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A Review on Antibody-Drug Conjugates Components for the Treatment of Cancer

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Abstract

Cytotoxic drugs are generally utilized as chemotherapeutic agents for the therapy of different sorts of tumors. The disadvantage of utilizing cytotoxic medications is their non-explicitness, which might prompt harming healthy human cells alongside the cancerous cells. Thus, it can cause various damaging effects on human health. However, anticancer drugs and antibody-drug conjugates (ADCs) are used to avoid the aforementioned harmful effects. This review presents the components of antibody-drug conjugates and the effect of Maytansinoids for the treatment of cancer. Moreover, this review also presents the formation and mechanism of action of Antibody-Maytansinoid Conjugates. In addition, it summarizes the Antibody-Maytansinoid Conjugate Products that may be helpful for the researchers working in the field of cancer treatment through Antibody-Maytansinoid Conjugate.

Keywords: Conjugates Components; Anticancer Drugs; Cancerous Cells

Introduction

Cytotoxic drugs are traditionally used as chemotherapeutic agents for the treatment of various types of cancers. One of the major disadvantages of using cytotoxic drugs alone is their non-specificity, which may lead to damaging healthy cells along with the cancer cells. Consequently, numerous adverse effects are associated with the use of such agents. In order to avoid these adverse effects, and to enhance the specificity, safety and efficacy of anticancer drugs, antibody-drug conjugates (ADCs) are used. ADCs are composed of a monoclonal antibody (mAb) as well as a cytotoxic payload, joined together through a linker group, where the cancer cell targeting ability of antibody and the cancer cell killing potential of cytotoxic payload are combined [1]. Considering the specificity of antibodies, targeting only the disease-causing agents, without damaging the healthy cells, the German scientist Paul Ehrlich regarded them as "zauberkugel" which means "magic bullet" [2]. The first clinical trial of ADCs on human body was conducted in 1983 [3]. Later on, further advances in this field lead to generation of more efficacious, target specific and less immunogenic ADCs [4].

Components of Antibody-Drug Conjugates

There are three components of ADCs, a monoclonal antibody, a linker molecule and a cytotoxic drug [5].

Antibody: Selection of a suitable antibody, with high specificity for the target cells, is the most vital aspect of ADC design [6]. There are five types of immunoglobulins, i.e., IgG, IgA, IgM, IgE and IgD, among which IgG is the most widely used for manufacturing ADC [7].

Linker molecule: Linkers are the chemical agents which are used to bind the antibody with the cytotoxic drug. The efficacy, specificity and safety of ADC depend upon the linker molecule because it aids the antibody to deliver the cytotoxic ayload to the site of tumour [8]. Linkers are of two types, cleavable and non-cleavable linkers. As the name indicates, cleavable linkers cleave on the tumour site, due to pH change or enzymatic effect, and release the cytotoxic payload for killing the cancer cells. On the contrary, non-cleavable linkers do not cleave, rather the ADC enters the lysosome of tumour cell, where the antibody and linker are destroyed, and the cytotoxic payload is released and kills the tumour cell. Hence, non-cleavable linkers are considered to be safer and more target specific than cleavable linkers [9].

Cytotoxic payload: Another vital component of ADC is the cytotoxic drug, attached to the antibody, also known as cytotoxic payload or warhead, having the ability to kill the tumour cells [10]. The cytotoxic payload should be highly efficacious, that it may kill the tumour cells even in less quantity [11]. Generally,

cytotoxic payloads or warheads have two types, i.e., microtubule disrupting agents and DNA damaging agents. Microtubule disrupting agents interfere with the mitosis step during the cell division of tumour cells and hence seize the cells from dividing [12]. Examples of microtubule disrupting agents are Auristatin [13] and Maytansinoids [14]. Conversely, the DNA damaging agents target the DNA of tumour cells and cause breakage of DNA double strand, leading to death of tumour cells [15]. Examples of DNA damaging agents include Calicheamicins [16], Duocarmycin [17] and Doxorubicin [18].

Maytansinoids

Maytansine was discovered by Kupchan and his colleagues in 1972 from the bark of plant Maytenus ovatus [19]. It is a benzoansamacrolide, with highly potent anti-mitotic activity [20]. Maytansinol also has a similar chemical structure as of maytansine, and both are Maytansinoids, included in the class of microtubule disrupting agents [21]. Maytansinoids stop the mitotic phase of cell division by interacting with the tubulin at the binding sites of Vinca alkaloids [22]. However, the cytotoxic potency of Maytansinoids is 100 times higher than the Vinca alkaloids [23]. Hence, by interacting with the tubulin, maytansinoids disrupt the formation of microtubules, causing arrest of cell in G2/M phase of cell division and eventually cause death of the affected cell [14]. However, when used alone for the treatment of cancer, in certain human trials, maytansinoids failed to exhibit desired therapeutic efficacy [24].

Formation of Antibody-Maytansinoid Conjugates

In order to enhance the therapeutic efficacy and targeted cytotoxic effect of maytansinoids, for the treatment of cancer, they are used as Adtibody-Drug Conjugates (ADCs). The ADCs having maytansinoids as cytotoxic payload are also known as Antibody-Maytansinoid Conjugates (AMCs). Ado-Trastuzumab emtansine is an AMC that has been approved for therapeutic use [25]. This AMC is composed of an anti-HER2 antibody, which is attached to maytansinoid, through a non-cleavable linker, and used for the therapy of breast cancer [26]. Among the AMCs, two thiol-based maytansinoids are being used as cytotoxic payloads for killing cancer cells, i.e., DM1 [N2′-deacetyl-N2′- (3-mercapto-1-oxopropyl) -maytansine] and DM4 [N2′-deacetyl-N2′- (4-mercapto-4-methyl-1-oxopentyl) -maytansine] [27,28].

AMCs are produced chemically by joining the amino group of lysine amino acid of antibody with the thiol group of a maytansinoid, either DM1 or DM4, through a cleavable or non-cleavable linker molecule [29]. The cleavable linkers are disulfide-based linkers, whereas the non-cleavable linkers are thioether based linkers. Moreover, depending upon the various combinations of linkers and cytotoxic payloads, AMCs can be classified into four groups, i.e., emtansines, mertansines, ravtansines and soravtansines [30].

Mechanism of Action of Antibody-Maytansinoid Conjugates

AMC is a targeted mode of treatment for various cancers and tumours, in which the cytotoxic payload is transported to the tumour cell by the attached antibody and the linker molecule, to ensure the safety and efficacy of the treatment [31]. Upon reaching the target site, the AMC is internalized in the target tumour cell, where the antibody and linker molecule are degraded by the lysosomal enzymes and active cytotoxic payload (maytansinoid) is released into the cytoplasm of tumour cell [32]. Consequently, maytansinoid interferes with the microtubule formation of the cell and hence causes cell death [33].

Antibody-Maytansinoid Conjugate Products

Maytansine

Maytansine has been teted in various clinical trials for treatment of cancer, and when tested on human, it caused rise in SGOT (AST) levels with increased doses, hence produced dose limiting toxicity [34]. Moreover, increased levels of bilirubin and transaminases were also observed in another trial on maytansine [35]. Furthermore, in animal models, on monkeys, dogs and mice, hepatotoxicity was observed with raised liver enzymes [36].

Emtansines (DM1 linked with non-cleavable thioether linker SMCC)

Ado-Trastuzumab Emtasine (T-DM1, Status: FDA approved)

T-DM1 with brand name Kadcyla ®, with payload class Maytansinoid DM1, is the first FDA approved AMC, in which HER2 humanized IgG1 antibody is bound to DM1, using non-cleavable thioether linker SMCC [37]. It was approved in February 2013 after successful phase III clinical trials [26]. T-DM1 (Kadcyla ®) is used for the treatment of breast cancer [38]. The most significant adverse effect associated with T-DM1 (Kadcyla ®) is onset of liver toxicity, especially in patients with raised liver enzymes (AST and ALT) [25].

Mertansines (DM1 linked with cleavable disulfide linker SPP)

According to current data, there is no approved mertansine AMC in the market, as all of them have been discontinued due to adverse effects. A few of the AMCs of this class include Lorvotuzumab mertansine (status: discontinued), Cantuzumab mertansine (status: discontinued), Bivatuzumab mertansine (status: discontinued), MLN 2704 (status: discontinued).

Ravtansines (DM4 linked with cleavable disulfide linker SPDB)

Currently, there are no approved ravtansine AMCs in the market, because many of them are under clinical trial phase and some have been discontinued. Some of the ravtansines include Coltuximab ravtansine (status: currently in phase II), Indatuximab ravtansine (status: currently in phase II), Anatumab ravtansine (status: currently in phase II), Cantuzumab ravtansine (status: discontinued).

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Soravtansines (DM4 linked with cleavable disulfide linker sulfo-SPDB)

Mirvetuximab soravtansine (IMGN853, Status: FDA approved)

Mirvetuximab soravtansine (IMGN853), with payload class Maytansinoid DM4, is an FDA approved AMC, which is available in market with brand name ELAHERE, comprising of humanized IgG1 antibody M9346A against FOLR1 (folate receptor 1), attached with DM4 maytansinoid, using cleavable disulfide linker sulfo-SPDB [39]. It is indicated for the treatment of platinum-resistant ovarian cancer [40]. The adverse effects associated with this AMC is slightly raised AST and ALT levels during the treatment [41].

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