Journal on Oncology

www.journalononcology.org

Review Article

Open Access, Volume 2

Antibody-Drug Conjugates (ADCs): A Novel Treatment for Hematologic Malignancies

Kajetan Karaszewski*; Wiesław Wiktor Jędrzejczak

Department of Hematology, Transplantation and Internal Medicine, Medical University of Warsaw, Warsaw, Poland.

Abstract

Antibody-drug conjugates are novel agents used in the treatment of hematologic malignancies. These drugs consist of a cytotoxin and monoclonal antibody, which enables this cytotoxin to target cancer cells while sparing other cells. These drugs are used in monotherapy or as an addition to existing chemotherapy schemes. Antibody-drug conjugates are currently used in patients with advanced hematologic malignancies under certain conditions, usually concerning prior refractoriness to other drugs. However, antibody-drug conjugates are gradually rescheduled to earlier phases of therapy due to numerous proofs of their clinical efficacy. Therefore, they may help to achieve cures for patients whose diseases remain incurable. Furthermore, many of these drugs were already approved, and many more are in various phases of clinical trials. Altogether these drugs represent a new and very promising direction in the development of anti-cancer pharmacotherapeutics. Therefore, further research on drugs of this category may yield breakthroughs in future hematology and medicine.

Keywords: Antibody-drug conjugate; Hematology; Anti-cancer agent; Neoplasia; Malignancy.

Abbreviations: AML: Acute Myeloid Leukemia; HL: Hodgkin Lymphoma; ALCL: Anaplastic Large Cell Lymphoma; ALL: Acute Lymphoblastic Leukemia; DLBCL: Diffuse Large B-Cell Lymphoma; MM: Multiple Myeloma: HCL: Hairy Cell Leukemia: R/R: Relapsed/Refractory.

Manuscript Information: *Received: May 10, 2022; Accepted: May 27, 2022; Published: Jun 03, 2022*

Correspondance: *Kajetan Karaszewski, Department of Hematology, Transplantology and Internal Medicine, Medical University of Warsaw, Warsaw, Poland. Email: s077751@student.wum.edu.pl*

Citation: *Karaszewski K, Jędrzejczak WW. Antibody-Drug Conjugates (ADCs): A Novel Treatment for Hematologic Malignancies. J Oncology. 202; 2(1): 1026.*

Introduction

The discovery that some cytotoxic agents may be helpful in the treatment of cancer was hampered by the concomitant finding that they were also toxic to normal cells and that their specificity for cancer cells is limited. Hence, one of the significant research directions has focused on either finding or developing agents that would specifically target cancer cells. The breakthrough was the development of monoclonal antibodies that could bind to specific molecules on the surface of cancer cells. Unfortunately, such antibodies have prompted the death of cells they have recognized in some cases. This was the case of anti-CD20 antibodies such as rituximab in B-cell lymphomas or anti-HER2 antibodies such as trastuzumab in breast cancer. However, such antibodies did not produce desired effects in many other situations: they have only recognized cancer cells without further consequences. Then the concept of arming such antibodies with toxins has emerged. Such armed antibodies were later termed antibody-drug conjugates (ADCs,) and some of them have already been introduced into clinical practice [1,2]. This review will only concern ADCs registered and used in hematology, which are: gemtuzumab ozogamicin, brentuximab vedotin, inotuzumab ozogamicin, polatuzumab vedotin, belantamab mafodotin, moxetumomab pasudotox, and loncastuximab tesirine. They are listed in Table 1.

The ADC, as mentioned, is composed of an antibody recognizing a specific molecule on the surface of specific cancer cells and a cytotoxic drug. This drug is attached to a monoclonal antibody with a linker, which must be stable enough not to get degraded by endogenous proteases before ADC is taken to cancer cells. Of course, the target antigen should be as specific for cancer cells as possible [1,2]. When the antibody binds to its target, the whole ADC is internalized. After endocytosis, the linker alone or both antibody and linker are degraded through enzymatic proteolysis in lysosomes. This leads to the release of the cytotoxic drug, which finally causes the death of cancer cells by interfering with their critical molecules [1-4]. The mechanism of their action is shown in Figure 1.

Apart from the classical mode of action of ADCs described in the previous paragraph, there exists a phenomenon termed «bystander killing effect». It refers to the situation when due to a high drug to antibody ratio, the drug may be released from the antibody prior to internalization of ADC and exert direct cytotoxic action [5]. This mechanism may allow achieving therapeutic activity of the drug even in tumors with low expression of a target molecule for an antibody carrier. The bystander killing effect has been described for therapy targeting HER2 in breast cancer [5,6] and in other solid tumors [7]. However, this effect has also been observed in experimental models of hematological malignancies [8].

Table 1: Antibody-drug conjugates registered by FDA for the use in hematologic cancers.

ADC name	Registration date	Indications	Conditions	Target antigen
gemtuzumab ozogamicin	May 2000	AML	R/R newly diagnosed	CD33
brentuximab vedotin	August 2011	HL, ALCL, T-cell lymphomas	Relapse (≥2 unsuccessful therapies)	CD30
inotuzumab ozogamicin	August 2017	ALL	R/R newly diagnosed	CD22
polatuzumab vedotin	June 2019	DLBCL	R/R (≥2 unsuccessful therapies)	CD79b
belantamab mafodotin	August 2020	MM	R/R (≥4 unsuccessful therapies)	BCMA
moxetumomab pasudotox	September 2018	HCL	Relapse (≥2 unsuccessful therapies	CD22
loncastuximab tesirine	April 2021	DLBCL	R/R (≥2 unsuccessful therapies)	CD19

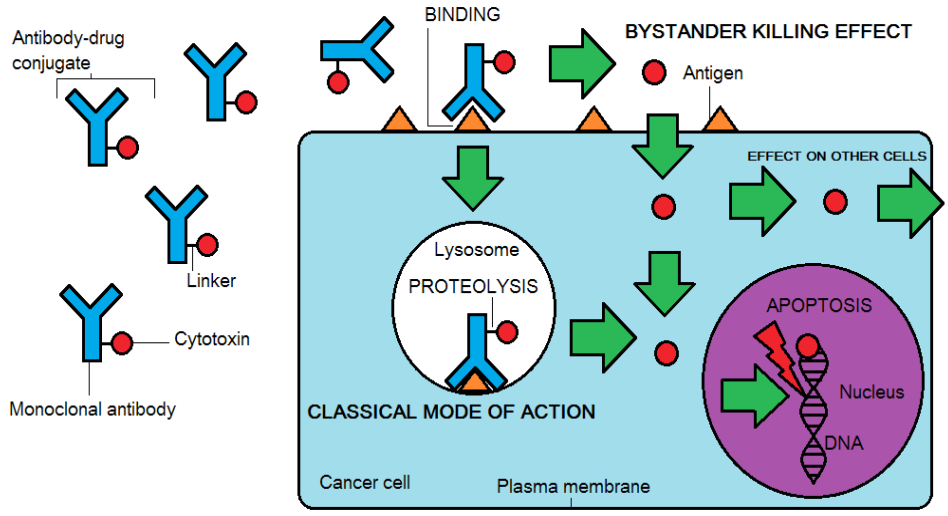

Figure 1: Principle of action of antibody-drug conjugates.

It has been observed that ADCs have a general preference to reach cancer cells located in the blood or at the vicinity of blood vessels since these locations are more accessible for them following i.v. administration. It is some limitations, but on the other hand, it seems sufficient for fighting blood neoplasia [1]. Like any other drug, the efficacy of ADCs is dependent on their pharmacokinetics. The optimization of chemical groups in linkers' structure seems to be the decisive factor in drug efficacy and specificity [4,9].

Gemtuzumab ozogamicin

Gemtuzumab ozogamicin (GO) is composed of calicheamicin linked to a humanized monoclonal antibody anti-CD33. CD33 is present on cells of approximately 90% of acute myeloid leukemia (AML), which was the basis for selecting this target [10,11]. Calicheamicin is a cytotoxic antibiotic isolated from *Micromonospora echinospora* subsp. *calichensis*. Monoclonal antibodies and calicheamicin are conjugated through an acid-labile hydrazone linker [12]. GO was first approved in May 2000 by FDA for patients in the first relapse of CD33-positive AML above 60 years of age, who did not qualify for aggressive chemotherapy [13]. Afterward, the drug was withdrawn in 2010 and re-approved in September 2017 for adults with newly diagnosed CD33+ AML and for R/R CD33+ AML patients ≥2 years old [14].

According to meta-analysis, the addition of GO to standard daunorubicin+cytarabine (DA) chemotherapy produced a reduction of relapse risk, as well as an increase of overall 5-year survival without a significant increase in complete remission (CR) rate [15,16]. In another study, induction therapy of adult AML patients with the combination of chemotherapeutics - fludarabine, cytarabine, idarubicin (FLAI) + GO - produced a CR rate of 82% [17]. Furthermore, in children for whom GO was added to induction treatment with cytarabine, daunorubicin, etoposide (ADE), there was a significant decrease in MRD levels [18]. Moreover, the drug was also evaluated in monotherapy, producing an overall response rate (ORR) of 26% [10].

Evaluation of the relationship between the level of CD33 expression and GO efficacy did not yield definitive results [19]. CD33 has a function of the inhibitory receptor. Its phosphorylation inhibits the secretion of pro-inflammatory cytokines (TNF-α, IL-1β, IL-8) and downregulates the myeloid line of hematopoiesis. Inversely, reduction of CD33 receptors on the surface might increase cell proliferation. Therefore, reducing the expression of CD33 receptors may contribute to a more aggressive phenotype of leukemia. Consequently, leukemic cells of favorable genotype with higher CD33 expression would be more sensitive to chemotherapy and destroyed more effectively [20]. Similarly, concerning cytogenetic alterations: some studies have only shown an improvement for patients with favorable cytogenetics [10,15], while others failed to confirm this phenomenon [19]. However, it is more probable that patients with CD33 activating mutations have more considerable benefits from the treatment [21]. For instance, this phenomenon was documented for NPM1 positive patients [22] or patients with acute promyelocytic leukemia (APL). In this case, GO was given in combination with arsenic trioxide and all-trans retinoic acid [23].

GO was ineffective as monotherapy in pediatric patients [11]. The drug used after post-consolidation therapy did not improve either median time to relapse or relapse rate. It was also ineffective in prolonging 5-year survival and event-free survival rates [24]. As before, the relationship to the level of CD33 expression remained unclear [25]. It also concerned the results of their next study, in which GO in combination with conventional chemotherapy significantly improved event-free survival and reduced relapse risk in *KMT2A*-r AML, both overall and in higher- and lower-risk *KMT2A*-subsets [26]. Although GO was reported to have a generally acceptable profile of adverse events significant neutropenia and thrombocytopenia were observed in almost all patients in the first weeks of the treatment [10,24]. The drug is even described to be toxic to platelet production [22]. Other significant adverse events were: hyperbilirubinemia [15], sepsis [10], and veno-occlusive disease [27]. Especially this last complication, which was initially associated with the transplantation of hematopoietic cells, is unique as drug toxicity. It hinges on the occlusion of small veins in the liver resulting in ascites and hyperbilirubinemia. If severe, it may cause the death of affected patients [28].

Brentuximab vedotin

Brentuximab vedotin (BV) is composed of chimeric anti-CD30 antibody and cytotoxic drug auristatin E [29]. CD30 molecule on lymphoma cells stimulates their growth and survival [30,31] through the activation of the NF-κB pathway. Auristatin is a natural cytostatic microtubule inhibitor isolated from mollusk *Dorabella auricularia*. Monomethyl auristatin E (MMAE) is attached to a monoclonal antibody with peptide valine-citrulline linker [12,32]. BV was first approved in August 2011 by FDA [9] to treat classical Hodgkin's lymphoma (HL) and systemic anaplastic large cell lymphoma (ALCL) after a relapse (≥2 ineffective therapies) or after previous hematopoietic stem cell transplantation (HSCT). This situation concerns 15-30% of HL patients [33]. This approval was expanded in 2017 to cutaneous anaplastic large cell lymphoma and CD30-expressing mycosis fungoides [34]. Further approvals in 2018 expanded use of BV to first-line treatment of stage III and IV classical Hodgkin lymphoma in combination with chemotherapy [35] and to previously untreated systemic anaplastic large cell lymphoma or other CD30-expressing peripheral T-cell lymphomas also in combination with chemotherapy [36].

Standard chemotherapy in newly diagnosed HL produces PFS of 75-80%, but is substantially less effective in R/R disease. Therefore, it implies a need for modern chemotherapeutics, like ADCs [37,38]. ORR depending on the study, was 60% [29,39] or 75% [30] of patients with relapsed/refractory HL and 88% [39] or 86% [30] cases of R/R ALCL. In these two diseases together, ORR was estimated to be 68 % [39], 75% [40]. Another study estimated overall survival (OS) after 20 months as 73.8% [37]. Notably, BV prolonged 5-year progression-free survival (PFS) (59% vs. 41%) versus placebo, as consolidation treatment in patients at high risk of a relapse or progression [41].

BV was also tested with promising results in patients with other hematologic malignancies. These diseases included diffuse large B cell lymphoma (DLBCL), primary mediastinal lymphoma and Sézary syndrome [42,43]. Naturally, in all these diseases, there might be an expression of CD30, but no correlation between antigen expression and response to BV has been observed for peripheral T-cell lymphomas, as an example. Sometimes the response was even possible while CD30 remained undetected [43].

Interestingly, there is an ability to successfully perform the allo-HSCT procedure after BV treatment, although the high incidence of graft versus host disease has been reported [40].

Common adverse effects of BV treatment included: peripheral sensory or motor neuropathy, which was the most significant, but also present were less severe – nausea, diarrhea, arthralgia, or pyrexia [39]. Other authors also reported pulmonary toxicity [30], hyperkalemia [43], thrombocytopenia and neutropenia, or severe states, such as arrhythmia or septic shock [38]. Sensory neuropathy was described to occur in 42-66% of patients. It tended to resolve after 12 weeks of therapy with physical exercises sessions [37,44].

Inotuzumab ozogamicin

Inotuzumab ozogamicin (IO) is composed of humanized anti-CD22 monoclonal antibody conjugated through acid-labile hydrazone linker with calicheamicin [12]. This ADC was registered in August 2017 for patients with refractory/resistant acute lymphoblastic leukemia (R/R ALL). CD22 is present on the surface of >90% of normal B lymphocytes [9,45] and is also expressed on cells of the majority of B cell lymphomas, for example, chronic lymphocytic leukemia (CLL), follicular lymphoma (FL), marginal zone lymphoma (MZL) and DLBCL. Therefore, it may lead to IO approval in new indications in the near future [46].

A randomized study showed a significant increase in CR rate (80.7% vs. 29.4%) [47]. Moreover, duration of remission, OS, PFS, and the rate of MRD negativity among patients with CR was higher. This time IO in monotherapy was compared to a 'standard therapy', which included several treatment possibilities chosen by an investigator. In this study, both Philadelphia chromosome (Ph) positive and negative patients were included [47]. The obtained results were similar, but in this case, IO therapy was also proven to increase patients' chance for HSCT after the treatment [48]. In another study increased rate of patients with MRD-negativity and longer PFS was observed in the IO group [49].

There are also studies evaluating the effect of IO concerning mutations underlying ALL. Lower response rates are generally achieved in Ph+ patients with ALL (negative predictive factor), and also these with translocation (4;11) or chromosome 17 alterations [50]. Even if Ph+ patients manage to achieve CR or MRD-negativity after IO therapy, they often experience relapses [51], and IO does not affect their survival time, even after HSCT. Considering the fact that Ph+ patients have limited treatment options and the occurrence of resistance mutations is high (BCR-ABL kinase inhibitors), there is a need for new agents in this indication [52].

ALL is more common in pediatric patients (about 30 % of all diagnoses), in whom standard chemotherapy gives much better results than in adult patients. Nevertheless, there are also pediatric ALL patients who are not cured by chemotherapy, and they need new therapeutic approaches. Moreover, there is a need for less toxic therapies [53]. Initial results of phase I studies of IO seem promising since investigated patients achieved ORR of 80% and MRD-negativity of 84%. However, 1-year OS of 40% was yet far from desired. The treatment was generally well tolerated by investigated pediatric patients [54].

In combination with mini hyper-cyclophosphamide, vincristine, and dexamethasone (Mini-HCVD), IO was reported to produce CR in 98% (vs. 88% in HCVAD control) of elderly patients. Moreover, IO increased 3-year event-free survival rate (49% vs 29%), and OS rate (54% vs 32%). All investigated patients were Ph-negative. Some patients from the IO+Mini-HCVD group were also treated with blinatumomab, which could affect final results [55]. Blinatumomab is a bispecific antibody registered for R/R ALL and considered by some as the first-choice treatment in this case [56].

The most significant adverse effects of IO treatment are veno-occlusive disease (which is considered the most dangerous for patients), increased bilirubin, increased liver enzymes, hypotension [45,47], abdominal pain [50], leukopenia. In addition, like in other ACDs, thrombocytopenia and neutropenia were often reported [46].

Polatuzumab vedotin

Polatuzumab vedotin (PV) is made of humanized anti-CD79b monoclonal antibody conjugated through peptide valine-citrulline linker with MMAE. CD79b antigen has a function of B-cell signaling component and is naturally present on the surface of most normal B lymphocytes and malignant ones [57,58]. PV was registered in June 2019 for patients with R/R DLBCL who did not respond to at least 2 prior therapies (≥2 in the US, ≥1 in EU) [57,59,60].

So far, this drug is suggested to be used only in combination with bendamustine and rituximab (polatuzumab-BR treatment) in patients who did not qualify for bone marrow transplantation [60,61]. However, clinical trials have promising results for the efficacy of PV in combinations with bispecific antibodies, venetoclax, or immunomodulating agents. Moreover, trials in patients with FL are in progress [62,63]. Polatuzumab-BR therapy is sometimes accompanied by chimeric antigen receptor T-cell therapy (CAR-T) [61].

CR rate achieved with polatuzumab-BR was estimated as 40% vs. 17.5% for BR alone. The increase of OS and PFS rates was also observed in the PV group, regardless of cytogenetic status in subgroups, for instance, those with MYC or BCL2 overexpression. However, more research in this field is necessary to produce precise data [57]. Another study reported an ORR of 61%, where 40% were complete responses [59].

Common adverse effects of PV were neutropenia, anemia, thrombocytopenia, pulmonary infection [59], diarrhea, nausea, and the most significant one – peripheral neuropathy, already described for BV. This last complication was sometimes responsible for treatment discontinuation [61].

Belantamab mafodotin

Belantamab mafodotin (BM) is composed of humanized anti-BCMA (anti-B cell maturation antigen) monoclonal antibody and monomethyl auristatin F (MMAF). Both substances are connected via a protease-resistant maleimidocaproyl linker. BCMA, also termed TNFRSF17 or CD269, is essential for myeloma and normal plasma cells' proliferation [64-66]. BM was approved in August 2020 for patients with R/R MM who had previously been treated with ≥4 unsuccessful therapies [65,67,68]. These therapies must include anti-CD38 treatment with monoclonal antibodies, immunomodulatory agents, and proteasome inhibitors (triple-class refractory MM). These patients have a very poor prognosis – median survival is less than 1 year. The approval of this drug was accelerated by FDA since phases II and III of clinical trials for mono-

therapy, as well as drugs combinations, are still ongoing [68,69].

ORR in the case of BM used as monotherapy was estimated to be 32% [67,70], while the 1-year survival rate was 58% among responders [67]. There is a need for more precise data, especially from controlled trials, about the drug's survival rates, response rates, data among cytogenetic subgroups, or usage in combinations with other agents.

As for other ADCs, thrombocytopenia and neutropenia were reported as common adverse effects of BM treatment. Other less severe were pyrexia, diarrhea, chills, or tachycardia. The most characteristic ones were keratopathy of corneal epithelium, visual acuity, or blurred vision [64,67]. Despite the temporary character of these events, patients treated with BM require a multidisciplinary approach from hematologists, ophthalmologists, and specialists to cope with these events. Specific information about the management has already been created [71].

Moxetumomab pasudotox

Moxetumomab pasudotox (MP) consists of the recombinant murine anti-CD22 monoclonal antibody and bacterial exotoxin of Pseudomonas species (PE38). They are connected via a furin-cleavable linker [60]. PE38 is a 38 kDa fragment of exotoxin A. Therefore, MP is an immunotoxin and not a classical ADC, but it is included here as belonging to a similar category of compounds [72]. Its mechanism of action finally leads to a decrease of concentration of myeloid cell leukemia 1 (Mcl-1) protein (antiapoptotic agent), which may lead to apoptosis of leukemia cells [73]. The drug was first registered in September 2018 for patients with hairy cell leukemia who had been treated with ≥2 failed therapies, including purine analog. This rare B-cells malignancy generally has a good response to standard therapy (purine analogs, pentostatin, rituximab). However, relapses occur in about half of patients after several years of remission [74-77].

MP caused OR in about 80% of patients and durable CR in 30% of patients. MRD-negativity was achieved in 85% of responders [75]. In another study, similar values were estimated as 36% (durable CR) and 82% (MRD-negativity in responders). Moreover, among complete responders, the duration of CR at ≥5 years was 61% [78].

Adverse effects of MP differ from events in therapies with other ADCs. In this case, common incidents are peripheral edema, hemolytic uremic syndrome (HUS), infections, capillary leak syndrome (CLS). Less severe events, like headache, nausea, or pyrexia, also happen during therapy [73,75-77]. Anemia, lymphopenia, and thrombocytopenia were rare compared to other ADCs [78].

Loncastuximab tesirine

Loncastuximab tesirine (LT) is comprised of humanized anti-CD19 monoclonal antibody and pyrrolobenzodiazepine dimer (PBD) toxin. Both structures are linked through a peptide valine-alanine linker [79]. LT was registered in April 2021 for patients with R/R DLBCL after ≥2 failed standard therapies [80]. However, there are also trials for R/R ALL as a possible indication, which would be another ADC option for ALL patients, apart from IO [79]. Moreover, it is also being developed for FL and mantle cell lymphoma in monotherapy and combinations. Numerous potential indications for this drug are possible due to the familiar presence of the target antigen on the surface of B cells [80].

It is still too early to assess this drug's efficacy in clinical practice. However, promising results of the phase I clinical trials are already available [81].

Common adverse events of LT therapy are nausea, neutropenia, peripheral edema, liver parameters abnormalities [79], thrombocytopenia, anemia, pneumonia [80].

Conclusion and future directions

Antibody-drug conjugates are novel and promising pharmacotherapeutics for patients with hematologic malignancies. Apart from the ADCs described here, over 100 other drugs are currently being developed for various indications [60]. Examples include denintuzumab mafodotin [82], pinatuzumab vedotin [83], and coltuximab ravtansine [84].

Currently, ADCs are not as effective as desired since they did not produce cures in cases of hematologic neoplasias in which they were used. However, they have been used mainly in patients with advanced stages of their disorders whose cells were preselected for resistance to many other agents. Possibly their impact would be much more significant if they were moved to use in the early phases of treatment, as this was already documented for GO and IO [85]. Moreover, further perfection of this technology may provide us with more effective compounds. This is the reason why ADCs technology will probably remain the object of interest for future scientific research.

References

1. Hamilton GS. Antibody-drug conjugates for cancer therapy: The technological and regulatory challenges of developing drug-biologic hybrids. Biologicals. 2015; 43: 318-32.
2. Adair JR, Howard PW, Hartley JA, Williams DG, Chester KA. Antibody-drug conjugates - a perfect synergy. Expert Opin. Biol. Ther. 2012; 12: 1191-1206.
3. Kovtun YV, Goldmacher VS. Cell killing by antibody-drug conjugates. Cancer Lett. 2007; 255: 232-240.
4. Chari RV, Miller ML, Widdison WC. Antibody-drug conjugates: an emerging concept in cancer therapy. Angew Chem Int Ed Engl. 2014; 53: 3796-3827.
5. Rinnerthaler G, Gampenrieder SP, Greil R. HER2 Directed Antibody-Drug Conjugates beyond TDM-1 in Breast Cancer Int J Mol Sci. 2019; 20: 1115.
6. Corti C, Giugliano F, Nicolò E, Ascione L, Curigliano G. Antibody-Drug Conjugates for the Treatment of Breast Cancer. Cancers. 2021; 13.
7. Burton JK, Bottino D, Secomb TW. A System Pharmacology Model for Drug Delivery to Solid Tumors by Antibody-Drug Conjugates: Implications for Bystander Effect. The AAPS J. 2020; 22: 12.
8. Schönberger S, van Beekum C, Götz B, Nettersheim D, Schorle H, Schneider DT et al. Brentuximab Vedotin exerts profound antiproliferative and proapoptotic efficacy in CD30-positive as well as cocultured CD30-negative germ cell tumour cell lines. J Cell Mol Med. 2018; 22: 568-575.
9. Matsuda Y, Mendelsohn BA. An overview of process development for antibody-drug conjugates produced by chemical conjugation

technology. Expert Opin Biol Ther. 2021; 21: 963-975.

10. Larson RA, Sievers EL, Stadtmauer EA, Löwenberg B, Estey EH, Dombret H et al. Final report of the efficacy and safety of gemtuzumab ozogamicin (Mylotarg) in patients with CD33-positive acute myeloid leukemia in first recurrence. Cancer. 2005; 104: 1442-1452.

11. Zwaan CM, Reinhardt D, Corbacioglu S, van Wering ER, Bökkerink JPM, Tissing WJE et al. Gemtuzumab ozogamicin: first clinical experiences in children with relapsed/refractory acute myeloid leukemia treated on compassionate-use basis. Blood. 2003; 101: 3868-3871.

12. Nolting B. Linker Technologies for Antibody-Drug Conjugates. Methods Mol Biol. 2013; 1045: 71-100.

13. Rowe JM, Löwenberg B. Gemtuzumab ozogamicin in acute myeloid leukemia: a remarkable saga about an active drug. Blood. 2013; 121.

14. Selby C, Yacko LR, Glode AE. Gemtuzumab Ozogamicin: Back Again. J Adv Pract Oncol. 2019; 10: 68-82.

15. Appelbaum FR, Bernstein ID. Gemtuzumab Ozogamicin for Acute Myeloid Leukemia. Blood. 2017; 130: 2373-2376.

16. Hills RK, Castaigne S, Appelbaum FR, Delaunay J, Petersdorf S, Othus M et al. Addition of gemtuzumab ozogamicin to induction chemotherapy in adult patients with acute myeloid leukaemia: a meta-analysis of individual patient data from randomised controlled trials. Lancet Oncol. 2014; 15: 986-96.

17. Candoni A, Papayannidis C, Martinelli G, Simeone E, Gottardi M, Iacobucci I et al. Flai (fludarabine, cytarabine, idarubicin) plus low-dose Gemtuzumab Ozogamicin as induction therapy in CD33-positive AML: Final results and long term outcome of a phase II multicenter clinical trial. Am J Hematol. 2018; 93: 655-663.

18. O'Hear C, Inaba H, Pounds S, Shi L, Dahl G, Bowman WP et al. Gemtuzumab ozogamicin can reduce minimal residual disease in patients with childhood acute myeloid leukemia. Cancer. 2013; 119(22): 4036-4043.

19. Olombel G, Guerin E, Guy J, Perrot JY, Dumezy F, de Labarthe A et al. The level of blast CD33 expression positively impacts the effect of gemtuzumab ozogamicin in patients with acute myeloid leukemia. Blood. 2016; 127.

20. 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 (Basel). 2021; 13.

21. Fournier E, Duployez N, Ducourneau B, Raffoux E, Turlure P, Caillot D et al. Mutational profile and benefit of gemtuzumab ozogamicin in acute myeloid leukemia. Blood. 2020; 135: 542-546.

22. Castaigne S. Why is it so difficult to use gemtuzumab ozogamicin? Blood. 2013; 121: 4813-4814.

23. Aribi A, Kantarjian HM, Estey EH, Koller CA, Thomas DA, Kornblau SM et al. Combination Therapy With Arsenic Trioxide, All-trans Retinoic Acid, and Gemtuzumab Ozogamicin in Recurrent Acute Promyelocytic Leukemia. Cancer. 2007; 109.

24. Hasle H, Abrahamsson J, Forestier E, Ha SY, Heldrup J, Jahnukainen K et al. Gemtuzumab ozogamicin as post-consolidation therapy does not prevent relapse in children with AML: results from NOPHO-AML 2004. Blood. 2012; 120.

25. Pollard JA, Alonso TA, Loken M, Gerbing RB, Ho PA, Bernstein ID et al. Correlation of CD33 expression level with disease characteristics and response to gemtuzumab ozogamicin containing chemotherapy in childhood AML. Blood. 2012; 119.

26. Pollard JA, Guest E, Alonso TA, Gerbing RB, Loken M, Brodersen LE et al. Gemtuzumab Ozogamicin Improves Event-Free Survival and Reduces Relapse in Pediatric KMT2A-Rearranged AML: Results From The Phase III Children's Oncology Group Trial AAML0531. J Clin Oncol. 2021; 39: 3149-3160.

27. Piccaluga PP, Martinelli G, Rondoni M, Malagola M, Gaitani S, Isidori A et al. Gemtuzumab Ozogamicin for Relapsed and Refractory Acute Myeloid Leukemia and Myeloid Sarcomas. Leukemia & Lymphoma. 2004; 45: 1791–1795.

28. Corbacioglu S, Jabbour EJ, Mohty M. Risk Factors for Development of and Progression of Hepatic Veno-Occlusive Disease/Sinusoidal Obstruction Syndrome. Biol Blood Marrow Transplant. 2019; 25: 1271-1280.

29. Rothe A, Sasse S, Goergen H, Eichenauer DA, Lohri A, Jäger U et al. Brentuximab vedotin for relapsed or refractory CD30+ hematologic malignancies: the German Hodgkin Study Group experience. Blood. 2012; 120: 1470-1472.

30. Ansell SM. Brentuximab vedotin. Blood. 2014; 124: 3197-200.

31. Chen R, Gopal AK, Smith SE, Ansell SM, Rosenblatt JD, Savage KJ et al. Five-year survival and durability results of brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma. Blood. 2016; 128: 1562-1566.

32. Vaklavas C, Forero-Torres A. Safety and efficacy of brentuximab vedotin in patients with Hodgkin lymphoma or systemic anaplastic large cell lymphoma. Ther Adv Hematol. 2012; 3(4): 209-225.

33. Garciaz S, Coso D, Peyrade F, Fürst S, Duran S, Chetaille B et al. Brentuximab vedotin followed by allogeneic transplantation as salvage regimen in patients with relapsed and/or refractory Hodgkin's lymphoma. Hematol Oncol. 2014; 32: 187-91.

34. Welborn M, Duvic M. Antibody-Based Therapies for Cutaneous T-Cell Lymphoma. Am J Clin Dermatol. 2019; 20: 115-122.

35. Choi Y, Diefenbach CS. An evaluation of brentuximab vedotin as a treatment option for stage III/IV Hodgkin lymphoma. Expert Rev Hematol. 2019; 12: 801-808.

36. Nizamuddin I, Galvez C, Pro B. Management of ALCL and other CD30+ peripheral T-cell lymphomas with a focus on Brentuximab vedotin. Semin Hematol. 2021; 58: 85-94.

37. Zinziani PL, Viviani S, Anastasia A, Vitolo U, Luminari S, Zaja F et al. Brentuximab vedotin in relapsed/refractory Hodgkin's lymphoma: the Italian experience and results of its use in daily clinical practice outside clinical trials. Haematologica. 2013; 98: 1232-1236.

38. Minich SS. Brentuximab vedotin: a new age in the treatment of Hodgkin lymphoma and anaplastic large cell lymphoma. Ann Pharmacother. 2012; 46: 377-383.

39. Bartlett NL, Chen R, Fanale MA, Brice P, Gopal A, Smith SE et al. Retreatment with brentuximab vedotin in patients with CD30-positive hematologic malignancies. J Hematol Oncol. 2014; 7.

40. Chen R, Palmer JM, Thomas SH, Tsai NC, Farol L, Nademanee A et al. Brentuximab vedotin enables successful reduced-intensity allogeneic hematopoietic cell transplantation in patients with relapsed or refractory Hodgkin lymphoma. Blood. 2012; 119: 6379-6381.

41. Moskowitz CH, Walewski J, Nademanee A, Masszi T, Agura E, Holowiecki J et al. Five-year PFS from the AETHERA trial of brentuximab vedotin for Hodgkin lymphoma at high risk of progression or relapse. Blood. 2018; 132: 2639-2642.

42. Berger GK, McBride A, Lawson S, Royball K, Yun S, Gee K et al. Brentuximab vedotin for treatment of non-Hodgkin lymphomas: A systematic review. Crit Rev Oncol Hematol. 2017; 109: 42-50.

43. Horwitz SM, Advani RH, Bartlett NL, Jacobsen ED, Sharman JP, O'Connor OA et al. Objective responses in relapsed T-cell lymphomas with single-agent brentuximab vedotin. Blood. 2014; 123(20): 3095-3100.

44. Pastorelli F, Derenzini E, Plasmati R, Pellegrini C, Broccoli A, Casadei B et al. Severe peripheral motor neuropathy in a patient with Hodgkin lymphoma treated with brentuximab vedotin. Leuk Lymphoma. 2013; 54: 2318-21.

45. George B, Kantarjian HM, Jabbour E, Jain N. Role of inotuzumab ozogamicin in the treatment of relapsed/refractory acute lymphoblastic leukemia. Immunotherapy. 2016; 8: 135-143.

46. Shor B, Gerber HP, Sapra P. Preclinical and clinical development of inotuzumab-ozogamicin in hematological malignancies. Mol Immunol. 2015; 67: 107-116.

47. Kantarjian HM, DeAngelo DJ, Stelljes M, Martinelli G, Liedtke M, Stock W et al. Inotuzumab Ozogamicin versus Standard Therapy for Acute Lymphoblastic Leukemia. N Engl J Med. 2016; 375: 740-53.

48. 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: 2474-2487.

49. Jabbour EJ, Gökbuket N, Advani A, Stelljes M, Stock W, Liedtke M et al. Impact of minimal residual disease status in patients with relapsed/refractory acute lymphoblastic leukemia treated with inotuzumab ozogamicin in the phase III INO-VATE trial. Leuk Res. 2020; 88: 106283.

50. Thota S, Advani A. Inotuzumab ozogamicin in relapsed B-cell acute lymphoblastic leukemia. Eur J Haematol. 2017; 98: 425-434.

51. Jain N, Maiti A, Ravandi F, Konopleva M, Daver N, Kadia T et al. Inotuzumab ozogamicin with bosutinib for relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukemia or lymphoid blast phase of chronic myeloid leukemia. Am J Hematol. 2021; 96: 1000-1007.

52. Stock W, Martinelli G, Stelljes M, DeAngelo DJ, Gökbuget N, Advani A et al. Efficacy of inotuzumab ozogamicin in patients with Philadelphia chromosome-positive relapsed/refractory acute lymphoblastic leukemia. Cancer. 2021; 127: 905-913.

53. de Vries JF, Zwaan CM, De Bie M, Voerman JSA, den Boer ML, van Dongen JJM et al. The novel calicheamicin-conjugated CD22 antibody inotuzumab ozogamicin (CMC-544) effectively kills primary pediatric acute lymphoblastic leukemia cells. Leukemia. 2012; 26: 255-264.

54. Brivio E, Locatelli F, Lopez-Yurda M, Malone A, Diaz-de-Heredia C, Bielorai B et al. A phase 1 study of inotuzumab ozogamicin in pediatric relapsed/refractory acute lymphoblastic leukemia (ITCC-059 study). Blood. 2021; 137: 1582-1590.

55. Jabbour EJ, Sasaki K, Ravandi F, Short NJ, Garcia-Manero G, Daver N et al. Inotuzumab ozogamicin in combination with low-intensity chemotherapy (mini-HCVD) with or without blinatumomab versus standard intensive chemotherapy (HCVAD) as frontline therapy for older patients with Philadelphia chromosome-negative acute lymphoblastic leukemia: A propensity score analysis. Cancer. 2019; 125: 2579-2586.

56. Tvito A, Rowe JM. Inotuzumab ozogamicin for the treatment of acute lymphoblastic leukemia. Expert Opin Biol Ther. 2017; 17: 1557-1564.

57. Malecek MK, Watkins MP, Bartlett NL. Polatuzumab vedotin for the treatment of adults with relapsed or refractory diffuse large B-cell lymphoma. Expert Opin Biol Ther. 2021; 21: 831-839.

58. Lu D, Lu T, Gibiansky L, Li X, Li C, Agarwal P et al. Integrated Two-Analyte Population Pharmacokinetic Model of Polatuzumab Vedotin in Patients With Non-Hodgkin Lymphoma. CPT Pharmacometrics Syst Pharmacol. 2020; 9:48-59.

59. Segman Y, Ribakovsky E, Avigdor A, Goldhecht Y, Vainstein V, Goldschmidt N et al. Outcome of relapsed/refractory diffuse large B-cell lymphoma patients treated with polatuzumab vedotin-based therapy: real-life experience. Leuk Lymphoma. 2021; 62: 118-124.

60. Burke JM, Morschauser F, Andorsky D, Lee C, Sharman JP. Antibody-drug conjugates for previously treated aggressive lymphomas: focus on polatuzumab vedotin. Expert Rev Clin Pharmacol. 2020; 13: 1073-1083.

61. Walji M, Assouline S. An evaluation of polatuzumab vedotin for the treatment of patients with diffuse large B-cell lymphoma. Expert Rev Hematol. 2020; 13: 933-942.

62. Choi Y, Diefenbach CS. Polatuzumab Vedotin: a New Target for B Cell Malignancies. Curr Hematol Malig Rep. 2020; 15: 125-129.

63. Deeks ED. Polatuzumab Vedotin: First Global Approval. Drugs. 2019; 79(13): 1467-1475.

64. Sheikh S, Lebel E, Trudel S. Belantamab mafodotin in the treatment of relapsed or refractory multiple myeloma. Future Oncol. 2020; 16: 2783-2798.

65. Lassiter G, Bergeron C, Guedry R, Cucarola J, Kaye AM, Cornett EM et al. Belantamab Mafodotin to Treat Multiple Myeloma: A Comprehensive Review of Disease, Drug Efficacy and Side Effects. Curr Oncol. 2021; 28: 640-660.

66. Becnel MR, Lee HC. The role of belantamab mafodotin for patients with relapsed and/or refractory multiple myeloma. Ther Adv Hematol. 2020; 11.

67. 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: 4198-4212.

68. Markham A. Belantamab Mafodotin: First Approval. Drugs. 2020; 80: 1607-1613.

69. Nooka AK, Weisel K, van de Donk NW, Routledge D, Rodriguez Otero P, Song K et al. Belantamab mafodotin in combination with novel agents in relapsed/refractory multiple myeloma: DREAMM-5 study design. Future Oncol. 2021; 17: 1987-2003.

70. Tzogani K, Penttilä K, Lähteenvuo J, Lapveteläinen T, Lopez Anglada L et al. EMA Review of Belantamab Mafodotin (Blenrep) for the Treatment of Adult Patients with Relapsed/Refractory Multiple Myeloma. Oncologist. 2020; 26: 70-76.

71. Lonial S, Nooka AK, Thulasi P, Badros AZ, Jeng BH, Callander NS et al. Management of belantamab mafodotin-associated corneal events in patients with relapsed or refractory multiple myeloma (RRMM). Blood Cancer J. 2021; 11.

72. Dosio F, Brusa P, Cattel L. Immunotoxins and anticancer drug conjugate assemblies: the role of the linkage between components. Toxins (Basel). 2011; 3: 848-883.

73. Dhillon S. Moxetumomab Pasudotox: First Global Approval. Drugs. 2018; 78: 1763-1767.

74. Yurkiewicz IR, Coutre S, Ghesquieres H, Pastan I, Kreitman RJ. Moxetumomab pasudotox as re-treatment for heavily-pretreated relapsed hairy cell leukemia. Leuk Lymphoma. 2021; 62: 2812-2814.

75. Abou Dalle I and Ravandi F. Moxetumomab pasudotox for the treatment of relapsed and/or refractory hairy cell leukemia. Expert Rev Hematol. 2019; 12: 707-714.

76. 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: 1768-1777.

77. Janus A, Robak T. Moxetumomab pasudotox for the treatment of hairy cell leukemia. Expert Opin Biol Ther. 2019; 19: 501-508.

78. Kreitman RJ, Dearden C, Zinzani PL, Delgado J, Robak T, le Coutre PD et al. Moxetumomab pasudotox in heavily pre-treated patients with relapsed/refractory hairy cell leukemia (HCL): long-term follow-up from the pivotal trial. J Hematol Oncol. 2021; 14.

79. 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 Adv. 2020; 4: 449-457.

80. Lee A. Loncastuximab Tesirine: First Approval. Drugs. 2021; 81: 1229-1233.

81. Hamadani M, Radford J, Carlo-Stelta 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: 2634-2645.

82. Jones L, McCalmont H, Evans K, Mayoh C, Kurmasheva RT, Billups CA et al. Preclinical activity of the antibody-drug conjugate denintuzumab mafodotin (SGN-CD19A) against pediatric acute lymphoblastic leukemia xenografts. Pediatr Blood Cancer. 2019; 66: e27765.

83. Advani RH, Lebovic D, Chen A, Brunvand M, Goy A, Cheng JE et al. Phase I Study of the Anti-CD22 Antibody-Drug Conjugate Pinatuzumab Vedotin with/without Rituximab in Patients with Relapsed/Refractory B-cell Non-Hodgkin Lymphoma. Clin Cancer Res. 2017; 23: 1167-1176.

84. Kantarjian HM, Lioure B, Kim SK, Atallah E, Leguay T, Kelly K et al. A Phase II Study of Coltuximab Ravtansine (SAR3419) Monotherapy in Patients With Relapsed or Refractory Acute Lymphoblastic Leukemia. Clin Lymphoma Myeloma Leuk. 2016; 16: 139-45.

85. McNeer JL, O'Brien MM, Rheingold SR, Devidas M, Chen Z, Bhojwani D et al. A Phase 3 Randomized Trial of Inotuzumab Ozogamicin for Newly Diagnosed High-Risk B-ALL: Safety Phase Results from Children's Oncology Group Protocol AALL1732. Blood. 2021; 138: 3398-3400.