# Antibody Drug Conjugates: New Weapons Against Cancer

BY REBECCA WILSON

In recent years, targeted cancer therapy has reached a whole new level with antibody drug conjugates (ADCs). Researchers are now chemically linking powerful cytotoxic agents with tumor-specific antibodies to deliver cell-killing capabilities with, hopefully, far fewer systemic safety concerns.

"Traditional cytotoxic chemotherapy can be very effective for numerous malignancies and [it has] revolutionized how we began to treat cancers," according to Christine M. Walko, PharmD, a Personalized Medicine Specialist at the H. Lee Moffitt Cancer Center and Research Institute in Tampa, Fla.

Unfortunately, this approach targets fast-growing cells indiscriminately, according to Walko, often leading to toxicity and side effects such as myelosuppression, hair loss, nausea, and neuropathy. "By linking these cytotoxic drugs to a specific antibody expressed predominantly on cancer cells, we are able to decrease the toxicity seen to healthy cells while still killing the cancer cells."

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"ADCs represent a treatment modality for patients with advanced/metastatic disease who have failed multiple therapies and are left with few therapeutic choices," explained William Douglas Figg, Sr., PharmD, senior investigator at the NCI. "They also represent another viable approach for diseases that have limited treatment options or unmet medical need."

With several options already approved and more than 100 under investigation, the field is blooming (*Lancet* 2019; doi: 10.1016/S0140-6736(19)31774-X). Researchers are a long way from solving all of the technical issues that plague this unique class of therapy, but what has been accomplished so far has experts excited for what the future holds.

## ADC Promise

This new biologic treatment approach has been under investigation for at least 50 years, but the relatively recent approval of several drugs has spurred considerable interest from oncologists and the pharmaceutical industry at large.

ADCs are designed to use a cancer-specific antibody linked to a cytotoxic drug with a "linker protein." Currently, the approved therapeutics target the CD33, CD30, CD20, CD79b, and HER2 receptors and are approved to treat patients with certain types of leukemia, lymphoma, and breast cancer.

"The goal of ADCs is for them to act similar to a 'smart bomb' where the antibody component of the drug is specific for a certain type of cancer cell that will allow the drug to target that cell and then drop the 'payload' of the cytotoxic drug attached to it," explained Walko. "In theory, this would allow for the destruction of the cancer cells while minimizing toxicity to the healthy cells."

Currently, seven ADCs have made it to market and are described below.

**Gemtuzumab ozogamicin,** a monoclonal antibody targeting CD33 linked with calicheamicin, is used as a monotherapy and in combination with daunorubicin and cytarabine for the treatment of adult patients with newly diagnosed CD33-positive acute myeloid leukemia (AML). First approved in 2000, this ADC was voluntarily removed from the market in 2010 after follow-up studies showed no improved outcomes and increased early deaths in newly diagnosed AML patients receiving a combination of gemtuzumab ozogamicin and standard chemotherapy (*Expert Rev Clin Pharmacol* 2018; doi: 10.1080/17512433.2018.1478725). The drug was re-approved in 2017 with an updated dosing regimen and target patient population.

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Studies show gemtuzumab ozogamicin with standard induction chemotherapy resulted in an event-free survival of 13.6 months compared with 8.8 months for those receiving chemotherapy alone (*Clin Cancer Res* 2018; doi: 10.1158/1078-0432.CCR-17-3179). As a monotherapy for patients treated without curative intent, gemtuzumab ozogamicin provided a median overall survival of 4.9 months compared with 3.6 months for those on supportive care only.

**Brentuximab vedotin,** which consists of the chimeric monoclonal antibody brentuximab linked with the antimitotic agent monomethyl auristatin E (MMAE), is approved for the treatment of certain patients with Hodgkin lymphoma (HL). In 2017, it received two new indications: for patients previously treated for primary cutaneous anaplastic large cell lymphoma and those with CD30-expressing mycosis fungoides. For HL patients who experienced failure with autologous stem cell transplant, treatment with brentuximab vedotin every 3 weeks for up to 16 treatments provided an overall response rate of 75 percent and a complete response in 34 percent (*Hematology Am Soc Hematol Educ Program* 2018; doi: 10.1182/asheducation-2018.1.207). The favorable outcomes have led to its use, in combination with chemotherapy, as a frontline treatment of advanced-stage patients.

**Inotuzumab ozogamicin** is a humanized anti-CD22 monoclonal antibody paired with the cytotoxic agent calicheamicin and is approved to treat relapsed B-cell precursor acute lymphoblastic leukemia (ALL). A phase III randomized trial of 326 adults with relapsed/refractory ALL found 73.8 percent of patients treated with inotuzumab ozogamicin experienced improved complete remission compared with just 30.9 percent treated with standard-of-care chemotherapy (*Cancer* 2019; doi: 10.1002/cncr.32116). Researchers are now investigating its efficacy as frontline treatment in combination with chemotherapy (*Drug Des Devel Ther* 2018; doi: 10.2147/DDDT.S150317).

**Polatuzumab vedotin-piiq,** a monoclonal antibody against CD79b linked with MMAE, is approved as a combination therapy with bendamustine and a rituximab product for relapsed or refractory diffuse large B-cell lymphoma. An open-label multicenter trial of 80 patients showed those treated with the combination of polatuzumab vedotin-piiq, bendamustine, and a rituximab product experience a complete response of 40 percent compared with 18 percent of those treated with bendamustine alone (*Drugs* 2019; doi: 10.1007/s40265-019-01175-0). Another recent study found polatuzumab vedotin combined with bendamustine and rituximab provided transplant-ineligible patients a 58 percent reduced risk of death compared with bendamustine and rituximab (*J Clin Oncol* 2020; doi: 10.1200/JCO.19.00172).

**Ado-trastuzumab emtansine** consists of the anti-HER2 monoclonal antibody trastuzumab linked with emtansine. While ado-trastuzumab emtansine was initially approved to treat HER2-positive metastatic breast cancer, it was recently approved to also treat patients with HER2-positive early breast cancer who have residual invasive disease. An open-label trial of 1,486 patients found that adjuvant ado-trastuzumab emtansine treatment lowered the risk of recurrence or death by half compared with trastuzumab alone (*N Engl J Med* 2019; doi: 10.1056/NEJMoa1814017). A recent trial testing its use for patients with HER2-mutant lung cancers found it provided a median progression-free survival of 5 months—a result the researchers note is promising and warrants further study (*J Clin Oncol* 2018; doi: 10.1200/JCO.2018.77.9777).

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**Enfortumab vedotin** was approved by the FDA on Dec. 18, 2019, for the treatment of patients with advanced or metastatic urothelial cancer who have failed on prior treatments. The first to target the Nectin-4 protein, this antibody links with MMAE. The trial that led to enfortumab vedotin's accelerated approval included 125 patients with progression on or after platinum or checkpoint inhibitor therapy. At the study conclusion, participants had an overall response rate of 42 percent, 9 percent of whom had a complete response (*J Clin Oncol* 2019; doi: 10.1200/JCO.2019.37.18_suppl.LBA4505). Enfortumab vedotin "represents a much-needed treatment option for this patient population who had limited options after initial therapies failed," Figg noted.

**Trastuzumab deruxtecan,** approved just 2 days after enfortumab vedotin on Dec. 20, 2019, is for patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior therapies. The ADC is composed of an anti-HER2 antibody linked with a cytotoxic topoisomerase I inhibitor. Of 184 patients with a median of six prior therapies, 60.9 percent responded to trastuzumab deruxtecan, with a median progression-free survival of 16.4 months (*N Engl J Med* 2019; doi: 10.1056/NEJMoa1914510).

"Trastuzumab deruxtecan will benefit patients with metastatic HER2-positive breast cancer as a late-line treatment option for those who have been heavily pretreated and progressed on several regimens," explained Figg. "Looking ahead, it will be interesting and exciting to see whether trastuzumab deruxtecan can extend the benefit to patients with HER2-low disease."

## Hurdles

Given the complexity of the ADC design, four parameters are key to a successful therapy, each of which present unique challenges:

1. *Tumor targeting*. Although the number of surface markers only needs to be slightly increased in tumor cells compared with healthy cells for ADC therapy to work, the more markers present, the more potent the ADC. In addition, researchers continue to investigate ways to account for the shedding of the relevant antigenic determinant on cell surface membranes, which could inadvertently reduce the targeted delivery. The homogeneity of the tumor marker on the cell surface has proven a challenge as well, as homogenous expression tends to improve efficacy for most ADCs; however, heterogeneity may be beneficial for ADCs with bystander killing activity.

2. *Antibody.* A successful ADC must start with an antibody that has a highly specific target and minimal immunogenicity. The antibody's binding affinity to the tumor marker is also important, although researchers have yet to fully understand the required binding affinity for ADC success. Likewise, the way in which the antibody is internalized remains under investigation. Studies suggest different antibodies that share the same tumor marker exhibit different internalization rates. In addition, where the antibody is deposited in the tumor cell affects its ability to release the cytotoxic agent.

3. *Cytotoxic payload*. Because antibodies can only carry so much, any chosen payload must be extremely toxic to kill the majority of the tumor cells with a minimal delivery—as little as 0.003 percent to 0.08 percent of an injected dose per gram is taken up by tumor cells (*Avicenna J Med Biotechnol* 2019; PMCID: PMC6359697). Because of the toxicity, researchers have to choose carefully to ensure efficacy with minimal immunogenic potential. The cytotoxic agent poses several problems beyond its potency. It must also remain stable during the preparation, storage, and blood circulation phases to avoid undesirable effects. They must also be hydrophilic for preparation and to permeate the tumor cell, but preferably form a hydrophobic metabolite after intercellular cleavage to improve blood clearance and safety—a tall order. Most ADCs (95-99%) are metabolized before binding to tumor cells, raising concerns of systemic toxicity and driving the search for safer and more effective options.

4. *Linking method.* Forming a successful ADC hinges on the ability to link the antibody to the cytotoxic drug. This linking process involves careful consideration of where the two are linked, the drug-antibody ratio, homogeneity, and stability. Currently, most ADCs use interchain disulfide bridges and surface-exposed lysines to create between 0 and 8 links with significant ADC heterogeneity. This is where much of the ADC research is focused in an attempt to homogenize the linking process.

"Advancements in technology have led to improved iterations of ADCs with each successive generation, with improvements in target specificity and linker and payload selection," Figg explained. "Research is also underway to evaluate for innovative linker systems and next-generation conjugation chemistry."

Yet, as with all therapeutics, recent studies show the emergence of drug resistance to ADC therapy—a new hurdle researchers are trying to understand, according to Figg. "More importantly, we need to understand and learn how to manage the more serious toxicities associated with the particular ADCs, as well as identify those at risk for the toxicity."

## Future Implications

Researchers are excited for the promise of ADCs for many reasons. Several of the more recent trials and approvals prove their efficacy beyond advanced/metastatic disease that has failed multiple therapies.

"We should be prepared to see some of the ADCs being used earlier in the disease continuum, in the frontline settings, and/or in combination with immune-oncology drugs as data for some of the ongoing studies investigating these avenues come to fruition," Figg stated.

In addition to earlier treatment, ADCs harbor the promise of new treatment options for many cancer populations. As investigators discover antigens unique to specific forms of cancer tumors, they can also work to build an ADC with the right antibody/cytotoxic agent combination to kill it.

"ADC agents are a fascinating example of combined biochemical engineering and pharmacology expertise to create both a carrier and cytotoxic agent targeted to the cancer cells," Walko explained. "Continued advances will help to expand the targetable antigens, and thus diversity of cancers that can be targeted by ADCs." OT

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### Learning Objectives for This Month's Activity:

After participating in this activity, readers should be better able to: 1. Evaluate the use of antibody drug conjugates (ADCs) for patients with advanced/metastatic disease. 2. Describe the indications for those ADCs that have been approved.

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