Sohag University Sohag Medical Journal Faculty of Medicine

Antibody-Drug conjugate, historical and future overview

Sahar NoorEldeen Hammam

* Lecturer of clinical oncology. Faculty of medicine, Sohag University

Abstract

Antibody-drug Conjugates (ADCs)which are composed of a monoclonal antibody (MoAb), a linker, and a payload; are a type of highly targeted biopharmaceutical drug that conjugate "monoclonal antibodies'. They are specific to antigens present on the surface of particular tumour cells with highly effective anti-cancer agents, all of which are linked to one another via a chemical linker. Recent advances in biotechnology have resulted in significant leaps in therapeutic potential for (ADCs). This review aims to demonstrate the concept of ADC and its based chemotherapies that are used in management of different kinds of cancer in the last few years. This review represents an integrated reference for many researchers and those interested in the field of cancer treatments, as it summarizes all antibody-based drugs, their effectiveness, and the types of cancer they treat, making it easier for researchers to view all antibody-based drugs.

Background: In the field of cancer, ADCs are among the most rapidly expanding therapeutic areas. In theory, these therapeutic entities, which are made up of monoclonal antibodies (mAbs) linked to cytotoxic medications, can expand the therapeutic window of the cytotoxic agents by delivering the chemicals only to cells that display the target antigen of the chosen mAb.

Aim: This review aims to demonstrate the concept of ADC and its based chemotherapies that are used in management of different kinds of cancer in the last few years

Key Findings: For decades, academics and pharmaceutical companies have worked together to develop numerous ADC therapies that have helped thousands of cancer patients.

- Increased interest in this still-emerging but incredibly challenging field of study has been spurred by recent approvals of 14 new ADC drugs and encouraging preliminary results from other ADC-in-development candidates
- However, many studies have shed light on the primary factors that influence ADCs' final behavior, and these findings have been made public. It is imperative that the proper methods for evaluating each component of an ADC in vitro and in vivo are established as soon as possible.
- Finding new antigens, proving their efficacy against cancer cells and developing new payloads with optimal toxicity appear to be the most important steps in the development of the next generation of anti-drug conjugates
- Given the ongoing efforts of researchers, it is easy to anticipate that ADCs are going to be the future therapy for cancer that will and decrease the expected side effects .ortality rateofchemotherapy achieve a lower m

Keywords: Chemotherapy, Anti-body drug conjugate, Cancer therapy, payload
DOI : 10.21608/SMJ.2023.199323.1376

Introduction

In the field of cancer, ADCs are among the most rapidly expanding therapeutic areas. In theory, these therapeutic entities, which are made up of monoclonal antibodies (mAbs) linked to cytotoxic medications, can expand the therapeutic window of the cytotoxic agents by delivering the chemicals only to cells that display the target antigen of the chosen mAb. Emerging evidence suggests that the efficacy of an ADC is determined by antibody, linker, and payload-specific parameters, each of which is a function of intricate interactions between the ADC and numerous components of the tumour and the tumour microenvironment (TME). While numerous ADCs have shown impressive activity against treatmentrefractory cancers, leading to approvals in a wide range of indications. Their wider use is hampered by a number of obstacles. These include toxicities, highly inefficient predictive biomarkers, unidentified clinical value in combination with traditional therapies, and poorly kn-own mechanisms of chemoresistance. (1)

It has recently come to light as a potential clinical strategy to combine highly cytotoxic agents with molecules that target specific cells in this setting. ADCs, have the revolutionize cancer chemotherapy. These ADCs can be humanized or human monoclonal antibodies, and they are linked to cytotoxic small molecules by chemical linkers. Using this platform, it is possible to selectively target cancer cells and deliver highly cytotoxic drugs (2)

Concurrent with the launch of this novel drug development strategy, a new class of pharmaceutical medications known as ADC emerged as a promising option for the targeted management of solid tumors. Recent biotechnology breakthroughs have resulted in considerable improvements in the therapeutic potential of ADCs, which are made up of a monoclonal antibody (MoAb), a linker, and a payload. ADCs have made these advancements possible.(3)

The development of novel linkers and payloads, in example, has resulted in improved drug delivery to tumor cells as well as increased activity in malignancies defined by variable expression of the targeted antigen. Until now, ADC development has mostly concentrated on cytotoxic medicines, despite the fact that a payload could theoretically come from any category of anticancer treatments. In recent years, much emphasis has been placed on very potent cytotoxic drugs, which, if not conjugated, frequently result in intolerable toxicities.(4)

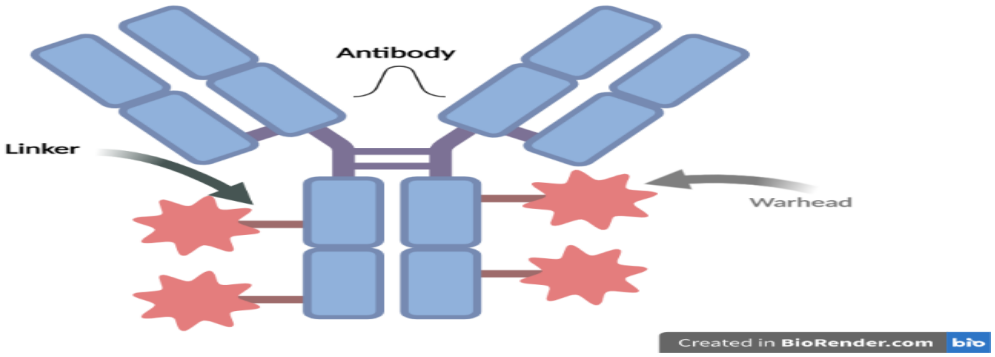

Figure 1: structure of Antibody drug conjugates

Figure (1) depicts the ADC structure. It is possible to think of immunoglobulin-drug conjugates in this context as a kind of pharmaceutics Trojan horse that kills cancer cells. [5]

Historical background

A wide variety of therapeutic conditions, such as cardiovascular disease, infection, disorders of the immune system, and cancer, have all been targeted by the development of pharmaceuticals that are based on approved biopharmaceutical monoclonal antibodies. The last two therapeutic fields are currently the most popular ones, and this popularity is reflected in both sales and the number of antibody products that are currently in development. There are very few exceptions to the rule, which is why it is understandable that significant research efforts are being devoted to "arming" monoclonal antibodies with bioactive payloads. "Naked" immunoglobulins have some therapeutic potential, but there are very few exceptions (e.g., drugs, cytokines, radionuclides) [6(

When Paul Ehrlich first envisioned the magic bullet concept, he had in mind drugs that would directly affect the structure of cells while being non-toxic to healthy tissues. As a result of this concept, targeted drug delivery was developed, which is not a new idea.[7]

The use of chemotherapies, which specifically target cancer cells that are rapidly dividing, has traditionally been the primary focus of cancer drug treatment. This chemotherapy regimen included both folate and purine analogues, such as "6-mercaptopurine"and "methotrexate" aswell as "microtubule polymerization inhibitors/promoters", such as "taxanes", "vinca alkaloids", and DNA damaging agents "anthracyclines and nitrogen mustard"[8and9] Figure (2) shows the mechanism of anthracyclines as anticancer treatment (ex, Doxorubicin)

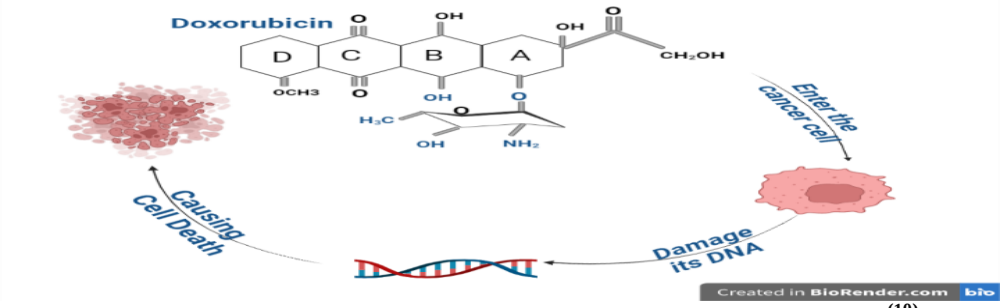

Figure 2: Anthracyclines as anticancer treatment (Doxorubicin) [10]

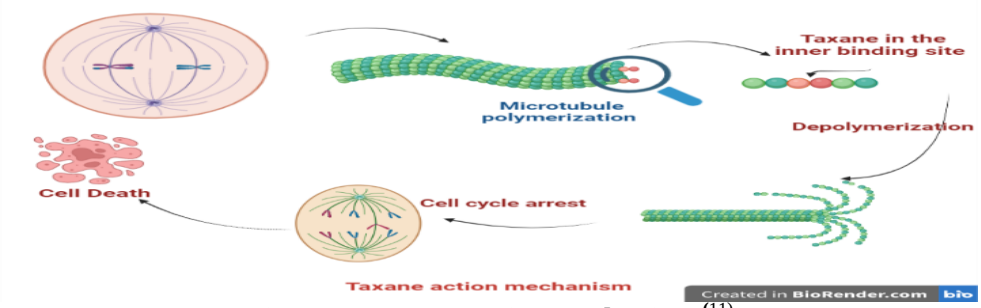

Figure 3: Taxane action mechanism [11]

Because the compounds in inquiry target not only cancerous cells as well as other dividing cells in the body when administered to cancer patients, the maximum dose that can be administered is significantly reduced. Drugs with a low therapeutic index (the ratio of the maximum tolerated dose to the lowest effective dosage) have a narrow therapeutic window. There were several reasons why researchers used ADCs in order to get around this roadblock and increase the therapeutic index of a drug [12]

As a primary trial for ADC drug; an anti-CD33 conjugate developed by Wyeth and Celltech (Mylotarg®) for m-anaging acute myeloid leukemia impr-oved on this early ADCs (AML). In order to enhance effectiveness, "Gemtu-zumab ozogamicin"a very powerful calicheamicin derivative was introduced. A reduced immunogenicity antibody was also incorporated into the formulation. [13]

In the 1980s, the first clinical trials of ADCs were performed in the treatment of cancer; however, the results were discouraging: high toxicity and no signs of efficacy were discovered. "The Food and Drug Administration" (FDA) gave its approval to the first ADC in the year 2000; it was gemtuzumab ozogamicin, an anti-CD33–targeted agent. For its promising result; Gemtuzumab ozogamicin earned an accelerated approval by the FDA in 2000. The agency justified this decision by citing the drug's promising clinical activity as well as subsequent clinical data that raised concerns regarding the drug's safety and efficacy when combined with the standard of care for first-line treatment [14]

Treatment for classical "Hodgkin lymphoma" and "systemic anaplastic large cell lymphoma" with "brentuximab vedotin" approved in 2011 and is now widely available. A decade had passed since the drug's initial trials when this occurred. T-DM1, an ADC that aims the "human epidermal growth factor receptor 2" (HER2), was the 1st ADC to be permitted to manage solid tumour a short time later, back in 2013 for managing metastatic breast cancer, it was given the green light (BC).[15]

ADCs decrease toxicity of chemotherapy

Since anticancer medications are cytotoxic for both normal and neoplastic cells, they generate a wide variety of side effects. The majority of the unwanted effects are either extremely dangerous or extremely inconvenient. Many can be easily misunderstood as being direct or indirect (paraneoplastic) effects of the cancer itself. This problem has been solved with the aid of ADCs since its key point is to target the cancer cell only. ADCs participated in decreasing the toxicity of chemotherapy and limit but not avoid it. Cytotoxic drugs can be delivered selectively to cancer cells, sparing normal cells from harm using ADC

platform. Despite the fact that antibodies are used to target antigens that are highly expressed or ubiquitous in cancer cells, dose-limiting toxicities (DLTs) in normal cells and tissues are frequently reported (i.e., target cells). Hematologic, hepatic, neurological, and ocular adverse effects are among the most common and dose-limiting of ADCs. These incidents most likely stem from the unintentional release of a previously released payload.[16, 17]

There is a wide range of target antigens that can be successfully combated by using cleavable linkers. Lysosomal delivery of the target antigen is not strictly necessary for ADC activity because payload secretion can be triggered early in the endocytic pathway for most cleavable linkers. This versatility allows for the use of a wider variety of target antigens, including some that may readily comprehend upon ligation but recycle back to the cell surface instead of progress to the lysosome. Additionally, cleavable linkers allow employing payloads that are ineffective unless they are in their natural state, and thus cannot be modified. Cleavable linkers have the possibility for payload release during ADC circulating prior to targeted therapy. If the payload is released systemically too soon, there may be off-target, daily dosage toxicities as well as a decline in the effectiveness of the residual circulating ADC.[18 ,19]

The concept of ADCs is simple, but developing an ADC that is effective and has a high therapeutic index has proven to be difficult. For this reason, a definite mAb, linker, and toxic payload must be carefully combined to create an ADC [40]

In spite of the fact that only few kinds of ADCs have been authorized for the management of solid and hematological malignancies, a significant number of ADCs are currently undergoing clinical testing at one of several different stages. [38,41]"Relapsed Hodgkin lymphoma" and "systemic anaplastic large cell lymphoma" can be treated with brentuximab. One of the most powerful tubulin inhibitors, "monomethyl auristatin E (MMAE)" has been conjugated to an anti-CD30 (mAb) via a cleavable linker [20]

By using a stable linker, the T-DM1 drug for HER2-positive metastatic breast cancer combines (HER2) antibody trastuzumabwith the potent emtansine (DM1) tubulin inhibitor. Trastuzumab is also known as Herceptin® [21]

The first ADC to be authorized by FDA for use as monotherapy for acute myeloid leukaemia (AML) patients in the year 2000 was gemtuzumab ozogamicin, marketed under the brand name Mylotarg® and manufactured by Wyeth, Pfizer' subsidiary. The drug was eventually taken off the market in 2010 [44, 46]

Generic gemtuzumab and inotuzumab ozogamicin (Besponsa® by Wyeth) have recently been authorized by FDA to be utilized in calicheamicin-based payloads for AML and Acute Lymphoblastic Leukemia (AML). More than 60 ADCs are currently being investigated in various clinical trials as a direct result of new drug development in ADCs since 2013 [22]

Two of the most commonly used cytotoxic payloads for ADCs that are being tested in clinical trials[48,49] are agents that damage DNA and proteins that inhibit tubulin. [23]

Investigators are using either auristatins (e.g., the "monomethyl auristatin F" [MMAF]) or maytansinoids as the cytotoxic payload in ADCs under development (including DM1 and ravtansine [DM4]). Microtubule assembly is inhibited in both classes of cytotoxic paylo-

ads, and these results in cell cycle arrests [24]

Consequently, numerous ADCs in development share a payload or linker-payload and only differ in the mAb portion designed to target a specific cellular receptor [25]

Antigens and antigenic targets

The monoclonal antibody (mAb) component of an (ADC) is an essential component in the process of developing therapies for cancer. The treatment that is based on antibodies uses 328 different antigens as a target. [26]

Before the antigen can be utilized, it must first fulfil a number of prerequisite conditions. To get things rolling, the target antigen ought to have high levels of expression in cancerous cells but not in healthy ones. [27]

As an example, the "HER2 receptor", that is 100 times more abundant in tumour cells than in healthy ones, is highly expressed in tumors. Second, target antigen on the cancer cells' surface must be introduced for (mAb) to be easily recognized. [28]

In the end, for the cytotoxic agent to be more effective, the target antigen needs to be able to be internalized by the ADC. This is the final consideration. [29]

Even though several studies have shown that "non-internalized ADC" products that target parts of the tumour microenvironment can release their drug into the extracellular space and have a strong therapeutic effect in some cases, and even though ADCs often have a strong "bystander effect," it is important to note that these results aren't the same. This happens because ADCs often have a strong "bystander effect." [30]

Antigens that are specific to cancer and are present throughout the body hold the most promise for therapeutic intervention. The most promising targets for immunotherapy are cancer antigens that can be attacked either locally or systemically by the patient's own antibodies [31]

Using a wide variety of target identification methods, such as antigen identification by serological expression cloning (SEREX), researchers were able to discover a large number of antigens that are associated with tumors.[32]

There are a few cancer antigens that have already been examined for their viability as targets, and these cancer antigens are now being investigated in clinical trials for immunotherapy of cancer [33]

A screening method that is extremely efficient is called transgenic cDNA expression cloning (also known as SEREX). This method is used to identify serum antibody-type tumour indicators. [34]

SEREX has the potential to be utilized for the immunological screening of cDNA libraries produced from tumour tissues with either autologous or allogeneic sera. In addition, sequencing the cDNA clones that were obtained made it easier to identify the antigens. Because of this, SEREX is suitable for conducting large-scale tumour antigen screening. Through the use of SEREX on a wide range of human tumour types, more than a thousand novel tumour antigens, also known as SEREX antigens, have been discovered.[35]

In addition to this, it was discovered that the tumour suppressor p53 was present in 21 of the antigens, along with the oncoprotein "phosphatidylinositol 3-kinase "and "stathmin".[36]

The anti-p53 antibody marker was successfully used in the diagnosis of both "gastric cancer" (GC) and "colon cancer" (CC). It's possible that the amount of antibodies against SEREX antigens play a part in both GC and CC. Antibodies against ESCC As a direct consequence

of this, SEREX antigens were examined to determine their prevalence in cancers of digestive organs [37]

New ADCs in the last 5 years

The specific proteins that are typically overexpressed in cancer cells serve as receptors for the anticancer drugs that are currently available. In solid tumors, these proteins include EGFR HER2, nectin4, and trop2; in hematological malignancies, they include "CD19", "CD22", "CD33", "CD30", "BCMA", and "CD79b" [38]

Given the bright future of ADCs, it is worthwhile to do considerable research into the identification of a highly effective ADC target with broad expression across all stages of cell development. What we have here is a target that is extremely selective, and it applies to every single type of cancer. One such target is CD19, which is abundantly expressed in B cells and nearly all cases of NHL and B-cell "Acute Lymphoid Leukemia" (B-ALL). Several ADCs, such as "SAR3419 SGN-CD19A", "MDX-1206", and "ADCT-402", have CD19 as a target.[39]

Finding cytotoxic payloads that are powerful enough with restricted DAR (Up to 7 medicines per antibody) is another major issue in ADC development. Among the many factors considered when selecting cytotoxic payloads are their aqueous solubility, lack of immunogenicity, and stability during storage and circulation. The development of novel approaches to modify ADCs' cytotoxic payloads with flexible functional groups (e.g., thiol, amine groups) simplifies the conjugation process and is thus an intriguing topic in its own right. Another difficulty with ADCs is that it is difficult to uniformly connect an optimal number of payloads to the antibody in a specific place using linkage and conjugation chemistry. Successful site-specific conjugation and homogenous ADCs are expected to be achieved by interdisciplinary and multidisciplinary efforts and associated studies, such as recombinant DNA technology, bioconjugation, and chemistry.[40]

Table 1: Advantages and disadvantages of ADCs [40]

Advantages	Disadvantages
ADCs are target specific	It could stimulate the body's immunological response
productivity when AB is employed on its own	The high cost of manufacturing.
Decrease toxicity of the payload	There was no discernible progress shown in some of the clinical trials.
	it is difficult to uniformly connect an optimal number of payloads to the antibody in a specific place using linkage and conjugation chemistry [40]

Drugs approved in 2017

In the past five years, (FDA) approved a number of drugs that are based on ADCs, and this pattern is anticipated to continue.

In 2017, the FDA gave its reaffirmation of approval for the use of "***gemtuzumabozogamicin"*** for managing acute myeloid leukaemia. The drug combination gemtuzumab ozogamicin has been granted accelerated approval for management of CD33+ AML patients who are

older than 60 years and are unable to receive intensive chemotherapy (GO) [41]
As part of the post-approval commit-ent made by the drug sponsor, the Southwest Oncology Group worked together with the drug sponsor to develop the study S0106[42]
The dose of daunorubicin in the GO arm was reduced from 60 mg/m2 to 45 mg/m2 in order to better allocate toxic effects between the two arms of the research. This was done in order to achieve a more even distribution of toxic effects. Because the results of the trial showed no overall benefit in survival related mortality -and increased treatment in the experimental arm, GO was taken toff the marke for commercial sale in October of2010. This decision was made because of the findings of the trial. The most recent reapplication for the drug, as well as its approval by FDA in USA, is founded on a deeper comprehension of GO dosing, specific findings from the particular research.[43]
Meanwhile; Pfizer and UCB were developing daunorubicinfor which is used for the treatment of haematological-cancer using (ADC) ***Besponsa®. Inotuzumab ozogamicin*** is another name for this ADC. [44]
Inotuzumab ozogamicin consists of a cytotoxic "N-acetyl—calicheamicin dimethylhydrazide" (Calich-DMH) molecule which is covalently attached to the antibody and a humanized "IgG4 mAb" that recognizes CD22 of the human. These are the two constituents that make up the medication as a whole.[45]
Inotuzumab ozogamicin (solution for infusion) can now be given to adults with CD22-positive B-cell precursor acute lymphoblastic leukaemia that has become worse or is resistant to treatment. previously been These patients have unable toreceive this treatment.[46]
Before, this medicine could only be given to children. Use of ***inotuzumab ozogamicin*** is limited to adults with Philadelphia chromosome-positive (Ph-positive), deteriorated CD22-positive B-cell precursor ALL who have already tried and failed at least one tyrosine kinase inhibitor.[45]
This is because ***inotuzumab ozogamicin*** is only effective in treating patients who have already been treated with at least 1tyrosine kina. ***Inotuzumab ozogamicin*** is the first ADC to be made obtainable for patients in the European Union who have this type of leukaemia.[46]
The European Medicines Agency (EMA) granted approval for the drug according to phase III trial results known as INO-VATE ALL (NCT01564784) [47]
Before beginning treatment with ***inotuzumab ozogamicin***, it is important to have a baseline CD22 positive of greater than 0 percent using an assay that has been validated and demonstrated to be sensitive. It is suggested that "***inotuzumab ozogamicin"*** be given in cycles that last for between three and four weeks each time [45]

Drugs approved in 2018

AstraZeneca, have developed "***Moxetumomabpasudotox-tdfk"***(LUMOXITI-TM), a recombinant anti-CD22 immunotoxin, for management of "hairy cell leukaemia". The immunotoxin CAT-3888, now known as IT, has been enhanced. ***Moxetumomabpasudotox*** consists of the "Fv" segment of an anti-CD22 mAb attached to a PE38 fragment of 38 kDa that is produced from "Pseudomonas exotoxin A". The Fv component of "**Moxetumomabpasudotox**" gets attached to CD22, which is expressed on different types of cancer B-cells. This results in the direct delivery of the PE38 portion of the toxin to the tumour cell [48]

To be eligible for chemotherapy with Moxetumomabpasudotox to treat recurent or resistant HCL; patients must have had at least two previously systemic therapies, one of which must have included management of the disease using purine nucleoside analogue. FDA just gave their blessing to this medication [49]

Moxetumomab pasudotox was granted its 1st approval at the level of the globe on September 13, 2018, in the United States of America for the management of adult patients with recurrent or resistant HCL who had received at least previous two treatment modalities, including treatment with a purine nucleoside analogue. The approval was given for the treatment of adults with relapsed or refractory HCL [48]

Drugs approved in 2019

"Polatuzumabvedotin" is an ADC that consists of a mAb against "CD79b". It is marketed under the brand name Polivy-TM (a B-cell receptor component moderately to strongly express in a majority of malignant lymphomas [49]

After that, a cleavable linker is used to attach this antibody in a covalent fashion to the microtubule (MMAE). Following the internalization of polatuzumabvedotin and the subsequent breaking of its linker, the MMAE that has been released is the factor that is responsible for supressing cell growth and inducing apoptosis. Genentech, which is a subsidiary of Roche, is now focusing on the development of polatuzumabvedotin as a potential treatment for haematological-tumours.[50]

In the USA, ***polatuzumabvedotin*** was approved for the first time on June 10th, 2019 for managing cases with recurrent and resistant DLBCL, after at least two previous bendamustine and rituximab treatments [51]

"Enfortumabvedotin" is used for management of cases with locally advanced mucin la/mUC who have earlier received "platinum-based chemotherapy" and a programmed death receptor-1 in addition to receiving treatment with programmed death-ligand 1 (PD-1/L1) inhibitor. It is also used to treat patients who are not eligible for cisplatin-based chemotherapy who have received one or more treatment regimens previously. Only in the United States is this treatment offered. Enfortumabvedotin was studied in two global clinical trials in patients with la/mUC: EV-201 (NCT03219333), a phase II, single-arm trial in patients who had previously received a PD-1/L1 inhibitor and platinum-based chemotherapy (Cohort 1),13 and EV-301. Patients were involved in both of these studies[52]

Enfortumabvedotinwasauthorized for the first time in 2019 [52]

Daiichi Sankyo Company Ltd. and AstraZeneca are working together to develop "***Trastuzumabderuxtecan"*** (ENHERTU®), used for treatment of solid tumors that express HER2, including breast cancer, stomach cancer, colorectal cancer, and non-small cell lung cancer, with a HER2-targeted antibody and DNA topoisomerase I inhibitor combination [53]

On December 20, 2019, the FDA approved "fam-trastuzumabderuxtecan-nxki" (DS-8201a, T-DXd, ENHERTU®) for the treatment of adults with metastatic HER2-positive breast cancer who have received two or more anti-HER2-based regimens in the metastatic setting.[54]

One percent (4/640) of patients who were evaluated after receiving treatment with fam-trastuzumabderuxtecan-nxki developed anti-drug antibodies (ADA). Efficacy and safety cannot be inferred from the limited number of patients who tested positive for immunogenicity. The

ability of anti-T-DXd antibodies to neutralize T-DXd has not been evaluated. (54 (

Drugs approved in 2020

Immunomedics developed the antibody–drug conjugate ***Sacituzumabgovitecan*** (sacituzumabgovitecan-hziy;
TrodelvyTM) for managing solid tumors,includes breastand urothelial malignancies, respectively. Irinotecan's active metabolite (SN-38), which is covalently linked to a humanized mAb(hRS7) against tropoblastic"cell-surface antigen-2" (Trop-2), was synthesized using a site-specific conjugation of SN-38 to hRS7 (55)

Rapid approval of intravenous "sacituzumabgovitecan" for managing adult cases with "metastatic triple-negative breast cancer" (mTNBC) received on 22 April 2020 in the United States.(56)

GlaxoSmithKline has developed the 1st mAbcalled"***Belantamabmafodotin"*** specifically for managing multiple myeloma. This ADC is known as belantamabmafodotin-blmf. An antibody that recognizes "B-cell maturation antigen" (BCMA) is coupled to monomethyl auristatin F to form (MMAF) (57)

Early August 2020 saw the approval of ***BelantamabMafodotin*** in USA based on preliminary findings from the multinational "DREAMM-2" study. The drug was authorized for the treatment of adult patients with recurrent and resistant multiple myeloma; who have been treated with nearly 4 prior chemotherapies included proteasome inhibitor, an anti-CD38 mAb, and an immunomodulatory drug(58)

Cetuximabsarotalocan was approved for the treatment of locally advanced or recurrent squamous cell carcinoma in head and neck. The drug was approved by the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) in September 2019. Approval was granted after a phase 2a trial with an open label and multiple sites produced positive results (59)

It is possible that the combination of ***CetuximabSarotalocan*** and cancer cells would result in their death due to the activation of the red laser emitted from the optical fiber. Additionally, laser-activated biophysical mechanisms are utilized in order to act as an inducer for very accurate rapid death of cancer cells without causing any damage to the normal tissues that are located in the surrounding area. This results in high tumour specificity (60)

Drugs approved in 2021

The most recently approved antibody drug conjugate (ADC) is called ***Tisotumabvedotin.*** Antiproliferative agent (MMAE) and an antiproliferative agent (mc-VC-PABC-PABC linker) are included in the average DAR of 4.(61)

The only tissue factor-directed ADC therapy, Tivdak®, was authorize by the FDA in September 2021for management ofpatients with advanced cervical cancer who have had disease progression during or following chemotherapy treatment for the management of adult patients with recurrent or metastatic cervical cancer who had disease progression during or after chemotherapy treatment.(39)

Humanized mAb CD19 (***Loncastuximabtesirine***, ADCT-402), which is also known as ADCT-402, is conjugated to PBD dimer via an enzyme-degradable (valine-alanine dipeptide) linker. After 2 or more rounds of systemic therapy, the FDA granted ***Zynlonta***® accelerated approval in April 2021 for managing adult cases with recurrent large B-cell lymphoma. There are three subtypes of diffuse large B-cell lymphoma (DLBCL): low-grade lymphoma, diffuse large B-cell ly-

mphoma arising from low-grade lymphoma, and high-grade lymphoma. For the managing recurrent and refractory DLBCL,

Loncastuximabtesirine was the 1st and the only CD19 ADC that received approval as a single agent.(62) On June 15, 2021, the "Chinese National Medical Products Administration" (NM-PA) approved the use of ***Disitamabvedotin*** conditionally as ADC for patients with advanced GI cancer, including adenocarcinoma of gastroeso-phageal junction. These patients must have previously been treated with at least two different kinds of systemic chemotherapy. The first drug of its kind to be developed in China and given the green light for use in commercial sett-ings is an ADC drug. The approval was granted on the basis of the findings of the RC48-C008 study, which demons-trated that patients who were given RC-48 experienced a clinically meaningful response as well as an improvement in their chances of survival.(63) Figure 3 demonstrates the timeline of ADC approval in the last 5 years. Table (2) summarizes the approved ADCs.

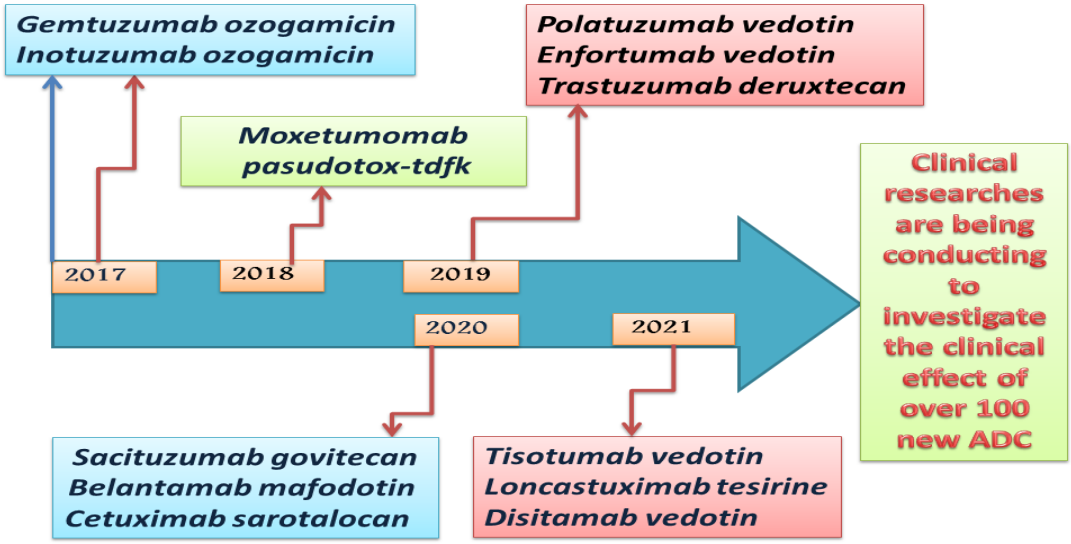

Figure 5: Timeline for the approved ADCs over the last 5 years (64)

Table 2: summarization of approved ADCs (65)

ADC	Lead indication	Target	Payload	Linker type	Linker composition	Drug to antibody ratio (DAR)
Brentuximabvedotin (Adcetris®)	Hodgkin lymphoma, anaplastic large-cell lymphoma	CD30	Auristatin	Cleavable	Valine–citrulline	4
Trastuzumabemtansine (Kadcyla®)	HER2-positive metastatic breast cancer	HER2	DM1	Non-cleavable	Valine–citrulline	3.5
Gemtuzumab ozogomicin (Mylotarg®)	Relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL)	CD33	Calicheamicin	pH- and redox-sensitive	AcBut–Disulphide	2–3
Inotuzumab ozogomicin (Besponsa®)	Acute lymphoblastic leukaemia (ALL)	CD22	Calicheamicin	pH- and redox-sensitive	AcBut–Disulphide	4–7
Moxetumomab pasudotox (Lumoxiti®)	Hairy-cell leukaemia	CD22	Pseudotox (Fragment of Pseudomonas exotoxin-A; PE38)	Cleavable	N/A	N/A
Tagraxofusp-erzs (Elzonris®)	Blasticplasmacytoid dendritic cell neoplasm (BPDCN)	CD123	Diphtheria toxin	Fusion	N/A	N/A

Conclusion

For decades, academics and pharmaceutical companies have worked together to develop numerous ADC therapies that have helped thousands of cancer patients. Howe-ver, many studies have shed light on the primary factors that influence ADCs' final behavior, and these findings have been made public. It is imperative that the proper methods for evaluating each component of an ADC in vitro and in vivo are established as soon as possible. Finding new antigens, proving their efficacy against cancer cells and deve-loping new payloads with optimal toxi-city appear to be the most important ste-ps in the development of the next gen-eration of anti-drug conjugates. Given the ongoing efforts of researchers, it is easy to anticipate that ADCs are going to be the future therapy for cancer that will decrease the expected side effects of chemotherapy and achieve a lower mortality rate

Declarations:

#Ethics approval and consent to participate:

This review was approved and granted ethical approval from Medical Research Ethics Committee of faculty of Medicine-Sohag University under Registration NumberSoh-Med-22-08-22

Consent for publication:

Single author (Not applicable for that section).

#Availability of data and materials:

Not applicable for that section.

 # Competing interests:
Not applicable for that section.
#Funding:
Author declares that she did not receive any funding from any institution or organization to conduct this review.
#Authors' contributions:
Single author: Collection of data and writing the manuscript.

References

1- Drago JZ, Modi S, Chandarlapaty S. Unlocking the potential of antibody–drug conjugates for cancer therapy. Nature Reviews Clinical Oncology. 2021 Jun;18(6):327-44.

2- Diamantis N, Banerji U. Antibody-drug conjugates—an emerging class of cancer treatment. British journal of cancer. 2016 Feb;114(4):362-7.

3- Drago JZ, Modi S, Chandarlapaty S. Unlocking the potential of antibody–drug conjugates for cancer therapy. Nature Reviews Clinical Oncology. 2021 Jun;18(6):327-44.

4- Beck A, Goetsch L, Dumontet C, Corvaïa N. Strategies and challenges for the next generation of antibody–drug conjugates. Nature reviews Drug discovery. 2017 May;16(5):315-37.

5- Tarantino P, CarmagnaniPestana R, Corti C, Modi S, Bardia A, Tolaney SM, Cortes J, Soria JC, Curigliano G. Antibody–drug conjugates: Smart chemotherapy delivery across tumor histologies. CA: a cancer journal for clinicians. 2022 Mar;72(2):165-82.

6- Nelson AL, Dhimolea E, Reichert JM. Development trends for human monoclonal antibody therapeutics. Nature reviews drug discovery. 2010 Oct;9(10):767-74.

7- Aronson JK. When I use a word.... Medical magic.bmj. 2022 Apr 29;377.

8- van den Boogaard WM, Komninos DS, Vermeij WP. Chemotherapy Side-Effects: Not All DNA Damage Is Equal. Cancers. 2022 Jan 26;14(3):627.

9- Benjamin B. Cytotoxic Drugs 63. Abialbon Paul NishanthiAnandabaskarJayanthiMathaiyan. 2021:1077.

10- Saleh Y, Abdelkarim O, Herzallah K, Abela GS. Anthracycline-induced cardiotoxicity: mechanisms of action, incidence, risk factors, prevention, and treatment. Heart failure reviews. 2021 Sep;26:1159-73.

11- Lim PT, Goh BH, Lee WL. Taxol: Mechanisms of action against cancer, an update with current research. InPaclitaxel 2022 Jan 1 (pp. 47-71). Academic Press.

12- Yaghoubi S, Karimi MH, Lotfinia M, Gharibi T, Mahi-Birjand M, Kavi E, Hosseini F, SinehSepehr K, Khatami M, Bagheri N, Abdollahpour-Alitappeh M. Potential drugs used in the antibody–drug conjugate (ADC) architecture for cancer therapy. Journal of cellular physiology. 2020 Jan;235(1):31-64.

13- Hibma J, Knight B. Population pharmacokinetic modeling of gemtuzumab ozogamicin in adult patients with acute myeloid leukemia. Clinical Pharmacokinetics. 2019 Mar;58(3):335-47.

14- Chia CB. A Patent Review on FDA-Approved Antibody-Drug Conjugates,

Their Linkers and Drug Payloads. ChemMedChem. 2022 Apr 5:e202200032.

15- Barta SK, Gong JZ, Porcu P. Brentuximabvedotin in the treatment of CD30+ PTCL. Blood, The Journal of the American Society of Hematology. 2019 Dec 26;134(26):2339-45.

16- Mahalingaiah PK, Ciurlionis R, Durbin KR, Yeager RL, Philip BK, Bawa B, Mantena SR, Enright BP, Liguori MJ, Van Vleet TR. Potential mechanisms of target-independent uptake and toxicity of antibody-drug conjugates. Pharmacology & Therapeutics. 2019 Aug 1;200:110-25.

17- Tolcher AW. The evolution of antibody-drug conjugates: A positive inflexion point. American Society of Clinical Oncology Educational Book. 2020 Mar 31;40:127-34.

18- Chuprakov S, Ogunkoya AO, Barfield RM, Bauzon M, Hickle C, Kim YC, Yeo D, Zhang F, Rabuka D, Drake PM. Tandem-Cleavage Linkers Improve the In Vivo Stability and Tolerability of Antibody–Drug Conjugates. Bioconjugate Chemistry. 2021 Mar 9;32(4):746-54.

19- Ubink R, Dirksen EH, Rouwette M, Bos ES, Janssen I, Egging DF, Loosveld EM, van Achterberg TA, Berentsen K, van der Lee MM, Bichat F. Unraveling the interaction between carboxylesterase 1c and the antibody–drug conjugate SYD985: improved translational PK/PD by using Ces1c knockout mice. Molecular Cancer Therapeutics. 2018 Nov;17(11):2389-98.

20- Khongorzul P, Ling CJ, Khan FU, Ihsan AU, Zhang J. Antibody–drug conjugates: a comprehensive review. Molecular Cancer Research. 2020 Jan 1;18(1):3-19.

21- Advani R, Lebovic D, Brunvand M, Chen AI, Goy A, Chang JE, Maeda LS, Ho W, Kahn R, Lu D, Su Z. A phase I study of DCDT2980S, an antibody-drug conjugate (ADC) targeting CD22, in relapsed or refractory B-cell non-hodgkin's lymphoma (NHL). Blood. 2012 Nov 16;120(21):59.

22- Chuprakov S, Ogunkoya AO, Barfield RM, Bauzon M, Hickle C, Kim YC, Yeo D, Zhang F, Rabuka D, Drake PM. Tandem-Cleavage Linkers Improve the In Vivo Stability and Tolerability of Antibody–Drug Conjugates. Bioconjugate Chemistry. 2021 Mar 9;32(4):746-54.

23- Fu Y, Ho M. DNA damaging agent-based antibody-drug conjugates for cancer therapy. Antibody therapeutics. 2018 Sep;1(2):43-53.

24- Best RL, LaPointe NE, Azarenko O, Miller H, Genualdi C, Chih S, Shen BQ, Jordan MA, Wilson L, Feinstein SC, Stagg NJ. Microtubule and tubulin binding and regulation of microtubule dynamics by the antibody drug conjugate (ADC) payload, monomethyl auristatin E (MMAE): Mechanistic insights into MMAE ADC peripheral neuropathy. Toxicology and Applied Pharmacology. 2021 Jun 15;421:115534.

25- Bartlett N, Brice P, Chen RW, Fanale MA, Gopal AK, Matous J, Rosenblatt JD, Grove LE, Forero-Torres A. Retreatment with brentuximabvedotin in

CD30-positive hematologic malignancies: A phase II study.

26- Strohl WR. Current progress in innovative engineered antibodies.Protein & cell. 2018;9(1):86-120.

27- Majzner RG, Mackall CL. Tumor antigen escape from CAR T-cell therapy. Cancer discovery. 2018 Oct 1;8(10):1219-26.

28- Diamantis N, Banerji U. Antibody-drug conjugates--an emerging class of cancer treatment. British journal of .cancer.7-362:(4)114,2016.

29- Di J, Xie F, Xu Y. When liposomes met antibodies: Drug delivery and beyond. Advanced Drug Delivery Reviews. 2020 Jan 1;154:151-62.

30- Casi G, Neri D. Noninternalizing Targeted Cytotoxics for Cancer Therapy. Molecular Pharmaceutics. 2015;12(6):1880-4.

31- Kepp O, Marabelle A, Zitvogel L, Kroemer G. Oncolysis without viruses—Inducing systemic anticancer immune responses with local therapies. Nature Reviews Clinical Oncology. 2020 Jan;17(1):49-64.

32- Chen YT. Cancer vaccine: identification of human tumor antigens by SEREX. Cancer J 2000;6(Suppl 3):S208–S217.

33- Seil I, Frei C, Sültmann H, Knauer SK, Engels K, Jäger E, Zatloukal K, Pfreundschuh M, Knuth A, Tseng-Chen Y, Jungbluth AA. The differentiation antigen NY-BR-1 is a potential target for antibody-based therapies in breast cancer. International journal of cancer. 2007 Jun 15;120(12):2635-42.

34- Sahin U, Türeci O, Schmitt H, Cochlovius B, Johannes T, Schmits R, Stenner F, Luo G, Schobert I, Pfreundschuh M. Human neoplasms elicit multiple specific immune responses in the autologous host. Proceedings of the national academy of sciences. 1995 Dec 5;92(25):11810-3.

35- Cancer immunome database: http://www2.licr.org/CancerImmunomeDB/

36- Kobayashi S, Hiwasa T, Arasawa T, Kagaya A, Ishii S, Shimada H, Ito M, Suzuki M, Kano M, Rahmutulla B, Kitamura K. Identification of specific and common diagnostic antibody markers for gastrointestinal cancers by SEREX screening using testis cDNA phage library. Oncotarget. 2018 Apr 6;9(26):18559.

37- Hiwasa T, Shimada H. Autoantibody in cancer. InBiomarkers in Cancer Therapy 2019 (pp. 25-40). Springer, Singapore.

38- Nejadmoghaddam MR, Minai-Tehrani A, Ghahremanzadeh R, Mahmoudi M, Dinarvand R, Zarnani AH. Antibody-drug conjugates: possibilities and challenges. Avicenna journal of medical biotechnology. 2019 Jan;11(1):3.

39- Nejadmoghaddam MR, Minai-Tehrani A, Ghahremanzadeh R, Mahmoudi M, Dinarvand R, Zarnani AH. Antibody-drug conjugates: possibilities and challenges. Avicenna journal of medical biotechnology. 2019 Jan;11(1):3.

40- Strop P, Tran TT, Dorywalska M, Delaria K, Dushin R, Wong OK, Ho WH, Zhou D, Wu A, Kraynov E, Aschenbrenner L. RN927C, a Site-Specific Trop-2 Antibody–Drug Conjugate (ADC) with Enhanced Stability, Is Highly Efficacious in Preclinical Solid Tumor ModelsSite-Specific Trop-2 ADC with Enhanced

Stability. Molecular cancer therapeutics. 2016 Nov 1;15(11):2698-708.

41- Jen EY, Ko CW, Lee JE, Del Valle PL, Aydanian A, Jewell C, Norsworthy KJ, Przepiorka D, Nie L, Liu J, Sheth CM. FDA Approval: Gemtuzumab Ozogamicin for the Treatment of Adults with Newly Diagnosed CD33-Positive Acute Myeloid LeukemiaFDA Approval Summary: Gemtuzumab Ozogamicin. Clinical cancer research. 2018 Jul 15;24(14):3242-6.

42- Petersdorf SH, Kopecky KJ, Slovak M, Willman C, Nevill T, Brandwein J, Larson RA, Erba HP, Stiff PJ, Stuart RK, Walter RB. A phase 3 study of gemtuzumab ozogamicin during induction and postconsolidation therapy in younger patients with acute myeloid leukemia. Blood, The Journal of the American Society of Hematology. 2013 Jun 13;121(24):4854-60.

43- Appelbaum FR, Bernstein ID. Gemtuzumab ozogamicin for acute myeloid leukemia. Blood, The Journal of the American Society of Hematology. 2017 Nov 30;130(22):2373-6.

44- Thota S, Advani A. Inotuzumab ozogamicin in relapsed B-cell acute lymphoblastic leukemia. European journal of haematology. 2017 May;98(5):425-34.

45- .Besponsa approved in the EU for adult patients with relapsed or refractory B-cell percursor acute lymphoblastic leukemia [media release]. 30 Jun 2017. http://www.pfizer.com/.

46- Kantarjian HM, DeAngelo DJ, Stelljes M, Martinelli G, Liedtke M, Stock W, Gökbuget N, O'Brien S, Wang K, Wang T, Paccagnella ML. Inotuzumab ozogamicin versus standard therapy for acute lymphoblastic leukemia. New England Journal of Medicine. 2016 Aug 25;375(8):740-53.

47- Dhillon S. Moxetumomab pasudotox: first global approval. Drugs. 2018 Nov;78(16):1763-7.

48- Kang C. Moxetumomab Pasudotox in Hairy Cell Leukaemia: A Profile of Its Use. Clinical drug investigation. 2021 Sep;41(9):829-34. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761104s000lbl.pdf.

49- FDA. FDA approves moxetumomab pasudotox-tdfk for hairy cell leukemia [media release]. 13 Sept 2018. https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm620473.htm.

50- The Human Protein Atlas. CD79B. 2019. https://www.proteinatlas.org/ENSG00000007312-CD79B/pathology.Accessed 28 June 2019.

51- Lacouture ME, Patel AB, Rosenberg JE, O'Donnell PH. Management of Dermatologic Events Associated With the Nectin-4-directed Antibody-Drug Conjugate EnfortumabVedotin. The Oncologist. 2022 Mar;27(3):e223-32.

52- Keam SJ. Trastuzumabderuxtecan: first approval. Drugs. 2020 Apr;80(5):501-8.

53- Narayan P, Osgood CL, Singh H, Chiu HJ, Ricks TK, Chow EC, Qiu J, Song P, Yu J, Namuswe F, Guiterrez-Lugo M. FDA Approval Summary: Fam-trastuzumabderuxtecan-nxki for the treatment of unresectable or metastatic HER2-positive breast cancer. Clinical Cancer Research. 2021 Aug 15;27(16):4478-85.

54- Syed YY.Sacituzumabgovitecan: first approval. Drugs. 2020 Jul;80(10):1019-25.

55- Immunomedics. TRODELVYTM (sacituzumabgovitecan-hziy) for injection, for intravenous use:

US Prescribing Information.2020. https://www.fda.govAccessed 20 May 2022.

56- US FDA. FDA grants accelerated approval to sacituzumabgovitecan-hziy for metastatic triple negative breast cancer [media release]. 20 May2022. https://www.fda.gov.

57- Offidani M, Corvatta L, Morè S, Olivieri A. Belantamabmafodotin for the treatment of multiple myeloma: An overview of the clinical efficacy and safety. Drug Design, Development and Therapy. 2021;15:2401.

58- Cognetti DM, Johnson JM, Curry JM, Mott F, Kochuparambil ST, McDonald D, Fidler MJ, Stenson K, Vasan NR, Razaq M, Campana JP. Results of a phase 2a, multicenter, open-label, study of RM-1929 photoimmunotherapy (PIT) in patients with locoregional, recurrent head and neck squamous cell carcinoma (rHNSCC).

59- Kitamura N, Sento S, Yoshizawa Y, Sasabe E, Kudo Y, Yamamoto T. Current trends and future prospects of molecular targeted therapy in head and neck squamous cell carcinoma. International Journal of Molecular Sciences. 2020 Dec 29;22(1):240.

60- Alley SC, Harris JR, Cao A, Gresnigt-van den Heuvel E, Velayudhan J, Satijn D, Verploegen S, Dominguez T, Breij EC. Tisotumabvedotin induces anti-tumor activity through MMAE-mediated, Fc-mediated, and Fab-mediated effector functions in vitro.

61- Lee A. LoncastuximabTesirine: First Approval. Drugs. 2021 Jul;81(10):1229-33.

62- Pysz I, Jackson PJ, Thurston DE. Introduction to antibody–drug conjugates (ADCs).

63- Deeks, E. D. (2021). Disitamab vedotin: first approval. Drugs, 81(16), 1929-1935.

64- Fu, Z., Li, S., Han, S. et al. Antibody drug conjugate: the "biological missile" for targeted cancer therapy. Sig Transduct Target Ther 7, 93 (2022). https://doi.org/10.1038/s41392-022-00947-7

65- Dahlgren D, Lennernäs H. Antibody-drug conjugates and targeted treatment strategies for hepatocellular carcinoma: a drug-delivery perspective. Molecules. 2020 Jun 21;25(12):2861.