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# Efficacy and safety of anlotinib in patients with advanced colorectal cancer and analysis of prognostic factors

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Anlotinib, as the new RTK inhibitor molecule, has gained significant interest among researchers in drug development targeting tumors. In this study, we investigated the efficacy and safety of anlotinib in patients with advanced colorectal cancer and analyzed the prognostic factors. A total of 116 patients with advanced colorectal cancer who were treated in the oncology center of our hospital from March 2018 to March 2019 were selected. All patients were divided into a control group and an observation group according to the random number table method, with 58 cases in each group. The patients in the group were given docetaxel treatment, and the observer patients were given anlotinib treatment on this basis. The short-term efficacy, disease control rate, tumor progression time, median survival time and 1-year survival rate of the two groups after treatment were compared; The incidence of adverse reactions during treatment in the two groups; Kaplan-Meier method was used to analyze the prognostic factors of colorectal cancer patients. The total effective rate of patients in the observation group after treatment with anlotinib in the near future was 44.83%, which was significantly higher than 25.86% in the control group, the difference was statistically significant. The disease control rate and 1-year survival rate of the observation group after treatment with anlotinib were significantly higher than the control group, the difference was statistically significant, and the tumor progression time and survival time of the observation group were significantly longer than the control group. There was no significant difference in the total incidence of adverse reactions such as diarrhea, nausea and vomiting, leukopenia, thrombocytopenia, oral mucositis between the two groups of patients during treatment. Kaplan-Meier method analysis found that age, treatment plan, lymph node metastasis, and residual tumor diameter are all risk factors affecting the prognosis of colorectal cancer patients.

**Keywords:** Anlotinib, RTK inhibitor

Colorectal cancer is one of the most common malignant tumors in the digestive system. According to GLOBACON 2020 report, colorectal cancer is rated as 3rd most common cancer affecting humans after breast and lung cancer. Incidence of colorectal cancer is estimated to be 10% of total 19.3 million cases of all types. It accounts for 9.4% of total 10 million cancer deaths reported worldwide[1]. The rate of incidence of colorectal cancer has attracted many researchers to work on its pathology, developing effective drugs, association with gene polymorphisms and prognosis, etc.[2-5].

The onset of colorectal cancer is closely related to lifestyle, genetics, and colorectal adenoma. The patient has no obvious symptoms in the early stage. As the cancer develops, it can show changes in stool habits and abdominal pain, blood in the stool, with or without systemic symptoms such as anemia and fever, threatens the safety of human life[6]. In recent years, the incidence of colorectal cancer in China has increased, ranking third in the incidence of malignant tumors, and its early detection rate is slow. It is prone to metastasis. Radiotherapy and chemotherapy can cause a variety of toxic and side effects such as hair loss and gastrointestinal side reactions, making the patients less tolerant to treatment[7,8]. Targeted therapy has become a new direction for cancer therapy. Molecular targeted therapy refers to the interference of signal transduction pathways between cells in the process of tumor development. These drugs have the characteristics of targeting and non-cytotoxicity, and have been studied It was confirmed that molecular targeted therapy drugs played an important role in NSCLC drug therapy[9].

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Anlotinib is a self-developed multi-target molecular drug[10]. It is a new type of highly selective oral small molecule tyrosine kinase inhibitor. It has anti-tumor angiogenesis and tumor growth inhibitory effects. Anlotinib can significantly inhibit the growth of liver cancer, colorectal cancer, and lung cancer mouse tumors and reduce the area of tumor spread[11]. In this study, we analyzed the efficacy and safety of anlotinib in patients with advanced colorectal cancer and also observed the prognostic factors.

## Materials and methods

### Object source

A total of 116 patients with advanced colorectal cancer who were treated in the oncology center of our hospital from March 2018 to March 2019 were selected as the research object. This study was approved by the hospital ethics committee and necessary informed consent was obtained priorly. Inclusion criteria: (i) All patients meet the clinical diagnostic criteria for colorectal cancer; (ii) Diagnosed as colorectal cancer by pathological biopsy or impactology examination; (iii) According to the International Anti-Cancer Union TNM stage are all stage IV; (iv) Patients with intolerable chemotherapy regimen; (v) Age ≥17 years old, expected survival time >3 months; and (vi) Patients and family members know and cooperate with treatment. Exclusion criteria:(i) Critically ill, Carn's score <50; (ii) Combined with respiratory failure and severe organic diseases; (iii) Estimated survival time <3 months; (iv) Those who have participated in other anti-tumor drug clinical studies within one month; (v) Patients with obvious mental disorders; and (vi) Patients with poor treatment compliance caused by various reasons are excluded. All patients were randomly divided into a control group and an observation group, with 58 cases in each group, including 36 males and 22 females in the observation group, aged 6-18 years, with an average age of (6.40±8.5) years, and a disease course of 0.4-3.0 years, with an average (1.45±0.29) years, including 15 cases of well-differentiated adenocarcinoma, 18 cases of moderately-differentiated adenocarcinoma, 11 cases of poorly differentiated adenocarcinoma, 14 cases of mucinous adenocarcinoma; 25 cases of liver metastasis, 16 cases of lung metastasis, and 17 cases of pelvic abdominal metastasis. In the control group, there were 34 males and 24 females, aged 7-18 years, with an average age of (5.28±10.54) years, with a disease duration of 0.4-3.0 years, with an average (1.50±0.31) years, including 16 cases of well-differentiated adenocarcinoma and moderately differentiated adenocarcinoma 32 cases, six cases of poorly differentiated adenocarcinoma, four cases of mucinous adenocarcinoma; 29 cases of liver metastases, 13 cases of lung metastases, 16 cases of pelvic and abdominal metastases. After statistical testing, the general data of the two groups were comparable ($P$ >0.05).

### Treatment method

Patients in the control group were given cisplatin for treatment: given docetaxel (specification 20 mg/ branch, Jiangsu Hengrui Pharmaceutical Co., Ltd., production lot number 160721) 75 mg/m$^2$, adding 250 mL of 0.9% sodium chloride solution, intravenous infusion for one hour, each Period 21 d, until the patient's disease progression or intolerance of adverse reactions, the drug was discontinued. Patients in the observation group were given oral anrotinib hydrochloride capsules (specification: 12 mg/capsule, Zhengda Tianqing Pharmaceutical Group Co., Ltd., production batch number: 180204) on the basis of the control group, 12 mg, orally before breakfast, once a day, continuous medication Withdrawal for two weeks for one week, every three weeks is a course of treatment, four consecutive courses of treatment. During treatment, the two groups should pay attention to diet, fasting spicy and stimulating food, and strengthen psychological care.

### Observation index

(i) Clinical efficacy: Complete remission: All measurable tumor lesions completely disappeared and maintained for more than one month; Partial remission: The sum of the largest vertical and horizontal diameter products of tumor lesions was reduced by 50% and maintained for more than one month; Stable: Tumor area was reduced by less than 50% Or increase no more than 25%; Progress: At least one lesion increased more than 25% or new lesions appeared. Objective effective rate = (complete remission + partial remission) / total number of cases × 100%, disease control rate = (complete remission + partial remission + stable) / total number of cases × 100%. (ii) Follow-up was conducted by outpatient service or telephone call. The cut-off time was March 2018 or death occurred. The tumor progression time, median survival time and 1-year survival rate of the two groups were compared. (iii) Observe the

occurrence of adverse reactions during treatment in both groups, including fatigue, nausea and vomiting, leukopenia, thrombocytopenia, and oral mucositis.

**Statistical analysis**

The measurement data in this study are represented by ( $\bar{x}\pm s$), the comparison between the observation group and the control group by *t* test, all the count data are represented by [n (%)], the comparison of the data between the two groups by $\chi^2$ test, Kaplan-Meier method analysis Factors affecting the prognosis of patients with colorectal cancer, The value of $P < 0.05$ was considered statistically significant, and the data of this study were analyzed using SPSS 21.0 software package.

## Results

**Comparison of the short-term efficacy of the two groups of patients after treatment**

The total effective rate of the observation group after anlotinib treatment was 44.83%, which was significantly higher than that of the control group, 25.86%. The difference was statistically significant ($P < 0.05$). These results are shown in Table 1.

**Comparison of long-term efficacy of two groups of patients after treatment**

The disease control rate and 1-year survival rate of the observation group after treatment with anlotinib were significantly higher than the control group, the difference was statistically significant ($P < 0.05$). And the tumor progression time and survival time of the observation group were significantly longer than the control group ($P < 0.05$). These results are shown in Table 2.

**Comparison of the incidence of adverse reactions between the two groups**

There was no significant difference in the total incidence of adverse reactions between the two groups of patients during the treatment, such as fatigue, nausea and vomiting, leukopenia, thrombocytopenia, oral mucositis ($P > 0.05$). These results are shown in Table 3.

Table 1 — Comparison of short term efficacy of Control and Observation groups of patients after treatment [n (%)]

| Efficacy | Control | Observation |
|---|---|---|
| Partial relief | 14 (24.14) | 25 (43.10) |
| Stable | 17 (29.31) | 18 (31.03) |
| Improvement | 27 (46.55) | 15 (25.86) |
| Efficient | 14 (24.14) | 25 (43.10) |

[$\chi^2$= 4.674; and *P*= 0.031. Each group had 58 cases No group had complete relief]

**Analysis of factors affecting prognosis of patients with colorectal cancer**

Kaplan-Meier method analysis found that age, treatment plan, lymph node metastasis, and residual tumor diameter are all risk factors affecting the prognosis of colorectal cancer patients ($P<0.05$). These results are shown in Table 4.

## Discussion

Colorectal cancer is more common in the elderly, the patients are more prolonged, and there are no obvious symptoms in the early stage, and most of them are in the advanced stage. However, occurrence among children and young adults cannot be ruled out. At present, the main methods of clinical treatment of lung cancer include surgery, radiation therapy, chemotherapy, traditional Chinese medicine treatment, etc. Since more than 50% of patients are in advanced stages at the time of treatment, the lesions gradually spread to the body and it is not suitable for surgical treatment. Patients will still relapse and metastasize after receiving treatment. Remote

Table 2 — Comparison of long-term efficacy of two groups (Control and Observation) of patients after treatment (x±s)

| Parameters | Control | Observation | $\chi^2$ | *P* |
|---|---|---|---|---|
| Disease control rate (%) | 37 (63.79) | 48 (82.76) | 5.375 | 0.020 |
| 1-year survival rate (%) | 4 (6.90) | 18 (31.03) | 10.994 | <0.001 |
| Tumor progression time (d) | 185.36 ±15.17 | 234.08 ±24.74 | 12.785 | <0.001 |
| Lifetime (d) | 218.16 ±13.55 | 390.15 ±20.87 | 52.640 | <0.001 |

[Each group had 58 cases]

Table 3 — Comparison of the incidence of adverse reactions between the two groups [n (%)]

| Adverse reactions | Control group | Observation group |
|---|---|---|
| Fatigue | 2 (3.45) | 2 (3.45) |
| Feel sick and vomit | 1 (1.72) | 3 (5.17) |
| Leukopenia | 1 (1.72) | 2 (3.45) |
| Thrombocytopenia | 1 (1.72) | 2 (3.45) |
| Oral mucositis | 2 (3.45) | 3 (5.17) |
| Total incidence | 7 (12.07) | 12 (24.14) |

[$\chi^2$= 2.849; and *P*= 0.091. Each group had 58 cases]

Table 4 — Analysis of factors affecting the prognosis of colorectal cancer patients

| Influence factor | | No. of Cases | Live for 3 years | $\chi^2$ | *P* |
|---|---|---|---|---|---|
| Age | 17 year | 59 | 41 (69.49) | 4.991 | 0.025 |
| | ≥18 year | 57 | 28 (49.12) | | |
| Treatment programs | Observed | 58 | 40 (68.97) | 4.328 | 0.037 |
| | Control group | 58 | 29 (50.00) | | |
| Lymph node metastasis | Yes | 34 | 6 (17.65) | 34.929 | <0.001 |
| | No | 82 | 63 (76.83) | | |
| Residual tumor diameter | ≤2cm | 94 | 65 (69.15) | 19.215 | <0.001 |
| | >2cm | 22 | 4 (18.18) | | |

metastasis is the main cause of death in colorectal cancer patients[12,13]. Relevant data show that the 5-year survival rate of patients with colorectal cancer after early radical resection can be as high as 90%, and the survival rate of patients with metastasis is less than 10%. And as the age increases, the lower the survival rate, so the early treatment of patients with rectal cancer is of great significance to improve the prognosis and survival of patients[14]. In recent years, with the advancement of molecular biology technology, based on the molecular biology of tumor cells, people use cell receptors, key genes and regulatory molecules as targets for treatment, so as to achieve the purpose of inhibiting tumor growth to treatment. At present, the action sites of molecular targeted drugs are mainly the traditional signaling pathways related to vascular endothelial growth factor and epidermal growth factor receptor, which will promote the treatment of colorectal cancer to the molecular level[15].

Anlotinib hydrochloride is a multi-targeted receptor tyrosine kinase inhibitor, which has been approved for the third-line treatment of advanced non-small cell lung cancer, which can prolong the survival of patients and improve clinical symptoms. Vascular endothelial cell growth factor and platelet-derived growth factor receptor thereby, blocking the signal transmission between epidermal factors and inhibiting the progression of tumor cells[16]. The signaling pathway mediated by c-Kit plays an important role in the occurrence, development and metastasis of various malignant tumors. Anlotinib can inhibit the downstream signaling pathway mediated by the stem cell factor receptor, thereby inhibiting tumor growth, interfering with multiple biological processes of tumor cells[17]. In addition, anlotinib significantly inhibits fibroblast growth factor and its receptors and other signaling pathways, thereby inhibiting tumor angiogenesis, the proliferation and spread of tumors play an antagonistic role[18]. Animal experiments have found that anlotinib hydrochloride can effectively inhibit the growth of transplanted tumors and reduce the number of microvessels in the tumor[19]. Anlotinib is commonly used in the treatment of lung cancer in clinic. Some scholars found that the lung tumor of patients with advanced sarcomatoid carcinoma showed obvious necrosis and cavity formation after two cycles of treatment, and the rest of the lesions did not increase significantly, and the condition was stable[20]. Some scholars have used anlotinib in patients with advanced metastatic colorectal cancer, and found that 26 patients had a disease control rate of 75% after a course of treatment, and the patient's overall treatment was well tolerated[17]. Oralinib hydrochloride can avoid serious toxic and side effects such as nausea and vomiting caused by traditional chemotherapy, and do not require intravenous injection. It is simple and convenient to use, and relatively few auxiliary drugs provide another treatment for patients who cannot receive chemotherapy method.

The results of this study showed that the total effective rate, disease control rate, and one year survival rate of the observation group afteranlotinib hydrochloride treatment were significantly higher than the control group. The tumor progression time and survival period were also significantly longer than the control group ($P$ <0.05). These findings demonstrate use of anlotinib in the treatment of patients with advanced colorectal cancer with improved clinical efficacy and prolonged survival of the patients. In addition, in this study, Kaplan-Meier method analysis found that age, treatment plan, lymph node metastasis, and residual tumor diameter are all risk factors that affect the prognosis of colorectal cancer patients ($P$ <0.05). As the age increases, the patient's immune system declines, and cancer cells are more prone to metastasis; the smaller the residual tumor diameter after surgery, the longer the patient's survival time. It can be seen that complete surgical resection of the tumor can help prolong the survival time of the patient and improve the prognosis.

## Conclusion

The findings of this study indicates that application of anlotinib in patients with advanced colorectal cancer for improves clinical efficacy, prolong patient survival and quality of life. It is also observed that factors such as prognosis and age, treatment plan, lymph node metastasis, residual tumor diameter and other clinical case factors are closely related and influence recovery.

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