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Original Article

Apatinib therapy as the third line of colorectal cancer therapy

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Abstract: Purpose: This study was conducted to review the efficacy and safety of Apatinib in colorectal cancer patients who failed previous chemotherapy. Methods: The clinical information of 14 patients with colorectal cancer who failed in prior chemotherapy and subsequently received Apatinib treatment was collected. Apatinib was given 500 mg/daily over a cycle of 4 weeks. Progression free survival (PFS), overall survival (OS), and treatment-related adverse effects were reviewed and evaluated. Results: The data of fourteen patients who met the inclusion criteria were analyzed. The patients were administered Apatinib for 0 to 12 cycles with a median of 6.7 cycles. Ten of the fourteen patients who received at least two complete cycles of Apatinib treatment were eligible for the efficacy analysis. The median PFS was 6.0 months. Four were identified as having partial responses (PR), six with stable disease (SD), four with progressive disease (PD) and no complete response (CR) was observed. The main adverse effect of apatinib is hypertension (21%), hand-foot skin reaction (HFSR) (36%), and proteinuria (36%). No drug-related severe adverse events occurred. Conclusions: Apatinib treatment in this third line treatment exhibited efficacy and manageable toxicity in colorectal cancer patients who failed in previous chemotherapy. This result supports future random controlled trial to further define Apatinib activity in colorectal cancer.

Keywords: Colorectal cancer, Apatinib, third-line treatment, efficacy, safety

Introduction

Colorectal cancer (CRC) is the third most common cancer with nearly 1.2 million new cases expected each year globally [1]. When colorectal cancer is localized, there is a five-year survival rate of about 90%, but it drops to near 12% once there are distant metastases [2]. For the majority of CRC patients, platinum-based doublet chemotherapy is the standard treatment option for advanced CRC [3]. However, most advanced CRC patients experience disease progression within 8 months from first-line therapy and progression within 3 months of second-line therapy [4]. Despite the fact that a considerable proportion of patients (36%-52%) are suitable for third line therapies, regorafenib, which is a targeted agent with worldwide approval for third-line treatment in metastatic CRC, is difficult to obtain in mainland China, and the quality and quantity of the available drugs in this setting are poor [5, 6].

Apatinib is a small molecule vascular endothelial growth factor receptor-2 (VEGFR-2) tyrosine kinase inhibitor (TKI), which has been approved in PRC for use as a subsequent line of treatment for advanced gastric cancer [7, 8]. It highly selectively binds and inhibits VEGFR-2, blocks downstream signaling, prevents VEGF-mediated endothelial cell migration and proliferation, and inhibits neovascularization with potential anti-angiogenic and antitumor activity [9]. It is similar to PTK787/ZK222584 (Valatanib) and has shown a superior in vivo efficacy in heterologous transplantation studies compared to valatanib [10]. Phase I and phase II Apatinib trials have demonstrated encouraging antitumor activities and manageable toxicities in gastric cancer, mammary cancer and non-small-cell lung cancer [11-13]. Apatinib was approved by the China Food and Drug Administration (CFDA) in 2014 for the treatment of advanced gastric cancer or adenocarcinomas of the esophagogastric junction. In this study, CRC patients who

Table 1. Baseline demographic and clinical characteristics of the 14 patients with advanced CRC

Characteristic	Apatinib (n = 14)
Age (years)	
≤ 65	3 (11.4%)
> 65	11 (78.6%)
Sex	
Male	7 (50%)
Female	7 (50%)
Primary tumor site	
RCC	2 (14.3%)
LCC & RECC	12 (85.7%)
Number of metastasis	
≤ 2	5 (35.7%)
> 2	9 (64.3%)

failed in chemotherapeutic treatments have experimented with Apatinib treatment and showed a response. Here, we review these data and evaluate the efficacy and safety of Apatinib as a single agent in these CRC patients.

Methods

Patients

Patients between 18 and 70 years old with histologically confirmed advanced colorectal cancer were eligible for enrollment. Patients had to have at least two lines of chemotherapy fail before participating in the study. Treatment failure was defined as intolerable adverse effects or disease progression during treatment with chemotherapy. All of these patients had a strong desire to receive further treatment and provided written informed consent before participating in the study. The application of Apatinib was in accordance with the declaration of Helsinki and this work was approved by the ethics committees of Anhui Medical University Cancer Hospital. All patients volunteered to participate in this trial and provided written informed consent.

Study design and treatment

This study was a single center, single-aim, open-label, prospective study to investigate the efficacy and safety of apatinib in patients with extensive-stage CRC after the failure of second or third-line chemotherapy. The patients received oral apatinib 500 mg in tablet form once daily. A treatment cycle was defined as 28 days (4 weeks). Treatment interruptions resulting from toxicities were allowed for no more than 14 days (either continuously or cumulatively) and no more than two times in a given treatment cycle. The patients continued treatment until they experienced disease progression or intolerable toxicity or withdrew consent from the study.

Table 2. Efficacy evaluation of the 14 patients

N = 14	N	%
CR	0	0
PR	4	28.57
SD	6	42.86
PD	4	28.57
ORR (CR+PR)	4	28.57
DCR (CR+PR+SD)	10	71.43

Efficacy and safety assessments

Postoperatively, the patients were routinely followed up. The follow-up was conducted every 3 months for 1 year. The follow-up proceeded through telephone calls or mail correspondence. Patient deaths were recorded. The last follow-up was in April 2017. Local recurrence was defined as either a clinically, radiologically, or pathologically evident tumor of the same histological type occurring contiguously to the previous tumor resection site. Distant recurrence was defined as a tumor of the same histological type occurring far away from the primary site of disease. Overall survival (OS) was calculated from the time of operation to death. Progression free survival (PFS) was assessed by investigators and verified by independent radiologists.

Statistical analysis

Data was presented as the mean ± standard deviation for continuous variables and as numbers and percentages for categorical variables after adjusting for age, sex, tumor sites and number of metastatic sites. All statistical analyses were performed using SPSS 19.0 (IL, USA). All *P* values were two sided, and a value less than 0.05 was considered to be statistically significant.

Results

Baseline patient characteristics

A total of nineteen patients were enrolled in this study with a median age of 53, but only

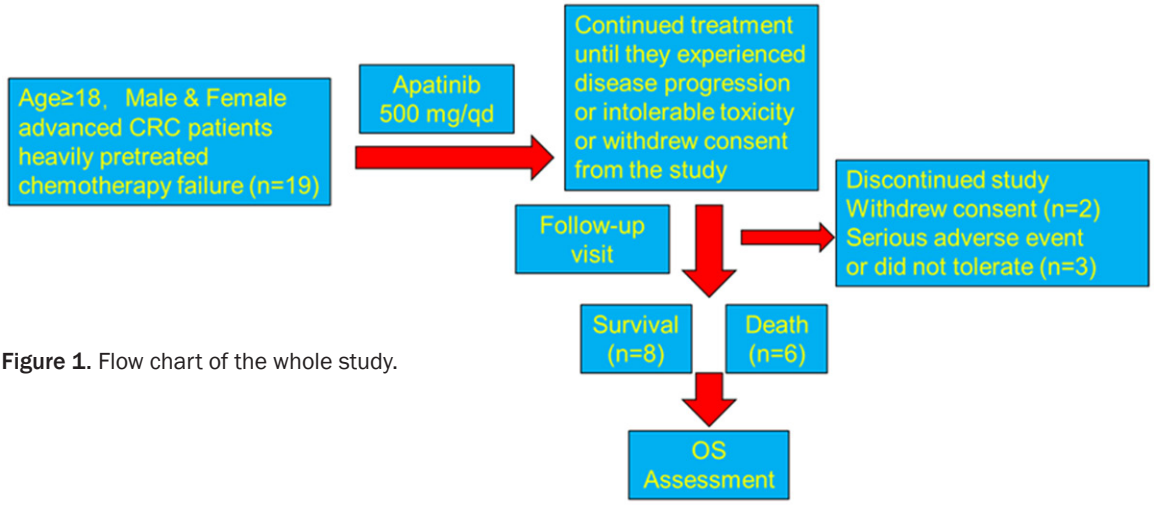

Figure 1. Flow chart of the whole study.

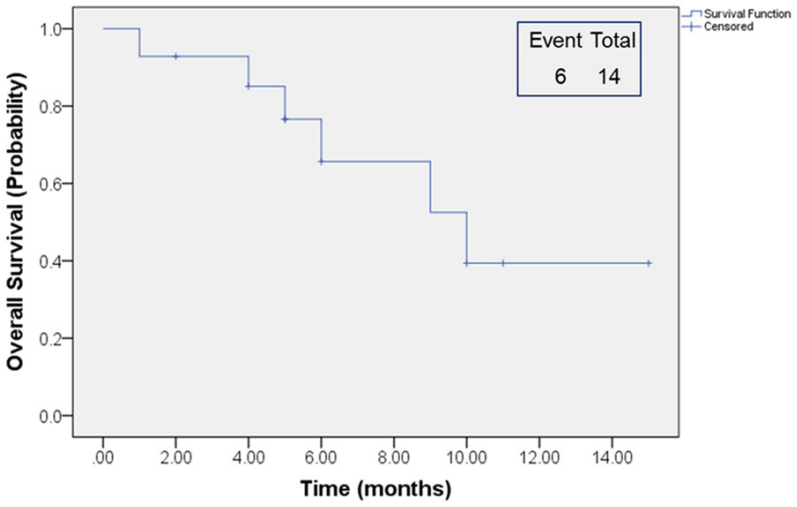

Figure 2. Kaplan-Meier estimates of overall survival (OS).

fourteen patients competed the study through April 2017. We lost contact with two patients during the study, and 3 patients did not tolerate the drug. All the patients who finished the study received 6.7 cycles of medication on average for the third line therapies, and 72% percent of the patients were treated over two or more cycles. The results are shown as **Tables 1**, **2** and **Figure 1**. In all the cases (n = 14), 14.3% (n = 2) of the patients had right-side colon cancer (RCC), and 85.7% (n = 12) had left-side colon cancer (LCC) or rectal cancer (RECC).

Efficacy

At the time of the data cut-off (04/01/2017), six patients had died in this study. The median OS was 10.0 months. Further analysis indicated that the 6-month OS rate was 65.7%, and the 12-month OS rate was 39.4% (**Figure 2**). Among these 14 patients who were treated with apatinib, 4 were identified as having a partial response (PR), 6 had stable disease (SD) and 4 had progressive disease (PD). No complete response (CR) was observed. The progression free survival (PFS) was also determined (**Figure 3**). The median PFS was 6.0 months (95% CI, 2.2-9.8). In univariate analyses, age ≥ 65 years, sex, number of metastatic sites, and primary tumor site were not found to be negative prognostic factors for OS (**Table 3**).

Safety

All the patients included in this study were investigated for the safety of the drug. The main adverse effect of apatinib is hypertension (21%), hand-foot skin reaction (HFSR) (36%), and proteinuria (36%). The most common adverse events with incidences of 10% or greater are summarized in **Table 4**. No unexpected adverse events were found in this study.

Discussion

With the in-depth study of the pathological mechanisms of cancer, tumor therapy has now

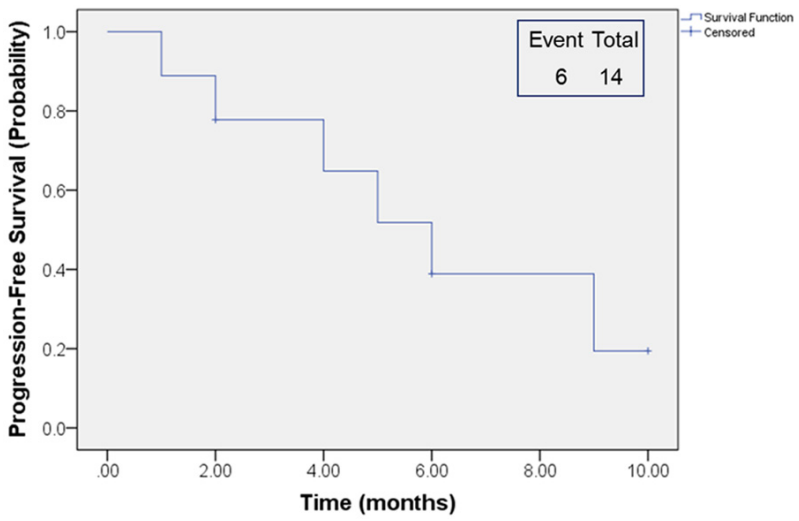

Figure 3. Kaplan-Meier estimates of progression-free survival (PFS).

Table 3. Univariate analyses (Cox proportional hazards model) of patient and tumor factors influencing overall survival after treatment with Apatinb of the 14 patients with advanced CRC

	HR (95 CI)	P
Age (year)		
< 65	1	
≥ 65	2.09 (0.19-23.12)	0.549
Sex		
Male	1	
Female	0.90 (0.18-4.53)	0.898
Numbers of metastatic sites		
≥ 2	1	
< 2	0.66 (0.12-3.80)	0.634
Tumor site		
RCC	1	
LCC & RECC	0.90 (0.10-7.95)	0.926

entered the field of molecular targeted therapy [14]. In 1971, Folkman firstly proposed that "tumor growth is dependent on the formation of new blood vessels", suggesting a new theoretical basis for the control of cancer progression. Over the years, it has been an important research direction in oncology to prevent the growth of new blood vessels for tumor control. Extensive studies have confirmed that tumor growth and metastasis depend on angiogenesis, and several angiogenic factors such as vascular endothelial growth factor (VEGF), MMP, TGF-β1, CD34, bFGF, cyclooxygenase-2 (COX-2), and c-KIT are associated with the prognosis of CRC [15]. The expression of VEGF in CRC is closely related to the early recurrence, metastasis and the prognosis of the tumor [16].

Apatinib is an oral VEGFR2 inhibitor which can injure the function of endothelial cells, including proliferation, migration, and tube formation. It also inhibits the germination of rat aortic rings and affects the growth of xenografts, either alone or combined with other chemotherapeutic agents [17]. It can be targeted to side population cells and ABCB1-overexpressing leukemia cells to enhance the efficacy of chemotherapeutic drugs [18].

Due to the high heterogeneity of the pathological subtypes of CRC, the sensitivity to chemotherapy is variable. Overall, the metastatic CRC has a low 5 year survival rate. Thus, new therapeutic strategies for CRC are needed. Hereby, we report the first clinical study of Apatinib in CRC to evaluate its efficacy and safety. Our analysis revealed four PR, six SD and four PD patients according to RECIST criteria. For the long term benefit, the median PFS is 6.0 months and the OS rate after Apatinib administration was 65.7% at the sixth month and became stable after that. These data suggest that CRC patients could acquire a longer benefit from Apatinib treatment. These results are encouraging for the efficacy and seem better than or at least comparable with what was reported in previous studies involved single-agent angiogenesis inhibitors, such as bevacizumab. In a phase III trial of pazopanib reported by Tournigand et al., 208 CRC patients were enrolled, 20 patients achieved PR, 126 patients SD, and 42 patients PD [19].

Considering the safety of Apatinib treatment, the most frequently observed adverse events are hand-foot syndrome, proteinuria, and hypertension, which are consistent with those reported in gastric cancer and triple negative breast cancer studies. Hypertension can also be controlled by antihypertensive drugs (such

Table 4. Analysis of safety after treatment with 500 mg/qd apatinib of the 14 patients

Adverse effect	All	Grade 3/4
Hematologic		
Anemia	4 (29%)	1 (7%)
Thrombocytopenia	1 (7%)	0 (0%)
Leukocytopenia	1 (7%)	1 (7%)
Nonhematologic		
Oral mucositis	3 (21%)	0 (0%)
Hypertension	3 (21%)	1 (7%)
Proteinuria	5 (36%)	2 (14%)
Hand-foot syndrome	5 (36%)	2 (14%)
Elevated transaminase	5 (36%)	2 (14%)
ALP increased	5 (36%)	2 (14%)
Fatigue	3 (21%)	1 (7%)

as amlodipine, valsartan and so on) in addition to dose disruption or reduction. Hematologic toxicities, including neutropenia and thrombocytopenia during treatment, do not create a need to suspend the drug or reduce the dose to control them because they are mild or moderate.

In summary, our study provides supporting evidence that apatinib exhibits objective efficacy in CRC with manageable toxicity. Therefore, random controlled trials based on these data are warranted to further evaluate apatinib activity in advanced sarcomas.

Disclosure of conflict of interest

None.

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