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Application Progress of Bevacizumab in Neoadjuvant Therapy for Locally Advanced Rectal Cancer

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Abstract

Rectal cancer is a common malignant tumor of the digestive tract, and most patients with locally advanced stage cannot be directly surgically removed. Neoadjuvant therapy can reduce the tumor staging of patients, and then accept surgical treatment, improve the quality of life and the prognosis. Bevacizumab can inhibit the formation of tumor angiogenesis, in recent years, it has been used in neoadjuvant therapy for locally advanced rectal cancer, and has achieved certain clinical efficacy. In this summary, we have reviewed the recent literatures on bevacizumab in neoadjuvant therapy for locally advanced rectal cancer, and summarized them to provide some references for clinical application.

Keywords

Bevacizumab; Locally advanced stage; Rectal cancer; Neoadjuvant therapy.

1. INTRODUCTION

Rectal cancer is the cancer that occurs from the dentate line to the junction of the rectosigmoid colon, and it is one of the most common malignant tumors of the digestive tract, the position of rectal cancer is low, it is easy to be diagnosed by digital rectal touch and sigmoidoscopy, however, because its position go deep into in the pelvic cavity, its anatomical relation is complicated, it is not easy to remove in the operation, and its postoperative recurrence rate is high[1] The age of onset median of rectal cancer in China is 45 years old or so, and the incidence of young people is increasing[2]. At present the cause of rectal cancer is still unclear, and its incidence is related to social environment, eating habits, genetic factors, etc., most of the early rectal cancers are asymptomatic, when rectal cancer grows to a certain extent, changes in defecation habits appear, bloody stools, bloody purulent stools, tenesmus, constipation, diarrhea, etc.; the stools gradually become thinner, in the advanced stage, there are defecation obstruction, weight loss and even cachexia; when the tumor invades the bladder, urethra, vagina and other surrounding organs, urinary irritation symptoms, dung fluid discharges from vagina, the sacrum and perineum ache, and lower extremity edema occur[3]. With the extensive promotion of molecularly targeted drugs in clinical practice, bevacizumab has been applied in neoadjuvant therapy for locally advanced rectal cancer, and has a certain curative effect, the contents of this aspect are reviewed at this time.

2. ANTI-TUMOR MECHANISM AND USAGE OF BEVACIZUMAB

2.1. Anti-Tumor Mechanism of Bevacizumab

Anti-tumor mechanism of bevacizumab, vascular endothelial growth factor (VEGF) plays a major part in the formation of tumor angiogenesis, and its high expression stimulates angiogenesis and cause the recurrence and metastasis tumor to be earlier. The drug belongs to

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recombinant humanized antivascular endothelial growth factor monoclonal antibody, which can selectively inhibit its biological activity in combination with VEGF [4, 5]; bevacizumab includes framework segment containing human antibody and antigen-binding segment which can bind humanized mouse VEGF antibody; there are 214 kinds of amino acids in the drug, and the relative molecular mass is about 149×103. Bevacizumab can inhibit the binding of VEGF and the receptors Flt-1 and KDR on the surface of endothelial cells, thereby prompting the disappearance of the biological activity of VEGFR, reducing the formation probability of tumor blood vessel, and inhibiting tumor growth, as a result, the formed tumor blood vessels are normalized, reduces the permeability of tumor blood vessels, increases the concentration of chemotherapeutic drugs in tumor tissue, and can achieve the synergistic effect of chemotherapy. According to NO16966, ATIST, AVF2017, E3200 and other multi-center studies, it suggests that bevacizumab has a significant curative effect in the treatment of advanced colorectal cancer; furthermore, the anti-angiogenesis effect will prompt the sensitivity of tumors to radiotherapy reduced, and promote the necrosis and apoptosis of tumor cells [6]. Moreover, the drug will not be affected by the mutation of the KARS gene, according to relevant studies, it suggests that although bevacizumab treatment can be continued after disease progression, the original chemotherapy plan should be changed [7].

2.2. Usage and Do's and Don'ts of Bevacizumab in Neoadjuvant Therapy for Locally Advanced Rectal Cancer

On the 1st day of clinical use of bevacizumab, choose 5-10 mg/kg, dilute with 0.9% sodium chloride solution, prompt the concentration maintain at 1.4-16.5 mg/mL, and infuse intravenously before infusing other chemotherapy drugs, the first infusion time should be maintained for 90min, if the patient's tolerance to the first intravenous infusion is better, the second infusion time can be appropriately reduced to 60mim, if the patient can also tolerate the 60min infusion, then the infusion time can be adjusted to 30min. Moreover, bevacizumab cannot be used together or mixed with low-molecular-weight dextran and sugar solutions.

3. EFFECTIVENESS OF BEVACIZUMAB IN NEOADJUVANT THERAPY FOR LOCALLY ADVANCED RECTAL CANCER

Patients were treated with bevacizumab and neoadjuvant chemoradiotherapy based on 5-fluorouracil, the curative effect was evaluated about 30 days after completion, the treatment outcome includes: first, neoadjuvant radiotherapy and chemotherapy have significant effects, TME operation can effectively cure the disease, TME opertion will be carried out 28 days after neoadjuvant therapy, and most of them will choose to carry out surgical treatment on the 42nd day after operating. Second, the tumor has not progressed and has not been cured, this type of patients can continue to receive adjuvant chemotherapy with bevacizumab. Third, local tumor progression and distant metastasis, this type of patients of this type can continue to receive bevacizumab, but need to change the chemotherapy regimen [8, 9]. Research indicates that in the phase I clinical trial of neoadjuvant chemoradiotherapy for locally advanced rectal cancer, bevacizumab was applied to it, bevacizumab was used at two doses of 5 and 10 mg/kg (mainly 6 and 5 cases) on the 1st, 15th, and 29th days, the total dose reached 50.4Gy, which was divided into 28 times, from the 15th to the 52nd day, 5-fluorouracil (225mg/m2) was added during the treatment, all patients were operated at 7-9 weeks of radiotherapy; the results were: the complete remission (pCR) rate of patients in the 10 mg/kg group was 43.25%, according to the molecular analysis of the specimens, bevacizumab could prompt the apoptosis of tumor cells, moreover, bevacizumab was evaluated to increase the sensitivity of tumor cells to radiotherapy [10]. The phase II study of bevacizumab (5mg/kg) and capecitabine for locally advanced rectal cancer was carried out in study, the results were that the pCR rate was 31.95%, the basic pathology of 25.14% of the patients' tumor was complete eased, and the local recurrence rate

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of the tumor was 6.17% 2 years after the operation. The data of the phase II clinical study is analyzed, the pCR rate was about 21.05%, but the pCR rate without bevacizumab was about 12.54%; phase II clinical studies indicates that neoadjuvant chemoradiotherapy for locally advanced rectal cancer with bevacizumab can improve the pCR rate of the tumor; however, the results of phase III clinical studies in various countries and multi-centers suggested that the improvement extent of the pCR rate was not significant, and the results of some studies showed that it did not improve; and both phase II and III studies lacked the 5-year survival rate and local recurrence rate study on patients [11].

Various clinical studies indicates that there are certain differences in the pCR rate of bevacizumab, which may be related to the following factors: first, different combined chemotherapy regimens, and now commonly used combined chemotherapy regimens include FOLFOX4, FOLFIRI , XELOX, according to their differences, At present, there is no favorable evidence to confirm which chemotherapy regimen is most effective in combination with bevacizumab [12]; second, the dose of bevacizumab, choose 10mg/kg and 5mg/kg dose for application, the 10mg/kg pCR rate is higher than 5mg/kg group, and because the 10mg/kg group had more than grade 3 adverse reactions related to bevacizumab than the 5mg/kg group, severe diarrhea, colitis are common, therefore, the following phase II and III studies chose to use the dose of 5 mg/kg; third, different radiotherapy regimens, generally used short-course intensive radiotherapy (1-week regimen) and long-term regimen (namely 5-week regimen); fourth, the staging method of tumors before operating, although the staging before operating has been significantly improved based on the gradual improvement of inspection equipment (high-resolution magnetic resonance/CT and intracavitary ultrasound), however, it is still difficult to assess whether there is lymph node metastases and the number of metastases before operating; fifth, there is no controlled trial, now there are no controlled trial for pathological response rates in locally advanced colorectal cancer.

3 Safety of Bevacizumab in Neoadjuvant Therapy for Locally Advanced Rectal Cancer

ater bevacizumab is applied to patients clinically, induced adverse effects is associated with antiangiogenic, for example, severe bleeding, hypertension, wound healing complications, gastrointestinal perforation, etc. [9]. Its adverse reactions in other tumor treatments include: bleeding, such as gatrointestinal bleeding, hemoptysis, epistaxis can increase up to 5 times, and also induce severe bleeding and fatal bleeding;The incidence of gastrointestinal perforation is about 1.37%, if serious, it even threaten the patient's life, complications of surgery and wound healing, the application of bevacizumab will increase slow wound healing and surgical complications; patients who have complications of wound healing require short-term stopping of bevacizumab until the wound heals [13]. It is expected that bevacizumab should be stopped for a short period of time during selective operation, and the most appropriate interval between withdraw, selective operation has not yet been determined. The drug should be stopped for at least 4 weeks before operating, and the safety is relatively high for 6-8 weeks. Bevacizumab is banned for 4 weeks after operating and until wound healing; the drug does not require dose adjustment in the elderly, and in randomized clinical studies, patients over 65 years old are more likely to have cerebrovascular accident and myocardial infarction than patients with younger age. In some studies, patients with locally advanced rectal cancer have been observed, and the adverse reactions induced by neoadjuvant therapy in combination with bevacizumab are usually mild, and only a few patients had grade 3 toxic side effects, no toxicity and adverse reactions exceeding grade 3 occurred [13]. According to a large number of studies, the safety of bevacizumab and fluorouracil-based neoadjuvant chemoradiotherapy in preoperative and postoperative adverse reactions is relatively high [14, 15]. Therefore, the use of bevacizumab and 5-fluorouracil-based preoperative chemoradiotherapy did not significantly increase the complications of locally advanced rectal cancer and the side effects of chemoradiotherapy.

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4. SUMMARY

the bevacizumab in applied in neoadjuvant chemoradiotherapy for locally advanced rectal cancer is highly safe and does not increase the toxicity and incidence of adverse reactions of radiotherapy and chemotherapy; the effectiveness of this drug in neoadjuvant chemoradiotherapy for locally advanced rectal cancer is still unclear. A large number of control, random, large-sample trials and Meta-analyses are still needed for clinical confirmation;

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