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Effectiveness and Safety of Apatinib Mesylate Tablet in the Treatment of Advanced Solid Tumors

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ABSTRACT

Angiogenesis is the most critical step in the development and progression of malignant tumors. Anti-tumor angiogenesis has become the most promising new strategy for tumor treatment. Rapidly growing tumor cells secrete a variety of vascular growth factors under hypoxia to stimulate tumor angiogenesis. One of the important growth factors is Vascular Endothelial Growth Factor (VEGF). Some small molecule compounds that inhibit VEGFR have been used to treat Tumors. In this study, we evaluated the effectiveness and safety of Apatinib Mesylate tablet in the treatment of advanced solid tumors. We found that Apatinib Mesylate tablet can treat advanced solid tumors.

Keywords: Apatinib Mesylate Tablet, Treatment, Advanced Solid Tumors

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Introduction

Angiogenesis is the most critical step in the development and progression of malignant tumors¹. Generally, angiogenesis in the tumor area provides nutrients for the tumor growth and takes away its metabolites^{2,3}. Additionally, tumor cells are transferred to other parts of body through the new blood vessels⁴. Therefore, effectively inhibiting angiogenesis in the tumor area could inhibit growth of tumor and reduce the occurrence of metastasis⁵. Currently, anti-tumor angiogenesis has become the most promising new strategy for tumor treatment⁶.

Tumor vascularization is closely related to a variety of vascular-related factors⁷. Rapidly growing tumor cells secrete a variety of vascular growth factors under hypoxia to stimulate tumor angiogenesis⁸. One of the important growth factors is Vascular Endothelial Growth Factor (VEGF). VEGF binds to VEGF receptor (VEGFR), stimulates VEGFR-mediated downstream signal transduction, and ultimately leads to tumor angiogenesis⁹. In 2004, the successful listing of a monoclonal antibody against VEGF (Bevacizumab) established the important role of anti-tumor angiogenesis in tumor treatment¹⁰. Angiogenesis-targeted drugs include monoclonal antibodies, such as bevacizumab, and small molecule compounds that inhibit the activity of VEGFR tyrosine kinases, such as Vatalanib (PTK787), Sunitinib, Sorafenib (Sorafenib) and Vandetanib (Vandetanib), etc^{11,12}.

Some small molecule compounds that inhibit VEGFR have been marketed, such as Sunitinib And Sorafenib¹³, while some are still undergoing clinical trials, such as van Detanib. PTK787, jointly developed by Novartis Pharma AG and Schering AG, mainly inhibits VEGFR with a single target^{14,15}. It can block the formation of blood vessels and lymphatic vessels. However, it failed because the combination of PTK787 with chemotherapy has not achieved a synergistic result. Drugs like Sunitinib, Sorafenib, and Vandetanib are multi-target inhibitors. They not only inhibit VEGFR but also have strong effects

on other tyrosine kinases¹⁶.

In a recent phase II clinical study, Docetaxel combined with ZD6474 was superior to Docetaxel monotherapy¹⁷. Sorafenib second-line treatment of NSCLC had a disease control rate of 59% and a median survival of 6.7 months¹⁸. For second-line treatment of NSCLC with Sunitinib, effective rate, disease control rate and median survival time were 09.5%, 52.2%, 23.9 months separately¹⁹.

Apatinib developed by Hengrui Pharmaceutical Co., Ltd. is a tyrosine kinase inhibitor that inhibits the VEGFR²⁰. Its molecular formula is C₂₅H₂₇N₅O₃S with a molecular weight of 493.58 (methanesulfonate). Apatinib can effectively inhibit VEGFR at a very low concentration. Furthermore, its higher concentration can also inhibit kinases like PDGFR, c-Kit, and c-Src²¹. Activity testing found that Apatinib binding capacity to VEGFR was more than 10 times stronger than PTK787²². Its action site is the intracellular ATP-binding site of the protein tyrosine receptor. Pharmacodynamic studies show that Apatinib can inhibit VEGFR tyrosine kinase activity, block signal transduction after VEGF binding, and lead to inhibition of tumor angiogenesis²².

Aim of study

To study Apatinib mesylate tablet in the treatment of advanced solid tumors including Disease Control Rate (DCR), Object Response Rate (ORR), Quality of Life (QoL) and safety.

Methods

Dose

Apatinib, 250-500mg, qd; 28 days as a cycle;

Object Response Rate (ORR)

The proportion of patients whose tumors have shrunk to a certain amount and maintained for a certain period of time, including cases of complete response (CR) and partial response (PR). The RECIST 1.1 was used to evaluate the objective tumor remission. Patients must be accompanied by measurable tumor lesions before treatment. Efficacy assessment criteria are divided into complete response (CR), partial

response (PR), stable disease (SD), and progressive disease (PD) according to RECIST 1.1^{23,24}.

Disease Control Rate (DCR)

The evaluation was performed according to the solid tumor remission assessment standard (RECIST 1.1). $DCR = (CR + PR + SD)\%$

Quality of life score (QoL):

QoL was evaluated by following EORTC QLQ-C30 (version 3, Chinese version)²⁵.

Briefly, changes in clinical symptoms and objective examination results of patients before and after treatment were scored at time points including before treatment, at the end of the second and third cycles during treatment, and at the end of every 2 cycles thereafter.

Safety

Adverse events (AE), adverse drug reactions (ADR), severe adverse events (SAE), and other events that should be treated as SAEs were recorded. The AE is evaluated by the researcher according to the definition of NCI-CTC AE version 4.0²⁶.

Degree I (mild): uncomfortable feeling but no effect on normal daily activities;

Degree II (moderate): reduce or affect normal daily activities;

Degree III (severe): unable to work or do normal daily activities;

Degree IV: life threatening or disabling;

Degree V: death.

Inclusion criteria

1. Age: 18 to 70 years;
2. Pathologically confirmed patients with advanced solid tumors;
3. ECOG PS scores: 0-2 points;
4. Expected survival ≥ 3 months;
5. The patients have recovered from damage caused by other treatments. They have received Nitroso or Mitomycin more than 6 weeks and other cytotoxic drugs, radiotherapy or surgery more than 4 weeks if any.

6. Patients may have a history of meningeal / meningeal metastases, but they must undergo treatment (surgery / radiotherapy) and be clinically stable for at least 2 months before inclusion. (Before or concurrent use of glucocorticoid drugs was allowed, but it must be a non-high and stable dose. High dose was defined as dexamethasone 20mg, other glucocorticoid drugs are converted accordingly);

7. The main organs function normally as the following criteria:

(1) The blood routine examination standards must meet:

- a. $HB \geq 90g / L$ (no blood transfusion within 14 days);
- b. $ANC \geq 1.5 \times 10^9 / L$;
- c. $PLT \geq 80 \times 10^9 / L$

(2) Biochemical examination must meet the following standards:

- a. $BIL < 1.25 \times ULN$
- b. ALT and $AST < 2.5 \times ULN$; if with liver metastases, ALT and $AST < 5 \times ULN$;
- c. Serum $Cr \leq 1.25 \times ULN$, endogenous creatinine clearance rate $> 45ml / min$ (Cockcroft-Gault formula)

8. Women of childbearing age must perform a pregnancy test (serum or urine) within 7 days before enrollment. They must be with a negative result of pregnancy and willing to use appropriate methods of contraception during the test and 8 weeks after the last test drug administration. For men, consent must be given to appropriate contraception or surgical sterilization during the trial and 8 weeks after the last test drug administration;

9. Patients voluntarily joined the study and signed informed consent with good compliance.

Exclusion criteria

1. pregnant or lactating women;

2. Patients who have hypertension and cannot be reduced to the normal range after treating with antihypertensive medication (systolic blood pressure > 140 mmHg, diastolic blood pressure > 90 mmHg), Patients have level I of higher myocardial ischemia or myocardial infarction, arrhythmia (including QT Interval \geq 440 ms) or class I cardiac insufficiency;
3. Patients have Multiple factors affecting of taking oral medication (such as inability to swallow, post-gastrointestinal resection, chronic diarrhea, and intestinal obstruction, etc.);
4. Abnormal coagulation function (PT or PT-INR > 1.5xULN, APTT > 1.5xULN), bleeding tendency (such as active peptic ulcer) or with thrombolytic or anticoagulant treatment;
5. Patients have pulmonary hemorrhage of more than CTCAE level 2 four weeks before inclusion. Patients have other sites bleeding more than CTCAE level 3 four weeks before the first use of study drug;
6. Long-term unhealed wounds or fractures;
7. Arterial / venous thrombosis events, such as cerebrovascular accidents (including transient ischemic attacks), deep vein thrombosis, pulmonary embolism 6 months before inclusion;
8. Urine routine results indicate urinary proteins \geq ++, and 24-hour urine protein quantification more than 1.0 g;
9. Patients treated with anticoagulants or vitamin K antagonists such as warfarin, heparin or its analogues
10. A history of psychotropic substance abuse
11. Participated in clinical trials of other anti-tumor drugs within four weeks;
12. Patients have been treated with VEGFR, PDGFR and s-SRC kinase inhibitor drugs (except Bevacizumab);

13. Past or concurrently accompanied by other malignancies, except for cured skin basal cell carcinoma and cervical carcinoma in situ.

Shedding / rejection criteria

1. Simultaneously receive SFDA-approved Chinese medicine preparations and immunomodulators for the treatment of lung cancer;
2. cannot follow this study protocol

Termination criteria:

1. Patient who want to quite the study
2. Radiological evidence of disease progression;
3. Pregnancy event during the study;
4. After dose adjustment, Patients still cannot tolerate the toxicity;
5. other circumstances necessary to withdraw patients from the study

Results

Disease Control Rate (DCR) after the treatment of Apatinib Mesylate Tablet in Advanced Solid Tumors

The DCR after the treatment of Apatinib Mesylate Tablet was in Figure 1.

Object Response Rate (ORR) after the treatment of Apatinib Mesylate Tablet in Advanced Solid Tumors

The ORR after the treatment of Apatinib Mesylate Tablet was in Figure 2.

QoL after the treatment of Apatinib Mesylate Tablet in Advanced Solid Tumors

Based on results of ECOG, QoL after the treatment of Apatinib Mesylate Tablet in Advanced Solid Tumors had no significant change.

Safety after the treatment of Apatinib Mesylate Tablet in Advanced Solid Tumors

Adverse events including fatigue, hand and foot skin reactions, urine protein and diarrhea were found in some patients (Figure 3)

Conclusion

This clinical study shows the treatment of tablet is effective. advanced solid tumors with Apatinib Mesylate

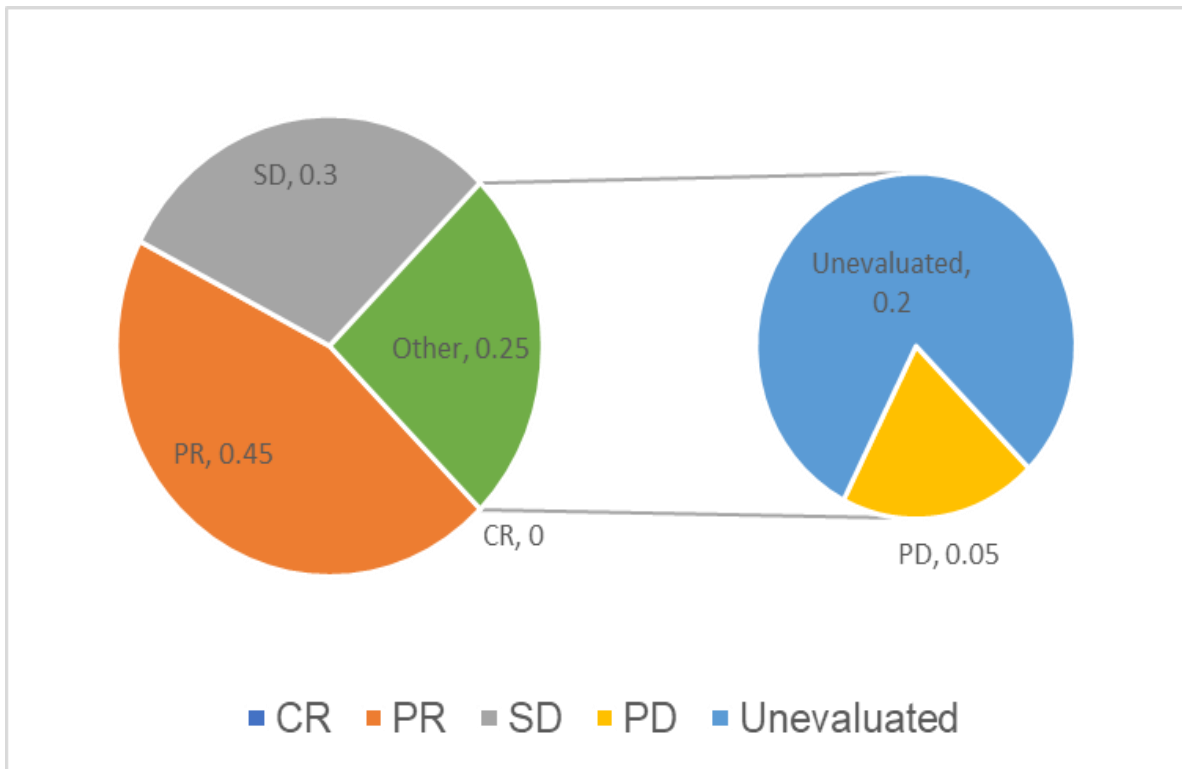


Figure 1 DCR after the treatment of Apatinib Mesylate Tablet in Advanced Solid Tumors. CR: complete response, PR: partial response, SD: stable disease, and PD: progressive disease.

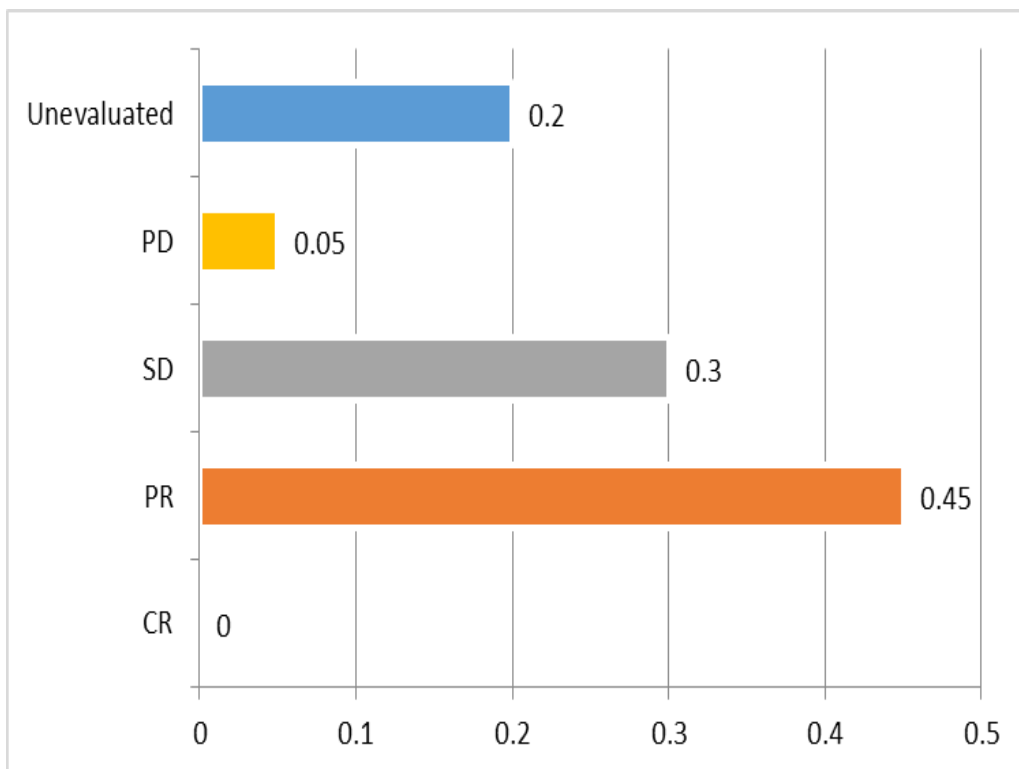


Figure 2 ORR after the treatment of Apatinib Mesylate Tablet in Advanced Solid Tumors. CR: complete response, PR: partial response, SD: stable disease, and PD: progressive disease. n=40

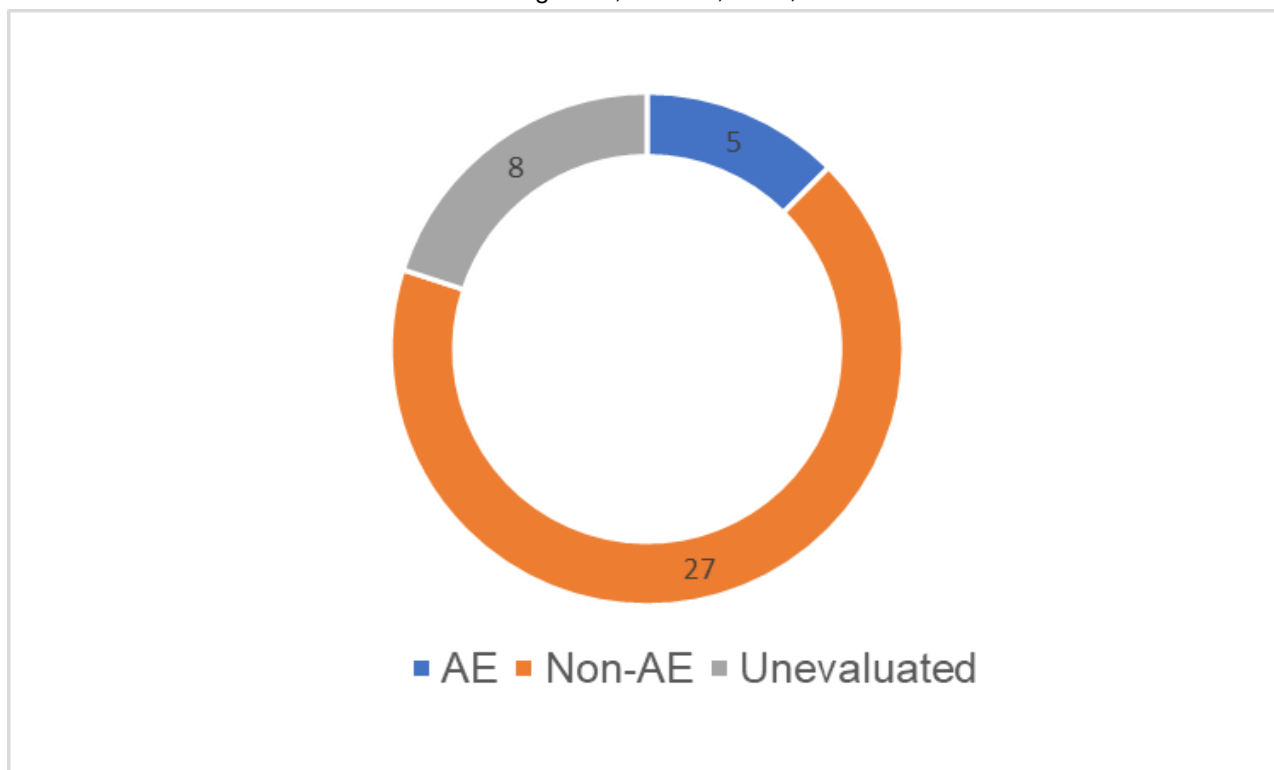


Figure 3 Patients with adverse events after the treatment of Apatinib Mesylate Tablet in Advanced Solid Tumors. AE: Adverse events, Non-AE: Non-adverse events.

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