



# The efficacy and safety of apatinib in patients with heavily pretreated end-stage cancer: a retrospective study

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**Background:** Anti-angiogenesis therapy has been a vital treatment option in a variety of cancers. Assessing the efficacy and safety of apatinib in patients with heavily pretreated end-stage cancer is essential.

**Methods:** Thirty patients with end-stage cancer who were heavily pretreated were enrolled in this study. All patients received oral administration of apatinib (125–500 mg/d) between May 2015 and November 2016. Dose reduction or elevation was conducted based on adverse events and doctors' judgments.

**Results:** Prior to the apatinib treatment, the enrolled patients received a median of 1.2 surgeries (range, 0–7), 1.6 sessions of radiotherapies (range, 0–6), and 10.2 cycles of chemotherapy (range, 0–60); 43.3% of patients had uncontrolled local lesions, 83.3% of patients had uncontrolled multiple metastases, and 30.0% of patients had both. After the treatment, 25 patients had valuable data, 6 (24.0%) patients achieved partial response (PR), and 12 (48.0%) patients had stable disease (SD). The disease control rate (DCR) was 72.0%. The PR and SD rates were 20.0% and 40.0%, respectively, and the DCR was 60.0% in the intent-to-treat (ITT) analysis. Meanwhile, the median progression-free survival (PFS) was 2.6 (range, 0.7–5.4) months, and the median overall survival (OS) was 3.8 (range, 1.0–12.0) months. Furthermore, the PR rate and DCR in patients with squamous cell cancer (SCC) were 45.5% and 81.8%, respectively; those in patients with adenocarcinoma (ADC) were 8.3% and 58.3%, respectively. The adverse events were generally mild. The most common adverse events were hyperbilirubinemia (53.3%), elevated transaminase (36.7%), anemia (30.0%), thrombocytopenia (30.0%), hematuria (30.0%), fatigue (26.7%), and leukopenia (20.0%).

**Conclusions:** The results of this study demonstrate the efficacy and safety of apatinib and support the further development of apatinib as a potential treatment option for patients with heavily pretreated end-stage cancer.

**Keywords:** Apatinib; end-stage cancer; disease control rate (DCR); survival; safety

Submitted Aug 24, 2022. Accepted for publication Jan 12, 2023. Published online Mar 27, 2023.

doi: 10.21037/tcr-22-2080

View this article at: <https://dx.doi.org/10.21037/tcr-22-2080>

## Introduction

The characteristics of end-stage cancer, including its high degree of malignancy, treatment resistance, and uncontrollable metastatic lesions, place a large burden on patients (1,2). Various trials have been conducted to explore possible treatments for patients with end-stage cancers. The trials mainly focused on immunotherapies and small molecular inhibitors. However, some treatments are accompanied by uncontrollable adverse effects (3-8). Careful evaluation of the potential benefits and harms of various palliative treatment options is crucial in determining strategies in clinical circumstances (9). The optimal options should be safe, convenient, and tolerable for patients and not simply focus on prolonging the lifespan of patients (10). However, there is no consensus regarding effective palliative treatment except for best supportive care (BSC; including pain release, communication, etc.) for patients with end-stage cancer who desire to live longer. Thus, the development of new therapeutic strategies for these patients is necessary.

Vascular endothelial growth factor (VEGF)-mediated angiogenesis plays a critical role in tumor growth and metastasis (11). Consequently, the targeting of angiogenesis by inhibiting VEGFs is a promising strategy for cancer treatment (12). Several reports have demonstrated the efficacy of this treatment strategy in lung, breast, renal,

hepatic, and colon cancers (12-15). Antiangiogenic treatment is also considered one of the potential treatment methods to benefit and increase the survival of patients with cancer and drug resistance, even in those who have been heavily pretreated (16-19).

Apatinib (YN968D1), an oral small-molecular tyrosine kinase inhibitor, selectively targets VEGFR-2 to decrease VEGF-mediated endothelial cell migration, proliferation, and microvascular tumor density (20). Preclinical experiments have indicated that apatinib might be considered a potential therapeutic agent for malignancies and could reverse the resistances to a variety of drugs (21,22). Furthermore, the clinical efficacy of apatinib has been proven in patients with gastric, hepatic, breast, lung, and colorectal cancers (23-29). Furthermore, apatinib is also effective in patients with chemotherapy-refractory or chemotherapy-resistant cancers, such as gastric, breast, and non-small cell lung cancer (NSCLC), who have failed 2 or more previous lines of treatment (30-32).

In this retrospective study, we assessed the clinical efficacy and safety of apatinib in patients with end-stage cancer who had previously received intensive treatment. These patients had uncontrollable local or metastatic lesions and failed or could not tolerate standard therapeutic options. Our analysis might offer new insights into apatinib for overcoming drug resistance and controlling the disease. We present the following article in accordance with the STROBE reporting checklist (available at <https://tc.amegroups.com/article/view/10.21037/tcr-22-2080/rc>).

### Highlight box

#### Key findings

- In patients with heavily pretreated end-stage cancer treated with low-dose apatinib, intent-to-treat analysis showed that the partial response and stable disease rates were 20.0% and 40.0%, respectively, with a disease control rate of 60.0%.
- The median progression-free survival was 2.6 months, and the median overall survival was 3.8 months in the entire population.
- The adverse events associated with the low-dose apatinib treatment were generally mild.

#### What is known and what is new?

- What is known: Recent studies have examined the use of low-dose apatinib monotherapy as a third-line treatment in patients with metastatic colorectal cancer.
- What is new: The treatment with low-dose apatinib was safe and effective in patients with end-stage cancer in a variety of tumors.

#### What is the implication, and what should change now?

- Low-dose apatinib is a potential treatment option for patients with heavily pretreated end-stage cancer.

## Methods

### Study design and participants

This study was a retrospective cohort analysis of the best response and survival data collected routinely in patients with end-stage cancer who had previously been heavily treated and who had received low-dose apatinib at the Cancer Center in Union Hospital, Wuhan, China, from May 2015 to November 2016. Thirty patients were enrolled in this study. All patients had uncontrollable progressive lesions, making them unsuitable for surgery, radiotherapy, and chemotherapy (intolerant or progressive disease) after combined chemotherapy). We excluded (I) patients treated with a combination of apatinib and other therapies, such as chemotherapy, radiotherapy, or targeted therapy; and (II) patients who were not at end-stage disease but who had

received mono-apatinib treatment.

### *Ethical approval*

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Institutional Review Board of the Huazhong University of Science and Technology and the Tongji Medical College Ethics Committee for Clinical Investigation (No. 2018S323). Informed consent was obtained from all individual participants.

### *Apatinib*

Patients received oral apatinib at a dose of 125 to 500 mg daily in tablet form and BSC. Dose reductions or elevation were conducted based on adverse events and the diagnosis of the doctor (33). Patients were given continuous treatment until they experienced disease progression or intolerable toxicity.

### *Outcome evaluation and adverse effects*

The response and progression of the disease were evaluated according to the international criteria proposed by the Response Evaluation Criteria in Solid Tumors Committee. The primary end point was the disease control rate (DCR). Disease control was defined as complete response (CR), partial response (PR), or stable disease (SD). In terms of the DCR, whether the patients had CR, PR, or SD in the fourth week of the study was recorded. Secondary end points included progression-free survival (PFS) and overall survival (OS). PFS was defined as the time from the beginning of treatment until disease progression or death, whichever occurred first. OS was defined as the time from treatment until death from any cause or the last follow-up. Toxicity was evaluated according to World Health Organization classification standard of acute and subacute toxicity of anticancer drugs (34).

### *Statistical analysis*

Categorical variables are presented as numbers and percentages. Continuous data are presented as the median with range. Median PFS and OS were estimated with a Kaplan-Meier curve.

## **Results**

### *Characteristics of the patients*

The 30 included patients had a median age of 57 years (range, 28–86 years) were included in this study; of these patients, 10 had head and neck carcinoma, 7 had gynecological cancer, and 13 had digestive cancer. Patients' characteristics are shown in *Table 1*. The average time from the initial pathology diagnosis to the progression of end-stage cancer was 33.4 months (range, 6.6–181.7 months). Patients received a median of 1.2 surgeries (range, 0–7), 1.6 sessions of radiotherapy (range, 0–6), and 10.2 cycles of chemotherapy (range, 0–60) before treatment with apatinib. Additionally, 13 (43.3%) patients had uncontrolled local lesions, 25 (83.3%) patients had uncontrolled multiple metastases, and 9 (30.0%) patients had both local uncontrolled lesions and multiple metastatic sites. The most frequently involved metastatic sites were the bone (14, 46.7%), lungs (12, 40.0%), peritoneum (10, 33.3%), pleura (9, 30.0%), liver (8, 26.7%), and brain (4, 13.3%). Of the patients, 14 (46.7%) were not tolerant to chemotherapy, 14 (46.7%) were refractory or resistant to chemotherapy, and 2 (6.7%) were both (*Table 1*). The detailed clinical characteristics of subgroups, including patients with squamous cell carcinoma (SCC), adenocarcinoma (ADC), uncontrollable local lesion, or uncontrollable metastatic lesion, are also shown in *Table 1*.

### *Efficacy*

Overall, 50% of patients received no more than 250 mg/d of apatinib, and the other 50% of patients received up to 500 mg/d; 5 patients abandoned apatinib therapy within 1 month. Thus, efficacy was evaluated in 25 patients who had valuable data. Of these, 6 (24.0%) patients achieved PR, 12 (48.0%) had SD, and 7 (28.0%) had PD, resulting in an objective response rate (ORR; defined as CR + PR) of 24.0% and a DCR of 72.0%. Median PFS (mPFS) was 2.6 months (range, 0.7–5.4 months), while median OS (mOS) was 3.8 months (range, 1.0–12.0 months) in the entire population (*Table 2*). The PR rate and SD rate were 20.0% and 40.0%, respectively, and the DCR was 60.0% in the intent-to-treat (ITT) analysis.

### *Efficacy by pathology*

Among patients with SCC, 11 patients had valuable data.

**Table 1** Characteristics of patients with end-stage cancer

Characteristics	Total patients (n=30)	SCC (n=14)	ADC (n=14)	Local-F (n=13)	Multi-M (n=25)
Age (years), median [range]	57 [28–86]	59 [47–86]	54 [28–60]	60 [47–86]	57 [28–81]
Gender, n (%)					
Male	15 (50.0)	9 (64.3)	5 (35.7)	7 (53.8)	12 (48.0)
Female	15 (50.0)	5 (35.7)	9 (64.3)	6 (46.2)	13 (52.0)
Pathology, n (%)					
SCC	14 (46.7)	14 (100.0)	0 (0.0)	11 (84.6)	9 (36.0)
ADC	14 (46.7)	0 (0.0)	14 (100.0)	1 (7.7)	14 (56.0)
Others*	2 (6.7)	0 (0.0)	0 (0.0)	1 (7.7)	2 (8.0)
Primary tumor, n (%)					
Head and neck cancer	10 (33.3)	9 (64.3)	0 (0.0)	6 (46.2)	6 (24.0)
Gynecological cancer	7 (23.3)	2 (14.3)	5 (35.7)	3 (23.1)	6 (24.0)
Digestive cancer	13 (43.3)	3 (21.4)	9 (64.3)	4 (30.8)	13 (52.0)
Previous treatment					
Average number of surgeries, median (range)	1.2 (0–7)	1.4 (0–7)	1.1 (0–2)	1.5 (0–7)	1.0 (0–3)
Average number of radiotherapy sessions, median (range)	1.6 (0–6)	2.3 (1–6)	1.1 (0–4)	2.2 (1–4)	1.6 (0–6)
Average number of chemotherapy cycles, median (range)	10.2 (0–60)	5.7 (0–18)	15.9 (5–60)	8.9 (0–46)	11.1 (1–60)
Course of disease (months), median (range)	33.4 (6.6–181.7)	22.3 (6.6–59.6)	45.6 (8.3–181.7)	29.5 (6.6–76.6)	36.1 (7.0–181.7)
Local failure after multiline treatment, n (%)	13 (43.3)	11 (78.6)	2 (14.3)	13 (100.0)	8 (25.0)
Tolerance to chemotherapy, n (%)					
No	16 (53.3)	10 (71.4)	6 (42.9)	8 (61.5)	12 (48.0)
Yes	14 (46.7)	4 (28.6)	8 (57.1)	5 (38.5)	13 (52.0)

\*, others included sarcoma and ACC. SCC, squamous cell cancer; ADC, adenocarcinoma; ACC, adenoid cystic carcinoma; Local-F, local failure; Multi-M, multiple metastases.

After treatment with apatinib, 5 (45.5%) patients achieved PR, 4 (36.4%) patients had SD, and 2 (18.2%) patients had PD. Therefore, the ORR and DCR were 45.5% and 81.8%, respectively. The mPFS and mOS were 2.1 months (range, 0.7–4.4 months) and 3.7 months (range, 1.0–12.0 months), respectively (*Table 2*).

Among the patients with ADC, 12 patients had valuable data, including 1 (8.3%) patient with PR, 6 (50.0%) patients with SD, and 5 (41.7%) patients with PD. Thus, the ORR and DCR were 8.3% and 58.3%, respectively. The mPFS was 3.0 months (range, 1.8–5.4 months), and the mOS was 4.0 months (range, 1.0–7.7 months; *Table 2*). Further comparison analysis revealed that although the ORR was

better in patients with SCC compared to those with ADC (45.5% *vs.* 8.3%), no statistical significance was observed ( $P=0.069$ ), which might be attributable to the small sample size (*Table S1*).

#### ***Efficacy by local failure or multiple metastases***

Ten patients had uncontrollable lesions. There were 4 (40.0%) patients with PR, 5 (50.0%) patients with SD, and 1 (10.0%) patient with PD. The ORR and DCR were 40% and 90%, respectively. The mPFS was 2.6 months (range, 0.9–5.2 months), and the mOS was 4.2 months (range, 1.0–12.0 months; *Table 2*).

**Table 2** Treatment response and survival profile

Items	Total patients	SCC	ADC	Local-F	Multi-M
Assessed, n	25	11	12	10	22
PR, n (%)	6 (24.0)	5 (45.5)	1 (8.3)	4 (40.0)	3 (13.6)
SD, n (%)	12 (48.0)	4 (36.4)	6 (50.0)	5 (50.0)	12 (54.5)
PD, n (%)	7 (28.0)	2 (18.2)	5 (41.7)	1 (10.0)	7 (31.8)
ORR, n (%)	6 (24.0)	5 (45.5)	1 (8.3)	4 (40.0)	3 (13.6)
DCR, n (%)	18 (72.0)	9 (81.8)	7 (58.3)	9 (90.0)	15 (68.2)
mPFS (months), median (range)	2.6 (0.7–5.4)	2.1 (0.7–4.4)	3.0 (1.8–5.4)	2.6 (0.9–5.2)	2.6 (0.7–5.4)
mOS (months), median (range)	3.8 (1.0–12.0)	3.7 (1.0–12.0)	4.0 (1.0–7.7)	4.2 (1.0–12.0)	3.5 (1.0–7.7)

PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate; mPFS, median progression-free survival; mOS, median overall survival; SCC, squamous cell carcinoma; ADC, adenocarcinoma; Local-F, local failure; Multi-M, multiple metastases.

**Table 3** Treatment response classified by the primary tumor

Outcome	Head and neck cancer	Gynecological cancer	Digestive cancer
Assessed, n	9	5	11
PR, n (%)	3 (33.3)	2 (40.0)	1 (9.1)
SD, n (%)	4 (44.4)	1 (20.0)	7 (63.6)
PD, n (%)	2 (22.2)	2 (40.0)	3 (27.3)
ORR, n (%)	3 (33.3)	2 (40.0)	1 (9.1)
DCR, n (%)	7 (77.7)	3 (60.0)	8 (72.7)

PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

In patients with uncontrollable metastatic lesions, 22 patients had valuable data. Of these, 3 (13.6%) patients achieved PR, 12 (54.5%) patients had SD, and 7 (31.8%) patients had PD, resulting in an ORR and DCR of 13.6% and 68.2%, respectively. The mPFS was 2.6 months (range, 0.7–5.4 months), and the mOS was 3.5 months (range, 1.0–7.7 months; *Table 2*).

#### *Efficacy by primary tumor site*

In patients with head and neck cancer, there were 3 (33.3%) patients with PR, 4 (44.4%) patients with SD, and 2 (22.2%) patients with PD, which resulted in an ORR of 33.3% and a DCR of 77.7%. In patients with gynecological cancer, 2 (40.0%) patients achieved PR, 1 (20.0%) patient had SD, and the other 2 (40.0%) patients had PD. The ORR and

DCR were 40.0% and 60.0%, respectively. In patients with digestive cancer, 1 (9.1%) patient achieved PR, 7 (63.6%) patients had SD, and 3 (27.3%) patients had PD. The ORR and DCR were 9.1% and 72.7%, respectively (*Table 3*).

#### *Safety*

Major observed toxicities of low-dose apatinib included hyperbilirubinemia (16 patients, 53.3%), elevated transaminase (11 patients, 36.7%), anemia (9 patients, 30.0%), thrombocytopenia (9 patients, 30.0%), hematuria (9 patients, 30.0%), fatigue (8 patients, 26.7%), and leukopenia (6 patients, 20.0%; *Table 4*). Most of the toxicities were of grades 1–2. The most common grades 3–4 toxicities were thrombocytopenia (5 patients, 16.7%) and hyperbilirubinemia (3 patients, 10.0%; *Table 4*).

Each patient's specific disease, apatinib administration, treatment response, survival, and grades 3–4 adverse events are listed in *Table S2* for reference.

#### **Discussion**

Our results illustrated that low-dose apatinib was a potentially effective anticancer agent with an acceptable safety profile that could be used for heavily pretreated patients with end-stage cancers or patients with uncontrollable lesions who failed or were not tolerant to chemotherapy. To the best of our knowledge, this was the first study of cancer patients who had received low-dose apatinib in the final stage of their lives. Notably, it also reported apatinib treatment in head and neck

**Table 4** Adverse events

Adverse events	Total	Grades 1–2	Grades 3–4
Hyperbilirubinemia, n (%)	16 (53.3)	13 (43.3)	3 (10.0)
Elevated transaminase, n (%)	11 (36.7)	10 (33.3)	1 (3.3)
Anemia, n (%)	9 (30.0)	7 (23.3)	2 (6.7)
Thrombocytopenia, n (%)	9 (30.0)	4 (13.3)	5 (16.7)
Hematuria, n (%)	9 (30.0)	9 (30.0)	0 (0.0)
Fatigue, n (%)	8 (26.7)	6 (20.0)	2 (6.7)
Leukopenia, n (%)	6 (20.0)	4 (13.3)	2 (6.7)
Hand-foot syndrome, n (%)	5 (16.7)	4 (13.3)	1 (3.3)
Hypertension, n (%)	4 (13.3)	4 (13.3)	0 (0.0)
Proteinuria, n (%)	3 (10.0)	3 (10.0)	0 (0.0)
Bleeding, n (%)	3 (10.0)	3 (10.0)	0 (0.0)

squamous cancers, esophageal squamous cell carcinoma, nasopharyngeal carcinoma, non-breast gynecological cancers, and adenoid cystic carcinoma. Among 13 cases, 5 PR, 6 SD, and 2 PDs were observed, and both patients with nasopharyngeal carcinoma showed PD disease. This study also suggested that apatinib had a better effect on SCC.

Several studies support the idea that apatinib may be effective in multiline-failed and end-stage patients who are chemo-refractory or have a high degree of malignancy or resistance. In a randomized controlled phase III trial of 267 patients with advanced gastric cancer who failed in the second-line chemotherapy, patients who were treated with apatinib (750 mg/d) achieved a DCR of 42.1% and an mPFS of 2.6 months; in the placebo group, the DCR was 8.8%, and the mPFS was 1.8 months (32). A possible reason for these findings could be that a high dose of apatinib might be intolerable in these patients, and they postponed apatinib administration, which might have led to poor survival. A phase II, multicenter, open, single-arm clinical study that included 36 patients with metastatic breast cancer for whom chemotherapy had failed and who were treated with apatinib (500 mg/d) reported an ORR of 16.7%, a DCR of 66.7%, and an mPFS of 4.0 months (35). This study pooled different types of end-stage cancer and obtained a DCR of 72%, an ORR of 24%, and an mPFS of 2.7 months, similar to the findings of the above-mentioned clinical trials (32,35). These results showed that even with low-dose apatinib (125–500 mg/d), effective outcomes could still be achieved, providing evidence for reducing the drug dose in clinical treatment for patients with multiline failure

and/or end-stage cancer.

Previous studies on the adverse events of apatinib have mainly focused on hypertension, hand-food syndrome, proteinuria, diarrhea, fatigue, and leukopenia (27,36–38). Most of published literature indicates that grade 3–4 adverse events rarely occur. In our study, the common adverse events were similar to those previously reported. Most of the adverse events were tolerable and manageable. Our study further indicated that apatinib could be a safe treatment in patients with end-stage cancer or patients with uncontrollable lesions who were not tolerant to chemotherapy or for whom chemotherapy had failed.

This study also evaluated the efficacy of apatinib in SCC and ADC. According to the published literature, in patients with previously treated SCC who had received apatinib treatment, the ORR ranged from 7.5% to 12.5%, while the DCR ranged from 65.0% to 72.5% (36–38). However, studies using apatinib monotherapy in patients with previously treated ADC are rare. Only one study was conducted on colorectal cancer, reporting a DCR of 23.0% (27). In our study, the ORR of low-dose apatinib in patients with ADC or SCC was 8.3% and 45.5%, respectively, and DCR with ADC or SCC was 58.3% and 81.8%, respectively. The treatment response in patients with SCC was similar to that previously reported. From our data, it could be observed that the treatment response was better in patients with SCC compared to patients with ADC. Thus, we propose that patients with SCC might be more sensitive to apatinib treatment compared to patients with ADC. Therefore, further randomized clinical studies are highly recommended to assess the use of low-dose apatinib in patients with SCC.

The results of this study show that a low-dose of apatinib (125–500 mg/day) also exerted effective antitumor activity. Previously, high and unacceptable toxicity was observed in patients with a standard dose of apatinib treatment. In a phase II trial of metastatic breast cancer, the apatinib dose was reduced from 750 to 500 mg/day due to the unacceptable toxicity of the 750 mg/day dose (31). A low-dose of apatinib was shown to be effective. A phase I clinical trial reported that, in 37 patients with gastrointestinal, bronchus/lung, breast, and other cancers treated with oral apatinib at a dose ranging from 250 to 1,000 mg/day, the DCR of the 250, 500, 750, 850, 1,000 mg dose cohorts was 66.7%, 66.7%, 100.0%, 90.9%, and 66.7%, respectively (39). Thus, it is worth investigating the efficacy and toxicity of apatinib at lower doses in patients with end-stage cancer. In patients with end-stage cancer, the balance

of adverse events and survival benefits should be considered. In the current study, a low dose of apatinib was effective and tolerable, and thus might be a potential choice for patients with end-stage cancer (40,41).

This study has some limitations. First, there was no randomized, double-blind control group that received a placebo compared with low-dose apatinib. Second, the sample size of this study was insufficiently large to draw definitive conclusions. Third, studies on different aspects of quality of life should also be included. Fourth, the quality of life was not evaluated in this study. Fifth, we enrolled patients with various types of end-stage cancer, including head and neck cancer, gynecological cancer, breast cancer and digestive cancer, which might have confounded the results. Further studies should consider these limitations to verify the conclusions.

## Conclusions

Collectively, apatinib can be administered as an alternative monotherapy with a high DCR and moderate adverse events in patients with heavily pretreated end-stage cancer. As low-dose apatinib yielded a good response in patients with SCC, it is worth further investigating its therapeutic effects in this specific group.

## Acknowledgments

*Funding:* This work was supported by the National Natural Science Foundation of China (grant Nos. 81302019, 81472201, and 81672979), and Henry CSCO Cancer Research Fund (grant No. Y-HR2017-033).

## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at <https://tcr.amegroups.com/article/view/10.21037/tcr-22-2080/rc>

*Data Sharing Statement:* Available at <https://tcr.amegroups.com/article/view/10.21037/tcr-22-2080/dss>

*Peer Review File:* Available at <https://tcr.amegroups.com/article/view/10.21037/tcr-22-2080/prf>

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <https://tcr.amegroups.com/article/view/10.21037/tcr-22-2080/coif>). The authors

have no potential conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Review Boards of the Huazhong University of Science and Technology, and Tongji Medical College Ethics Committee for Clinical Investigation (No. 2018S323), and informed consent was obtained from all individual participants.

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**Cite this article as:** Li Z, Zhou X, Wang S, Shi L, Meng R, Dai X, Liu Y, Lin X, Xiao Y, Peng G. The efficacy and safety of apatinib in patients with heavily pretreated end-stage cancer: a retrospective study. *Transl Cancer Res* 2023;12(4):904-912. doi: 10.21037/tcr-22-2080

**Supplementary**

**Table S1** Comparison of ORR and DCR between patients with SCC and ADC

Outcome	SCC	ADC	P value*
Assessed, n	11	12	–
ORR, n (%)	5 (45.5)	1 (8.3)	0.069
DCR, n (%)	9 (81.8)	7 (58.3)	0.371

\*Fisher exact test between patients with SCC and ADC. SCC, squamous cell carcinoma; ADC, adenocarcinoma; ORR, objective response rate; DCR, disease control rate.

**Table S2** Detailed information of each patient

Patient No.	Age (years)	Gender	pathology	Primary tumor	Stage	Previous surgery times	Previous radiotherapy times	Previous chemotherapy cycles	Course of disease (months)	Local-F	Multi-M	Response	Apatinib dose (mg)	PFS (mo)	OS (mo)	Adverse events in grades III-IV
1	58	Male	SCC	Esophagus	IIB	1	3	4	59.6	Yes	Yes	PR	250	1.2	1.6	
2	86	Female	SCC	Neck skin	II	2	2	0	6.6	Yes	No	PR	125–250	4.4	4.7	Hand-foot syndrome
3	60	Male	SCC	Hypopharynx	III	1	1	8	17.3	Yes	No	PR	250	1	1	
4	32	Female	ADC	Breast	IIA	1	2	60	88.6	No	Yes	PR	250–500	5.4	5.4	
5	59	Male	SCC	Inner canthus	IV	7	1	11	40.6	Yes	No	PR	250–500	3.1	12	Thrombocytopenia and leukopenia
6	81	Female	SCC	Vulvar	IV	3	3	3	39.2	Yes	Yes	PR	250–500	1.8	3.5	Hypoglycemia and hypopotassemia
7	58	Male	SCC	Esophagus	IIIc	1	3	4	14.6	Yes	Yes	SD	125–250	0.9	1.2	
8	64	Male	SCC	Esophagus	IV	0	1	9	14.7	Yes	Yes	SD	125–250	2.8	2.8	
9	67	Female	SCC	Tongue	IVa	2	2	1	7.8	Yes	Yes	SD	125–250	2.7	2.8	Thrombocytopenia
10	38	Female	ADC	Ovary	IV	1	1	5	40.3	No	Yes	SD	250–500	2.7	4.7	Thrombocytopenia and hyperbilirubinemia
11	52	Male	SCC	Parotid gland	IVa	1	1	4	7	No	Yes	SD	250	0.7	1.7	
12	57	Female	ADC	Gastric	IV	1	0	10	14.2	No	Yes	SD	500	3.8	> 6.8	
13	58	Female	ADC	Pancreas	IV	1	0	9	12.5	No	Yes	SD	250	2.3	2.6	
14	57	Female	ADC	Gastric	IV	1	0	14	18.4	No	Yes	SD	250–500	>7.7	> 7.7	
15	65	Male	Sarcoma	Inguina	IIB	1	1	2	22.6	Yes	Yes	SD	250–500	>5.3	>5.3	Thrombocytopenia, anemia and leukopenia
16	58	Male	ADC	Gastric	IV	1	0	6	20.3	No	Yes	SD	500	2	>3.1	
17	32	Female	ADC	Oropharynx	II	1	0	2	27.2	No	Yes	SD	250–500	> 3.2	>3.2	
18	52	Male	ADC	Gastric	III	2	0	8	34.5	No	Yes	SD	500	1.8	2.5	Hyperbilirubinemia and elevated transaminase
19	48	Male	SCC	NPC	IV	0	6	4	10.1	No	Yes	PD	250	<1	5	Thrombocytopenia
20	65	Male	SCC	NPC	IV	0	1	4	10.4	No	Yes	PD	125–250	<1	1	
21	36	Female	ADC	Breast	II	0	4	21	85.2	No	Yes	PD	250	<1	1.7	
22	56	Male	ADC	Rectum	IV	1	1	5	8.3	No	Yes	PD	500	<1	2.4	
23	60	Male	ADC	Gastric	IV	1	0	21	17.7	No	Yes	PD	500	<1	3.2	Hyperbilirubinemia
24	48	Female	ADC	Breast	III	1	3	46	76	Yes	Yes	PD	500	<1	1	
25	28	Male	ADC	Gastric	IV	1	1	7	13.3	No	Yes	PD	500	<1	6.8	
26	68	Female	SCC	NPC	IVa	1	4	18	50.9	Yes	Yes	NE	250	NE	0.1	Sudden change
27	52	Female	ADC	Gastric	III	2	1	5	28.2	No	Yes	NE	250–500	NE	0.9	Sudden change
28	57	Female	Medullary	Breast	II	1	2	6	181.7	No	Yes	NE	250	NE	>5.8	Sudden change
29	50	Female	SCC	Cervix	IIIb	0	3	7	23.6	Yes	No	NE	250	NE	>6.1	Intolerable fatigue
30	47	Male	SCC	Oropharynx	IVa	0	1	3	9.8	Yes	No	NE	250	NE	>1.1	Intolerant fatigue and vertigo

SCC, squamous cell carcinoma; ADC, adenocarcinoma; Local-F, local failure; Multi-M, multiple metastases; NE, not evaluable; PFS, progression-free survival; OS, overall survival; PR, partial response; SD, stable disease; PD, progressive disease; >, patient alive at the time of analysis.