World Journal of Biology Pharmacy and Health Sciences
eISSN: 2582-5542
Cross Ref DOI: 10.30574/wjbphs
Journal homepage: https://wjbphs.com/

(REVIEW ARTICLE)

Check for updates

Conjugated monoclonal antibodies and their role against cancer

David Fabián Alpízar-Miranda [1], Celeste Núñez-Monge [1], Zulema Vargas-Guido [1], Rolando Vargas-Zúñiga [2, 3], Daniela Matarrita-Brenes [2, 3], German Madrigal-Redondo [2, 3] and Juan José Mora-Román [2, 3, *]

[1] *Pharmacy student, Faculty of Pharmacy, Universidad de Costa Rica, San José, Costa Rica.*
[2] *Industrial Pharmacy Department, Faculty of Pharmacy, Universidad de Costa Rica, San José, Costa Rica.*
[3] *Instituto de Investigaciones Farmacéuticas (INIFAR), Faculty of Pharmacy, Universidad de Costa Rica, San José, Costa Rica.*

World Journal of Biology Pharmacy and Health Sciences, 2024, 19(03), 029–044

Publication history: Received on 10 June 2024; revised on 25 June 2024; accepted on 21 August 2024

Article DOI: https://doi.org/10.30574/wjbphs.2024.19.3.0532

Abstract

Cancer involves the proliferation of abnormal cells at an accelerated rate, which can have metastatic and invasive qualities. This illness is a significant public health problem worldwide. Usual treatments are surgery, radiotherapy, and chemotherapy. The drawback of these strategies is their adverse effects, which is why more specific options have been sought. Conjugated monoclonal antibodies have been manufactured to achieve this goal. Their structure comprises a monoclonal antibody, a cytotoxic agent or payload, and a linker, which holds the first two components together. Thanks to this technology, novel medications have yielded better results than traditional therapies. Through these findings, 11 drugs in this therapeutic category are being marketed worldwide. As a complement, significant advances in treating this pathology have led to continued research. In the short term, more conjugated monoclonal antibodies are expected to be approved by health authorities such as the United States Food and Drug Administration and the European Medicines Agency.

Keywords: Cancer; Biological Drug; Monoclonal Antibody; Linker; Payload.

1. Introduction

Cancer is the first disease to provoke death before the age of 70 in most countries [1]. This disorder is characterized by the proliferation of abnormal cells at an accelerated rate, which can have metastatic and invasive qualities. It is not caused exclusively by external agents [2-4].

Currently, there are various therapeutic options, the most common being chemotherapy, radiotherapy, and surgery [3]. However, the search continues for more specific therapies with fewer adverse effects [5], among which biological therapies can be mentioned, such as monoclonal antibodies [6]. An antibody or immunoglobulin is a glycoprotein complex produced and secreted by plasma cells, a specific type of B lymphocytes [7]. The main classification is based on the ability to recognize and bind to epitopes. Monoclonals exclusively recognize one epitope, while polyclonals respond to multiple targets [7, 8].

Monoclonal antibodies result from the fusion of a stem cell and a B lymphocyte clone, integrating the characteristics of both elements [9]. Their mechanism of action is that, due to their high specificity and reproducibility, they block the responses of abnormal proteins and genes with the subsequent destruction of malignant cells [10, 11].

In addition, their utilization as conjugates with cytotoxic agents linked by a chemical linker has been investigated. These molecules combine the specificity of monoclonal antibodies to develop a therapy that targets surface receptors

* Corresponding author: Juan José Mora-Román

associated with a tumor and, upon binding, releases the agent, causing cell death [12, 13]. Since this strategy reduces the side effects on healthy cells and is presented as an effective treatment against cancer, numerous drugs have been approved for human use. Therefore, the present review aims to investigate the production of conjugated monoclonal antibodies and their applications in cancer treatment.

2. General description of an antibody

Antibodies have a structure comprising four polypeptides, two heavy chains, and two light chains [14]. These chains have a constant and a variable portion, joined by non-covalent bonds of disulfide bridges, which get a "Y" shape. In the upper part of the arms, there is the antigen-binding fragment (Fab), whose function is antigenic binding. This union can be monovalent if it occurs in only one arm or bivalent if it happens in both. At the bottom of the molecule is the crystallizable fragment (Fc), constituted of the two heavy chains. This domain has effector functions such as activating specialized lymphocytes and complement and phagocytosis [8, 15].

3. Classification of monoclonal antibodies

According to their origin, they can be classified into four types. Those of murine origin were the first to be produced in large quantities for clinical employment [10]. Subsequently, chimeric antibodies were the first fabricated through genetic engineering. They retain only mouse genetic sequences for the variable regions of the glycoprotein [8]. Then, humanized antibodies were generated by including the mouse complementarity-determining regions in the human immunoglobulins [15]. 95 % of its structure is human [16]. Finally, human glycoproteins were achieved thanks to strategies such as transgenic animals with human Ig genes. They are better tolerated, less antigenic, and remain in circulation longer than the other classes [16].

4. Principal characteristics of conjugated monoclonal antibodies

In a conjugated monoclonal antibody, the Ig is combined with a radioactive particle or a cytotoxic drug or payload through a chemical linker [17-19], as seen in **Figure 1**. The first allows specific antigen recognition in tumor cells, leading to a decrease in systemic toxicity and resistance generation [17, 18]. The target tumor antigen must be overexpressed in the cancer cells, the agent must be highly cytotoxic as the molecules in the Ig is low, and the binding must be stable in the bloodstream and must release the agent in the target cells [20].

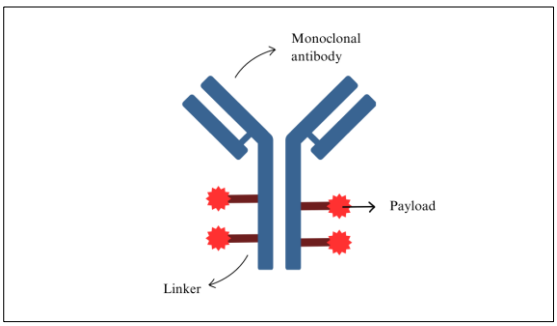

Figure 1 General structure of a conjugated monoclonal antibody.

These molecules enhance the balance between tolerance and efficacy of the cytotoxic agents, given that they have high specificity, allowing the pharmacodynamics and pharmacokinetics to be improved [21], including distribution, metabolism, excretion, and parameters such as volume of distribution (Vd), half-life (t1/2), clearance, and area under the curve (AUC) [22, 23]. The pharmacokinetics of these drugs are mainly affected by the antibody characteristics because it represents 90 % of its molecular weight, so the optimal isotype must be sought to provide remarkable efficacy and appropriate parameters [22]. Most of the payloads in clinical studies used the IgG1 isotype, which is additionally capable of generating antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cellular cytotoxicity (ACC) [19].

On the other hand, the chemical linker allows the release of the cytotoxic component at the site of action. The linker must remain stable in the blood circulation to allow the payload to remain bound to the antibody as it is distributed to cancer cells but to tolerate efficient release when internalization occurs [23].

Two linker types are currently utilized: cleavable and non-cleavable [23]. The former can be used to design internalizing or non-internalizing conjugated monoclonal antibodies since the cytotoxic agent release must be within the lysosome, cytosol, or extracellular tumor environment. The proteases release the payload [24]. Once released, it can induce cancer cell death, and this mortality can provoke the release of proteolytic enzymes, generating additional liberation of the cytotoxic agent [25].

On the other side, conjugated monoclonal antibodies with non-cleavable linkers need to be internalized because to release the cytotoxic agent, the antibody has to be degraded by endosomal or lysosomal proteases. This type of linker has greater efficacy for treating cancer that expresses an antigen at high levels and for hematological tumors [24]. Furthermore, they can occasion less off-target toxicity, given that they have more stability in plasma [26].

Besides, the molecule coupled to the monoclonal antibody is responsible for the cytotoxic effect on cancer cells [27]. It must meet a series of characteristics: the covalent attachment to the linker must not interfere with its activity, has physicochemical properties that allow the antibody to be formulated for intravenous (IV) administration, be stable at the lysosome pH, and has an average inhibitory concentration lower than the nanomolar range since only 1 to 2 % reach its intracellular target [18]. Nonetheless, due to their low efficacy and high toxicity, payloads are employed as conjugates with antibodies to provide targeted therapy and augment the therapeutic index [28].

Finding cytotoxic agents that comply with all the above is difficult. Most drugs that have been developed belong to the maytansinoid, calicheamicin, and auristatin families [18]. Also, payloads such as pyrrolobenzodiazepine (PBD), duocarmycins, and camptothecin derivatives have been manufactured [29]. The main characteristics of these substances are summarized in **Table 1**.

Table 1 Characteristics of the families of cytotoxic drugs employed to develop conjugated monoclonal antibodies.

Family	Description
Maytansinoids [15, 26, 30-32]	They are natural cytotoxic agents that inhibit tubulin, an essential protein for the formation of microtubules. They are derived from the macrolide maytansine, isolated from the bark of the *Maytenus serrata* plants. The semisynthetic maytansinoid compounds emtansine (DM1) and ravtansine (DM4) are frequently contemplated.
Calicheamicins [16, 27, 30-33]	They are enediyne antibiotics isolated from the bacteria *Micromonospora echinospora*. They bind to the minor groove of DNA, causing the breakage of the double helix chain and leading to cell cycle arrest and apoptotic cell death. Some types of calicheamicin are γ1, α2, α3, and N-acetyl-γ1.
Auristatins [15, 26, 30-32]	Auristatin is a synthetic analog of dolastatin, isolated from the mollusk *Dolabella auricularia*, with the ability to block tubulin polymerization. Its derivatives, monomethyl auristatin E (MMAE) and monomethyl auristatin F (MMAF) have been studied. Structurally, MMAF has a phenylalanine at the C-terminus, which implies that it is impermeable to the membrane, while MMAE can diffuse and attack more cells.
Camptothecin [16, 26, 31, 34-36]	It is a natural alkaloid with cytotoxic properties that induce double-strand DNA breakage, forming a stable complex between DNA and topoisomerase I (TOPO-I) and causing apoptosis. SN-38 and DXd are camptothecin analogs. The first is an active metabolite of irinotecan, which is three times more potent, and DXd is an exatecan derivative.
PBD [31, 32, 37-39]	They are natural products with anti-tumor properties obtained from bacteria of the *Streptomyces* genus. They alkylate minor grooves in the DNA by binding to guanine, damaging the genetic material, which leads to cell cycle arrest and cell apoptosis. Some examples are SG1882, SG2057, and SG3199.

There is a limited number of payloads that can be efficiently administered into target cells since only 1.56 % of the administered cytotoxic molecules manage to enter them, assuming that the biodistribution efficiency, antigen binding, internalization, release, intracellular stability, and target binding are 50 %. However, it is estimated that this percentage may be much lower, so to maximize efficacy, the cytotoxic potency has to be high enough to eradicate cancer cells effectively [20].

Moreover, these drugs are administered intravenously, avoiding degradation by gastric acid in the gastrointestinal tract [40]. When it reaches the blood, the antibody finds and binds to the antigen, with the consequent internalization of the drug-antigen complex through endocytosis in the target cells. There, it will be processed within the lysosomes, provoking linker cleavage due to the proteases in the lysosome or acidic pH, which allows the payload to be released within the cancer cell, triggering its death [40, 41].

5. Applications of conjugated monoclonal antibodies against cancer

Cancer is a significant public health problem worldwide, being the second cause of death in the United States, with nearby 608,570 deaths in 2021 (around 1,700 people daily). The types that originate the most significant number of deceases are lung, breast, and colorectal in women and lung, colorectal, and prostate in men [42]. Although there is a considerable number of new anticancer drugs, millions of people continue to die [43].

Nevertheless, the number of survivors is continually growing because of advances in early detection and treatment [44, 45]. Despite all the advances, there is still a long way to go to achieve safer and more effective therapies that improve patients' quality of life. That is why scientists have investigated conjugated monoclonal antibodies in cancer treatment. Several have been approved by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) [29, 46, 47].

6. Approved conjugated monoclonal antibodies

6.1. Gemtuzumab ozogamicin

It is a humanized IgG4 monoclonal antibody directed against CD33. It is covalently linked to the payload N-acetyl-gamma-calicheamicin [48]. Among the indications that the FDA has approved for this medication are the treatment of newly diagnosed CD-33 positive acute myeloid leukemia (AML) in adults and relapsed or refractory CD-33 positive in adults and children from 2 years of age [49].

CD33 is a transmembrane protein expressed on the surface of cells associated with myeloid differentiation that belongs to the sialic acid-binding immunoglobulin-like lectin family [50]. CD33 has an inhibitory function. When the cytoplasmic immunoreceptor tyrosine-based inhibitory motif (ITIM) sequence is phosphorylated, the phosphatases SHP-1 and SHP-2 are recruited, causing negative regulation of cellular activation in myeloid cell lines. When it binds to an antibody, the complex is internalized, allowing it to be an excellent therapeutic target, especially since around 90 % of adult and pediatric individuals with AML are CD-33 positive [51].

This medication was approved by the FDA in 2000 under accelerated conditions. In 2010, the confirmatory trial failed to demonstrate clinical benefits among safety concerns [52] due to excessive toxicity potential at doses greater than 6 mg/m^2 [53]. Nonetheless, different randomized clinical trials were performed, allowing the EMA to reintegrate into the market in 2018 [54].

One of these phase III investigations was intended to demonstrate the addition of the biological drug to induction and/or consolidation chemotherapy in young patients who had not been previously treated without significantly increasing the toxicity of the therapy. 1113 patients, mostly under 60 years of age, participated. Those who received a single dose of gemtuzumab ozogamicin of 3 mg/m^2 on the first day of the induction cycle were randomly assigned to one of the three regimens: 1) fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin, 2) cytarabine, daunorubicin, and etoposide, and 3) daunorubicin and cytarabine. In addition, in remission, 948 persons were randomly assigned to receive the drug in course three in combination with amsacrine, cytarabine, and etoposide or high-dose cytarabine. It was determined that the presence of the conjugated monoclonal antibody was well tolerated without a toxicity increase. In this population, there was an improvement in survival by adding gemtuzumab ozogamicin [55].

In another trial, the objective was to assess the improvement in overall survival during induction therapy in an elderly population (51 to 84 years) with AML or high-risk myelodysplastic syndrome. Of the 1115 patients, 559 received gentuzumab ozogamicin 3 mg/m^2 therapy together with daunorubicin/ara-C or daunorubicin/clofarabine and the rest did not add biological therapy. There were no significant differences in mortality at 30 or 60 days, nor a significant toxicity rise when adding the drug. Likewise, three-year survival was considerably higher, and this medication's cumulative relapse incidence in an identical period was significantly lower [56].

Finally, a randomized, open-label, phase III trial was carried out, the objective of which was to add low fractionated-dose gemtuzumab ozogamicin to specific chemotherapeutic regimens for the improvement of people with AML without generating excessive toxicity [57, 58]. For this, 280 patients aged between 50 and 70 years were randomized 1:1, to whom the conjugated monoclonal antibody in a 3 mg/m^2 dose was administered or not on days 1, 4, and 7 during the induction stage, along with daunorubicin and cytarabine. After this therapy, individuals in remission were given two consolidation therapy courses with the same chemotherapy, with or without the biological drug, at the same dose, under the initial randomization. Even though the results showed a favorable panorama for the biological drug, the difference was not significant [58].

6.2. Brentuximab vedotin

It is a recombinant chimeric IgG1 molecule covalently linked to MMA. It is directed against CD30, allowing inhibition of microtubules. This medication is used as a therapeutic option against CD30-positive Hodgkins' lymphoma in stage III or IV patients, in conjunction with dacarbazine, doxorubicin, and vinblastine, when the disorder has come back or has not responded to an autologous stem cell transplant or at least two other therapies, and the consideration of the transplant or multi-agent chemotherapy is not possible or is likely to come back or get worse after that transplant. As a complement, it is considered for non-Hodgkins' lymphoma, specifically in systemic anaplastic large cell lymphoma alone with cyclophosphamide, doxorubicin, and prednisone, and cutaneous T-cell lymphoma in persons who have received at least one previous systemic treatment [59, 60].

CD30 is a transmembrane receptor that belongs to the tumor necrosis factor (TNF)-receptor superfamily. It is overexpressed in different lymphomas such as Hodgkins' and systemic anaplastic large cell lymphomas [61, 62]. Its expression in normal tissue is low and is limited to a small subset of activated B and T lymphocytes [63]. Its binding with the monoclonal antibody allows it to be internalized and release the payload, triggering a cascade of events that will lead to the cellular apoptosis of the tumor [64].

In an open-label, multicenter, randomized phase III investigation, 1334 patients with previously untreated stage III or IV classic Hodgkins' lymphoma received brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine or doxorubicin, bleomycin, vinblastine, and dacarbazine. Of the 664 people who received the therapeutic option with the conjugated monoclonal antibody, the two-year modified progression-free survival rate was 82.1 %. At the same time, without this drug, it corresponded to 77.2 %. Thus, its addition has superior efficacy for treating these individuals [65].

For its part, a double-blind, double-dummy, randomized, placebo-controlled, active-comparator phase III study attempted to compare the safety and efficacy of the biological drug added to cyclophosphamide, doxorubicin, and prednisone versus cyclophosphamide, doxorubicin, vincristine, and prednisone in CD30-positive peripheral T-cell lymphomas. The 452 patients were randomized 1:1 to receive either of the two regimens for six to eight 21-day cycles. The dose of brentuximab vedotin was 1.8 mg/kg IV. The results showed that progression-free survival and overall survival hazard ratios were higher for the therapy where the biological medication was included. Also, the safety profile was adequate, with no toxicity increase [66].

6.3. Ado-trastuzumab emtansine

The drug comprises a humanized IgG1 monoclonal antibody covalently linked through a thioether bond to DM1 [67]. It is administered in adults for the adjuvant treatment of early human epidermal growth factor receptor 2 (HER2)-positive breast cancer who have residual invasive cancer in the breast and/or lymph nodes after applying neoadjuvant taxane therapy and therapy directed at the said receptor. Additionally, it is considered in people with unresectable metastatic or locally advanced HER2-positive breast cancer who have received trastuzumab and a taxane together or separately and who have received prior therapy for locally advanced or metastatic pathology or present any recurrence during the adjuvant regimen or in the six months after its completion [68].

HER2 is a transmembrane protein found in normal tissues in small amounts and overexpressed in approximately 20 % of breast cancer patients. It has been associated with a poor prognosis regarding disease-free survival and overall survival [69-71] by promoting the growth of cancer cells through the activation of signaling pathways PI3K-AKT and RAS-MAPK. The drug has improved this scenario significantly because the interaction between the conjugated monoclonal antibody and HER2 modulates the signals of these pathways. Then, internalization of the drug-receptor complex allows the payload release and the antitumor action [69].

In a randomized, open-label, international phase III study involving patients with HER2-positive, unresectable, locally advanced, or metastatic breast cancer (previously treated with trastuzumab and a taxane), the efficacy and safety of the conjugated monoclonal antibody against lapatinib plus capecitabine was determined. 991 people participated in this

trial, being randomized 1:1. The main results included median progression-free survival of 9.6 months for ado-trastuzumab emtansine versus 6.4 months with lapatinib plus capecitabine and median overall survival at the second interim analysis of 30.9 months versus 25.1 months, respectively. Therefore, the biological drug improved these parameters, along with lower toxicity [72].

Furthermore, its safety and efficacy were studied in a single-arm, open-label, phase IIIb trial. Persons with HER2-positive locally advanced/metastatic breast cancer with prior HER2-targeted therapy and chemotherapy participated. They received 3.6 mg/kg IV every three weeks until unacceptable toxicity, withdrawal of consent, or disease progression. It was noted that adverse effects related to the nervous system were more frequent in patients with brain metastases, although the profile of side effects was similar despite this condition. Likewise, the best overall response rate in the 126 patients with measurable brain metastases was 21.4 %. The clinical benefit rate corresponded to 42.9 %, and in 398 patients with baseline brain metastases, the median progression-free survival was calculated at 5.5 months and survival at 18.9 months. Moreover, the therapy was active and well tolerated [73].

6.4. Inotuzumab ozogamicin

It consists of a recombinant humanized IgG4 protein directed towards CD22 and covalently linked to N-acetyl-gamma-calicheamicin dimethylhydrazine. It is indicated in adults as an individual therapeutic option in relapsed or refractory CD22-positive B cell precursor acute lymphoblastic leukemia (ALL) and in those who suffer from Philadelphia chromosome-positive relapsed or refractory B cell precursor ALL and for whom treatment with at least one tyrosine kinase inhibitor had failed [74].

CD22 is a sialic acid-binding immunoglobulin-like lectin (Siglec), part of the superfamily of immunoglobulins expressed in B lymphocytes during their life cycle, except in plasma cells. It is expressed in 90 % of B-cell ALL cases but not in hematopoietic stem cells or other tissues. This characteristic makes it an attractive therapeutic target for this pharmaceutical product [75-77].

In an open-label, two-arm, randomized phase III trial, 326 patients over 18 years of age with relapsed or refractory CD22-positive, Philadelphia chromosome-positive, or -negative ALL, who received their first or second salvage therapy were selected. The purpose was to find the tolerability and efficacy of the conjugated monoclonal antibody in standard-of-care chemotherapy. The median overall survival was 7.7 versus 6.2 months, while the two-year overall survival rate was 22.8 and 10.0 %, respectively. In this way, the biological treatment provided a better response, with prolonged progression-free survival and overall survival. Regarding secondary events, veno-occlusive pathology was a central non-hematologic effect [78, 79].

6.5. Moxetumomab pasudotox

This drug consists of a chimeric recombinant monoclonal anti-CD20 antibody fused to a fragment of *Pseudomonas* exotoxin A. The drug is not a chemical conjugate because the entire product is produced in *Escherichia coli* [80-82]. Upon binding to CD22 (B-lymphocyte lineage-restricted transmembrane protein) on the surface of malignant cells, internalization of the complex occurs, and PE38 is released, inhibiting the synthesis of anti-apoptotic protein myeloid cell leukemia 1 (Mcl-1) and promoting apoptosis [81, 83]. In 2018, it received FDA approval for hairy cell leukemia (HCL), which failed at least two prior lines of therapy, including a purine analog [83, 84]. This illness has a high expression of CD22 [85].

During a pivotal, multicenter, single-arm, open-label phase III trial, the rate of durable complete response with moxetumomab pasudotox in patients with multiply relapsed HCL was evaluated. 80 patients received the biologic drug at 40 μg/kg IV on days 1, 3, and 5 every 28 days for six or fewer cycles. The values obtained indicated that the durable complete response, the complete response, and the objective response rate were 30, 41, and 75 %, respectively. In addition, 64 patients experienced hematologic remission. The most common adverse effects included headache, fatigue, nausea, and edema. This way, a high rate of independently assessed durable response and minimal residual disease was achieved (85 % of complete responders), together with acceptable tolerability [85].

Besides, the complete response rate was evaluated in an international, multicenter, phase II research. The work was with 32 pediatric patients, whose ages ranged between 6 months and less than 18 years, with relapsed or chemotherapy-refractory precursor B-cell ALL or lymphoblastic lymphoma who had received at least one front-line and one salvage regimen of chemotherapy or a prior allogeneic hematopoietic stem cell transplantation. The dose administered was 40 μg/kg IV every other day for six doses in a 21-day cycle until progressive disease, up to six cycles, or until they otherwise became ineligible. Although there was clinical activity, the trial was terminated, as the desired objective in phase I was not achieved [86].

In July 2023, the company permanently discontinued this medication in the United States. Its withdrawal was not related to its safety or efficacy but rather to its low clinical acceptance since its approval, the availability of different therapeutic options, its complex administration, the toxicity prophylaxis, and the safety monitoring needs [87].

6.6. Polatuzumab vedotin

This pharmaceutical product comprises a humanized monoclonal antibody covalently conjugated to MMAE. The protein binds to the CD79b receptor of B cells, which is actively expressed in most malignant lymphomas, such as relapsed or refractory diffuse large B-cell lymphoma (DLBCL) [88, 89]. CD79b is part of the B cell receptor (BCR) signaling complex. It plays an essential role in the development and function of mature B cells [90, 91]. When binding with the antibody occurs, it is internalized and allows the payload release, which binds to tubulin and disrupts the microtubule network, consequently inhibiting cell division and growth [92].

Polatuzumab vedotin was approved in combination with bendamustine plus rituximab for adults with relapsed/refractory DLBCL who have received at least two prior therapies. Data from an open-label, phase Ib/II, multi-center clinical investigation in relapsed or refractory DLBCL after at least one prior line of therapy were considered. In the phase II cohort, 80 individuals with relapsed or refractory disorder after at least one prior line of therapy were randomized 1:1 to either polatuzumab vedotin 1.8 mg/kg IV in combination with the other two medications or only bendamustine and rituximab every 21 days for six cycles. The complete response rate was 40 versus 18 %, and the overall response rate was 63 versus 25 %, respectively [89].

In another double-blind, placebo-controlled, international phase III research, the efficacy and safety of the polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, and prednisone regimen versus rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone was studied in patients with untreated intermediate-risk or high-risk DLBCL. The trial included 879 patients between 18 and 80 years of age who randomly received, in a 1:1 ratio, six cycles of one of the regimens plus two cycles of rituximab alone. After two years, the percentage of patients who survived without progression was significantly higher in the conjugated monoclonal antibody group (76.7 %) compared to the other pharmacological combination (70.2 %) and with a similar safety profile [93].

6.7. Enfortumab vedotin

The medication involves a fully human IgG1 monoclonal antibody conjugated to MMAE. It is currently administered for people with locally advanced or metastatic urothelial carcinoma who have previously received a programmed cell death protein 1 (PD-1) or programmed cell death protein ligand 1 (PD-L1) inhibitor and platinum-containing chemotherapy in the neoadjuvant or adjuvant, locally advanced, or metastatic therapy. The glycoprotein binds nectin-4, expressed in breast, lung, pancreatic, ovarian, and urothelial cancers. The cytotoxic agent is then delivered, with consequent cell death [94, 95].

A cohort (125 individuals) of a single-arm, multicenter phase II investigation in adults who previously received platinum-containing chemotherapy and a PD-1/PD-L1 inhibitor was established to determine its efficacy and safety. The drug was given at a dose of 1.25 mg/kg IV on days 1, 8, 15, and 28 of the cycle until some improvement was observed or a very high toxicity level was reached. The confirmed objective response rate in this group was 44 %. Some toxicity cases were related to the payload, while others were explained by the on-target effects correlated with nectin-4 expression. The efficacy was found to be clinically relevant and with an appropriate safety profile [94].

Another global, open-label, randomized phase III trial investigated the efficacy and safety of enfortumab vedotin and pembrolizumab compared to platinum-based chemotherapy in individuals with previously untreated locally advanced or metastatic urothelial carcinoma. 886 people were randomized 1:1 to receive three-week cycles of the biological medicine (1.25 mg/kg IV on days 1 and 8) and pembrolizumab (200 mg IV on day 1) or gemcitabine and either cisplatin or carboplatin. Progression-free survival and overall survival were longer in the conjugated monoclonal antibody group (12.5 versus 6.3 months and 31.5 versus 16.1 months, respectively). Regarding adverse events, the incidence was higher in the group where chemotherapeutic agents were provided [96].

6.8. Fam-trastuzumab deruxtecan

This product's conjugation is performed with DXd. The humanized IgG1 glycoprotein binds to HER2, and it is administered for adult patients with HER2-positive metastatic breast cancer who have received two or more prior anti-HER2 regimens in the metastatic setting and patients with metastatic breast cancer HER2-low who have received prior chemotherapy [97-99].

Regarding clinical investigations, in an open-label, randomized, multicenter, phase III trial, therapy with trastuzumab deruxtecan was compared with trastuzumab emtansine. Once individuals aged 18 years or older with HER2-positive unresectable or metastatic breast cancer previously treated with trastuzumab and a taxane were randomized, 261 received trastuzumab deruxtecan (5.4 mg/kg IV), and 263 trastuzumab emtansine (3.6 mg/kg IV) every three weeks. The group concerning the first drug showed improvement since the median progression-free survival was 28.8 months compared to 6.8 months for the other biological therapy. Its safety profile was appropriate, with interstitial lung illness and pneumonitis being common [100-101].

Another randomized, two-group, open-label, phase III study involving persons with HER2-low, unresectable, or metastatic breast cancer who previously received one or two chemotherapy lines was achieved. The purpose was to evaluate effectiveness and safety. Of the 557 individuals enrolled (2:1 randomization), 373 received 5.4 mg/kg trastuzumab IV every three weeks, and 184 received the chemotherapy chosen by their respective treating physician (capecitabine, eribulin, gemcitabine, nab-paclitaxel, or paclitaxel). Moreover, the separation was made based on the presence of positive hormone receptors, obtaining 361 and 163 people, respectively. The primary data revealed that the hormone receptor-positive patients in the biological drug group achieved a median progression-free survival of 10.1 months, and in the other group with similar characteristics at the receptor level was 5.4 months, while the overall survival was 23.9 against 17.5 months, respectively. For the group of total individuals, regardless of the characteristic associated with the hormone receptor, the median progression free-survival was 9.9 months in the trastuzumab deruxtecan group and 5.1 in the chemotherapy group. Additionally, the overall survival corresponded to 23.4 and 16.8 months, respectively. Thus, those who received therapy with trastuzumab deruxtecan had significantly longer progression-free survival and overall survival than those associated with chemotherapy [102].

6.9. Sacituzumab govitecan

The drug consists of SN-38 and a humanized monoclonal antibody (hRS7) that interacts with the trophoblastic cell-surface antigen-2 (Trop-2). It is indicated for metastatic triple-negative breast cancer (mTNBC) in patients who have received at least two therapies for this condition [103-105].

Trop-2 is a transmembrane protein identified in more than 85 % of epithelial tumors, including TNBC, with little expression in normal tissue. It stimulates the growth of cancer cells and is associated with a poor prognosis [103-105].

One of the trials accomplished was a single-arm, open-label, multicenter phase I/II investigation, including a dose-escalation and a cohort expansion phase. The safety and effectiveness were evaluated in 495 people over 18 years of age with distinct types of advanced epithelial cancers, including TNBC and mTNBC, who had relapsed after or were refractory to at least one prior standard therapeutic regimen. The conjugated monoclonal antibody was administered at 8, 10, 12, and 18 mg/kg IV on days 1 and 8 in 21-day cycles. The most common adverse effects were nausea, diarrhea, fatigue, alopecia, and neutropenia. Regarding efficacy, it was validated that the antigen was appropriate as a therapeutic target for these disorders [106].

Also, in a randomized, phase III trial, the biological medication was evaluated against single-agent chemotherapy of the physician's choice (capecitabine, eribulin, gemcitabine, or vinorelbine) in persons with relapsed or refractory mTNBC, and prior utilization of a taxane. After 1:1 randomization, 245 patients received 10 mg/kg IV on days 1 and 8 of each 21-day cycle, and 233 acknowledged chemotherapy. The median progression-free survival was 5.6 versus 1.7 months, and the median overall survival was 12.1 against 6.7 months, respectively. In this way, both values were significantly longer. The most frequent secondary events related to sacituzumab govitecan were neutropenia, leukopenia, diarrhea, anemia, and febrile neutropenia [107].

6.10. Belantamab mafodotin

It is an acufosylated humanized IgG1 monoclonal antibody conjugated with MMAF. It binds to the B-cell maturation antigen (BCMA), which is essential for the proliferation and survival of malignant plasma cells [108-111]. This medication is approved for relapsed or refractory multiple myeloma after administration of four or more therapies, including anti-CD38 treatment [108]. Binding to this receptor destroys multiple myeloma by inducing apoptosis through a multimodal mechanism, with the intervention of ADCC, antibody-dependent cellular phagocytosis (ADCP), and immunogenic cell death [111].

In an open-label, two-arm, phase II investigation, persons aged 18 or older with relapsed or refractory multiple myeloma, with illness progression after three or more therapeutic lines, and who were refractory to immunomodulatory drugs and proteasome inhibitors and refractory or intolerant (or both) to an anti-CD38 monoclonal antibody were recruited. 97 individuals received 2.5 mg/kg, and 99 were administered 3.4 mg/kg IV every three weeks

on day 1 of each cycle until pathology progression or unacceptable toxicity. For the primary analysis data cutoff date, 31 and 34 % of individuals, respectively, experienced an overall response. The most common adverse effects were keratopathy, thrombocytopenia, and anemia. In the end, 2.5 mg/kg was recommended for future studies, exhibiting anti-myeloma activity with a favorable safety profile [111].

This drug was approved in 2020 based on the information gathered in the previous trial [112]. Nevertheless, in November 2022, its withdrawal from the market began after the FDA request, following data from a subsequent phase III trial [113].

6.11. Loncastuximab tesirine or ADCT-402

It comprises a humanized anti-CD19 glycoprotein stochastically conjugated to SG3199 [114-116]. It was approved for adults with relapsed or refractory DLBCL after two or more systemic treatments [117].

CD19 is a surface protein expressed on healthy and malignant B cells throughout their maturation. It has been observed in a broad spectrum of malignant lymphoid neoplasms [118]. This transmembrane receptor regulates BCR signaling and its efficient internalization [114].

In an open-label, single-arm, phase II research involving 145 people over 18 years of age with relapsed or refractory DLBCL after two or more multi-agent systemic treatments, the antitumor activity and safety of the biological drug were assessed. A dose of 150 μg/kg IV was applied in the first two cycles and subsequent cycles of 75 μg/kg IV for up to one year or until disorder relapse or progression, unacceptable toxicity, death, significant protocol deviation, pregnancy, or decision taken by the patient, investigator, or sponsor. 35 patients experienced a complete response, and the same number generated a partial response. Common adverse effects included neutropenia and thrombocytopenia. Substantial antitumor activity and durable response were obtained with an acceptable safety profile [116].

Regarding the analysis of this medication's effects, symptoms, and tolerability, most participants reported improved pain, lumps/swelling, and weight loss. More than 60 % described little or no discomfort from side effects [119].

6.12. Tisotumab vedotin

The drug consists of a fully human monoclonal antibody conjugated to MMAE. It interacts with tissue factor (TF), a protein detected in multiple solid tumors, such as cervical cancer [120, 121]. It was approved for adults with recurrent or metastatic cervical cancer with progression during or after chemotherapy [122].

TF is a transmembrane receptor expressed in cells near blood vessels and body surfaces and has an essential role in homeostasis and the coagulation cascade. Diverse types of cancer express TF in high amounts, which has been associated with poor prognosis. Such is the case of breast, colorectal, pancreatic, and prostate cancer. TF has been described as an enhancer of tumor growth through various mechanisms, increasing angiogenesis by stimulating proteins such as vascular endothelial growth factor (VEGF). As a complement, high levels are associated with metastasis in some tumors, including colorectal, gastric, and pancreatic [123, 124].

In a phase I/II, open-label, dose-escalation and dose-expansion trial, safety, tolerability, pharmacokinetic profile, and antitumor activity were studied in patients with locally advanced or metastatic (or both) solid tumors comprising esophagus, bladder, prostate, cervix, ovary, endometrium, squamous cell carcinoma of the head and neck, and non-small cell lung cancer (NSCLC), known to express TF. For the dose-escalation stage (27 individuals), people were treated with 0.3 and 2.2 mg/kg IV of the conjugated monoclonal antibody every three weeks in a 3 plus 3 design. Furthermore, in the dose-expansion stage (147 persons), they were treated at the recommended phase two dose. Thanks to the first phase, the lowest dose was established as recommended, with the main side effects being diabetes mellitus, mucositis, and neutropenic fever. Then, in phase two, the objective response represented 15.6 %, with several adverse events, such as alopecia, epistaxis, fatigue, nausea, and vomiting. The antitumor activity was relevant, and the safety profile was manageable [120].

Next, a multicenter, open-label, single-arm, phase II study was performed, recruiting patients 18 years and older with recurrent or metastatic squamous cell, adenocarcinoma, or adenosquamous cervical cancer, who had progressive disease during or after doublet chemotherapy (paclitaxel plus either platinum or topotecan) plus bevacizumab, if eligible), or had received two or fewer previous systemic regimens for recurrent or metastatic cervical cancer, among other characteristics. 101 patients received at least one drug dose. The confirmed objective response rate was 24 % (17 partial and seven complete responses), with common adverse effects being alopecia, conjunctivitis, nausea, and fatigue. These findings were similar to the previous trial [121].

Finally, a single-arm, open-label phase I/II study determined the safety and efficacy outcomes of this medication in Japanese patients with recurrent or metastatic cervical cancer. In terms of efficacy, pharmacokinetics, and safety, the results were similar to those of research conducted on non-Japanese people [125].

6.13. Mirvetuximab soravtansine

It is a chimeric IgG1 macromolecule conjugated to DM4. Its therapeutic target is folate receptor alpha (FRα). Upon binding, the payload internalizes and releases itself, which, when exerting its action, causes the arrest of the cell cycle and the consequent apoptosis. It is approved for adult patients with FRα-positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received one to three prior systemic therapies [126-127].

FRα is a surface protein that is scarce in healthy tissues but overexpressed in epithelial tumors such as ovarian, endometrial, TNBC, and NSCLC. Its high expression is associated with a poor prognosis, with more aggressive tumors and resistance to conventional chemotherapy [127].

Regarding clinical studies, a single-arm, phase II investigation evaluated the efficacy and safety in individuals with platinum-resistant epithelial ovarian cancer, high FRα tumor expression, and who had received one to three prior therapies, including bevacizumab. In total, 105 patients between 35 and 85 years old received 6 mg/kg IV every three weeks until progressive pathology, unacceptable toxicity, consent withdrawal, or death. The objective response rate was 32.4 % (29 partial and five complete responses), and the median duration of response corresponded to 6.9 months. Common adverse effects were blurred vision, keratopathy, and nausea. These events led to administration delays, dose reductions, and treatment discontinuations [128].

Likewise, a global, confirmatory, open, randomized, and controlled phase III clinical trial was made to compare its efficacy and safety in comparison with the chemotherapy chosen by the investigator (paclitaxel, doxorubicin, or topotecan) in patients with platinum-resistant epithelial ovarian cancer. 453 patients aged between 29 and 88 years were randomized. Of them, 227 received the conjugated monoclonal antibody (6 mg/kg IV every three weeks), and 226 received the chemotherapeutic agent. Those treated with biologic therapy showed more benefit in progression-free survival and objective response [129].

7. Conclusions

Cancer treatment is one of the main challenges for the pharmaceutical industry today. Chemotherapy and radiotherapy have been employed for many years. However, they generate many adverse effects, affecting healthy and abnormal tissues without distinction. Besides, surgery is a highly invasive procedure that can have significant complications.

Conjugated monoclonal antibodies have emerged as a solution to the lack of specificity, improving the percentages of efficacy and tolerance. Despite the approval of 13 drugs (two were withdrawn from the market), some aspects must be evaluated, such as the barriers in the tumor microenvironment. Therefore, significant advances in treating this pathology have continued, and in the short term, health authorities such as the FDA and EMA should approve more of these biological therapies.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

References

[1] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA: A Cancer Journal for Clinicians. 2021; 71(3):209-49.

[2] Hausman DM. What Is Cancer? Perspectives in Biology and Medicine. 2019; 62(4):778-84.

[3] Yin W, Wang J, Jiang L, James Kang Y. Cancer and stem cells. Experimental Biology and Medicine. 2021; 246(16):1791-801.

[4] Vaghari-Tabari M, Ferns GA, Qujeq D, Andevari AN, Sabahi Z, Moein S. Signaling, metabolism, and cancer: An important relationship for therapeutic intervention. Journal of Cellular Physiology. 2021; 236(8):5512-32.

[5] Aghebati-Maleki A, Dolati S, Ahmadi M, Baghbanzhadeh A, Asadi M, Fotouhi A, et al. Nanoparticles and cancer therapy: Perspectives for application of nanoparticles in the treatment of cancers. Journal of Cellular Physiology. 2020; 235(3):1962-72.

[6] Esfahani K, Roudaia L, Buhlaiga N, Del Rincon SV, Papneja N, Miller WH Jr. A review of cancer immunotherapy: from the past, to the present, to the future. Current Oncology. 2020; 27(Suppl 2):S87-S97.

[7] Carrasco-Yalán A. Anticuerpos Monoclonales. Diagnóstico. 2021; 60(4):204-12.

[8] Torres Villasante A. Anticuerpos recombinantes como herramientas en neurobiología: producción y caracterización de anticuerpos monoclonales recombinantes para detectar proteínas sinápticas [degree final project]. Valencia: Universitat Politècnica de València; 2020.

[9] Flores Ramírez JF, García Bernal H, Morales León EU, Islas Martínez CU. Usos de anticuerpos monoclonales en medicina. TEPEXI Boletín Científico de la Escuela Superior Tepeji del Río. 2019; 6(11):25-8.

[10] Gorovits B, Koren E. Immunogenicity of Chimeric Antigen Receptor T-Cell Therapeutics. BioDrugs. 2019; 33(3):275-84.

[11] Malik D, Mahendiratta S, Kaur H, Medhi B. Futuristic approach to cancer treatment. Gene. 2021; 805:145906.

[12] Si Y, Melkonian AL, Curry KC, Xu Y, Tidwell M, Liu M, et al. Monoclonal antibody-based cancer therapies. Chinese Journal of Chemical Engineering. 2021; 29(2):301-7.

[13] Towner M, Marcus J. Antibody–Drug Conjugates for the Treatment of Gynecologic Cancer. Advances in Oncology. 2024; 4:73-81.

[14] Suurs FV, Lub-de Hooge MN, de Vries EGE, de Groot DJA. A review of bispecific antibodies and antibody constructs in oncology and clinical challenges. Pharmacology & Therapeutics. 2019; 201:103-19.

[15] Chiu ML, Goulet DR, Teplyakov A, Gilliland GL. Antibody Structure and Function: The Basis for Engineering Therapeutics. Antibodies. 2019; 8(4):55.

[16] Doevendans E, Schellekens H. Immunogenicity of Innovative and Biosimilar Monoclonal Antibodies. Antibodies. 2019; 8(1):21.

[17] Bayer V. An Overview of Monoclonal Antibodies. Seminars in Oncology Nursing. 2019; 35(5):150927.

[18] Melgarejo-Rubio G, Pérez-Tapia SM, Medina-Rivero E, Velasco-Velázquez MA. Anticuerpos conjugados a fármaco: la nueva generación de terapias biotecnológicas contra el cáncer. Gaceta Médica de México. 2020; 156(3):229-36.

[19] Lu RM, Hwang YC, Liu IJ, Lee CC, Tsai HZ, Li HJ, et al. Development of therapeutic antibodies for the treatment of diseases. Journal of Biomedical Science. 2020; 27(1):1.

[20] Tsuchikama K, An Z. Antibody-drug conjugates: recent advances in conjugation and linker chemistries. Protein Cell. 2018; 9(1):33-46.

[21] Paci A, Desnoyer A, Delahousse J, Blondel L, Maritaz C, Chaput N, et al. Pharmacokinetic/pharmacodynamic relationship of therapeutic monoclonal antibodies used in oncology: Part 1, monoclonal antibodies, antibody-drug conjugates and bispecific T-cell engagers. European Journal of Cancer. 2020; 128:107-18.

[22] Porta-Oltra B, Merino-Sanjuán M. Personalized pharmacotherapy in oncology: Application of pharmacokinetic-pharmacodynamic criteria. Farmacia Hospitalaria. 2021; 45(Suppl 1):45-55.

[23] Birrer MJ, Moore KN, Betella I, Bates RC. Antibody-Drug Conjugate-Based Therapeutics: State of the Science. Journal of the National Cancer Institute. 2019; 111(6):538-49.

[24] Ponziani S, Di Vittorio G, Pitari G, Cimini AM, Ardini M, Gentile R, et al. Antibody-Drug Conjugates: The New Frontier of Chemotherapy. International Journal of Molecular Science. 2020; 21(15):5510.

[25] Dal Corso A, Cazzamalli S, Gébleux R, Mattarella M, Neri D. Protease-Cleavable Linkers Modulate the Anticancer Activity of Noninternalizing Antibody-Drug Conjugates. Bioconjugate Chemistry. 2017; 28(7):1826-33.

[26] Schlam I, Moges R, Morganti S, Tolaney SM, Tarantino P. Next-generation antibody-drug conjugates for breast cancer: Moving beyond HER2 and TROP2. Critical Reviews in Oncology/Hematology. 2023; 190:104090.

[27] Abdollahpour-Alitappeh M, Lotfinia M, Gharibi T, Mardaneh J, Farhadihosseinabadi B, Larki P, et al. Antibody-drug conjugates (ADCs) for cancer therapy: Strategies, challenges, and successes. Journal of Cellular Physiology. 2019; 234(5):5628-42.

[28] Nguyen TD, Bordeau BM, Balthasar JP. Mechanisms of ADC Toxicity and Strategies to Increase ADC Tolerability. Cancers. 2023; 15(3):713.

[29] Joubert N, Beck A, Dumontet C, Denevault-Sabourin C. Antibody-Drug Conjugates: The Last Decade. Pharmaceuticals. 2020; 13(9):245.

[30] Gogia P, Ashraf H, Bhasin S, Xu Y. Antibody-Drug Conjugates: A Review of Approved Drugs and Their Clinical Level of Evidence. Cancers. 2023; 15(15):3886.

[31] Wang Z, Li H, Gou L, Li W, Wang Y. Antibody-drug conjugates: Recent advances in payloads. Acta Pharmaceutica Sinica B. 2023; 13(10):4025-59.

[32] Ma H, Sawas A. Combining Biology and Chemistry for a New Take on Chemotherapy: Antibody-Drug Conjugates in Hematologic Malignancies. Current Hematologic Malignancy Reports. 2018; 13(6):555-69.

[33] Vollmar BS, Frantz C, Schutten MM, Zhong F, Del Rosario G, Go MAT, et al. Calicheamicin Antibody-Drug Conjugates with Improved Properties. Molecular Cancer Therapeutics. 2021; 20(6):1112-20.

[34] Li W, Veale KH, Qiu Q, Sinkevicius KW, Maloney EK, Costoplus JA, et al. Synthesis and Evaluation of Camptothecin Antibody-Drug Conjugates. ACS Medical Chemistry Letters. 2019; 10(10):1386-92.

[35] Wang X, Zhuang Y, Wang Y, Jiang M, Yao L. The recent developments of camptothecin and its derivatives as potential anti-tumor agents. European Journal of Medicinal Chemistry. 2023; 260:115710.

[36] Hegedüs L, Okumus Ö, Mairinger F, Ploenes T, Reuter S, Schuler M, et al. TROP2 expression and SN38 antitumor activity in malignant pleural mesothelioma cells provide a rationale for antibody-drug conjugate therapy. Lung Cancer. 2023; 178:237-46.

[37] Lai W, Zhao S, Lai Q, Zhou W, Wu M, Jiang X, et al. Design, Synthesis, and Bioevaluation of a Novel Hybrid Molecular Pyrrolobenzodiazepine-Anthracenecarboxyimide as a Payload for Antibody-Drug Conjugate. Journal of Medicinal Chemistry. 2022; 65(17):11679-702.

[38] Staben LR, Chen J, dela Cruz-Chuh J, del Rosario G, Go MA, Guo J, et al. Systematic Variation of Pyrrolobenzodiazepine (PBD)-Dimer Payload Physicochemical Properties Impacts Efficacy and Tolerability of the Corresponding Antibody-Drug Conjugates. Journal of Medicinal Chemistry. 2020; 63(17):9603-22.

[39] Goel B, Jain SK. Natural products as a source of cytotoxic warheads in antibody-drug conjugates. Natural Product Research. 2023; 37(17):2973-85.

[40] Nagayama A, Vidula N, Ellisen L, Bardia A. Novel antibody-drug conjugates for triple negative breast cancer. Therapeutic Advances in Medical Oncology. 2020; 12:1758835920915980.

[41] Yu B, Liu D. Antibody-drug conjugates in clinical trials for lymphoid malignancies and multiple myeloma. Journal of Hematology & Oncology. 2019; 12(1):94.

[42] Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. CA: A Cancer Journal for Clinicians. 2021; 71(1):7-33.

[43] Hafeez U, Parakh S, Gan HK, Scott AM. Antibody-Drug Conjugates for Cancer Therapy. Molecules. 2020; 25(20):4764.

[44] Miller KD, Nogueira L, Mariotto AB, Rowland JH, Yabroff KR, Alfano CM, et al. Cancer Treatment and Survivorship Statistics, 2019. CA: A Cancer Journal for Clinicians. 2019; 69(5):363-85.

[45] Miller KD, Nogueira L, Devasia T, Mariotto AB, Yabroff KR, Jemal A, et al. Cancer Treatment and Survivorship Statistics, 2022. CA: A Cancer Journal for Clinicians. 2022; 72(5):409-36.

[46] Baah S, Laws M, Rahman KM. Antibody-Drug Conjugates-A Tutorial Review. Molecules. 2021; 26(10):2943.

[47] Tong JTW, Harris PWR, Brimble MA, Kavianinia I. An Insight into FDA Approved Antibody-Drug Conjugates for Cancer Therapy. Molecules. 2021; 26(19):5847.

[48] Committee for Medicinal Products for Human Use. Assessment Report: Mylotarg. London: European Medicines Agency; 2018.

[49] United States Food and Drug Administration. MYLOTARG™ (gemtuzumab ozogamicin) for injection, for intravenous use. Maryland: United States Food and Drug Administration; 2017.

[50] Gbadamosi M, Meshinchi S, Lamba JK. Gemtuzumab ozogamicin for treatment of newly diagnosed CD33-positive acute myeloid leukemia. Future Oncology. 2018; 14(30):3199-213.

[51] Molica M, Perrone S, Mazzone C, Niscola P, Cesini L, Abruzzese E, et al. CD33 Expression and Gentuzumab Ozogamicin in Acute Myeloid Leukemia: Two Sides of the Same Coin. Cancers. 2021; 13(13):3214.

[52] Norsworthy KJ, Ko CW, Lee JE, Liu J, John CS, Przepiorka D, et al. FDA Approval Summary: Mylotarg for Treatment of Patients with Relapsed or Refractory CD33-Positive Acute Myeloid Leukemia. The Oncologist. 2018; 23(9):1103-8.

[53] Xu Q, He S, Yu L. Clinical Benefits and Safety of Gemtuzumab Ozogamicin in Treating Acute Myeloid Leukemia in Various Subgroups: An Updated Systematic Review, Meta-Analysis, and Network Meta-Analysis. Frontiers in Immunology. 2021; 12:683595.

[54] Agencia Española de Medicamentos y Productos Sanitarios. Informe de Posicionamiento Terapéutico de gentuzumab ozogamicina (Mylotarg®) en el tratamiento de pacientes con leucemia mieloide aguda de novo que exprese CD33 previamente no tratados. Madrid: Ministerio de Sanidad, Consumo y Bienestar Social; 2019.

[55] Burnett AK, Hills RK, Milligan D, Kjeldsen L, Kell J, Russell NH, et al. Identification of patients with acute myeloblastic leukemia who benefit from the addition of gemtuzumab ozogamicin: results of the MRC AML15 trial. Journal of Clinical Oncology. 2011; 29(4):369-77.

[56] Burnett AK, Russell NH, Hills RK, Kell J, Freeman S, Kjeldsen L, et al. Addition of gemtuzumab ozogamicin to induction chemotherapy improves survival in older patients with acute myeloid leukemia. Journal of Clinical Oncology. 2012; 30(32):3924-31.

[57] Castaigne S, Pautas C, Terré C, Raffoux E, Bordessoule D, Bastie JN, et al. Effect of gemtuzumab ozogamicin on survival of adult patients with de-novo acute myeloid leukaemia (ALFA-0701): a randomised, open-label, phase 3 study. The Lancet. 2012; 379(9825):1508-16.

[58] Lambert J, Pautas C, Terré C, Raffoux E, Turlure P, Caillot D, et al. Gemtuzumab ozogamicin for *de novo* acute myeloid leukemia: final efficacy and safety updates from the open-label, phase III ALFA-0701 trial. Haematologica. 2019; 104(1):113-9.

[59] European Medicines Agency. Adcetris (brentuximab vedotin). Amsterdam: European Medicines Agency; 2023.

[60] European Medicines Agency. Adcetris: EPAR - Product information. Amsterdam: European Medicines Agency; 2023.

[61] Prince HM, Hutchings M, Domingo-Domenech E, Eichenauer DA, Advani R. Anti-CD30 antibody-drug conjugate therapy in lymphoma: current knowledge, remaining controversies, and future perspectives. Annals of Hematology. 2023; 102(1):13-29.

[62] Jagadeesh D, Horwitz S, Bartlett NL, Kim Y, Jacobsen E, Duvic M, et al. Response to Brentuximab Vedotin by CD30 Expression in Non-Hodgkin Lymphoma. The Oncologist. 2022; 27(10):864-73.

[63] van der Weyden CA, Pileri SA, Feldman AL, Whisstock J, Prince HM. Understanding CD30 biology and therapeutic targeting: a historical perspective providing insight into future directions. Blood Cancer Journal. 2017; 7(9):e603.

[64] Scott LJ. Brentuximab Vedotin: A Review in CD30-Positive Hodgkin Lymphoma. Drugs. 2017; 77(4):435-45.

[65] Connors JM, Jurczak W, Straus DJ, Ansell SM, Kim WS, Gallamini A, et al. Brentuximab Vedotin with Chemotherapy for Stage III or IV Hodgkin's Lymphoma. New England Journal of Medicine. 2018; 378(4):331-44.

[66] Horwitz S, O'Connor OA, Pro B, Illidge T, Fanale M, Advani R, et al. Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial. The Lancet. 2019; 393(10168):229-40.

[67] European Medicines Agency. Kadcyla: EPAR - Product information. Amsterdam: European Medicines Agency; 2023.

[68] F. Hoffmann-La Roche S.A. Información para el profesional: Kadcyla® Trastuzumab emtansina. Buenos Aires: F. Hoffmann-La Roche S.A.; 2021.

[69] Rassy E, Rached L, Pistilli B. Antibody drug conjugates targeting HER2: Clinical development in metastatic breast cancer. The Breast. 2022; 66:217-26.

[70] Mukohara T, Hosono A, Mimaki S, Nakayama A, Kusuhara S, Funasaka C, et al. Effects of Ado-Trastuzumab Emtansine and Fam-Trastuzumab Deruxtecan on Metastatic Breast Cancer Harboring HER2 Amplification and the L755S Mutation. The Oncologist. 2021; 26(8):635-9.

[71] Najjar MK, Manore SG, Regua AT, Lo HW. Antibody-Drug Conjugates for the Treatment of HER2-Positive Breast Cancer. Genes. 2022; 13(11):2065.

[72] Verma S, Miles D, Gianni L, Krop IE, Welslau M, Baselga J, et al. Trastuzumab Emtansine for HER2-Positive Advanced Breast Cancer. New England Journal of Medicine. 2012; 367(19):1783-91.

[73] Montemurro F, Delaloge S, Barrios CH, Wuerstlein R, Anton A, Brain E, et al. Trastuzumab emtansine (T-DM1) in patients with HER2-positive metastatic breast cancer and brain metastases: exploratory final analysis of cohort 1 from KAMILLA, a single-arm phase IIIb clinical trial☆. Annals of Oncology. 2020; 31(10):1350-8.

[74] European Medicines Agency. Besponsa: EPAR - Product information. Amsterdam: European Medicines Agency; 2024.

[75] Rubinstein JD, O'Brien MM. Inotuzumab ozogamicin in B-cell precursor acute lymphoblastic leukemia: efficacy, toxicity, and practical considerations. Frontiers in Immunology. 2023; 14:1237738.

[76] Xu J, Luo W, Li C, Mei H. Targeting CD22 for B-cell hematologic malignancies. Experimental Hematology & Oncology. 2023; 12(1):90.

[77] Zheng S, Gillespie E, Naqvi AS, Hayer KE, Ang Z, Torres-Diz M, et al. Modulation of CD22 Protein Expression in Childhood Leukemia by Pervasive Splicing Aberrations: Implications for CD22-Directed Immunotherapies. Blood Cancer Discovery. 2022; 3(2):103-15.

[78] Kantarjian HM, DeAngelo DJ, Stelljes M, Liedtke M, Stock W, Gökbuget N, et al. Inotuzumab Ozogamicin Versus Standard of Care in Relapsed or Refractory Acute Lymphoblastic Leukemia: Final Report and Long-Term Survival Follow-Up from the Randomized, Phase 3 INO-VATE Study. Cancer. 2019; 125(14):2474-87.

[79] Kantarjian HM, DeAngelo DJ, Stelljes M, Martinelli G, Liedtke M, Stock W, et al. Inotuzumab Ozogamicin versus Standard Therapy for Acute Lymphoblastic Leukemia. New England Journal of Medicine. 2016; 375(8):740-53.

[80] Feurtado J, Kreitman RJ. Moxetumomab Pasudotox: Clinical Experience in Relapsed/Refractory Hairy Cell Leukemia. Clinical Journal of Oncology Nursing. 2019; 23(3):E52-E59.

[81] Dhillon S. Moxetumomab Pasudotox: First Global Approval. Drugs. 2018; 78(16):1763-7.

[82] Kuruvilla D, Chia YL, Balic K, Yao NS, Kreitman RJ, Pastan I, et al. Population pharmacokinetics, efficacy, and safety of moxetumomab pasudotox in patients with relapsed or refractory hairy cell leukaemia. British Journal of Clinical Pharmacology. 2020; 86(7):1367-76.

[83] Nobre CF, Newman MJ, DeLisa A, Newman P. Moxetumomab pasudotox-tdfk for relapsed/refractory hairy cell leukemia: a review of clinical considerations. Cancer Chemotherapy and Pharmacology. 2019; 84(2):255-63.

[84] Lin AY, Dinner SN. Moxetumomab pasudotox for hairy cell leukemia: preclinical development to FDA approval. Blood Advances. 2019; 3(19):2905-10.

[85] Kreitman RJ, Dearden C, Zinzani PL, Delgado J, Karlin L, Robak T, et al. Moxetumomab pasudotox in relapsed/refractory hairy cell leukemia. Leukemia. 2018; 32(8):1768-77.

[86] Shah NN, Bhojwani D, August K, Baruchel A, Bertrand Y, Boklan J, et al. Results from an international phase 2 study of the anti-CD22 immunotoxin moxetumomab pasudotox in relapsed or refractory childhood B-lineage acute lymphoblastic leukemia. Pediatric Blood & Cancer. 2020; 67(5):e28112.

[87] United States Food and Drug Administration. Important Prescribing Information: Important Information for LUMOXITI® (moxetumomab pasudotox-tdfk) for Injection Intravenous Use – Permanent Withdrawal of Luxomoti® from the US Market. Maryland: United States Food and Drug Administration; 2022.

[88] Deeks ED. Polatuzumab Vedotin: First Global Approval. Drugs. 2019; 79(13):1467-75.

[89] Shultes KC. Polatuzumab Vedotin-Piiq (Polivy®). Oncology Times. 2020; 42(4):9.

[90] Sehn LH, Herrera AF, Flowers CR, Kamdar MK, McMillan A, Hertzberg M, et al. Polatuzumab Vedotin in Relapsed or Refractory Diffuse Large B-Cell Lymphoma. Journal of Clinical Oncology. 2020; 38(2):155-65.

[91] Ormhøj M, Scarfò I, Cabral ML, Bailey SR, Lorrey SJ, Bouffard AA, et al. Chimeric Antigen Receptor T Cells Targeting CD79b Show Efficacy in Lymphoma with or without Cotargeting CD19. Clinical Cancer Research. 2019; 25(23):7046-57.

[92] Fuh FK, Looney C, Li D, Poon KA, Dere RC, Danilenko DM, et al. Anti-CD22 and anti-CD79b antibody-drug conjugates preferentially target proliferating B cells. British Journal of Pharmacology. 2017; 174(8):628-40.

[93] Tilly H, Morschhauser F, Sehn LH, Friedberg JW, Trněný M, Sharman JP, et al. Polatuzumab Vedotin in Previously Untreated Diffuse Large B-Cell Lymphoma. New England Journal of Medicine. 2022; 386(4):351-63.

[94] Chang E, Weinstock C, Zhang L, Charlab R, Dorff SE, Gong Y, et al. FDA Approval Summary: Enfortumab Vedotin for Locally Advanced or Metastatic Urothelial Carcinoma. Clinical Cancer Research. 2021; 27(4):922-7.

[95] Mantia CM, Sonpavde G. Enfortumab vedotin-ejfv for the treatment of advanced urothelial carcinoma. Expert Review of Anticancer Therapy. 2022; 22(5):449-55.

[96] Powles T, Valderrama BP, Gupta S, Bedke J, Kikuchi E, Hoffman-Censits J, et al. Enfortumab Vedotin and Pembrolizumab in Untreated Advanced Urothelial Cancer. New England Journal of Medicine. 2024; 390(10):875-88.

[97] Nguyen X, Hooper M, Borlagdan JP, Palumbo A. A Review of Fam-Trastuzumab Deruxtecan-nxki in HER2-Positive Breast Cancer. Annals of Pharmacotherapy. 2021; 55(11):1410-8.

[98] Keam SJ. Trastuzumab Deruxtecan: First Approval. Drugs. 2020; 80(5):501-8.

[99] Swain SM, Shastry M, Hamilton E. Targeting HER2-positive breast cancer: advances and future directions. Nature Reviews Drug Discovery. 2023; 22(2):101-26.

[100] Cortés J, Kim SB, Chung WP, Im SA, Park YH, Hegg R, et al. Trastuzumab Deruxtecan versus Trastuzumab Emtansine for Breast Cancer. New England Journal of Medicine. 2022; 386(12):1143-54.

[101] Hurvitz SA, Hegg R, Chung WP, Im SA, Jacot W, Ganju V, et al. Trastuzumab deruxtecan versus trastuzumab emtansine in patients with HER2-positive metastatic breast cancer: updated results from DESTINY-Breast03, a randomised, open-label, phase 3 trial. The Lancet. 2023; 401(10371):105-17.

[102] Modi S, Jacot W, Yamashita T, Sohn J, Vidal M, Tokunaga E, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. New England Journal of Medicine. 2022; 387(1):9-20.

[103] Bardia A, Mayer IA, Vahdat LT, Tolaney SM, Isakoff SJ, Diamond JR, et al. Sacituzumab Govitecan-hziy in Refractory Metastatic Triple-Negative Breast Cancer. New England Journal of Medicine. 2019; 380(8):741-51.

[104] Syed YY. Sacituzumab Govitecan: First Approval. Drugs. 2020; 80(10):1019-25.

[105] Spring LM, Nakajima E, Hutchinson J, Viscosi E, Blouin G, Weekes C, et al. Sacituzumab Govitecan for Metastatic Triple-Negative Breast Cancer: Clinical Overview and Management of Potential Toxicities. The Oncologist. 2021; 26(10):827-34.

[106] Bardia A, Messersmith WA, Kio EA, Berlin JD, Vahdat L, Masters GA, et al. Sacituzumab govitecan, a Trop-2-directed antibody-drug conjugate, for patients with epithelial cancer: final safety and efficacy results from the phase I/II IMMU-132-01 basket trial. Annals of Oncology. 2021; 32(6):746-56.

[107] Bardia A, Hurvitz SA, Tolaney SM, Loirat D, Punie K, Oliveira M, et al. Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer. New England Journal of Medicine. 2021; 384(16):1529-41.

[108] Lonial S, Lee HC, Badros A, Trudel S, Nooka AK, Chari A, et al. Longer Term Outcomes With Single-Agent Belantamab Mafodotin in Patients with Relapsed or Refractory Multiple Myeloma: 13-Month Follow-Up From the Pivotal DREAMM-2 Study. Cancer. 2021; 127(22):4198-212.

[109] Weisel K, Krishnan A, Schecter JM, Vogel M, Jackson CC, Deraedt W, et al. Matching-Adjusted Indirect Treatment Comparison to Assess the Comparative Efficacy of Ciltacabtagene Autoleucel in CARTITUDE-1 Versus Belantamab Mafodotin in DREAMM-2, Selinexor-Dexamethasone in STORM Part 2, and Melphalan Flufenamide-Dexamethasone in HORIZON for the Treatment of Patients With Triple-Class Exposed Relapsed or Refractory Multiple Myeloma. Clinical Lymphoma, Myeloma, and Leukemia. 2022; 22(9):690-701.

[110] Trudel S, Lendvai N, Popat R, Voorhees PM, Reeves B, Libby EN, et al. Antibody-drug conjugate, GSK2857916, in relapsed/refractory multiple myeloma: an update on safety and efficacy from dose expansion phase I study. Blood Cancer Journal. 2019; 9(4):37.

[111] Lonial S, Lee HC, Badros A, Trudel S, Nooka AK, Chari A, et al. Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2): a two-arm, randomised, open-label, phase 2 study. The Lancet Oncology. 2020; 21(2):207-21.

[112] Ray U, Orlowski RZ. Antibody-Drug Conjugates for Multiple Myeloma: Just the Beginning, or the Beginning of the End? Pharmaceuticals. 2023; 16(4):590.

[113] GSK. GSK provides an update on Blenrep (belantamab mafodotin-blmf) US marketing authorisation [Internet]. London: GSK; 2022 [cited 2024 April 29]. Available from: https://www.gsk.com/en-gb/media/press-releases/gsk-provides-update-on-blenrep-us-marketing-authorisation/.

[114] Jain N, Stock W, Zeidan A, Atallah E, McCloskey J, Heffner L, et al. Loncastuximab tesirine, an anti-CD19 antibody-drug conjugate, in relapsed/refractory B-cell acute lymphoblastic leukemia. Blood Advances. 2020; 4(3):449-57.

[115] Hamadani M, Radford J, Carlo-Stella C, Caimi PF, Reid E, O'Connor OA, et al. Final results of a phase 1 study of loncastuximab tesirine in relapsed/refractory B-cell non-Hodgkin lymphoma. Blood. 2021; 137(19):2634-45.

[116] Caimi PF, Ai W, Alderuccio JP, Ardeshna KM, Hamadani M, Hess B, et al. Loncastuximab tesirine in relapsed or refractory diffuse large B-cell lymphoma (LOTIS-2): a multicentre, open-label, single-arm, phase 2 trial. The Lancet Oncology. 2021; 22(6):790-800.

[117] United States Food and Drug Administration. ZYNLONTA™ (loncastuximab) for injection, for intravenous use. Maryland: United States Food and Drug Administration; 2017.

[118] Zinzani PL, Minotti G. Anti-CD19 monoclonal antibodies for the treatment of relapsed or refractory B-cell malignancies: a narrative review with focus on diffuse large B-cell lymphoma. Journal of Cancer Research and Clinical Oncology. 2022; 148(1):177-90.

[119] Spira A, Zhou X, Chen L, Gnanasakthy A, Wang L, Ungar D, et al. Health-Related Quality of Life, Symptoms, and Tolerability of Loncastuximab Tesirine in Patients With Relapsed or Refractory Diffuse Large B-Cell Lymphoma. Clinical Lymphoma, Myeloma, and Leukemia. 2022; 22(3):158-68.

[120] de Bono JS, Concin N, Hong DS, Thistlethwaite FC, Machiels JP, Arkenau HT, et al. Tisotumab vedotin in patients with advanced or metastatic solid tumours (InnovaTV 201): a first-in-human, multicentre, phase 1-2 trial. The Lancet Oncology. 2019; 20(3):383-93.

[121] Coleman RL, Lorusso D, Gennigens C, González-Martín A, Randall L, Cibula D, et al. Efficacy and safety of tisotumab vedotin in previously treated recurrent or metastatic cervical cancer (innovaTV 204/GOG-3023/ENGOT-cx6): a multicentre, open-label, single-arm, phase 2 study. The Lancet Oncology. 2021; 22(5):609-19.

[122] United States Food and Drug Administration. TIVDAK™ (tisotumab vedotin-tftv) for injection, for intravenous use. Maryland: United States Food and Drug Administration; 2021.

[123] Hisada Y, Mackman N. Tissue Factor and Cancer: Regulation, Tumor Growth, and Metastasis. Seminars in Thrombosis and Hemostasis. 2019; 45(4):385-95.

[124] Ahmadi SE, Shabannezhad A, Kahrizi A, Akbar A, Safdari SM, Hoseinnezhad T, et al. Tissue factor (coagulation factor III): a potential double-edge molecule to be targeted and re-targeted toward cancer. Biomarker Research. 2023; 11(1):60.

[125] Yonemori K, Kuboki Y, Hasegawa K, Iwata T, Kato H, Takehara K, et al. Tisotumab vedotin in Japanese patients with recurrent/metastatic cervical cancer: Results from the innovaTV 206 study. Cancer Science. 2022; 113(8):2788-97.

[126] Dilawari A, Shah M, Ison G, Gittleman H, Fiero MH, Shah A, et al. FDA Approval Summary: Mirvetuximab Soravtansine-Gynx for FRα-Positive, Platinum-Resistant Ovarian Cancer. Clinical Cancer Research. 2023; 29(19):3835-40.

[127] Gonzalez-Ochoa E, Veneziani AC, Oza AM. Mirvetuximab Soravtansine in Platinum-Resistant Ovarian Cancer. Clinical Medicine Insights: Oncology. 2023; 17:11795549231187264.

[128] Matulonis UA, Lorusso D, Oaknin A, Pignata S, Dean A, Denys H, et al. Efficacy and Safety of Mirvetuximab Soravtansine in Patients With Platinum-Resistant Ovarian Cancer With High Folate Receptor Alpha Expression: Results From the SORAYA Study. Journal of Clinical Oncology. 2023; 41(13):2436-45.

[129] Moore KN, Angelergues A, Konecny GE, García Y, Banerjee S, Lorusso D, et al. Mirvetuximab Soravtansine in FRα-Positive, Platinum-Resistant Ovarian Cancer. New England Journal of Medicine. 2023; 389(23):2162-74.