Review article

ADCs propelled back into the oncology spotlight

The pharmaceutical industry's renewed interest in antibody-drug conjugates (ADCs) following a marked lull has, in part, been brought about by the US Food and Drug Administration's (FDA) accelerated approval of Seattle Genetics Inc's new-generation ADC, Adcetris (brentuximab vedotin). This is the company's first commercial approval as well as the first drug authorised in the US for the treatment of Hodgkin's lymphoma in more than 30 years.[1]

Though ADCs have been the subject of extensive research for decades, the only such therapy currently on the US market is Adcetris; no ADCs have been authorised in the European Union (Adcetris is currently under review there). The two companies that have made the most clinical advances in ADC technology are Seattle Genetics and ImmunoGen Inc, both of which are based in the US. (For a discussion of the status of ADCs in clinical studies globally and the spectrum of potential indications that are being pursued by their developers, please see article on pages 10 and 11.)

The technology behind Adcetris and other ADCs is being touted by some as the blockbuster that we've all been waiting for in the battle against cancer because it targets tumours in a way that allows a highly potent cytotoxic agent to be released only once it is inside the cell, avoiding the systemic toxicity that is a major disadvantage of traditional chemotherapy. Of course there are sceptics, too.

But what exactly are ADCs? 'Antibody conjugates', which have been around since the 1980s, are monoclonal antibodies that selectively deliver potent anti-cancer agents to tumour-associated antigen targets. The cytotoxic agent can be a small molecule, a radionuclide, a protein toxin or an enzyme. It is covalently bound to the antibody by a synthetic linker that is designed to be stable in the bloodstream but allow the agent to detach when it reaches the targeted cancer cells.

As the most significant progress to date has been made with small molecules, this article focuses on antibody-drug conjugates.

To better understand ADCs, it is helpful to look at the individual components, all of which need to be optimised for the therapy to be effective:

- the *monoclonal antibody* (mAb) is 'empowered' by being combined with a chemical linker and a cytotoxic agent. It targets a specific antigen (eg CD30 in the case of Adcetris) and causes the ADC to bind to that antigen;
- the *linker* is based on chemicals including disulfides, hydrazones or peptides (cleavable) or thioethers (non-cleavable). It is essential to ADC technology because it ensures the cytotoxic agent is not released before it reaches the target cell; and
- the *cytotoxic agent*, also referred to as the 'payload', is a highly potent tubulin-directed or DNA-directed cell-killing drug. The linker conjugates the agent with the antibody and releases the agent once it is inside the cell.

It is a simple enough concept, yet early ADCs tested in the clinical setting faced problems relating to immunogenicity, lack of potency and insufficient target selectivity. Now that these issues have largely been addressed, the industry has started to sit up and take note again.

One critical difference between current and early ADCs is that first-generation ADCs were prepared with mouse antibodies, whereas now they are either fully human or high-quality humanised antibodies, explains Beverly Teicher, who heads up the Molecular Pharmacology Branch's Developmental Therapeutics Program at the US National Cancer Institute.[2] Furthermore, the antibodies used today are "much more tight binding with appropriate binding constants and off-rates", she says. Earlier antibodies were not as rigorously characterised for these properties; today, the structure-activity relationship of antibodies is analysed much like small molecules.

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There is also more attention paid to the abundance of the target on the surface of the tumour cells versus the expression of the target on the surface of normal tissues, according to Dr Teicher.

In addition, scientists now have a better grasp on the stability of linkers in circulation. Although ADCs have a somewhat shorter circulating half-life than unconjugated antibodies, "the circulating half-lives are still several days (in most cases). So the stability of the linkers and the ADCs are characterised in depth before going *in vivo*," explains Dr Teicher.

The key prerequisites for successful ADC therapy are appropriate target selection, as well as optimisation of the antibody, the linker and the cytotoxic agent.

The traditional view is that the target antigen must be highly expressed on tumour cells and not present on normal tissue. However, John Lambert, executive vice president and chief science officer of ImmunoGen, has pointed out that the target can be on normal cells not undergoing frequent cell division if the cell-killing agent only impacts dividing cells (ie if a tubulin-acting agent is used rather than a DNA-acting agent).[3]

Furthermore, he suggests that the target can be on normal cells that undergo frequent cell division if a different epitope can be identified on the cancer cells, but the antibodies must be developed and evaluated accordingly.

Indeed, antibody optimisation is essential. According to

Dr Lambert, antibodies are generally selected based on their binding properties, but he notes that selection should also be based on their purpose. For example, more weight should be given to the antibody's functional properties for antigens that have a role in the disease process, whereas more emphasis should be placed on payload delivery capabilities for antigens that are solely targets.

As for linkers, the main criteria are that they must be stable in circulating blood so that the drug will not be released before it reaches the cell, and they must be labile inside the target cell so the drug can then be released. Linker stability is determined by, among other things, laboratory analyses of half-life and 'free drug' (cytotoxic agent released). Because linkers usually have shorter half-lives than 'naked' antibodies, they have to be adjusted to ensure stability.

As such, it is not possible to have a one-size-fits-all linker, ImmunoGen's executive director of investor relations and corporate communications, Carol Hausner, told *MedNous*. This is why ImmunoGen's modular approach to its Targeted Antibody Payload (TAP) technology allows researchers to test different linkers with different cell-killing agents.

Linker stability

Linker stability is a careful balancing act. Ms Hausner noted that "achieving 100% stability/safety compromises what you're trying to achieve. If you can get enough of the ADC into the patient to kill the cancer cells and yet not suffer from toxicity associated with 'free drug', the linker has all the stability needed. If there was no way for the cytotoxic agent to ever get released, then the ADC would be inactive".

She added that in most cases, an ADC with a cleavable linker is going to be more active than one with a non-cleavable linker, with a few exceptions. One of those exceptions is the company's T-DM1 (trastuzumab emtansine) for HER2-positive breast cancer, which is undergoing Phase 3 trials – the results are expected to form the basis for a global regulatory submission in 2012. The company uses a non-cleavable linker in T-DM1 because it allows the ADC to remain circulating in the blood longer, providing it with more time to build up in the tumour tissue.

Although the linker technology has been viewed as the main barrier to the clinical success of ADCs, Ms Hausner says that the primary obstacle is optimisation of the cytotoxic agent. The agent must be potent enough to kill the cell and be able to attach to the antibody, but it must also be able to detach without loss of potency.

The cytotoxic agents in ADCs need to be much more potent than traditional chemotherapy drugs such as doxorubicin because only a small quantity can be attached to the antibody. ImmunoGen's DM1, for example, is 100-10,000 times more potent than traditional chemotherapy agents. As a result, it can kill cells at a very low concentration.

Likewise, Seattle Genetics's highly potent class of antimicrotubule agents, called auristatins, are 100 to 1,000-fold more potent than traditional chemotherapy drugs. The company uses the microtubule disrupting agent monomethyl auristatin E (MMAE) in Adcetris.

Whether the agent is tubulin or DNA-targeted must also be taken into consideration. "Tubulin-acting agents only impact dividing cells, but are not effective for all cancers, whereas DNA-acting agents [ie calicheamicins and duocarmycins] are effective against a broader range of cancers, but require careful selection of appropriate targets," Dr Lambert said.

Too good to be true?

There are numerous advantages of ADCs, including selective delivery to tumour cells, a broad spectrum of therapeutic indications for both solid and liquid tumours (eg non-Hodgkin's lymphoma, breast cancer, non-small cell lung cancer, ovarian cancer) and reduced adverse effects compared with traditional cancer therapies.

However, the disadvantages must not be overlooked. There are still safety concerns, particularly following Pfizer's voluntary withdrawal of the first FDA-approved ADC, Mylotarg (gemtuzumab ozogamicin), in 2010 for recurrent CD33 positive acute myeloid leukemia.

Mario Brkulj of the German biotech company MorphoSys AG questions whether the linker can really be sustainable enough to hold the payload and whether the technology causes the antibody to be less effective. "The molecule is no longer equivalent to what we have in our body," he said to *MedNous*. The company has a large antibody library (HuCAL) but is not developing ADCs.

According to Ms Hausner, most of the disadvantages relate to targeting, ie there are certain properties that the target needs to have for the ADC therapy to be successful.

As such, the antigens must be well-characterised, so the tumour has to be tested for expression. Furthermore, if the target is expressed on normal tissue, there is an increased risk of toxicity. As mentioned by Mr Brkulj, there is also the possibility that some of the payload may release prematurely. Other potential obstacles to the commercial success of ADCs are that the cytotoxic agent will not be potent enough to kill the cell, or that antigen expression could be heterogeneous, especially in certain cancers.

These possible disadvantages are widely recognised and will still have to be addressed, perhaps through development of other types of antibody conjugates. Norwegian-based Algeta, for example, believes its thorium-227, a radionuclide that emits high-energy alpha particles, can be used as an effective payload in targeted cancer therapies.

The company says that targeted thorium conjugates have the potential to offer a number of unique advantages over current ADCs, including increased potency, highly localised effects and the ability to overcome drug-resistance by virtue of a direct tumour-killing alpha mechanism of action.

References: 1. Seattle Genetics press release, http://investor.seagen.com/phoenix.zhtml?c=124860&p=irol-newsArticle&ID=1598466&highlight, 19 August 2011.
2. Personal communication, Beverly Teicher, 7 November 2011.
3. John Lambert, Creating the Optimal ADC, World ADC Summit (San Francisco, California), 25-28 October 2011.

This article was written by Karen Finn, contributing editor to *MedNous*.