8%), and a high rate of stage 3 disease (53.8%) may have influenced the final results. Despite this possibility we believe there are still two potential benefits from our approach. First, the potential for a superior local tumor control with direct injection of PTS and second, the reduction in nonhematologic toxicities compared with concurrent chemoradiotherapy. In our study, most of nonhematologic toxicities were mild and recovered spontaneously. Myelosuppression occurred in 20% of patients, which is consistent with advanced NSCLC patients treated with the GEM/CIS regimen in China [29]. The safety of PTS injection is also known from prior studies showing its metabolism *in vivo* has little effect on the activities of the selected cytochrome P450 enzymes isoforms [10]. In this trial intratumoral PTS injection was safely combined with the chemotherapeutic agents.

In conclusion, GEM/CIS chemotherapy with concurrent intratumoral PTS injection is a well tolerated modality with potential activity in previously untreated locally advanced NSCLC Chinese patients. This combined approach will be tested directly against GEM/CIS chemotherapy in a multicenter randomized phase II trial.

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Conflicts of interest: none declared.

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