First-line albumin-bound paclitaxel/carboplatin plus apatinib in advanced pulmonary sarcomatoid carcinoma

A case series and review of the literature

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Abstract
Rationale: Pulmonary sarcomatoid carcinoma (PSC) is an uncommon type of non-small cell lung cancer, exhibiting aggressive behavior and resistance to the conventional chemoradiotherapy. To date, the optimal treatment for PSC has not been elucidated.

Patient concerns: Three male patients including a 69-year-old smoker (Case 1), a 45-year-old non-smoker (Case 2), and a 69-year-old smoker (Case 3) were admitted because of cough, back pain, and loss of body weight respectively.

Diagnoses: Radiographical examinations in these patients showed bulky intrathoracic lesions, which were pathologically diagnosed as PSC staging III–IV by computed tomography–guided percutaneous biopsy and endoscopy.

Interventions: Immunotherapy was not covered by their health insurance and they refused immune checkpoint inhibitors for financial reasons. In addition, a radical resection was not appropriate due to the advanced staging of these lesions. Therefore, first-line albumin-bound paclitaxel (nab-paclitaxel, 260mg/m2 of the body surface area) and carboplatin (area under curve 5) combined with oral apatinib (425 mg, daily) were administered empirically.

Outcomes: Two patients achieved a partial response and the other case showed stable disease lasting for more than 6 months. However, 1 of them indicated progression on the 7-month follow up.

Lessons: Nab-paclitaxel/carboplatin plus apatinib showed limited short-term efficacy in advanced, unresectable PSC. The rapid resistance of PSC to the current therapeutic regimen necessitates further researches, as more effective agents are urgently needed.

Abbreviations: AE = adverse events, CT = computed tomography, OS = overall survival, PD-L1 = programmed cell death-ligand-1, PSC = pulmonary sarcomatoid carcinoma.

Keywords: anti-angiogenesis, apatinib, immunotherapy, paclitaxel, pulmonary sarcomatoid carcinoma, targeted therapy

1. Introduction
Pulmonary sarcomatoid carcinoma (PSC) is a rare subtype of non-small-cell lung cancer (NSCLC), which has aggressive behavior with dismal prognosis. No consensus in the treatment protocol for this refractory disease has been established, and new therapeutic strategies are urgently needed because of the limited efficacy of surgery and conventional chemoradiotherapy.

Apatinib is reported to be effective in advanced sarcoma,[1] and is also effective for advanced NSCLC that failed prior chemotherapy.[2] The efficacy of albumin-bound paclitaxel (nab-paclitaxel) and carboplatin combined with apatinib in PSC has not been reported before. Herein, we presented 3 PSC patients who received this treatment regimen and obtained a median progression-free survival of more than 6 months. Furthermore, the updated literatures regarding the management of PSC were reviewed briefly.

2. Case presentation
2.1. Case 1
A 69-year-old male was hospitalized in January, 2019 because of cough and gradually aggravatd left-sided chest pain in the previous 2 months. He had a smoking history of nearly 80 pack-years. He was a 69-year-old smoker, which was a significant risk factor for the development of PSC. He had gradually aggravating left-sided chest pain associated with cough and weight loss. Computed tomography-guided percutaneous biopsy and endoscopy showed bulky intrathoracic lesions, which were pathologically diagnosed as PSC staging III–IV.

The patient was admitted to our hospital because of progressive dyspnea and cough. On admission, his body mass index was 18.2 kg/m². Physical examination revealed a 69-year-old man with weight loss and dyspnea. computed tomography (CT) scan showed a large intrathoracic mass in the left lung field, which was considered to be advanced-stage pulmonary sarcomatoid carcinoma. The patient was started on nab-paclitaxel (260mg/m²) and carboplatin (area under curve 5) combined with oral apatinib (425mg, daily). These agents were administered empirically due to the patient’s refusal of immunotherapy and the lack of an appropriate surgical option.

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years. The serum tumor biomarkers of neuron-specific enolase, cytokeratin-19 fragment, carcinoembryonic antigen, and progastrin-releasing peptide were all in normal range. Then the chest X-ray and computed tomography (CT) showed locally advanced pulmonary tumor approximately 111 mm × 114 mm, invading parietal pleura and adjacent ribs (Fig. 1). V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS), epidermal growth factor receptor, and echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK) were not identified in the specimen by immunohistochemistry (IHC) except positive expression of programmed death ligand-1 (PD-L1). Positron emission tomography was not carried out as it was not covered by his health insurance. Bone emission CT, emission computed tomography and cranial magnetic resonance imaging scan excluded other distant metastases. PSC was confirmed by CT-guided fine-needle biopsy, staging as T4NxM1 (IV) according to the 8th edition of the AJCC/UICC TNM staging system for lung cancer.\[3\] Then he received first-line chemotherapy using carboplatin (Qilu Pharmaceutical Co., Ltd., China; AUC 5, day 1) and nab-paclitaxel (Abraxane, American Pharmaceutical Partners. Inc, Melrose Park, Illinois, 260 mg/m² of body surface area, day 1 and 8) every 3 weeks for 4 cycles, in combination with oral apatinib (Jiangsu Hengrui Medicine Co., Ltd., China) at a dosage of 425 mg daily, with tolerable adverse events (AEs). In addition, zoledronic acid for injection (Jiangsu Hengrui Medicine Co., Ltd., China; 4 mg, once every month) was administered. Apatinib was continued as maintenance therapy thereafter until uncontrolled AEs or progressive disease. The efficacy was evaluated according to Response Evaluation Criteria in Solid Tumors 1.1. Partial remission of the tumor was indicated in the first 6 months since the treatment. Grade 2 thrombocytopenia, and Grade 3 hand-foot syndrome, according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0, were observed and controlled effectively. However, the lesion was significantly enlarged on the 7-month follow up. Then apatinib was discontinued. However, the patient was not suitable to be involved in an immunotherapy trial because of his compromised performance status. Therefore, best supportive care was started as palliative treatment.

2.2. Case 2
A 45-year-old male non-smoker was admitted on February, 2019 with severe pain of the left back for 1 month. Serum tumor markers including carcinoembryonic antigen, and neuron-specific enolase were within the normal range. CT revealed a giant soft mass (139 × 78 mm) located in the left upper lung, invading the adjacent pulmonary veins and mediastinum (Fig. 2). Then locally advanced PSC staging T4NxM0 (III) was diagnosed by fine-needle biopsy under bronchoscopy. The specimen was negative of epidermal growth factor receptor, ALK, KRAS, ROS proto-oncogene 1 (ROS1), human epidermal growth factor receptor-2 (HER2), and rearranged during transfection proto-oncogene (RET), except PD-L1 (>95%) by IHC. Nab-paclitaxel/carboplatin and apatinib (425 mg, daily) was administered for 4 cycles. On the 6-month follow up, the tumor remained stable. The major AEs were Grade 2 thrombocytopenia, and hypertension, without hemoptysis. His progression-free survival and overall survival (OS) were more than 6 months up to now.

2.3. Case 3
A 69-year-old male was admitted because of chest stiffness and loss of body weight in the previous 2 months in January 2019. X-ray and CT showed thoracic lesions in right upper lobe invading ribs with pleural effusion, and one of the tumors was about 68 mm × 40 mm in size (Fig. 3). He had a smoking history of 60 pack-years. Then he was diagnosed with systemically disseminated PSC (T3NxM1, IV) using CT-guided percutaneous biopsy. First-line carboplatin, nab-paclitaxel, and apatinib
(425 mg, daily), in addition to zoledronic acid were initiated timely. After 3 cycles of chemotherapy, the patient refused further intravenous treatment for financial reasons. Then apatinib (850 mg, daily) was continued as palliative therapy for another 1 month. However, the dosage was decreased to 425 mg daily thereafter because of Grade 3 leukocytopenia and hand-foot rash, although they were alleviated quickly after proper treatment. Encouragingly, both the osteolytic rib destruction and pulmonary mass of showed partial response nearly 7 months after the treatment.

3. Discussion

The incidence of PSC is nearly 0.5% of the NSCLC and 48% of them are staged IV at presentation, with a median OS of 5.8 months for stage III, and 5.4 months for stage IV patients.[4] Because of its rarity and heterogeneity, the treatment and prognosis of PSC have not been clearly described, lacking reliable efficacy-related biomarkers.

Previous reports regarding the treatment of PSC has been listed in Table 1, which shows that the efficacy of surgery combined with chemotherapy/chemoradiotherapy for PSC patients is quite

| First author, yr | Age, yr | Number of patients | Stage, I/II/III/IV | Treatment regimen | Median OS, mo |
|------------------|---------|--------------------|--------------------|------------------|--------------|
| Huang, 2013[5]   | 57.8 (30–80) | 51 | 2/25/14/10 | Surgery in 18 cases; Surgery + ChT in 19 cases | 6 |
| Vieira, 2014[6]  | 61 (53–69) | 77 | 16/33/23/5 | Surgery + ChT | 5-yr OS is 29% |
| Gu, 2015[7]      | 64 (43–80) | 95 | 23/26/30/16 | Surgery in 88 cases, and adjuvant ChT in 36 cases | 11.54 |
| Lin, 2016[8]     | 56 (17–81) | 69 | 11/26/23/9 | Complete resection in 50 cases, ChT/EGFR-TKI | 19.1 |
| Ung, 2016[9]     | 63 (40–85) | 93 | 17/11/24/10 | Surgery in 42 cases, ChT/BSC in 51 cases | NA |
| Roesel, 2017[10] | 64.9 (38–80) | 58 | 11/24/7/16 | Surgery + ChT/RT in 46 cases, ChT/RT in 12 cases | 5.6 in stage IV patients |
| Hou, 2018[11]    | 65 (37–88) | 114 | 7/16/18/73 | Surgery in 37 cases, ChT in 49 cases | 3.5 |
| Maneenil, 2018[12] | 68 (32–89) | 127 | 20/26/28/52 | Surgery + ChT/RT in 61 cases; ChT/RT in 41 cases; BSC in 25 cases | 9.9 |
| Karim, 2018[13]  | 57 (31–83) | 10 | I–II | Surgery alone | 23.5 |
|                 | 4        | I–II | surgery + ChT/RT | 15.1 |
|                 | 7        | III–IV | ChT, ChT + RT | NA |
|                 | 4        | IV | none | 6.8 |
| Sim, 2018[14]    | 69.5 (55–72) | 26 | 1/3/4/18 | ChT in 12, surgery in 6 | 9.5 |
| Seong, 2019[15]  | 62.2±1.9 | 37 | NA | Surgery | 68.3 |

BSC = best supportive care, ChT = chemotherapy, EGFR = epidermal growth factor receptor, RT = radiotherapy, TKI = tyrosine kinase inhibitor.
limited.\textsuperscript{11\textendash}15} PSC behaves in an aggressive way even in stage I-II compared to other subtypes of NSCLC.\textsuperscript{10} It represents a high risk for postoperative relapse,\textsuperscript{16} even in stage I after R0 resection.\textsuperscript{17} Because of its aggressive behavior, extended resection (bilobectomy, pneumonectomy, or even chest wall resection) are required, although the dismal prognosis still questions the role of surgery in PSC.

On the other hand, platinum-based chemotherapy is reported to be associated with a significant 8\% decrease of mortality in advanced PSC patients.\textsuperscript{18} Nevertheless, the overall response of locally advanced or metastatic cases to first-line chemotherapy is limited with a progression rate of 72\%, meanwhile, the median time to progression and OS are 2.7 and 4.3 months, respectively.\textsuperscript{19} Furthermore, neither neoadjuvant nor adjuvant chemotherapy improves the survival of early-stage PSC patients.\textsuperscript{18}

The high incidence of resistance to chemotherapy emphasizes the need of new strategies for the treatment of PSC. Due to high tumor mutation burden (TMB) and great prevalence for PD-L1 expression\textsuperscript{18\textendash}21 in PSC cases,\textsuperscript{\textendash}21 immunotherapy (immune checkpoint inhibitors) shows encouragingly enduring efficacy in PSC patients (Table 2).\textsuperscript{22\textendash}25 Furthermore, the registered trials of immunotherapy in PSC is listed in Table 3.

One of the limitations of anti-angiogenic treatment is the inevitable drug-resistance, as shown in Case 1. Genetic alterations in PSC suitable for targeted therapy are poorly known by its rarity. Next-generation sequencing enables genome-wide molecular profiling of PSC regarding specific signal pathways of tumorigenesis, which is critical to pave the way to new treatment strategies. Anaplastic lymphoma receptor tyrosine kinase gene (ALK) and MNNG HOS transforming gene (MET) seem to act synergistically in PSC.\textsuperscript{26} In addition, KRAS and MET mutations may contribute to PSC tumorigenesis, and the epithelial mesenchymal transition pathway may play a key role in sarcomatoid transformation.\textsuperscript{27} Moreover, potentially targetable genomic alterations and intermediate or high TMB are identified in most PSC cases.\textsuperscript{28} The activation of epithelial mesenchymal transition drives PSC phylogeny in vivo, and dasatinib reverts the sarcomatoid-associated phenotype efficiently.\textsuperscript{29} In addition, TP53 and KRAS mutations are the most common genetic alterations in PSC, and KRAS mutation is a prognostic biomarker.\textsuperscript{30,31}

### Table 2

| Author, yr | Number of patients | Age, yr | Staging | PD-L1 expression | Agent | Treatment lines | PFS, mo | OS, mo |
|------------|-------------------|---------|---------|------------------|-------|-----------------|---------|-------|
| Salati, 2018\textsuperscript{22} | 1 | 74 | IVB | ≥ 50% | Nivolumab | Third-line after surgery, AC, and docetaxel | > 22 | > 22 |
| Sukrithan, 2019\textsuperscript{23} | 5 | Median, 57 | Advanced | ≥ 75% | Pembrolizumab | First-line in 4 cases; third-line in 1 case | 11+ \(\sim\) 29+ | 14+ \(\sim\) 33+ |
| Kotlowiska, 2019\textsuperscript{24} | 1 | 53 | T3N2M1c, NB | > 95% | Not mentioned | Second-line following TC, RT, and lobeectomy | > 44 | > 44 |
| Roesel, 2019\textsuperscript{25} | 2 | 57 | T4N0M1c, NB | 80%\&\%90%, 100% | Nivolumab | Second-line after GP and surgery | > 6 | > 6 |

AC = pemetrexed and carboplatin, GP = gemcitabine and cisplatin, OS = overall survival, PFS = progression-free survival, PSC = pulmonary sarcomatoid carcinoma, TC = paclitaxel and carboplatin, VP = vinorelbine and cisplatin.

### Table 3

| Identifier | Yr | Gene mutation status | Gene mutation | Agent | Treatment lines | Estimated enrollment | Primary endpoint | Status | Country |
|------------|----|---------------------|---------------|-------|-----------------|---------------------|-----------------|-------|---------|
| NCT02834013 | 2016 | PD-L1 amplification | Anti-CTLA-4 (ipilimumab) + anti-PD-1 (nivolumab) | 2\textsuperscript{nd} and beyond | 707 | ORR | Recruiting | America |
| NCT02897479 | 2016 | MET Exon 14 mutation | Anti-MET savolitinib | 1\textsuperscript{st} and beyond | 50 | ORR | Recruiting | China |
| NCT03022500 | 2017 | Not mentioned | Anti-PD-L1 (duralumab) + anti-CTLA-4 (tremelimumab) | 1\textsuperscript{st} and beyond | 18 | Response rate | Active, not recruiting | South Korea |
| NCT04224337 | 2020 | Not mentioned | Anti-PD-L1 (duralumab) + doxorubicin + ifosfamide | 1\textsuperscript{st} and beyond | 22 | Response rate | Not yet recruiting | South Korea |

CTLA-4 = cytotoxic T-lymphocyte-associated antigen-4, ORR = objective response rate, PD-1 = programmed cell death-1, PD-L1 = programmed cell death-ligand-1.

### 4. Conclusions

First-line nab-paclitaxel/carboplatin plus oral apatinib showed limited short-term efficacy in advanced PSC. Besides the popular immune checkpoint inhibitors, more promising strategies for the treatment of PSC are still needed.

### Author contributions

Conceptualization: Feng-Wei Kong, Wei-Min Wang.

Data curation: Wei-Min Wang.

Funding acquisition: Wen-Bin Wu, Xiang Wang.

Methodology: Lei Liu, Long-Bo Gong.

Resources: Miao Zhang, Xiang Wang.

Writing – original draft: Feng-Wei Kong, Long-Bo Gong, Wen-Bin Wu.

Writing – review & editing: Lei Liu, Wen-Bin Wu, Miao Zhang.

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