

Apatinib for salvage treatment of advanced malignant pleural mesothelioma

A case report

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Abstract

Rationale: Malignant Pleural Mesothelioma (MPM) is rare cancer and has a poor prognosis with resistance to chemotherapy or radiotherapy. Until now there is no standard third-line treatment for patients who have failed second-line therapy.

Patient concerns: A 58-year-old non-smoking female peasant of ethnic Han was admitted to the oncology department of the 363 Hospital with a primary complaint of chest tightness and breathlessness from 3 months ago.

Diagnoses: Positron emission tomography-computed tomography (PET/CT) examination showed “dirty” pleural and parietal pleural involvement as well as mediastinal and pulmonary hilar lymph node enlargement. Finally, cancer cells were seen after repeated pleural effusion cell examination. Immunohistochemistry confirmed epithelioid of pleural mesothelioma.

Interventions: Apatinib as a third-line treatment after failure from pemetrexed/cisplatin (PC) as the first-line chemotherapy and gemcitabine/cisplatin (GP) as the second-line chemotherapy. At first, 250mg/day was given and 1 week later, the dose was increased to 500mg/day.

Outcomes: A 5-month progression-free survival was achieved and toxicity included severe hand-foot syndrome, mild proteinuria, and hypertension.

Lessons: Apatinib may be a potential therapeutic drug for MPM, particularly as a third-line treatment in cases resistant to chemotherapeutic options.

Abbreviations: CT = computed tomography, CTCAE = common terminology criteria for adverse events, VEGFR-2 = vascular endothelial growth factor receptor-2, MPM = malignant pleural mesothelioma, NCCN = National Comprehensive Cancer Network, OS = overall survival, PC = pemetrexed/cisplatin, PCB = bevacizumab and pemetrexed/cisplatin, PD = progressive disease, PFS = progress free survival, PS = performance status.

Keywords: apatinib, malignant pleural mesothelioma, targeted therapy, VEGF

1. Introduction

Malignant Pleural Mesothelioma (MPM) is rare cancer with poor prognosis.^[1] According to the National Comprehensive Cancer Network (NCCN),^[2] treatment for MPM patients include surgery, radiation therapy (RT), and chemotherapy, but no third-line treatment when the disease progresses after second-line treatment.

Apatinib, a small molecule receptor tyrosine kinase (RTK) inhibitor, targets the intracellular domain of the vascular

endothelial growth factor receptor-2 (VEGFR-2) ATP binding site, and is the first anti-angiogenic therapy approved by the China Food and Drug Administration in December 2014 for the treatment of metastatic gastric cancer in third-line or later treatment.^[3] With a tolerable side-effect profile and improved outcomes, apatinib has been proven to be a newly effective option for a variety of tumors, including advanced non-small cell lung cancer, metastatic triple-negative breast cancer, angiosarcoma, malignant fibrous histiocytoma, and myxoid/round cell liposarcoma.^[4–9]

However, to our knowledge, there is no case report about the application of apatinib for MPM. Here, we describe an advanced MPM case with resistance and intolerance to conventional first-line and second-line chemotherapy. However, the patient benefitted from apatinib as a salvage treatment. We also review the literature and compare the clinical efficacy of apatinib with that of other anti-angiogenic therapeutics used to target MPM. Finally, we discuss the possible mechanisms underlying the response to apatinib in MPM.

2. Case report

This case report was approved by the Medical Ethics Committee of the 363 Hospital and written informed consent was obtained from the patient for publication of this case report as well as accompanying images.

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ZD, YY, and DW contributed equally to this work.

The authors have no conflicts of interest to disclose.

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In September 2015, a 58-year-old non-smoking female peasant of ethnic Han was admitted to the oncology department of the 363 Hospital with a primary complaint of chest tightness and breathlessness from 3 months ago. Computed tomography (CT) (Fig. 1A) of the chest revealed pleural effusion and following puncture drainage, CT scans showed multiple right pleural nodules and a small amount of effusion in the right chest. Epithelial cells in the pleural effusion were found to be hyperplastic and adenocarcinoma could not be excluded. Unfortunately, the patient refused any treatment except traditional Chinese medicine. A month later, the patient could not breathe again. At this time, pleural biopsy did not find cancer cells. Positron emission tomography-computed tomography (PET/CT) (Fig. 1C) examination showed “dirty” pleural and parietal pleural involvement as well as mediastinal and pulmonary hilar lymph node enlargement. No signs of tumor metastasis were observed in the rest of the body. Finally, cancer cells were seen after repeated pleural effusion cell examination. Immunohistochemistry confirmed epithelioid of pleural mesothelioma (Fig. 1B).

Doublet chemotherapy of pemetrexed and cisplatin (PC) as a first-line chemotherapy was administered for 2 cycles from December 2015 with moderate anemia. However, therapeutic evaluation resulted in progressive disease (PD) (Fig. 2A) and the

patient showed chest pain. Therefore, palliative radiotherapy was given to reduce the pain. After radiotherapy, gemcitabine and cisplatin (GC) were prescribed as the second-line chemotherapy, which only lasted 1 cycle due to worsening anemia, exhaustion, a performance status (PS) of 3, and a therapeutic evaluation was PD (Fig. 2B). Hence, chemotherapy treatment was interrupted.

The patient was given apatinib as a third-line treatment on September 28, 2016, while a CT image showed PD (Fig. 2C). A dose of 250mg was given at the beginning following a comprehensive consideration for her poor PS, anemia, and medical history of hypertension. One week later, the dose was increased to 500mg/day. After 6 weeks of treatment with apatinib, a partial response (PR) was detected in multiple right pleural nodules and left lung lesion (Fig. 2D) according to the Response Evaluation Criteria in Solid Tumors (RECIST) and PS of the case improved from 3 to 1. Physical and chemical indicators improved (Table 1), such as hemoglobin increasing from 65 g/L to 123 g/L. Albumin also increased from 29.4 g/L to 40.1 g/L and a biochemical remission occurred with white blood cell counts dropping from $14.11 \times 10^9/L$ to $5.60 \times 10^9/L$. Apatinib was continued as maintenance therapy for 5 months as pleural and pulmonary lesions continued to stabilize (Fig. 2E). Treatment was stopped in February 2017, as the CT scanner showed liver metastasis and the therapeutic evaluation was PD. The toxicity

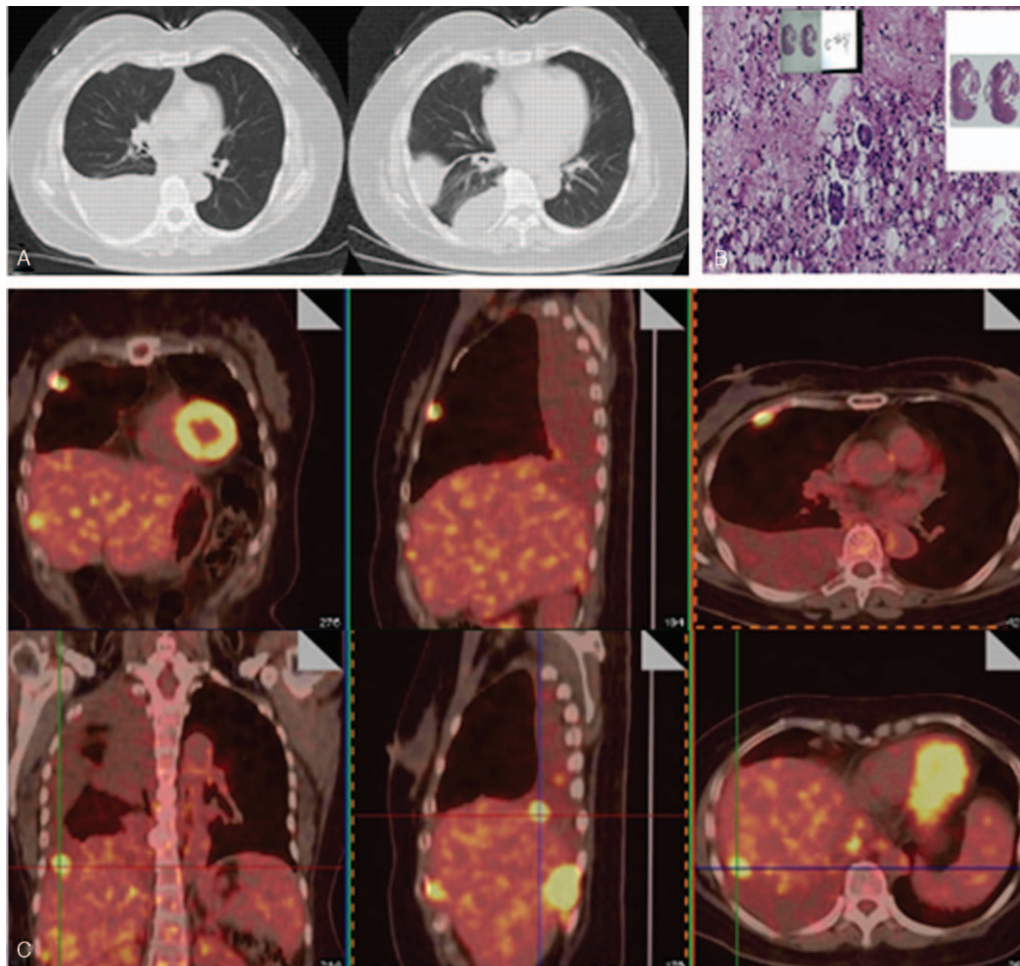


Figure 1. CT, PET/CT images, and cytopathology before treatment. A: CT images collected before treatment; B: hematoxylin and eosin images of cell blocks; C: PET/CT images collected before treatment. CT=computed tomography, PET/CT=positron emission tomography-computed tomography.

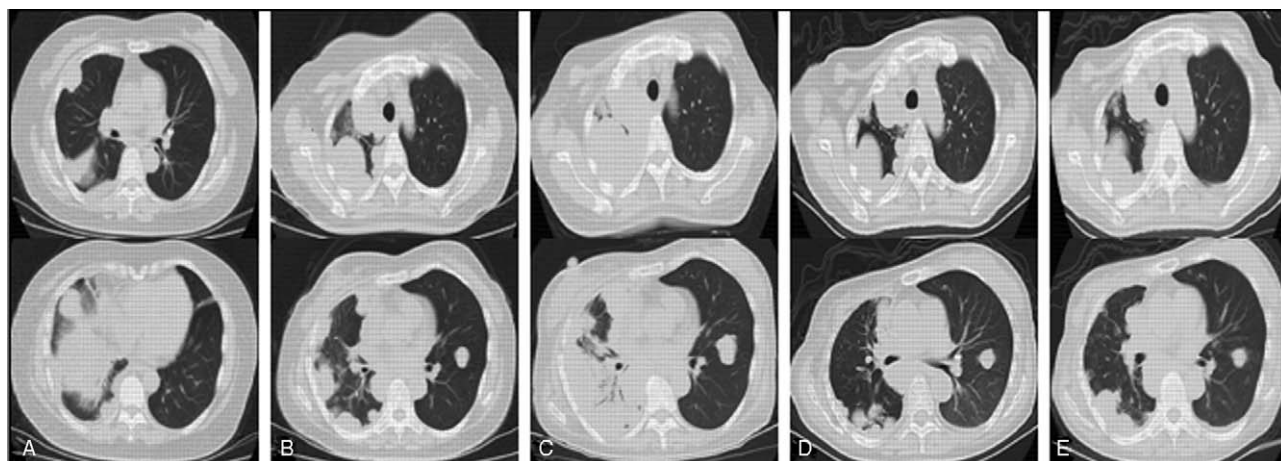


Figure 2. CT images after different treatments. A: 2 cycles of first-line chemotherapy (PC); B: 1 cycle of second-line chemotherapy (GC); C: Before treatment of apatinib; D: 6 weeks after apatinib treatment; E: 5 months after apatinib treatment. CT=computed tomography, PC=pemetrexed/cisplatin, GC=gemcitabine/cisplatin.

Table 1
Physical and chemical indicators.

| | Before apatinib treatment | After apatinib treatment |
|------------------|---------------------------|--------------------------|
| Hemoglobin | 65g/L | 123g/L |
| Albumin | 29.4g/L | 40.1g/L |
| White blood cell | 14.11*10 ⁹ /L | 5.60*10 ⁹ /L |

included severe hand-foot syndrome (grade 3, according to the Common Terminology Criteria for Adverse Events (CTCAE) v.4.03) (Fig. 3) and mild proteinuria (grade 2). Hypertension (grade 2) occurred in the fifth month and therefore, an anti-hypertension drug was added.

The fourth-line chemotherapy was by giving gemcitabine and pemetrexed plus apatinib. Only 1 cycle was finished, as the patient could not bear the severe toxicity. Subsequently, the disease progressed rapidly and PS score increased to 3. All treatments were then stopped, including apatinib, and only support care was maintained. Unfortunately, the patient died half a month later on March 11, 2017.

3. Discussion

MPM is the most common type of malignant mesothelioma, which can be difficult to treat as most patients have advanced

disease upon presentation and few patients are cured.^[1] Mesothelioma cells can secrete and express several angiogenic factors, including vascular endothelial growth factor (VEGF), VEGF receptor (VEGFR), platelet-derived growth factor (PDGF), and PDGF receptor (PDGFR), which are considered negative prognostic factors.^[10] The roles of VEGF and their receptors in tumor angiogenesis, lymphangiogenesis, cell proliferation, and metastasis are well established.^[11] VEGFR-2 is the major mediator of known VEGF-induced phenotypes, including microvascular permeability and neovascularization.^[12] VEGF/VEGFR-2 interaction effectively promotes tumor angiogenesis via strong ligand-receptor binding, which also downregulates signaling pathways favoring rapid tumorigenesis.^[13]

Apatinib is a tyrosine kinase inhibitor that selectively inhibits VEGFR-2, also known as kinase insert domain receptor (KDR), and can block downstream signaling and inhibit tumor angiogenesis. It is an orally bioavailable, small molecule agent, which is thought to inhibit angiogenesis in cancer cells, specifically by inhibiting VEGF-mediated endothelial cell migration and proliferation and thereby blocking the formation of new blood vessels in tumor tissue.^[14] In addition, this agent mildly inhibits c-Kit and c-Src tyrosine kinases. Some studies have demonstrated that apatinib is effective in some cancers, such as advanced gastric cancer^[3] and metastatic breast cancer.^[5] Furthermore, apatinib has produced promising clinical outcomes



Figure 3. Severe hand-foot syndrome.

in several other types of cancer^[9,15–18] and has a high binding affinity relative to other anti-angiogenic drugs. For example, apatinib ligand-receptor binding is 10 times greater than that of sorafenib.^[19] Apatinib also binds more strongly to VEGFR-2 than cediranib, a pan-VEGF inhibitor that mainly inhibits VEGFR-1, VEGFR-2, VEGFR-3, and PDGF.^[11] Additionally, there are a number of case reports, which have confirmed the benefit of apatinib in other types of cancer, including EGFR wild-type and ALK-negative advanced lung adenocarcinoma, metastatic triple-negative breast cancer, advanced epithelial ovarian cancer, angiosarcoma, and recurrent malignant glioma.^[5–8,15] Moreover, apatinib can reverse ABCB1- and ABCG2-mediated multidrug resistance by inhibiting transport, rather than blocking AKT or ERK1/2 signaling.^[20] The internal VEGFR-2 inhibitor, apatinib, inhibits intracellular VEGF signaling, suppresses cell proliferation *in vitro*, and delays xenograft tumor growth *in vivo*, while the anti-VEGF antibody, bevacizumab, demonstrates no such effects.^[21] Preclinical studies have demonstrated that VEGFR-TKIs, such as sunitinib (a VEGFR 2–3, RAF, PDGFR, and c-Kit inhibitor) and sorafenib (a Raf-1, B-Raf, and VEGFR-2 inhibitor), show limited activity in MPM. Furthermore, another strategy to inhibit angiogenesis is through the use of an inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase such as erlotinib. However, these agents were less effective in MPM.^[14,22]

In this case, the tumor histology and sex of our patient likely contributed to his survival. The histologic subtypes of mesothelioma include epithelioid, sarcomatoid, and biphasic (mixed), and patients with biphasic (mixed) or sarcomatoid mesothelioma have a worse outcome than those with epithelioid mesothelioma.^[23] However, we failed to get pathological tests and immunohistochemistry to strongly support our use of apatinib. Bevacizumab is a monoclonal antibody that binds to VEGF. A recent multicenter phase 3 randomized trial (MAPS) compared the combination of bevacizumab and pemetrexed/cisplatin (PCB) with pemetrexed/cisplatin (PC) alone for patients with unresectable MPM. This study showed that overall survival (OS) was significantly longer for PCB (median: 18.8 months; 95% CI: 15.9–22.6) than for PC (median: 16.1 months; 95% CI: 14.0–17.9) with a hazard ratio of 0.77 ([0.62–0.95]; $P=.0167$). These results showed that targeting the VEGF pathway can be a successful approach to treating unresectable MPM. Due to this study and other tumor types in which the addition of bevacizumab to chemotherapy has been shown to improve response rates (RR), progress free survival (PFS), and OS, the latest NCCN guidelines suggest PCB as the standard first-line treatment for MPM.^[24]

The patient with advanced MPM was pre-treated with PC and gemcitabine/cisplatin (GP) regimens as the first- and second-line chemotherapies, respectively. As the PS of the patient was poor, apatinib as a monotherapy was a good option to control the symptom. The disease was well controlled within 5 months, after which it progressed. The first-line chemotherapy PFS was only 3 months and the second-line chemotherapy PFS was even shorter than the first-line. However, the third-line PFS resulting from apatinib treatment was the longest, which was the most effective therapy for this patient. In all, the OS was 18 months, surpassing the estimated OS of 9 to 17 months after diagnosis.

However, this study has some limitations. Case reports cannot replace randomized controlled trials, whether apatinib is suitable for all MPM patients or what is the appropriate dose of apatinib for MPM patients? Further prospective studies are required to

optimize the usage of apatinib in the treatment for MPM and to identify which patients would benefit from the agent.

4. Conclusion

In conclusion, from this case report, apatinib significantly changed the quality of life for this patient and improved PFS and OS. Apatinib is a potentially therapeutic drug as a salvage treatment for MPM, especially as a third-line treatment. Further clinical trials are needed to confirm the effectiveness and toxicity of apatinib in MPM.

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