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Advances in monoclonal antibody therapy for colorectal cancer

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Abstract. As a disease phenomenon, the existence and recognition of cancer can be traced back to the medical literature long ago. However, the modern scientific understanding and classification of CRC are gradually formed with the deepening of medical research. Through long-term clinical observation, pathological research and the development of molecular biology technology, scientists have gradually revealed the pathogenesis, genetic characteristics and treatment of CRC. As for the invention of mAb for the treatment of CRC, it is the product of rapid development of biomedical technology in recent decades. In the treatment of CRC, a variety of mAb have been developed and applied clinically, such as monoclonal drugs targeting key signaling pathways such as EGFR and VEGF. The invention and application of these drugs provide new treatment options and hopes for CRC patients, and allow patients to have more choices to choose their own drugs to avoid some side effects during treatment.

Keywords: Colorectal cancer, monoclonal antibodies, EGFR, VEGF, cancer treatment.

1. Introduction

CRC is the third leading cause of cancer incidence in both men and women worldwide, and is the second leading cause of cancer-related death, particularly among gastrointestinal cancers. There are a wide range of risk factors for developing the disease, including an unhealthy diet, smoking habits, a history of intestinal inflammatory diseases, the presence of polyps, familial genetic predispositions, and aging. Statistics show that more than 90% of patients diagnosed with CRC are over 50 years old, and the average age is 64 years old. However, it is important to note that for those diagnosed at a younger stage, the disease tends to progress more rapidly and aggressively. According to the American Cancer Society, more than 49,700 people died of CRC in 2015 [1]. In the West, CRC is the most common type of solid tumor. Therapeutic strategies are developed based on the progression of the disease, the health status of the patient, and the evolving molecular properties of the tumor. In countries with surveillance systems, timely detection of tumors has reduced morbidity and mortality from the disease. It is important to note that there are significant differences between the guidelines of care for rectal cancer and the treatment options taken in the perioperative period of colon cancer [2]. The management of metastatic CRC has evolved significantly over the past few decades, with systemic chemotherapy establishing its role in improving outcomes beyond best supportive care. However, recent advancements have focused on targeted therapies that exploit specific molecular pathways involved in tumor growth and progression. One such therapy is Vectibix, a fully human mAb targeting the EGFR. This paper provides a comprehensive introduction to panitumumab.

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The main causes the cancer were lack of sport and, the rate of fat increase. There is a document that clearly shows the information on the cause of the problem, The highest CRC Between 1998 and 2002, registries in North America, Oceania and Europe recorded significant increases in incidence. This trend is likely due to increased risk factors associated with a "westernized" lifestyle, such as increased obesity and decreased physical activity. In contrast, registries in Asia, Africa and South America show the lowest levels of CRC incidence. Notably, CRC mortality has shown a downward trend in many long-term and emerging economies. However, in some resource-poor countries in South America and Eastern Europe, death rates from the disease continue to rise [3].

The content of this paper will discuss the treatment of CRC, the basic principle of this medicine, and show the work mechanism of medicine, medicines will have different speeds of treatment, different effects of treatment, what binding site the medicine will combine with different approach Including side effect and safety. What way needed to improve, to avoid some problems, such as drug resistance, conditions in the course of treatment for patients.

2. MAb binding site

2.1. EGFR

EGFR is membrane surface sensor with tyrosine kinase activity and is commonly expressed in human epidermal cells and stromal cells, EGFR is closely related to the proliferation of tumor cells, the formation, invasion and metastasis of blood vessels, and cell apoptosis and inhibition. Some studies have found that EGFR overexpression plays an important role in the evolution of malignant tumors, EGFR is highly or abnormally expressed in many solid tumors, such as lung cancer, prostate cancer, pancreatic cancer, and breast cancer. Especially in non-small cell lung cancer, EGFR gene mutations are more common in patients, and the mutation rate can reach 35%-40%. EGFR is widely distributed on the surface of mammalian epithelial cells, fibroblasts, glial cells, and keratinocytes. EGFR is divided into three regions: extracellular ligand-binding region, extracellular ligand-binding region, and extracellular ligand-binding region.

2.2. HER

It includes four highly homologous members EGFR, HER2, HER3, and HER4. These receptors play a role in both normal and tumor cells, mediating processes such as cell division, migration, survival and organ development. When mutations occur, they may produce abnormal signaling that stimulates cell survival and growth and is associated with cancer progression. HER can enhance Tumor angiogenesis, cancer cells' ability to secrete large amounts of VEGF, that can promote the division, proliferation and migration of the inner wall of blood vessels, thereby inducing the formation of tumor neovascularization.

2.3. VEGF

It is a glycoprotein with a strong ability to promote vascular endothelial cell proliferation, migration and lumen formation. VEGF can induce neovascularization, increase vascular permeability, and change the extracellular matrix, thereby supporting tissue growth and repair. When VEGF overexpress in tumor, that also can induce the formation of tumor. Overexpression of VEGF in tumors promotes the development of CRC, and the T/N ratio higher than 4.8 is a significant predictor of mRNA overexpression. Patients with this state had a worse prognosis than those without overexpression ($P<0.001$), and the risk of death was nearly two times higher ($P=0.005$). Studies have shown that VEGF is closely related to the deterioration, invasion and metastasis of CRC, and overexpression of VEGF mRNA in primary tumors is a poor prognostic indicator of CRC. In addition, the VEGF T/N ratio is expected to be an independent prognostic marker for CRC [4].

3. Working mechanism of mAbs

In the treatment of CRC, Panitumumab is used to treat metastatic colorectal cancer. By binding to EGFR, it prevents the EGFR on the surface of tumor cells from binding to ligands, thus inhibiting the

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proliferation and metastasis of tumor cells. This mechanism of action is based on interference with the EGFR signaling pathway and aims to block the growth signal of tumor cells for therapeutic purposes.

In the treatment of CRC, Pertuzumab binds specifically to the extracellular domain of the HER2 receptor, by binding to HER2, pertuzumab is able to prevent HER2 from forming heterodimers with other members of the HER2 family, such as HER3, thereby inhibiting the activation of the HER2 signaling pathway. This inhibition has a significant anti-proliferation effect on HER2 overexpressed tumor cells. In addition, pertuzumab can work with other drugs, collaboration with trastuzumab PertuZumab is mechanologically complementary to trastuzumab. Trastuzumab binds to the extracellular domain IV of the HER2 receptor, while pertuzumab binds to the domain l. The combination of the two can completely block the signaling of the HER2 channel, thereby enhancing the inhibition of tumor growth, and the antibody-dependent cell-mediated cytotoxic effect (ADCC): In addition to directly inhibiting the signaling, pertuzumab can also activate killer cells such as NK cells in the immune system to further destroy tumor cells through ADCC action.

Bevacizumab's primary mechanism of action targets VEGF, a molecule that plays a key role in tumor growth. The rapid growth of tumor cells requires the formation of new blood vessels to provide nutrients and oxygen, and Bevacizumab inhibits tumor angiogenesis by inhibiting the function of VEGF. This inhibition can slow or stop the growth and spread of tumors. Bevacizumab does not directly act on tumor cells, but acts on VEGF molecules that cause tumor angiogenesis. By blocking the binding of VEGF and its receptor, bevacizumab fundamentally closes the angiogenesis signaling pathway, inhibits endothelial cell mitosis, reduces neovascularization, and blocks tumor growt. Bevacizumab, as a treatment, works by precisely targeting and binding to circulating VEGF molecules. This process effectively blocks the interaction between VEGF and its receptors on the cell surface, thereby inhibiting the formation and expansion of microvessels in the tumor vascular network. This inhibition not only reduces the amount of blood flow to the tumor tissue and limits its nutrient supply, but also improves the permeability of blood vessels by reducing the pressure level of interstitial fluid. This series of effects may enhance the delivery efficiency of chemotherapy drugs to the tumor interior and create favorable conditions for promoting the programmed death of tumor endothelial cells [5]. Bevacizumab is an important anticancer drug that belongs to the class of angiogenesis inhibitors. By inhibiting tumor VEGF, it reduces tumor blood supply, thereby hindering tumor growth and metastasis. The drug is widely used in the treatment of CRC and is often combined with chemotherapy or radiotherapy to improve efficacy. However, the use of Bevacizumab is also associated with some side effects, such as high blood pressure and bleeding. At present, Bevacizumab, as a new anticancer drug, has important clinical application value and development prospect. With the in-depth study of its pharmacological effects and the continuous optimization of treatment programs, it is believed that it will play a more important role in the future cancer treatment, bringing hope and Gospel to more patients and better therapeutic effects

4. Evaluation of the effectiveness of mAbs in CRC

There is treatment outcome of panitumumab. The results of the retrospective evaluation reinforce the view that in patients with RAS (WT), right-sided primary tumors exhibit a more adverse prognosis than left-sided tumors, regardless of whether patients have received first-line therapy. Notably, for patients with RAS WT with left-sided tumors, the benefit of a treatment regimen containing pallizumab significantly exceeded the strategy of chemotherapy alone or the combination of bevacizumab, and this advantage was reflected in an increase in overall survival - 6.7 months according to the PRIME study. In the PEAK study, there was a significant increase of 11.4 months. However, given the relatively limited sample size of patients included in the analysis, no firm conclusions can be drawn about the best treatment for right-side mCRC in patients with RAS WT. Therefore, more in-depth research is needed in this field to fill this knowledge gap [6].

There is treatment outcome of pertuzumab. When comparing progression-free survival between the two groups, the control group had a median of 12.4 months, compared with 18.5 months for patients treated with pertuzumab. Further analysis of the interim data for overall survival clearly showed that the combination of pertuzumab with trastuzumab and docetaxel had a significant advantage. In terms of

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safety, overall consistency was maintained between the two treatment groups, and no additional burden on left ventricular systolic function was observed. However, it is worth noting that the proportion of cases with febrile neutropenia and grade 3 or higher diarrhea in the pertuzumab group was slightly higher than in the control group [7, 8]. Research on bevacizumab included seven randomized studies. In the analysis of the overall effect, PFS.

5. Conclusion

This paper provides an overview of CRC, including its mechanisms, current treatments, and drug-binding sites. The study compiles essential information on CRC, highlighting the advancements in treatment technologies. However, challenges remain, particularly concerning drug resistance, which is a significant issue in ongoing drug research. Drug resistance poses substantial obstacles to effective treatment, requiring considerable time and effort from scientists to understand and overcome it. Future treatment strategies for CRC will likely continue to emphasize the development and optimization of mAbs, along with the creation of new drugs to enhance and improve the effectiveness of CRC therapies.

References

[1] Granados-Romero J J Valderrama-Treviño A I Contreras-Flores E H et al 2017 Colorectal cancer: A review International Journal of Research in Medical Sciences 5 11 4667
[2] Stintzing S 2014 Management of colorectal cancer F1000prime Reports 6
[3] Center M M Jemal A Smith R A & Ward E 2009 Worldwide variations in colorectal cancer CA: A Cancer Journal for Clinicians 59 6 366-378
[4] Ishigami S I Arii S Furutani M Niwano M Harada T Mizumoto M & Imamura M 1998 Predictive value of vascular endothelial growth factor VEGF in metastasis and prognosis of human colorectal cancer British Journal of Cancer 78 10 1379-1384
[5] Shih T & Lindley C 2006 Bevacizumab: An angiogenesis inhibitor for the treatment of solid malignancies Clinical Therapeutics 28 11 1779-1802
[6] Boeckx N Koukakis R De Beeck K O & Vermorken J B 2017 Primary tumor sidedness has an impact on prognosis and treatment outcome in metastatic colorectal cancer: Results from two randomized first-line panitumumab studies Annals of Oncology 28 8 1862-1868
[7] Baselga J Cortés J Kim S B Im Y H Hegg R Im S A & Cleuter Y 2012 Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer New England Journal of Medicine 366 2 109-119
[8] Baraniskin A Buchberger B Pox C Graeven U Holch J Schmiegel W & Tannapfel A 2019 Efficacy of bevacizumab in first-line treatment of metastatic colorectal cancer: A systematic review and meta-analysis European Journal of Cancer 106 37-44