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ORIGINAL ARTICLE

A retrospective analysis of the safety and efficacy of apatinib in treating advanced metastatic colorectal cancer

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Abstract

Objective Colorectal cancer (CRC) is a heterogeneous disease in which both epigenetic alterations and gene mutations transform normal cells into cancer cells. Apart from a variety of standard treatments, there are few options available to improve a CRC patient's overall survival (OS) and quality of a life. The objective of the present retrospective study was to analyze the response and toxicity associated with apatinib in patients with metastatic CRC (mCRC).

Method Data on the use of apatinib as salvage therapy were collected from patients diagnosed with mCRC, Eastern Cooperative Oncology Group (ECOG) performance status ≤ 3, from the Luhe Hospital. A total of 17 patients with stage IV unresectable mCRC, who received at least one cycle of apatinib, between October 2015 and February 2017, were involved in this study. Our primary endpoints were the overall response rate (ORR) and disease control rate (DCR), and the secondary objectives were progression-free survival (PFS), OS and safety.

Result Seventeen patients with a median age of 62 years (34–83 years) were enrolled. Twelve patients were male, and the location of the primary tumor was in the colon and the rectum in 9 and 8 patients, respectively. Liver metastasis was observed in 9 patients and lung metastasis in 5. The ECOG performance status was 0 to 2 in 13 patients. The ORR at the first evaluation was 17.6 % (3/17). The DCR was 82.4% (14/17). The median PFS was 3.0 months (95% confidence interval (CI): 1.924–4.076 months) and the median OS was 5.4 months (95% CI: 3.383–7.417 months). Grade 1–2 adverse events included hypertension (52.9%), fatigue (64.7%), anorexia (29.4%), hoarseness (23.5%), proteinuria (23.5%), and development of rashes (17.6%). Grade 3 adverse events included thrombocytopenia (5.9%) and proteinuria (5.9%). There were no Grade 4 adverse events in our analysis.

Conclusions Apatinib was found to be both safe and effective in the treatment of advanced mCRC, and its associated toxicities were acceptable and manageable. However, further studies are required to validate these findings.

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Colorectal cancer (CRC) is the fifth most common malignancy in China. As per the National Central Cancer Registry of China (NCCR), an estimated 376,000 new cases of the disease and 191,000 associated deaths were reported, in China, in 2015. The incidence rates of CRC per 100,000 population, per year, are higher in men than in women (15.7 vs 11.7 per 100,000). Similarly, the mortality rate associated with CRC is substantially higher in men than in women (8.1 vs 5.8 per 100,000 [1]. Although surgical resection of metastatic lesions can significantly extend life and improve the quality of life, most patients lose the opportunity to receive radical surgery due to the presence of multiple metastatic sites. Systemic cytotoxic chemotherapy has become an important treatment option for metastatic CRC (mCRC); fluorouracil, irinotecan, oxaliplatin, and capecitabine, alone or in combination, have been shown to improve response rates, and prolong

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progression-free survival (PFS) and overall survival (OS) [2]. In addition, molecular targeted therapeutic drugs (cetuximab, panitumumab, bevacizumab, aflibercept, and ramucirumab) have been approved by the FDA for the treatment of mCRC [3]. Although many innovative drugs have been developed, some studies found that, in the case of mCRC, the median OS was no more than 41.3 months, and the median PFS was only 13.0 months [4–5]. Thus, it is important to develop new methods or drugs to treat CRC, especially recurrent mCRC.

Apatinib is a novel tyrosine kinase inhibitor that targets the vascular endothelial growth factor receptor-2 (VEGFR-2) with high specificity [6]. The vascular endothelial growth factor-A (VEGF-A)/ VEGFR-2 signal pathway is regarded as a key limiting step in tumor growth and metastasis. A variety of anti-angiogenesis approaches targeting the VEGF-A/ VEGFR-2 signal pathway have shown modest improvements in the OS and PFS associated with mCRC [7–8], and pre-clinical and clinical trials have shown that they are effective in treating non-small cell lung cancer, breast cancer, CRC, and gastric carcinoma [9–11]. In 2014, the China Food and Drug Administration approved apatinib for the treatment of chemotherapy-refractory advanced or metastatic adenocarcinoma of the stomach or gastro-esophageal junction. Although apatinib is effective in treating mCRC, published literature on the same is still limited. Therefore, this study aimed to explore the safety and efficacy of apatinib in the treatment of advanced mCRC, especially in patients in whom standard therapy failed or in whom chemotherapy was not recommended due to poor general conditions.

Materials and methods

Patients' characteristics

Patients with histologically or cytologically confirmed advanced (locally advanced or metastatic, unresectable) measurable CRC, for which no standard alternative curative therapy was available, were eligible. A total of 17 patients were enrolled, between August 2015 and February 2017. All these patients had received ≥ 1 cycle of apatinib therapy and were eligible for efficacy and toxicity assessments. The median age of the patients was 62 years, with a range of 34-83 years. Four patients were over 70 years old.

Assessments

Patients with measurable disease were evaluated by the modified Response Evaluation Criteria in Solid Tumors (mRECIST). All the patients underwent one computed tomography (CT) scan at the baseline, after one cycle, and after every two cycles or progression of the disease. Disease control was defined as complete remission (CR), partial remission (PR), or stable disease (SD). Patients in whom the disease progressed after two cycles of treatment were defined as having progressive disease (PD). PFS was defined as the time between the start of the treatment and disease progression or death. OS was considered as the duration from the start of therapy with apatinib to the date of death or the last day of follow-up. Adverse events were graded according to the NCI Common Toxicity Criteria version 3.0.

Statistics analysis

The patient cohort was characterized by descriptive statistics and frequency counts. Continuous variables were described with means, medians, and standard deviations; categorical variables are presented as proportions and 95% confidence intervals (CIs). Statistical significance was set at $P \leq 0.05$, with a two-tailed test. The PFS and OS were analyzed using the Kaplan–Meier method. SPSS software (version 19.0; SPSS, USA) was used for the data analysis.

The study protocol was approved by the institutional review board, and all the patients provided informed consent to participate in the study.

Results

Patients' characteristics

Between October 2015 and February 2017, 17 patients were enrolled to our study. Until May 28, 2017, the median follow-up time was 5.4 months (range: 1.6–14.0 months). The patients' characteristics were listed in Table 1. All the patients received at least one cycle of apatinib. The median age was 62 years (34–83). Of the patients, 12 were male and 13 patients had a performance status of 0 to 2 at the baseline. All patients were diagnosed with stage IV of the disease. The main site of the primary tumor was the colon in 9 patients, with majority of the metastases occurring in the liver. Of particular interest was that four of the patients were aged over 70 years. Thirteen patients had received 19 kinds of chemotherapy regimens before, including FOLFOX, FOLFIRI, and XELOX. The four elderly patients had not received any treatment due to their poor general conditions.

Treatment

Patients received oral apatinib (500 mg per day, in 28-day treatment cycles) in tablet form. Treatment

Table 1 The demographic and general characteristics of the 17 patients

Characteristics	*n*	%
Age (years)		
Median age	62	
Range	34–83	
Sex		
Male	12	70.6
Female	5	29.4
ECOG PS		
0	3	18
1	4	24
2	6	35
3	4	24
Stage		
IV	17	100
Location of primary tumour		
Colon	9	53
Rectum	8	47
Location of metastases		
Lung	5	23.8
Liver	9	42.8
Abdominal lymph node metastasis	3	14.3
Others	4	19
Histologic differentiation		
Well	2	11.7
Moderate	5	29.4
Poorly	8	47.1
Others	2	11.7
line of apatinib		
1	4	23.5
2	7	41.7
3	6	35.3
Prior treatment		
Oxaliplatin-containing	9	
Irinotecan-containing	10	

ECOG PS, Eastern Cooperative Oncology Group performance status.

interruption, resulting from adverse events, was allowed for no more than 14 days. Dose reductions of apatinib (from 500 mg to 250 mg per day) were permitted to manage treatment-related adverse events. Patients received treatment until disease progression, development of unacceptable toxicity, death, or discontinuation of apatinib for any other reason.

Efficacy

The efficacy of apatinib was analyzed in all 17 patients. The short-term efficacy of apatinib was described in Table 2. None of the patients experienced a confirmed partial response; 3 (17.6%) patients achieved a PR; SD was observed in 11 (64.7%) patients, and 3 (17.6%) patients had PD. The ORR was 17.6% (3/17) and DCR was 82.4% (14/17). The median PFS of the patients receiving apatinib was 3.0 months (95% CI: 1.924–4.076 months) (Fig. 1). The median OS was 5.4 months (95% CI: 3.383–7.417 months) (Fig. 2). Prolonged SD was observed in two heavily-pretreated patients. In a 47-year-old man with KRAS wild-type rectal cancer involving the lung, the disease progressed following treatment with XELOX, FOLFIRI, and two cycles of FOLFIRINOX. The patient refused cetuximab and bevacizumab. From October 15, 2015, he took apatinib orally (500 mg/d) and 6 months later, a CT scan showed that his lung lesions were larger; we increased the dosage to 750 mg/d, after which the patient had SD lasting 9 months. Another patient, an 81-year-old man, was diagnosed with stage IVb (T4aN1MIb) heterochrony colon cancer, with liver metastasis, in May 2014. On May 28, 2014, he underwent radical surgery for colon cancer. Pathology studies revealed a 3.5 cm long moderate differentiated adenocarcinoma. There were 5 lymph nodes in the fatty tissue around the intestine; in this patient, one of the nodes had metastasized. After the operation, the tumor was found to be of the stage IIIA (T4aN1M0) type. The patient received capecitabine for four months and the progress of the disease was stable, according to the guideline of the mRECIST. On September 1, 2016, a CT scan demonstrated disease progression, with two new lesions in the lung and liver. The levels of serum carcinoembryonic antigen and carbohydrate antigen 19-9 (CA199) rapidly increased by over three times. A 1-month dose of capecitabine was given, and the family members refused to let the patient undergo another round of chemotherapy. From September 25, 2016, the patient took apatinib (500 mg) once daily. Two weeks later, proteinuria (3+) appeared. Three weeks later, hypertension (Grade 2), leukopenia and thrombocytopenia appeared. The dose of apatinib was reduced to 250 mg, once daily. Meanwhile, fosinopril, amlodipine, ambrette capsule, G-CSF, and interleukin-11 were given simultaneously to control side reactions. When the adverse reactions disappeared, the dose of apatinib was increased to 500 mg, once daily. After this, the time taken for disease progression was 8 months, and the treatment was well-tolerated by the patient. Adverse reactions were also controllable.

Adverse events

Adverse events were graded according to the NCI Common Toxicity Criteria version 3.0. The main toxicities possibly related to therapy are listed in Table 3. The adverse events in the 17 patients were generally mild, mainly ranging from Grade 1 to Grade 2. Two patients experienced Grade 3 adverse events, including

Table 2 The short-term efficacy of apatinib

Efficacy	*n*	%
CR	0	0
PR	3	17.6
SD	11	64.7
PD	3	17.6
ORR		17.6
DCR		82.4

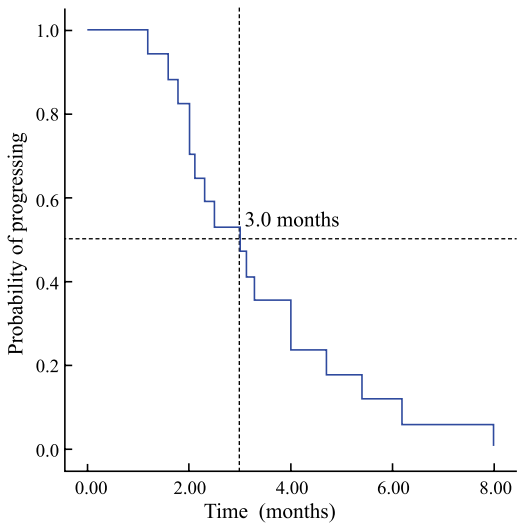

Fig. 1 Kaplan–Meier analysis of PFS

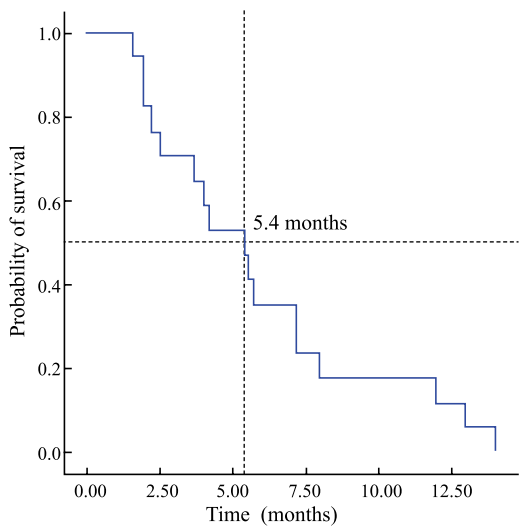

Fig. 2 Kaplan–Meier analysis of OS

proteinuria (1/17; 5.9%), and thrombocytopenia (1/17; 5.9%). There were no Grade 4 adverse events in our analysis. None of the patients died of drug-related causes during the study period.

Table 3 Adverse events

Toxicitya*	Toxicity grade					
	1		2		3	
	n	%	*n*	%	*n*	%
Hematological	0					
Neutropenia	0	0	1	5.9	0	0
Thrombocytopenia	1	5.9	1	5.9	1	5.9
Anemia	0	0	1	5.9	0	0
Non-hematological						
Hypertension	1	5.9	8	47.1	0	0
Proteinuria	3	17.6	1	5.9	1	5.9
Hand and foot syndrome	3	17.6	1	5.9	0	0
Rash	3	17.6	0	0	0	0
Anorexia	5	29.4	0	0	0	0
Hoarseness	4	23.5	0	0	0	0
Fatigue	11	64.7	0	0	0	0
Diarrhea	2	11.8	0	0	0	0
Liver dysfunction	0	0	1	5.9	0	0

* Intestinal perforation was reported in one patient and lung thromboembolism in one patient

Discussion

CRC is the third most commonly diagnosed type of cancer, worldwide. It is the fifth most common malignancy in China. An estimated 376,000 new cases of colon/rectum cancer were diagnosed in China in 2015 [1]. CRC is a heterogeneous multi-pathway disease with both epigenetic alterations as well as gene mutations that can transform normal cells into cancer cells [12].

The treatment of CRC consists of the radical resection of the colorectal carcinoma in the primary tumor and regional lymph nodes, as well as systemic cytotoxic chemotherapy and targeted therapy. Due to advancements in medical science, the 5-year survival rate associated with the disease has dramatically improved to 65% [13]. Fluorouracil-based regimens have become the cornerstone strategy of stage II or III colon cancers. In the mid-90s, Machover reported the efficacy of 5-fluorouracil (5-FU) combined with high-dose folinic acid for the treatment of patients with advanced CRC. The median time to disease progression reached 10 months and the median survival time reached 19.5 months, as a high dose of folinic acid enhances the effectiveness of 5-FU [14]. A French Intergroup Study modified the monthly schedule (intravenous (IV) LV 20 mg/m^2 plus bolus 5-FU 425 mg/m^2 for 5 days, every 4 weeks) to a bimonthly schedule (IV LV 200 mg/m^2 plus bolus 5-FU 400 mg/m^2 and 22 h infusion 5-FU 600 mg/m^2 for 2 consecutive days, every 2 weeks) subsequently. The response rates were 14.4% and 32.6% (P = 0.0004), while the median times to disease progression were 22 weeks and 27.6 weeks, respectively

(P = 0.0012) [15]. Four years later, fluoropyrimidine (capecitabine), that could be orally administered, was designed, and this helped in the achievement of an efficacy level that was comparable to that achieved when IV 5-FU/LV was used. In addition, the use of capecitabine was associated with lower incidences (P < 0.00001) of grade 3/4 stomatitis and neutropenia [16]. Irinotecan combined with fluorouracil as a first-line treatment of mCRC led to significantly higher (49 vs 31%, P < 0.001) RRs than fluorouracil monotherapy. The median time to disease progression was also longer (6.7 vs 4.4 months, P < 0.001) in the irinotecan group [17]. In addition to its combination with irinotecan, fluorouracil/ LV in combination with oxaliplatin significantly prolonged the median time to disease progression (9.0 v 6.2 months; P = 0.0003) and improved the RRs (50.7% v 22.3%; P = 0.0001) compared to the fluorouracil/LV group [18]. Due to the effectiveness of fluorouracil/LV combined with oxaliplatin, a capecitabine plus oxaliplatin (XELOX) regimen was tested by Cassidy J for patients with mCRC. After a minimum follow-up period of 2 years, the median time to disease progression was 7.7 months and the median OS was 19.5 months; these results are similar to those obtained when the FOLFOX-4 regimen was administered. After this, several modified FOLFOX trials were conducted and the progress made was promising [19].

Except for cytotoxic agents, several monoclonal antibodies and small molecular tyrosine kinase inhibitors (TKIs) that target angiogenesis exhibited excellent efficacy in treating mCRC, both as single agents or in combination with classic chemotherapy regimens [20].

Angiogenesis is the process by which new blood vessel develop from pre-existing vasculature. Angiogenesis and tumor growth are related. While tumor or tumor-associated macrophages release diffusible cytokines to the surrounding microenvironment and promote angiogenesis, tumor growth depends on the presence of an adequate blood supply [21]. Compared with normal blood vessels, tumor vasculature has different features, such as tumor vessel tortuosity, vessel permeability, increased interstitial pressure and the presence of thin and fragile tumor vessel walls. Under normal physiological conditions, the pro-angiogenic and anti-angiogenic factors are in balance [22]. When the vascular supply is insufficient, tumors produce hypoxia-inducible factor-1 which increases VEGF-A transcription. The VEGF superfamily consists of five related ligands--VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placenta growth factor. All of them act by binding with three structurally related typical tyrosine kinase receptors (TKRs), namely VEGFR1 (Flt-1), VEGFR-2 (KDR) and VEGFR3 [23]. Koch *et al* reviewed the interactions between VEGFs and TKRs extensively, and found that the receptors not only bind to its ligands but also through homodimerization or heterodimerization exerted biological functions [24]. VEGF-A is the main ligand for VEGFR-2. VEGF-A/ VEGFR-2 acts as a dominating transducer, promoting cancer cell survival, proliferation, invasion or metastasis [25]. In most solid tumors, VEGF-A and VEGFR-2 are overexpressed [26], making the inhibition of tumor angiogenesis and prevention of tumor progression by blocking the VEGF-A/VEGFR-2 pathway possible. Bevacizumab, a monoclonal antibody that targets the VEGF, was the first approved antiangiogenic agent for the treatment of mCRC. Bevacizumab plus irinotecan, bolus fluorouracil, and leucovorin (IFL) improved by 4.7 months in the median duration of survival compared to when IFL was used alone, and the median duration of progression improved by 4.4 months compared to when IFL was used alone. Bevacizumab plus oxaliplatin-based chemotherapy also helped in the achievement of meaningful results. The median PFS was 9.4 months in the bevacizumab group and 8.0 months in the oxaliplatin-based chemotherapy group (P = 0.0023). The median OS was 21.3 months in the bevacizumab group and 19.9 months in the oxaliplatin-based chemotherapy group (P = 0.077) [27]. Other antiangiogenic agents, such as ramucirumab—a human VEGFR-2 mAb, and Ziv-aflibercept—a soluble fusion protein with VEGF-A/B and placental growth factor, have been approved for the treatment of mCRC in combination with FOLFIRI, for patients in whom an oxaliplatin-containing regimen failed. Beyond the second line, the number of appropriate options was found to be low and the treatment outcomes were barely satisfactory.

As mentioned above, VEGF-A is overexpressed in solid tumors, resulting in the auto-phosphorylation of VEGFR-2 and induction of cell proliferation, migration, and permeability. As a consequence, tumor angiogenesis occurred. Apatinib is a novel small-molecule TKI that targets the VEGFR-2 with high specificity. Apatinib also mildly inhibits c-Kit and c-Src tyrosine kinases. Blocking the VEGF-A/VEGFR-2 pathway inhibited endothelial cell migration and tumor growth. For advanced gastric cancer patients, the use of apatinib has been shown to significantly increase the OS (195 d vs 140 d, HR = 0.71, 95% CI: 0.54-0.94) and PFS (78 d vs 53 d, HR = 0.44, 95% CI: 0.33-0.61) [28]. The results of the phase one study showed that three colon tumors had evaluable PRs. Another study found that in two patients with metastatic rectal cancer, in whom prior treatment with multiple chemotherapy regimens failed, treatment with apatinib increased the time to disease progression to more than seven months [29].

Three of our patients showed PRs, in whom prior treatment with FOLFOX and FOLFIRI had failed, and appeared to have multiple metastatic sites. Conventional strategies were not effective, and apatinib was accepted

for later-line therapy. A retrospective analysis evaluating the efficacy and safety of bevacizumab plus FOLFIRI or FOLFOX in mCRC patients, in whom FOLFIRI and FOLFOX treatment failed, was conducted previously. The results showed modest activity: the ORR was 9.5%, and the SD was 52.4%. The results of our study were similar to those of the abovementioned study's. However, in the other study, the median PFS (5.3 months) and median OS (9.5 months) were higher [30].

The safety profile of apatinib, as documented in this trial, was similar to that observed in previously conducted clinical trials. The frequencies of trial-related adverse events, such as hypertension and diarrhea, were within the ranges observed in previous reports. However, the incidence rate of thrombocytopenia, anemia, hand and foot syndrome, and proteinuria were lower than previously described. The incidence rate of fatigue was increased 2.8-fold compared to that observed in another study [31].

Conclusion

In conclusion, apatinib was shown to provide moderate therapeutic efficacy in cases of advanced mCRC. A multicenter prospective study is required to determine the value of apatinib single agents in treating advanced mCRC.

Limitations

The retrospective design of the present study and the small sample size resulted in evidence that was weaker than the evidences obtained in randomized clinical trials. However, we reported the use of apatinib in cases of advanced mCRC, systematically, and found that its efficacy and safety were significant in treating mCRC patients in whom prior treatment with multiple strategies failed. We believe that the potential therapeutic value of apatinib deserves further study, in the form of large multicenter clinical trials.

Conflicts of interest

The authors indicated no potential conflicts of interest.

References

1. Chen W, *et al*. Cancer statistics in China, 2015. CA Cancer J Clin, 2016. 66: 115–132.
2. Tournigand C, André T, Achille E, *et al*. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol, 2004, 22: 229–237.
3. Miyamoto Y, Suyama K, Baba H, *et al.* Recent Advances in Targeting the EGFR Signaling Pathway for the Treatment of Metastatic Colorectal Cancer. Int J Mol Sci, 2017, 18.
4. Heinemann V, von Weikersthal LF, Decker T, *et al*. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. Lancet Oncol, 2014, 15: 1065–1075.
5. Schwartzberg LS, Rivera F, Karthaus M, *et al*. PEAK: a randomized, multicenter phase II study of panitumumab plus modified fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) or bevacizumab plus mFOLFOX6 in patients with previously untreated, unresectable, wild-type KRAS exon 2 metastatic colorectal cancer. J Clin Oncol, 2014. 32: 2240–2247.
6. Tian S, Quan H, Xie C, *et al*. YN968D1 is a novel and selective inhibitor of vascular endothelial growth factor receptor-2 tyrosine kinase with potent activity in vitro and in vivo. Cancer Sci, 2011, 102: 1374–1380.
7. Grothey A, van Cutsem E, Sobrero A, *et al*. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet, 2013, 381: 303–312.
8. Loupakis F, Cremolini C, Masi G, *et al*. Initial therapy with FOLFOXIRI and bevacizumab for metastatic colorectal cancer. N Engl J Med, 2014, 371: 1609–1618.
9. Tian S, Quan H, Xie C, *et al*. YN968D1 is a novel and selective inhibitor of vascular endothelial growth factor receptor-2 tyrosine kinase with potent activity in vitro and in vivo. Cancer Sci, 2011, 102: 1374–1380.
10. Goel S, Duda DG, Xu L, *et al*. Normalization of the vasculature for treatment of cancer and other diseases. Physiol Rev, 2011, 91: 1071–121.
11. Ding L. The Use of apatinib in treating nonsmall-cell lung cancer: case report and review of literature. Medicine, 2016, 95: 3598.
12. Lao, V.V. and W.M. Grady, Epigenetics and colorectal cancer. Nat Rev Gastroenterol Hepatol, 2011, 8: 686–700.
13. Siegel, R.L., K.D. Miller and A. Jemal, Cancer Statistics, 2017. CA Cancer J Clin, 2017, 67: 7–30.
14. Machover D, Goldschmidt E, Chollet P, *et al*. Treatment of advanced colorectal and gastric adenocarcinomas with 5-fluorouracil and high-dose folinic acid. J Clin Oncol, 1986, 4: 685–696.
15. de Gramont A, Bosset JF, Milan C, *et al*. Randomized trial comparing monthly low-dose leucovorin and fluorouracil bolus with bimonthly high-dose leucovorin and fluorouracil bolus plus continuous infusion for advanced colorectal cancer: a French intergroup study. J Clin Oncol, 1997, 15: 808–815.
16. Van Cutsem E, Twelves C, Cassidy J, *et al*. Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: results of a large phase III study. J Clin Oncol, 2001, 19: 4097–4106.
17. Douillard JY, Cunningham D, Roth AD, *et al*. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. Lancet, 2000, 355: 1041–1047.
18. Kalofonos HP, Aravantines G, Kosmidis P, *et al*. Irinotecan or oxaliplatin combined with leucovorin and 5-fluorouracil as first-line treatment in advanced colorectal cancer: a multicenter, randomized, phase II study. Ann Oncol, 2005, 16: 869–877.
19. Cassidy J, Tabernero J, Twelves C, *et al*. XELOX (capecitabine plus oxaliplatin): active first-line therapy for patients with metastatic colorectal cancer. J Clin Oncol, 2004, 22: 2084–2091.
20. Riechelmann R, Grothey A. Antiangiogenic therapy for refractory colorectal cancer: current options and future strategies. Ther Adv Med Oncol, 2017, 9: 106–126.
21. Folkman J. Tumor angiogenesis: therapeutic implications. N Engl J Med, 1971, 285: 1182–1186.

22. Shibuya M. VEGF-VEGFR signals in health and disease. Biomol Ther, 2014, 22: 1–9.
23. Al-Husein B, *et al*. Antiangiogenic therapy for cancer: an update. Pharmacotherapy, 2012, 32: 1095–1111.
24. Koch S, Tugues S, Li X, *et al*. Signal transduction by vascular endothelial growth factor receptors. Biochem J, 2011, 437: 169–183.
25. Carmeliet P, Jain RK. Molecular mechanisms and clinical applications of angiogenesis. Nature, 2011, 473: 298–307.
26. Gerber HP, Ferrara N. The role of VEGF in normal and neoplastic hematopoiesis. J Mol Med, 2003, 81: 20–31.
27. Hurwitz H, *et al*. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med, 2004, 350: 2335–2342.
28. Qin S. Phase III study of apatinib in advanced gastric cancer: A randomized, double-blind, placebo-controlled trial. J Clin Oncol. 2014, 32: 4003.
29. Li J, Zhao X, Chen L, *et al*. Safety and pharmacokinetics of novel selective vascular endothelial growth factor receptor-2 inhibitor YN968D1 in patients with advanced malignancies. BMC Cancer, 2010, 10: 529.
30. Kang BW, Kim TW, Lee JL, *et al*. Bevacizumab plus FOLFIRI or FOLFOX as third-line or later treatment in patients with metastatic colorectal cancer after failure of 5-fluorouracil, irinotecan, and oxaliplatin: a retrospective analysis. Med Oncol, 2009, 26: 32–37.
31. Li J, Qin S, Xu J, *et al*. Apatinib for chemotherapy-refractory advanced metastatic gastric cancer: results from a randomized, placebo-controlled, parallel-arm, phase II trial. J Clin Oncol, 2013, 31: 3219–3225.

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