Review Article

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Antibody Drug Conjugates for Cancer Therapy

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ABSTRACT

BACKGROUND AND OBJECTIVE: In recent decades, the use of antibody drugs conjugates (ADCs) generated promise for the treatment of cancer. In this type of treatment, a monoclonal antibody against a cancer specific antigen is used, and a cytotoxic drug is attached to the antibody via a linker. This smart drug delivery system also named Armed Antibody. In this review, important factors for the design and performance of an ADC are described.

METHODS: Search by the keywords "Antibody Drug Conjugate" in databases Pubmed, Scopus and Web of Science were done and then 58 related articles that published in 2000-2017 were selected.

FINDINGS: To develop a suitable ADC different parameters should be considered. The choice of the type of antibody, drug and linker should be based on different factors to achieve an ADC with optimal performance. far, more than 671 clinical trials have been registered in Clinical Trial Database registry (www.clinicaltrials.gov) using the keyword 'antibody drug conjugate', but only three drugs with trade names, Mylotarg, Adcetris® and Kadcyla® have received FDA approve however the production of Mylotarg is stopped due to lethal effects.

CONCLUSION: Cancer treatment by traditional methods due to the effects of chemotherapy drugs on normal cells caused adverse effects but the use of ADCs can induces an apoptosis effects on tumor cells by targeted drug delivery.

KEY WORDS: *Chimeric Antibody, Cancer, Antibody Drugs Conjugates*.

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Introduction

Magic bullet was first used by Paul Ehrlich's Russian scientist. He suggested that if a substance has the ability to attach selectively to a pathogenic agent, it can cause the targeted transmission of the drug (poison) to the causative agent by binding a toxic agent on the substance. He won the Nobel Prize in medicine in 1908 for this theory (1-3). Antibody-drug conjugates (ADCs) are a new class of drugs designed to treat cancer patients. ADCs are a complex of antibodies and drugs (anticancer drugs) linked by a linker, so that monoclonal antibodies in the variable region have special paratopes for binding to cancer antigenic epitopes. In figure 1, the three constituent parts of a ADCs are depicted (4, 5).

Mechanism of action of ADCs: A complex of ADCs induces apoptosis in the cancerous cell at five stages. Stage I: Cellular Adherence: ADCs can be linked to a specific antigen (cancer antigen) by antigen-binding monoclonal antibody, thus forming an antigen antibody complex. Stage II) Internalization: The ADCs complex can be endocytosed through receptor-dependent endocytosis into the cancerous cell. The third step: separating the drug from the antibody: After the endocytosis of the ADCs into the cell, the ADCs are inserted into the primary vesicle, which then turns into a secondary vesicle causing the linker to be discontinued and the antibody is isolated from the antibody. Stage IV) Release: The drug is released into the cytoplasm. Stage 5) Cell death: The drug causes cancer cell apoptosis through various mechanisms such as interaction with DNA, microtubules or enzymes involved in cell proliferation (6-8).

Methods

This overview of antibody conjugated drugs is based on articles published in PubMed, Scopus and Web of Science databases. The search for articles was done using the Antibody Drug Conjugate vocabulary. In the initial search, a large number of articles were found, followed by a review of 58 related articles, mostly related to the years 2017-2000.

Results

In order to design an appropriate ADCs, a specific monoclonal antibody for cancer antigens should be produced and an appropriate linker should be used for antibody binding to the drug. Important points are mentioned in the selection of antibodies, linkers, and medications.

Antibody: In the past, mouse antibodies were used to produce ADCs , but today, due to the human immune response to this type of mouse antibody, humanized or fully humanized antibodies (Fully Humanized mAbs) produced by phage display methods are used (10, 9). When selecting antibodies, the biochemical activity of the antibody Fc fraction, which can interact with Fc receptor of cells (FcRs) should be considered. The design and construction of a monoclonal antibody in the construction of an APC complex is very important. Today, the human IgG1 is used as appropriate isotype for construction of ADC, because it is capable of stimulating both directions (antibody dependent cellular cytotoxicity) ADCC and (complement dependent cytotoxicity) CDC as well (11-13).

One of the factors affecting the effectiveness of ADCs is the amount of drug conjugated to an antibody or drug antibody ratio (DAR). If the number of drugs attached to the ADCs is high, it reduces its stability and also its pharmacokinetic profile. On the other hand, if the number of conjugated drugs is low in the antibody, it can reduce the potential for ADCs. Therefore, according to the conditions, the DAR value should be appropriately determined (14, 15).

Other influential cases in an appropriate ADCs are linker attachment to an antibody. Linker binding to the antibody is usually performed by binding to the amino acid cysteine or lysine antibody, each of which has its own characteristics (16).

There is currently a lot of research on the use of Fragment Antibody in the ADCs system. Due to its small size, these antibodies have a very good ability to penetrate tumor tissues. Different types of these antibodies are depicted in figure 2 (17-20).

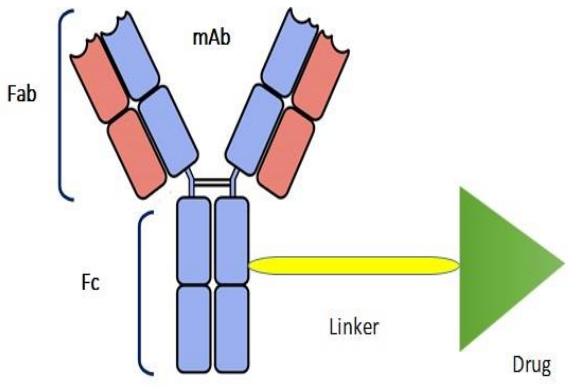

Figure 1. Components of the ADCs complex

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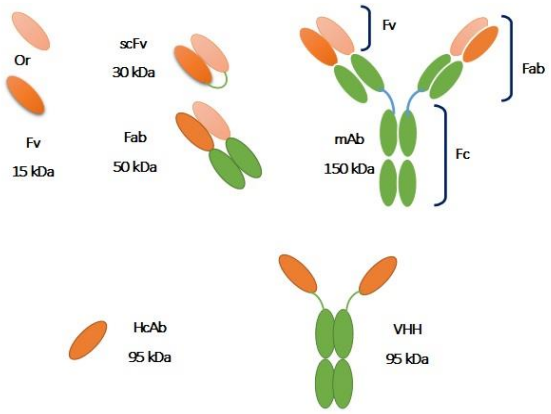

Figure 2. Different Types of Fragment Antibodies

Antigen: An antigen that is selected as a specific cancer cell antigen should be adequately expressed on the cell surface, and should also be present in a small amount on healthy cells to prevent the APCs complex from binding to normal cells. Another selective antigenic property is the ability to induce high endocytosis when it is attached to an antigen (21). Several examples of antigens suitable for targeting by APCs are introduced (table 1)(22-24).

Although the amount of antigen expressed at the target cell surface as a receptor plays a significant role in ADC's performance, it has been proven in many studies that antigens that are expressed quantitatively on the target cell surface also have the potential and potential for use in the ADC. For example, the CD33 receptor is expressed in a few amount on acute myeloid leukemia tumor cells (5,000 to 10,000), but the receptor could successfully be used in ADC design called Mylotarg® (25-27).

Linker: Generally, linkers are divided into two cleavable and non-cleavable categories. Cleavable linker groups are divided into three subunits: sensitive to pH-proteolysis sensitive and sensitive to glutathione. Linkers, which are sensitive to proteolysis, are split by catB in lysosome and release the drug from the antibody. In fact, these type of linkers have a valine-citrulline dipeptide linkage that is broken down by cathepsin B in the lysosome and causes release of the drug. This type of linker is available in the Adcetris drug, which is an ADC-based drug.

The second group of linkers is sensitive to pH and is broken down in the lower pH of lysosome which allows the release of the drug from the ADCs complex, but these linkers can easily release the drug by reducing the pH before entering the drug into lysosome and they are usually not suitable for construction of ADCs complexes. One of the drugs used this type of linker is Mylotarg, which was released into the bloodstream due to the poor linker of the drug and caused toxic effects. For this reason, the drug was collected from the market level. The third category of cleavable linker is thiol-sensitive linkers that are sensitive to glutathione, these linkers are leached into cancerous cells that have high glutathione concentrations and release the drug. Regarding the non-cleavable linkers, it should be noted that these linkers have high stability in the bloodstream and are currently used in the Kadcyla drug (28-34).

Endocytosis of ADCs: After antibody binding to cancer antigen, receptor-dependent endocytosis occurs. One of the most important factors that increase endocytosis is the choice of the type of anti-cancer epitope. The level of antigen antibody affinity also play an important role in increasing the internalization of ADCs into cancer cells.

Internalization is accomplished by three mechanisms: by claverine, caveolae and also with pinocytosis, the first two of which is dependent on the receptor and the latter is non-dependent on the receptor. After endocytosis, the ADCs are placed inside the primary vesicle, and subsequently converted to the secondary vesicles by binding of lysosomes and discontinued by low pH or the presence of cathepsin B and the drug is isolated from the antibody (35-37).

Drug: Generally, two types of drugs including microtubules inhibitors and DNA degrading drugs can be linked to ADCs to treat cancer. One of the factors that inhibits the polymerization and depolymerization of the microtubules is Dolastatin, which is used in Adcetris®. Tubulysins is similar to Auristatins and Maytansine, and induces apoptosis in cancerous cells through inhibition of polymerization and depolymerization of microtubules. Auristatin is the third type of drug that is produced by a marine rabbit Dolabella auricularia. Monomethyl auristatin E (MMAE), which is 1000 times more toxic than doxorubicin, is used in Kadcyla.®

The last type of medication that causes cell death through its effect on microtubules is Maytansinoids, which is highly toxic and has a apoptotic effect in picogram and is derived from Maytenus. Toxic agents that can induce apoptosis by affecting the DNA structure can be called Calicheamicinis. The toxin is derived from an indigenous bacterium in Texas and it is 4000 times more toxic than doxorubicin, and penetrates the small groove of DNA causing a breakdown in DNA and inducing cell death. This toxin was used in the Mylotarg® drug. Duocarmycin also

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influences the small groove of DNA and causes a breakdown in DNA and ultimately cell death. Drugs that have already been licensed by the FDA and found on the drug market include Adcetris and Kadcyla. (37-40). Although there are currently only two drugs at the market level, more than 30 other drugs are based on ADCs for the treatment of various types of cancer. In table 2, various types of these drugs are listed in various phases in the experiment (41-50).

Bystander effect: Several studies have proven that some ADCs have the ability not only to destroy target cells, but also to eliminate the cells around the tumor. The mechanism of this effect is due to the phenomenon of toxic propagation of hydrophobic molecules after separation from an antibody that can be transmitted to the surrounding cells of the tumor and cause the death of nearby cells (bystander cells). This transition is due to the ability of the hydrophobic toxic molecules to cross the membrane of the bystander cells, which does not have target antigens on the cell surface. Drugs that cannot pass through the cell membrane do not affect the bystander effect. The question now is whether it should be stopped or this effect can be helpful in treating cancer. Since the cells around the tumor tissue are involved in the nutrition and support of these cells, the bystander effect can be effective in treating cancer by eliminating these nutritional cells (48-51).

Table 1. Different types of antigens that can design antibodies against them (22-24)

Type of cancer	Used antigen
Breast cancer	CD174, GPNMB, CRIPTO & nectin-4 (ASG-22ME)
Ovarian cancer	MUC16 (CA125), TIM-1 (CDX-014) & mesothelin
Lung cancer	CD56, CD326, CRIPTO, FAP, mesothelin & GD2
pancreas cancer	CD74, CD227 (MUC-1) & nectin-4 (ASG-22ME)
Prostate cancer	PSMA, STEAP-1 & TENB2

Table 2. Different types of ADC-based drugs that are at different stages of clinical confirmation(22-24,41-47, 44-48)

Agent	Linker	Warhead	Target	Phase
IMMU-110	Hydrazone	Doxorubicin	CD74	2
Mylotarg®	Hydrazone	Calicheamicin	CD33	Withdrawn
CMC-544	Hydrazone	Calicheamicin	CD22	3
SAR3419	Disulfide	DM4	CD19	2
BT-062	Disulfide	DM4	CD138	1
BAY-94-9343	Disulfide	DM4	Mesothelin	1
SAR-566658	Disulfide	DM4	DS6	1
IMGN901	Disulfide	DM1	CD56	2
Kadcyla®	Thioether	DM1	HER2	Licensed
IMGN529	Thioether	DM1	CD37	1
SGN-75	MC	MMAF	CD70	1
Adcetris®	Peptide (Val-Cit)	MMAE	CD30	Licensed
RG-7596	Peptide (Val-Cit)	MMAE	CD79b	2
CDX-011	Peptide (Val-Cit)	MMAE	GPNMB	2
PSMA-ADC	Peptide (Val-Cit)	MMAE	PSMA	2
ASG-5ME	Peptide (Val-Cit)	MMAE	AGS-5	1
IMUU-130	Peptide (Phe-Lys)	SN-38	CEACAM5	2

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Discussion

In the treatment of cancer in traditional ways due to the effect of chemotherapy on natural cells, adverse effects occur in the patient's body, but the use of ADCs can selectively induce cellular toxicity or apoptosis in targeted cells through targeted drug delivery. The ADC complex is composed of an antibody that is specific for cancer cell linked to a drug (anti-cancer drug) via a linker. ADCs can deliver anti-cancer drug to target cancer cells and reduce the cytotoxic effect of drugs on non-cancerous cells and normal tissues.

However, many factors still remain to improve the efficiency of ADCs complexes, including the selection of cancer antigens, the preparation of specific monoclonal antibodies, and especially the type of linker selected, as well as the type of drugs. Therefore, the optimization of each one so that it can be used to treat cancer is a complicated process so that only three drugs have been marketed to the market today with the approval of the FDA.

The first drug that had FDA approval was gemtuzumab ozogamicin branded with the name of Mylotarg to treat acute myeloid leukemia (AML). In 2010, a clinical trial was conducted on the drug and the results of the study showed that Mylotarg's therapeutic effect is not significantly different from that of the traditional drugs used to treat cancer, but it has serious toxic effects on the liver. Therefore, the FDA abolished the marketing authorization for this drug and was abandoned around the world. This phenomenon was due to the fact that the linker used in these ADCs was not sufficiently stable and drug was isolated from the antibody in the bloodstream (52-54). Two other ADC-based drugs that received FDA approval for global markets were brentuximab vedotin (Adcetris) and ado-trastuzumab emtansine (Kadcyla). Both products contain antibodies conjugated with anti-mitotic drugs. Each ®Adcetris contains about 4 molecules of auristatin (MMAE), which is linked to a single human chimeric anti-CD30 IgG1 antibody molecule via a peptide linker sensitive to valine-citrulline.

The Kadcyla drug contains DM1, which binds to the HER2 monoclonal antibody with a thioether bond. Adcetris is used to treat Hodgkin's lymphoma and Kadcyla is used for the treatment of metastatic breast cancer (55-58). In general, and given the adverse side effects of cytotoxic drugs used in chemotherapy, the development of a new generation of targeted anti-cancer agents is an inevitable necessity. In this regard, research and development on ADCs are being pursued as a serious approach to cancer treatment.

Along with the various parameters mentioned above, many efforts are being made to develop ADCs formulation through advanced drug delivery systems, including targeting an enzyme-encapsulated drug in nanoparticles with monoclonal antibodies.

In addition, derivatives and various antibody fragments with targeted antigen targeting capabilities for use in ADC systems are under consideration, among which the advantages of these derivatives can be smaller, higher half-lives, better penetration and better pass through biological barriers and the ability to target different antigens. The therapeutic application of these new systems and their advancement to the clinic depends on the optimization of sustainable production methods, the effectiveness of clinical trials, and the confirmation of their superiority to existing drugs for side effects.

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