Analysis Of Research Status of Antibody-Drug Conjugate in The Treatment of Colorectal Cancer

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Abstract. As the most frequent malignant tumors in the digestive system, Colorectal Cancer (CRC) has a high incidence and mortality in recent years. Asymptomatic or asymptomatic symptoms are not obvious in CRC patients due to early clinical manifestations. The current treatment plan for CRC is a comprehensive treatment plan based on surgery, but about 30% of patients still have recurrence and metastasis and lead to death after receiving traditional treatment. The treatment of CRC is still being optimized, and more scientists are constantly investing in the discovery and development of novel medications. With the deepening of research and the improvement of clinical trial data, antibody-drug conjugate (ADC) targeting specific targets have gradually shown great potential therapeutic effects. In this paper, the basic principle of ADC, the research status of ADC for CRC and the application limitations of ADC drugs are reviewed. The development of ADC has brought new hope for the treatment of CRC patients, but the toxicity and drug resistance of ADC is still a great challenge to limit the efficacy of ADC. At present, how to combine ADC with personalized treatment of patients, effectively reduce toxicity, and find the next generation of high efficiency and low toxicity is the development direction of ADC.

Keywords: Colorectal cancer, antibody-drug conjugate, clinical manifestations.

1. Introduction

The colon and rectum are commonly affected by CRC, a malignant tumor of the digestive tract, and is one of the most common cancers in the world, with the third highest incidence in the world. According to the survey data, there will be 1.966,000 new cases and 904,000 deaths worldwide in 2022 [1], and it is expected that by 2040, the number of new CRC cases will reach 2.2 million [2]. The treatment methods of CRC mainly include surgery, radiotherapy, chemotherapy. At present, CRC is mainly treated by surgery. However, CRC is prone to recurrence after surgery, and adjuvant chemoradiotherapy alone cannot effectively reduce recurrence and metastasis. According to statistics, about 30% of patients will still have recurrence and metastasis after surgical treatment, and those who are unlucky will face death [3]. Therefore, in addition to the continuous optimization of traditional surgical protocols, researchers have been accelerating the speed of research and development of new drugs.

ADC is a new class of highly effective drugs, which is a perfect combination of chemotherapy and immunotherapy. ADC is a drug that uses antibodies that can selectively recognize antigens on the surface of cancer cells and attach them to a payload to kill cancer cells. It is a new effective means to fight against malignant tumors after chemotherapy, targeted therapy and immunotherapy.

In the early 20th century, the concept of ADC was proposed by German scientist Paul Ehrlich, who referred to ADC drugs as "magic bullets". Until the 1950s, scientists began to promote the research of ADC drugs. In 1958, Mathe first conjugated mouse antibodies with pterygine to treat leukemia. Due to different issues in immunogenicity and antibody production, the research of ADC has been stationary for decades. It was not until 1975 that Kohler and Milstein introduced hybridoma technology to produce monoclonal antibodies (mAbs), which was combined with the therapeutic application of mAb. In the 1980s, Greg Winter pioneered the technology of humanized mAbs. Major breakthroughs have been made in the development of ADC drugs. However, because the technology is still immature,serious catastrophic liver damage and no substantial survival advantage have occurred during use. Mylotarg, the first drug to be commercialized by ADC, was approved in 2000

and withdrawn from the market in 2010. As of 2024, there are currently 15 ADCs approved worldwide for the treatment of solid tumors and hematological malignancies. It leads a new era of targeted therapy and also brings new hope to CRC patients.

2. The fundamentals of ADC

2.1. The structure of ADC

ADC consists of three main components, mAb, Linker, and highly potent cytotoxic drug (Payload). Antibodies to ADCs are cytotoxic guidance systems that can specifically target a specific antigen that is highly expressed in tumor cells and low or non-expressed in normal cells. The non-specific binding activity with other tissue cells was the lowest. Linkers act as a bridge between antibodies and drugs and can control the release of drugs within cancer cells. As the payload of ADC, highly potent cytotoxic drugs are the main part of drugs that kill tumor cells.

2.2. The mechanism of action of ADC

In the early 20th century, the concept of ADC was first proposed on the assumption that there were specific targets within tumor cells through which tumors could be killed directly by certain compounds. In theory, these compounds can not only effectively kill tumor cells, but also do not harm other normal cells. Traditional cytotoxic drugs do not have tumor targeting, and specific antibody linking can make up for this deficiency. Antibodies in ADCs typically target antigens on the surface of tumor cells and bind to target cytotoxic drugs in tumor tissue. Therefore, the effect on normal cells is reduced, thus achieving a higher and less toxic effect.

ADC has three functions in killing tumor cells [4]. First, cytotoxic agents have antitumor activity. Second, mAb can directly or indirectly exert anti-tumor effects. For example, Cluster of Differentiation (CD) that can directly anti-tumor, human epidermal growth factor receptor 2 (HER2), programmed cell deathprotein1/ Programmed cell death 1 ligand 1, vascular endothelial growth factor (VEGF) and other mAb. Other antibodies can exert indirect anti-tumor effects through mechanisms such as "complement dependent cytotoxicity" and "antibody-dependent cell-mediated cytotoxicity" [5]. Third, cytotoxin exerts anti-tumor effect, and some ADCs have bystander effect. The bystander effect is also known as the bystander kill effect or bystander kill effect. Target antigen positive cells surrounding cells or cancer cells, which can also be normal cells are called "bystander" cells, and usually do not express the target antigen themselves. Under normal circumstances, ADC drugs can only kill cells with high expression of target antigen, but after endocytosis and decomposition of some ADC drugs, when the payload is released from the target cell or in the extracellular space, the drug enters and kills the cells around the target cell [6].

3. Clinical application and clinical manifestations of ADC in CRC

3.1. A major target for CRC

In patients with colorectal cancer, about 20% of patients initially present with metastatic colorectal cancer (mCRC). In addition, 50% of local diseases will eventually metastasize. Therefore, how to effectively deal with mCRC is an urgent clinical problem. mCRC has been found to be associated with mutations in v-raf murine sarcoma viral oncogene homologue B1 (BRAF), Kirsten ratsarcoma viral oncogene homolog (KRAS), and Tumor Protein p53 (TP53). The development of targeted drugs for specific McRc-related drive abnormalities is progressing rapidly, and the main targets include KRAS, HER2, Epidermal Growth Factor Receptor (EGFR), VEGF...

3.2. Approved ADCs

Currently 15 ADC drugs have been approved worldwide (Table 1). It covers the treatment of a variety of malignant tumors, including colorectal cancer, breast cancer, lymphoma, leukemia,

multiple myeloma, head and neck cancer, urothelial cancer, etc. More than 100 ADCs candidates are currently in clinical trials.

Table1. Globally approved ADCs.

TOP-1(DNA topoisomerase 1), Trop-2(Cell surface glycoprotein Trop-2), BCMA (B-cell maturation protein), FOLR1(Folate receptor 1).

Brand name	Drug name	Main enterprise	Global first approval time	Target spot
Mylotarg	Gemtuzumab Ozogamicin	Pfizer	2000/05-first approval 2010/06-romoved 2017/09/01-reapproval	CD33 + DNA
Adcetris	Brentuximab Vedotin	Seagen/Takeda	2011/8/19	CD30+Tubulin
Kadcyla	Trastuzumab Emtansine	Roche	2013/2/22	HER2+Tubulin
Besponsa	Inotuzumab Ozogamicin	Pfizer	2017/6/28	CD22 + DNA
Lumoxiti	Moxetumomab Pasudotox	AstraZeneca	2018/9/13	CD22
Polivy	Polatuzumab Vedotin	Roche	2019/6/10	CD79B+Tubulin
Padcev	Enfortumab Vedotin	Seagen/Astellas	2019/12/18	Tubulin+nectin-4
Enhertu	Trastuzumab Deruxtecan	Daiichi Sankyo Company Limited /AstraZeneca	2019/12/20	HER2+TOP-1
Trodelvy	Sacituzumab Govitecan	Immunomediics	2020/4/22	TOP-1+Trop-2
Blenrep	Belantamab Mafodotin	GSK	2020/8/5-first approval 2022/11/22-removed	BCMA
Akalux	Cetuximab Saratolacan	Rakuten Medical	2020/9/25	EGFR
Zynlonta	1oncastuximab tesirine	ADC Therapeutics	2021/4/23	CD19 + DNA
DisitamabVedotin For Injection	Disitamab Vedotin	Remegen Co., Ltd.	2021/6/8	HER2 +Tubulin
Tivdak	tisotumab vedotin	Genmab/Seagen	2021/9/20	Tubulin+tissue factor
Elahere	mirvetuximab	ImmunoGen/HuaDong Medicine	2022/11/14	FOLR1+Tubulin

3.3. Application of ADC in CRC clinical trials

With the deepening of the research on the molecular biological mechanism of CRC, the development of molecular targeted drugs for key signaling pathways has become a hot direction in the field of CRC. HER2 plays an important role in cell differentiation, cell survival and cell proliferation and has been identified as an effective therapeutic target in gastric carcinoma and pancreatic cancer. In the field of CRC, about 2%-3% of patients are found to be HER2-positive (IHC3+ or IHC2+/ISH+) by immunocytochemistry (IHC) testing and In situ hybridization (ISH) [7]; Positive studies have shown that the incidence of HER-2 amplification in RAS wild-type mCRC is about 5%, but HER2 amplification is rare in patients with KRAS mutation [8]. Trastuzumab, pertuzumab, Tucatinib, lapatinib and other large mab and small molecule drugs have been actively explored in the field of mCRC, and it is confirmed that HER2 can be used as an effective target for CRC (Table 2). However, in the current clinical practice of CRC treatment, the available anti-HER2 treatment options are still limited. The emergence of a new antibody coupling drug, T-DXd (Trastuzumab Deruxtecan), offers new hope for patients with HER2-positive CRC.

Table2. Treatment of HER2 positive mCRC

FISH (Fluorescence in situ hybridization), CISH (Chromogenic in situ hybridization)

	DESTINY-CRCO1research [7] (HER2 positive Cohort A)	HERACLES Research [9-10]		TRIUMPH Research [11]		MOUNTAINEER Research [12]	My Pathway Research [13]
		A	B	Tissue	ctDNA		
Therapeutic regimen	T-DXd(6.4 mg/kg)	Trastuzumab+ Lapatinib	Pertuzumab+T-DM1	Trastuzumab+ Pertuzumab		Trastuzumab+Tucatinib	Trastuzumab+Pertuzumab
Research stage	stage II	stage II	stage II	stage II		stage II	stage II
Lines of therapy	Tumor third line or later	Tumor third line or later	Tumor third line or later	Tumor third line or later		Tumor third line or later	Tumor third line or later
HER2 state	IHC3+2+/ISH+>10%Tumor cells (refer to gastric cancer interpretation criteria)	IHC3+2+/FISH+(HER2/CEP17>2)>50 % cancer cells	IHC3+ or IHC2+/FISH+	IHC3+ or ISH+(HER2/CEP17>2)	HER2 expansion	IHC3+ or 2+/ISH+(FISH), or HER2 expansion (NGS)	HER2 expansion (FISH/CISH)
Objective response rate ORR, %	45.3	30	9.7	35	33	38	32

T-DXd is a new drug in the ADC class, and the DESTINY-CRC01 study is the first to explore the use of T-DXd in HER2-expressing, RAS/BRAF wild-type mCRC patients who have previously received at least second-line therapy. The study divided mCRC patients into 3 cohort.The A cohort is determined by their HER2 expression status, with the other two cohorts being IHC3+ or

IHC2+/ISH+. IHC2+/ISH- is present in the B cohort. IHC1+ is present in the C cohort. None of the patients in the B and C achieved a confirmed objective response rate; The ORR and Disease Control Rate of cohort A were 45.3% and 83.0%, respectively, and the median survival time for progression-free survival was 6.9 months and the median survival time for overall survival was 15.5 months. Some studies have preliminarily confirmed the clinical benefit of T-DXd in mCRC. Its safety was confirmed in the study of DESTINY-CRC01 and was approved by the FDA for use in refractory HER-2 positive mCRC patients [14].

4. Challenges facing ADC development

Tumor toxicity and drug resistance to ADCs can also arise. Although ADC shows great technical advantages and clinical application prospects, toxicity is still a key factor limiting the improvement of the therapeutic window of ADC. After entering the clinic, many ADCs that showed therapeutic potential in the preclinical stage were terminated or not continued in the short term due to unacceptable toxicity problems such as ocular toxicity, blood toxicity (thrombocytopenia, neutropenia), peripheral neuropathy [15].

The effectiveness of the drug carrier largely determines whether ADCs can play a powerful role in anti-cancer. The ideal drug carrier is a small molecule compound with strong potency and no specificity. ADCs are designed to deliver effective drugs to the tumor site through antibody targeting, improving the accuracy of drug therapy. However, it is estimated that only about 0.1% of ADC can be delivered to the targeted diseased cell population after entering the human body, while most drugs are off-target in non-targeted healthy cells [16]. The "bystander" effect caused by excessive ADC action can produce non-targeted toxic effects on normal cells [17]. The off-target toxicity of ADC is influenced by the low expression of the target antigen.

Considering ADC has a complex mechanism of action, the causes of drug resistance may include down-regulated expression of tumor cell target antigen, loss of internalization pathway, and increased expression of active drug effector pump [18]. In view of these resistance mechanisms, the development of novel ADCs and the study of ADCs combined with other therapies (such as chemotherapy, targeted therapy, immunotherapy) are the ways to improve the efficacy. At this stage, various strategies to address ADC toxicity are expected to improve ADC safety, including optimal design of ADC source structure, promulgation and implementation of preclinical study guidelines, and timely adjustment of dosing schedules (low dose, multi-frequency) during clinical study and use phases.

5. Conclusion

In this paper, the basic principle of ADCs, the clinical application of ADCs in CRC and the challenges of ADCs development were analyzed and summarized. With the advancement in technology, the specificity and cytotoxicity of the new generation of ADCs are improving rapidly compared to those of previous generations. For example, the new ADC drug T-DXd not only breaks through the limitations of previous anti-HER-2 treatment, but also breaks through the limitations of RAS gene status, which is expected to create a new pattern of treatment of HER-2 positive mCRC. There are still challenges in the development of ADCs. In the research on ADCs, there are also many failed trials, some of which have insufficient efficacy and some of which are more toxic. To solve these problems, it is necessary to optimize the various parts of ADC, select more reasonable target antigens, develop new antibodies, more efficient loads, more stable and easier to crack linkers.

ADC therapy has demonstrated great potential in treating colorectal cancer, and with further research and clinical trials, ADC will bring more effective and personalized treatment options to CRC patients. Future research will continue to advance this field and open up new avenues for cancer treatment.

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