Clinical Roundtable Monograph

Antibody-Drug Conjugate Technology Development for Hematologic Disorders

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Abstract: Antibody-drug conjugates (ADCs) combine cytotoxic chemotherapy and antibody specificity. There are 4 components of ADC technology: the cancer, or target, antigen; the antibody to that target; the linker that connects the drug to the antibody; and the drug itself. The antibody directs the cytotoxic agent to the tumor cell, thereby diminishing the side effect profile of the cytotoxic agent and enabling delivery of a more potent therapeutic because of the ability to control the target and the side effects. ADC technology has vastly improved within the last several years. In early ADCs, the linkers were too labile, which led to the release of free drug in the circulation and consequent off-target toxicity. In the current generation of ADCs, the linkers are more stable, and the cytotoxic agents are significantly more potent. ADCs have been developed against a variety of antigens and receptors, including CD19, CD22, and CD30, and have been linked to multiple different cytotoxic agents, including calicheamicin and maytansinoid derivatives. The ADC brentuximab vedotin was recently approved by the US Food and Drug Administration for the treatment of patients with Hodgkin lymphoma after failure of autologous stem cell transplant or at least 2 prior multiagent chemotherapy regimens, and the treatment of patients with systemic anaplastic large cell lymphoma after failure of at least 1 prior multiagent chemotherapy regimen. Other ADCs in clinical trials for hematologic disorders include inotuzumab ozogamicin, SAR3419, and gemtuzumab ozogamicin.

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Overview of Antibody-Drug Conjugate Technology for the Clinician

Neil H. Bander, MD

The Rationale for ADCs

The goal in the development of antibody-drug conjugates (ADCs) was to marry the 2 concepts of cytotoxic chemotherapy and antibody specificity in an effort to overcome the limitations of the respective component technologies.[1] Cytotoxic chemotherapy, which has been in use since the 1940s, suffers from a lack of specificity. Patients experience significant toxicity from these agents, which can limit the amount of chemotherapy that can be delivered, thereby undermining the ability of cytotoxic chemotherapy to achieve its goal. In contrast, antibody therapy has enormous specificity but limited potency in its ability to kill targeted cells. Conceptually, ADCs arose as an effort to combine these 2 technologies and obtain the benefit of their complementarity. The antibody can be used to direct the cytotoxic agent to the tumor cell and thereby accomplish 2 objectives: diminish the side effect profile of the cytotoxic agent and enable delivery of a more potent therapeutic because of the ability to control the target and the side effects.

Components of an ADC

There are 4 components of ADC technology: 1] the cancer, or target, antigen; 2] the antibody to that target; 3] the linker that connects the drug to the antibody; and 4] the drug itself. Like the proverbial chain, an ADC is only as effective as its weakest link. Each component should work perfectly for the ADC to function satisfactorily.

The Target Antigen
The target antigen for an ADC should ideally have high expression on a tumor[2-12] and little or no expression in normal tissue.[11,13] These 2 characteristics—specificity and high-level expression—combine to generate the therapeutic index of the ADC. The target antigen should be present on the cell surface (Figure 1), in order to be accessible to the circulating antibody. It should be an internalizing antigen[3,14] so that, after binding, the ADC is transported into the cell where the cytotoxic agent can exert its effects. Attempts have been made to target

ADCs to non-internalizing antigens, so that the agent is released in the tumor milieu and will exert its effect by subsequent diffusion into the cell.[2] In my view, this approach severely undermines the potential of an ADC and is likely to fail. One way to overcome the issue of a non-internalizing antigen target would be to conjugate an agent that does not require internalization to be active. One class of agents/conjugates that meet this criterion are radioisotope emitters.[15]

The Antibody
The antibody must, of course, be specific to the target. Ideally, it should have limited or no immunogenicity and reasonable affinity, generally in the area of 1 nM.[16] Weaker affinities, or even stronger affinities, have been shown to be disadvantageous or not beneficial, respectively.

The Linker
The linker should be stable in the circulation so that the cytotoxic agent is not released systemically where it can be internalized into normal, nontarget cells. The linker should also maintain attachment of the cytotoxic agent (the conjugate to the antibody) until the ADC reaches the tumor and is internalized.[3] The early, cleavable linkers were too labile[17]; this led to release of free drug in the circulation and consequent off-target toxicity (Figure 2). Approximately 10 years ago, a non-cleavable linker was developed. This type of linker is extremely stable in the circulation, and it prevents premature release of the cytotoxic agent into the circulation (Figure 3).[17] The theoretical concern with the use of a non-cleavable linker was that the cytotoxic agent would not be released even when the ADC was internalized into the target cell. It turns out, however, that when the ADC is internalized into a lysosome, the antibody protein is digested by the lysosomal proteases, and that digestion process releases the cytotoxic agent. Under ideal circumstances, the type of linker should be selected on the basis of the tumor target and the metabolism of the ADC in a given tumor cell type.[17] I would expect that linker research may become an active area that may allow development of linkers with particular appropriateness for a given tumor type. Such a development would further improve an ADC's therapeutic window.
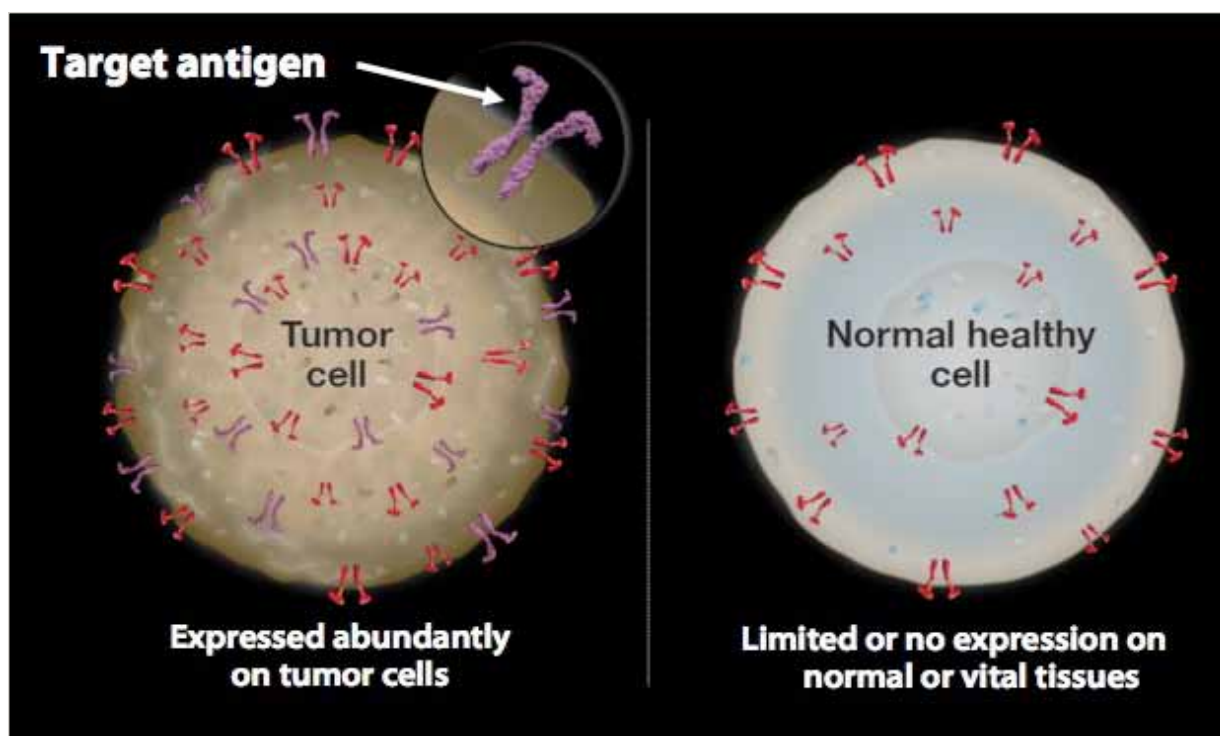
Figure 1. The target antigen of an antibody-drug conjugate should be abundantly present on the cell surface and have little or no expression on normal or vital tissues.

The Cytotoxic Agent

Early ADC efforts simply utilized conventional, readily available chemotherapy agents such as methotrexate or doxorubicin.[18] However, because drug entry in an ADC setting is "gated" by target antigen expression level and internalization kinetics, and effect is further influenced by ADC-drug release kinetics, it became apparent that more potent cytotoxic agents would be necessary.[18]

Another class of conjugates researched early in the field were plant toxins, such as ricin, or microbial toxins, such as pseudomonas exotoxin.[3,19-21] While these immunotoxins certainly made the grade with respect to activity or efficacy, they suffered from immunogenicity.[18]

The most common cytotoxic agents currently used in ADCs—maytansinoids and monomethyl auristatin E (MMAE), both anti-microtubule agents—have IC50s that are 100-1,000–fold more potent than those of conventional chemotherapeutic agents from the same or a similar class.[2] In fact, these agents are so cytotoxic that they could not be utilized without being tethered to a targeting moiety. Another, new class of cytotoxins approaching clinical use is the pyrrolobenzodiazepines (PBDs).[22] PBDs covalently bind the minor groove of DNA, forming interstrand crosslinks.[22] PBDs can be dimerized, and by various chemical substitutions, their level of cytotoxicity can be "tuned" from the nanomolar to the femtomolar range. This latter trait may aid in development of future ADCs that can be tailored to their respective targets.

There is active research into the development of cytotoxic agents with increased potency, which may allow improved ADC opportunities and, potentially, the ability to target tumor antigens with low expression. Development of agents to which a given tumor type is particularly sensitive would provide yet another avenue to increase the ADC therapeutic index. One example of this approach that is already available is the use of targeted isotopes in hematopoietic cancers, taking advantage of those cell types with particular sensitivity to radiation.

Most current ADCs use a ratio of cytotoxic drug to antibody in the range of 2:1 to 4:1.[17,23,24] Ideally, it would appear to be optimal to attach a large number of cytotoxic molecules to each antibody molecule, so that the antibody carried a large amount of agent into the cell. In reality, that approach is likely not feasible; anything more than roughly 4 cytotoxic molecules per antibody molecule leads to physicochemical problems with antibody precipitation, aggregation, or very short pharmacokinetics.[18,23,24] Several efforts in preclinical development are focused on ways to increase the number of cytotoxic agents per antibody molecule.
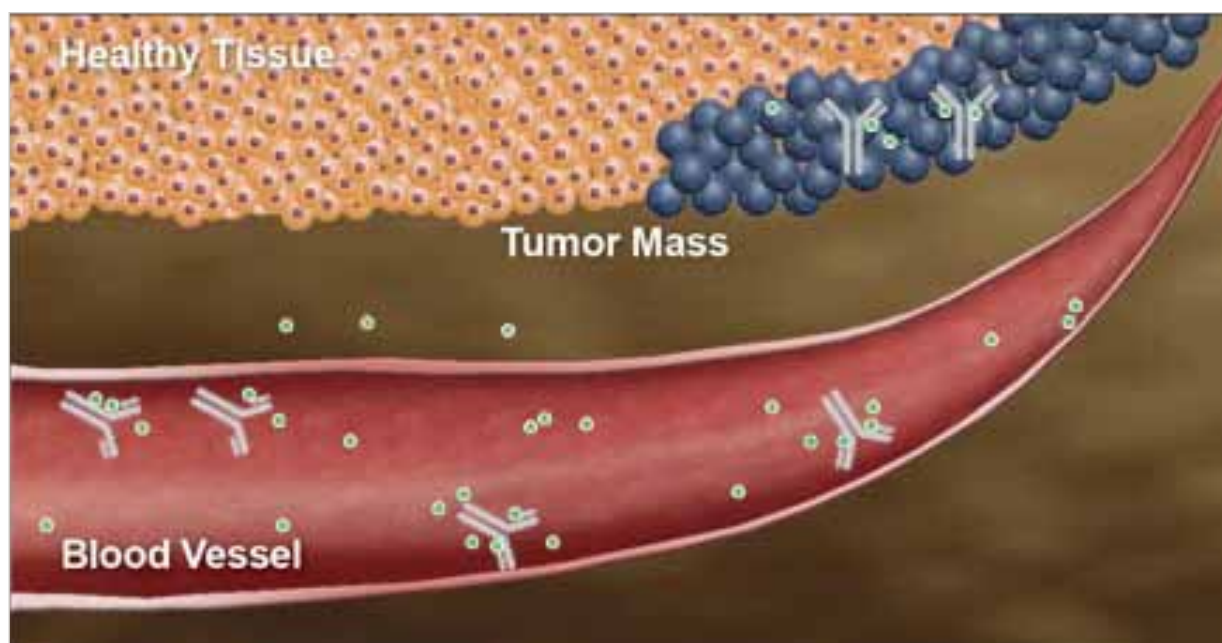
Figure 2. Limitations of early antibody-drug conjugate technology. The early, cleavable linkers were too labile, which led to release of free drug in the circulation and consequent off-target toxicity.
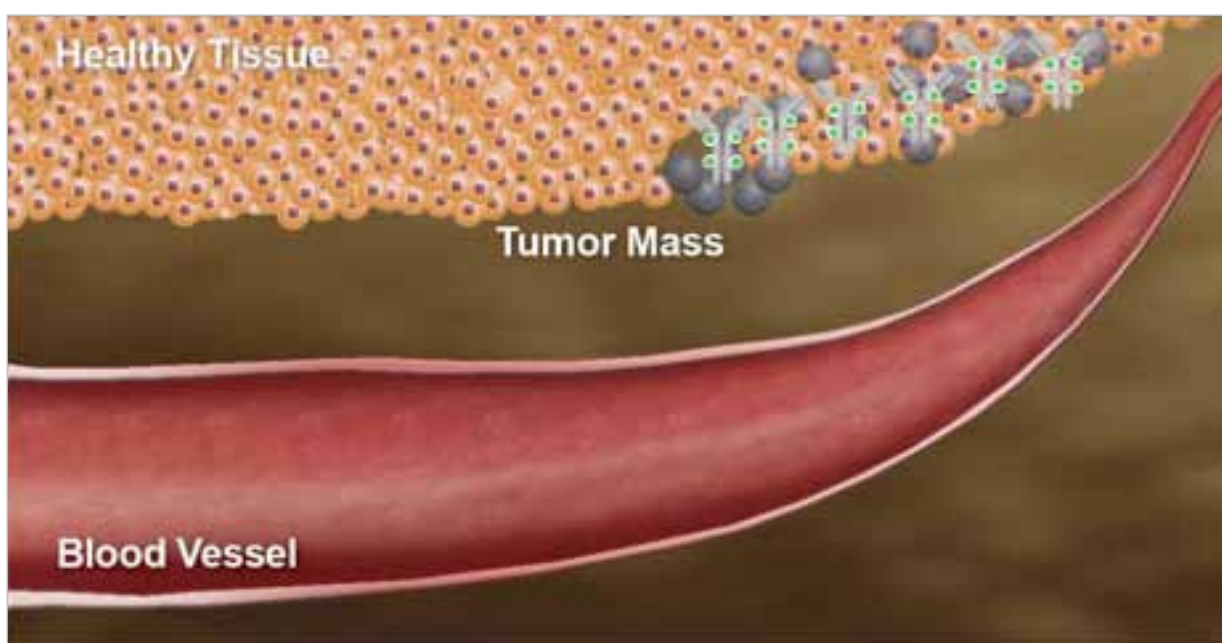
Figure 3. Approximately 10 years ago, a non-cleavable linker was developed. This type of linker is extremely stable in the circulation, and it prevents premature release of the cytotoxic agent into the circulation.

Early ADCs

The first-generation ADCs arose in the 1980s, early in the era of monoclonal antibody technology.[3] In retrospect, this initial development perhaps demonstrated the naïve over-enthusiasm of investigators. The early efforts at ADC development suffered from poor selection of targets, poor selection of antibodies, and a lack of understanding about the stability of the linkers that were being used.[25] None of these early efforts proved successful.

Each component of these early ADCs was inadequate.[26] It is now appreciated that each component should be optimized, and there is a much better understanding and selection of appropriate targets and

antibodies.[1,27-29] Murine antibodies are no longer used. All the antibodies that are now contemplated are at a minimum chimeric, or more likely either humanized or fully human.[26] Early linkers suffered from relatively poor stability, to the point that they released their cytotoxic agents before the antibody had even reached the tumor; they have now been replaced by much more stable linkers. There is also an understanding that the cytotoxic agent should be much more potent than conventional chemotherapeutic agents[26] because the transport of an ADC is limited by the number of target molecules on the cell surface. A more potent cytotoxic agent is necessary so that the small amounts that are internalized into the tumor cells will be sufficient to kill them.[26]

Gemtuzumab ozogamicin is a good example of a partially successful ADC that ultimately led to greater success. In 2000, this ADC was the first to be approved by the US Food and Drug Administration (FDA) for treatment of acute myeloid leukemia (AML). It was removed from the market in 2010 because clinical trials failed to demonstrate clinical benefit.[30] The original approval had been based on response data that had suggested some efficacy. Gemtuzumab ozogamicin used an antibody that binds to CD33 and a potent cytotoxic agent, calicheamicin.[3] This ADC had 2 main drawbacks, both of which undermined its efficacy. First, it used a hydrazone linkage,[3] which has been shown to be less than optimally stable.[17] This linker allowed an early release of the cytotoxic agent that led to significant toxicity in some patients.[18] Second, the target of gemtuzumab ozogamicin (CD33) was one that has weak expression in AML cells, with only 4,000–10,000 molecules per cell.[3] This low level of expression is likely insufficient to bind and deliver enough of the cytotoxic agent into the tumor and create an adequate therapeutic window. However, the use of this agent in fractionated doses may provide benefit. In a study presented at the 2011 American Society of Hematology (ASH) Annual Meeting, the addition of fractionated doses of gemtuzumab ozogamicin to standard chemotherapy significantly improved event-free survival and overall survival in AML patients ages 50–70 years.[31] The future of gemtuzumab ozogamicin is uncertain.

Current ADC Technology

ADC technology has vastly improved within the last several years. Brentuximab vedotin was approved by the FDA in 2011 for the treatment of previously treated Hodgkin lymphoma and systemic anaplastic large-cell lymphoma. In clinical trials, brentuximab vedotin has shown significant antitumor activity at well-tolerated doses.[32] This agent is a conjugate linking an anti-CD30 antibody to MMAE, a synthetic drug designed for ADC

technology.[33] MMAE is an antimitotic drug that binds to tubulin and thereby inhibits tubulin polymerization. MMAE is linked to anti-CD30 through a newer-generation peptide-based linker that is stable in circulation but labile once it is internalized into cells. Upon exposure to proteolytic enzymes in lysosomes, the linker breaks down, releasing the cytotoxic MMAE.

Another agent with impressive data is trastuzumab-DM1 (T-DM1), which uses a noncleavable linker to attach the maytansinoid DM-1 to trastuzumab, an anti-HER2 antibody.[34] T-DM1 is well tolerated and has demonstrated significant antitumor activity in patients with HER2-positive metastatic breast cancer, including patients who had progressed on trastuzumab plus chemotherapy.[35] Like brentuximab vedotin, T-DM1 is a good demonstration of how each component of an ADC has been optimized to overcome the shortcomings seen in earlier efforts.

Future Directions in ADC Technology

The current generation of ADCs differs from the previous generation of ADCs in that the linkers are much more stable and the cytotoxic agents are significantly more potent.[3] These developments have enabled the recent clinical successes. It is likely that we will see ADCs with PBD (discussed earlier) in the next few years. The current cytotoxic agents that are being used—DM1 and MMAE—are both antimicrotubular agents, but there are DNA-targeting agents, such as the duocarmycins and PBDs, that are approximately 2 years away from entering the clinic. These cytotoxic agents are also very potent, but they work by a completely different mechanism than the antimicrotubular agents.

Efforts are under way to develop new linkers that have more stability and perhaps more specificity. The new linkers may be "tuned," in a sense, to the particular tumor type that is being targeted. For example, they may release the cytotoxic agent only upon entry to a target cell with an appropriate metabolic profile.

ADCs with differing cancer targets are currently in preclinical development and will likely enter the clinical arena in the next few years. Obviously, there is much focus today on CD30 and HER2 because they are the 2 most advanced targets among the current ADCs. ADCs that utilize many other targets are in development. These new targets will hopefully have adequate specificity, expression levels, and internalization profiles.

I anticipate that there will be a series of ADCs evolving through the clinical development process in the next several years. As shown by the current ADCs, these types of agents can have significant efficacy and an improved toxicity profile. In my view, there is a high likelihood that

we will see the current success of brentuximab vedotin and trastuzumab-DM1 translated to several other targets and other tumor types.

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Clinical Development of Antibody-Drug Conjugate Technology Agents for Hematology

Myron S. Czuczman, MD

The past few years have witnessed the development of multiple ADCs for the treatment of hematologic malignancies. These advances have relied on the identification of appropriate ADC targets, the development of potent cytotoxic agents, and recent progress in linker technology (Figure 1). ADCs have been developed against a variety of antigens and receptors, including CD19, CD22, and CD30 and have been linked to multiple different cytotoxic agents, including calicheamicin, maytansinoid derivatives, and other drugs. Currently, more than 20 different ADCs are being evaluated in different stages of clinical trials.

Recent research has not only aided ADC development, but has also revealed new information on how ADCs exert antitumor activity. Interestingly, some ADCs appear to kill cells not only directly but also through a bystander effect in which the cytotoxic agent is delivered to cells in the vicinity of the antigen-expressing cell, thereby allowing the killing of nearby cells not expressing the target antigen.[1] This phenomenon has been observed with radiolabeled antibodies, in which neighboring cells are killed not through high levels of antigen expression but via a bystander effect.

Inotuzumab Ozogamicin (CMC-544)

Inotuzumab ozogamicin (CMC-544) is a humanized anti-CD22 antibody conjugated to calicheamicin, a potent DNA-binding antibiotic. Preclinical studies showed significant antitumor activity with inotuzumab ozogamicin, both as a single agent and in combination with other targeted agents, such as rituximab.[2,3]

The safety and activity of inotuzumab ozogamicin were evaluated in a phase I study, in which 79 patients with relapsed or refractory CD22-positive B-cell non-Hodgkin lymphoma received single-agent intravenous inotuzumab ozogamicin every 3 or 4 weeks at doses ranging from 0.4–2.4 mg/m².[4] The maximum tolerated dose (MTD) was 1.8 mg/m², with dose-limiting toxicities including thrombocytopenia, asthenia, nausea, and neutropenia. The ORR was 39% overall; among patients receiving the MTD, the ORR was 68% for patients with follicular NHL and 15% for patients with diffuse large B-cell lymphoma.

Based on the results of this study, additional clinical trials have been undertaken, including a phase II trial evaluating inotuzumab ozogamicin in combination with rituximab in patients with relapsed follicular lymphoma (n=38) or DLBCL (n=40).[5] ORRs in follicular lymphoma and DLBCL were 84% and 80%, respectively, and median progression-free survival (PFS) was 23.6 months and 15.1 months, respectively. The combination showed limited activity in the 25 patients with rituximab-refractory disease, in whom the ORR was 20% and the median PFS was 2 months.

SAR3419

Another ADC being evaluated in B-cell malignancies is SAR3419, a humanized IgG1 anti-CD19 mAb conjugated to the maytansinoid derivative DM4. DM4 binds to the vinca site on tubulin, causing inhibition of microtubule assembly and cell cycle arrest. Preclinical studies demonstrated the antitumor activity of SAR3419.[6] Clinical trials have begun to evaluate the safety and activity of SAR3419 in patients with hematologic malignancies. In a phase I study of patients with relapsed or refractory CD19-positive B-cell NHL, administration of SAR3419 by intravenous infusion every 3 weeks was associated with tumor shrinkage in 17 of 25 evaluable patients (68%).[7] However, SAR3419 was also associated with microcystic epithelial corneal changes that resulted in blurred vision.

In 2011, Coiffier and colleagues presented results from a phase I/II dose-escalation study in which 44 patients with relapsed/refractory CD19-positive B-cell NHL received intravenous SAR3419 administered at 10–70 mg/m² weekly for 8–12 weeks.[8] The study showed significant antitumor activity with SAR3419; of 22 patients receiving the MTD of 55 mg/m², the ORR was 36%. Ocular toxicity was also noted in this study, although the incidence was lower than that observed in the first study, and it occurred later during therapy. Additional clinical trials are being planned with this agent.

Gemtuzumab Ozogamicin

Gemtuzumab ozogamicin is an ADC conjugating anti-CD33 to calicheamicin. This ADC received accelerated FDA approval in 2000 for the treatment of acute myelogenous leukemia (AML) but was withdrawn from the market in 2010 due to a lack of clinical benefit and an unfavorable toxicity profile.[9] However, recent data sug-
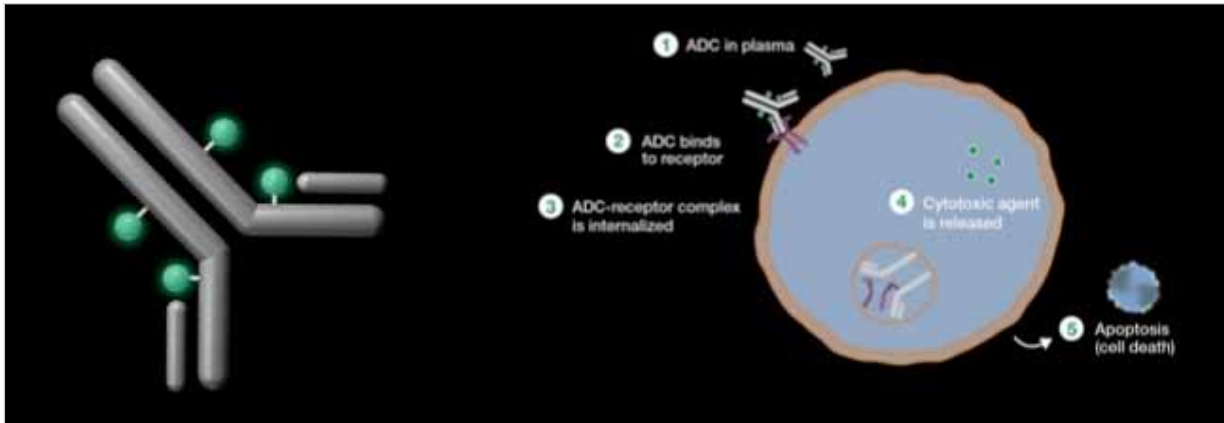
Figure 1. Advances in antibody-drug conjugate (ADC) technology have relied on the identification of appropriate targets, the development of potent cytotoxic agents, and progress in linker technology.

gest that the benefit of gemtuzumab ozogamicin may be greater than previously believed.[10,11] The future of gemtuzumab ozogamicin remains unknown.

Optimum Use of ADCs

ADCs rely on adequate antigen expression. Because of this requirement, ADCs can be used only in tumors with sufficient expression of antigen. Patients lacking broad expression of the target antigen on a high percentage of malignant cells would not be optimal candidates for ADC therapy. Therefore, as ADCs become more widely used, it may be necessary to test tumors to ensure adequate expression of the target antigen. In general, solid tumors are less "vascular" than hematologic tumors, thus it may be difficult for ADCs to reach solid tumor target cells in sufficient concentration to be lethal. Contrary to this concern are recent positive clinical data of high response rates seen in patients with relapsed/refractory metastatic breast cancer treated with trastuzumab-DM1.[12]

Conclusion

With the recent approval of brentuximab vedotin and the recent and ongoing trials with brentuximab vedotin, inotuzumab ozogamicin, SAR3419, and gemtuzumab ozogamicin, antibody-drug conjugates are having a significant impact on the treatment of hematologic malignancies.

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Development of Brentuximab Vedotin for Lymphoma

Anas Younes, MD

Brentuximab vedotin (formerly SGN-35) is an antibody-drug conjugate (ADC) consisting of an anti-CD30 monoclonal antibody linked to the cytotoxic agent monomethyl auristatin E (MMAE). In August 2011, the US Food and Drug Administration (FDA) granted accelerated approval to brentuximab vedotin for 2 indications: the treatment of patients with Hodgkin lymphoma after failure of autologous stem cell transplant or at least 2 prior multiagent chemotherapy regimens, and the treatment of patients with systemic anaplastic large cell lymphoma (ALCL) after failure of at least 1 prior multiagent chemotherapy regimen.

The path toward the development of brentuximab vedotin began decades ago with the discovery of CD30 expression on the surface of the Hodgkin Reed-Sternberg cells and ALCL cells, as well as select subtypes of B-cell–derived NHLs, mature T-cell lymphomas, and embryonal carcinomas.[1-3] Expression of CD30 on normal cells is highly restricted, limited to a small population of activated B cells and T cells and some eosinophils.[1,2,4]

The highly restricted expression pattern of CD30 is appealing for the use of CD30-targeted agents, allowing a selective treatment strategy with minimal toxicity. Early attempts at developing a CD30-targeted agent were unsuccessful, as these early custom-made ADCs were more toxic and produced only transient responses.[4] Subsequent research efforts turned to the development of unconjugated CD30-targeted antibodies. However, monoclonal antibody therapy using unconjugated anti-CD30 failed to produce clinically meaningful responses in patients with Hodgkin lymphoma, with response rates less than 10% and short durations of response.[5,6]

The previously described advances in ADC technology paved the way for the development of brentuximab vedotin, a CD30-directed ADC consisting of the chimeric IgG1 antibody cAC10 linked via a protease-cleavable linker to the microtubule-disrupting agent MMAE.[7] Approximately 4 molecules of MMAE are attached to each antibody molecule.[8]

Upon binding to CD30, brentuximab vedotin is rapidly internalized and transported to lysosomes. There, the peptide linker is selectively cleaved, releasing MMAE into the cell. The binding of MMAE to tubulin causes G2/M cell cycle arrest, which is usually followed by apoptosis.

The first clinical trial of brentuximab vedotin was a phase I, open-label, multicenter dose-escalation study in patients with relapsed or refractory CD30-positive hematologic malignancies.[9] A total of 45 patients were treated: 42 with Hodgkin lymphoma, 2 with systemic ALCL, and 1 with CD30-positive angioimmunoblastic T-cell lymphoma (AITL). The median age of enrolled patients was 36 years (range, 20–87). There was no restriction in the number of prior treatment regimens, although patients who had undergone allogeneic transplant were excluded. Enrolled patients had received a median of 3 previous chemotherapy regimens (range, 1–7), and 73% of patients had failed previous autologous stem cell transplant (ASCT).

Patients received brentuximab vedotin at doses ranging from 0.1–3.6 mg/kg of body weight every 3 weeks. The maximum tolerated dose was 1.8 mg/kg every 3 weeks. Adverse events were primarily grade 1/2 and included fatigue, pyrexia, diarrhea, nausea, neutropenia, and peripheral neuropathy. Objective responses were observed in 6 of 12 patients (50%) who received brentuximab vedotin at the maximally tolerated dose of 1.8 mg/kg. The median duration of response was at least 9.7 months. Tumor regression was observed in 36 of 42 evaluable patients (86%).

Based on the favorable results in the phase I study, 2 pivotal phase II trials were conducted—1 in relapsed or refractory Hodgkin lymphoma and 1 in relapsed or refractory systemic ALCL.[10,11] These parallel trials used the same dosing schedule of brentuximab vedotin of 1.8 mg/kg administered every 3 weeks in an outpatient setting.

The phase II study in Hodgkin lymphoma enrolled 102 patients with relapsed or refractory Hodgkin lymphoma who had failed a prior ASCT.[10] The median age was 31 years (range, 15–77), and patients had received a median of 3.5 prior regimens (range, 1–13). There was no limit to the number of prior treatment regimens; many patients had primary refractory disease and many had failed their last treatment regimen. In this population of heavily treated patients with relapsed or refractory Hodgkin lymphoma, brentuximab vedotin was associated with an ORR of 75%, including 34% complete responses (Table 1).[10] The median duration of response was 6.7 months overall and 20.5 months among patients in complete remission. Tumor regression was observed in 94%

Table 1. Outcomes With Brentuximab Vedotin in Relapsed or Refractory Hodgkin Lymphoma

Parameter	Median (months)	95% Confidence Interval (months)
Duration of objective response	6.7	3.6–14.8
Progression-free survival	5.6	5.0–9.0
Overall survival	22.4	21.7–not estimable

Data from Younes A et al. *J Clin Oncol.* 2012;30:2183-2189.[10]

of evaluated patients. Among patients who had received systemic therapy after autologous stem-cell transplantation before study enrollment, median progression-free survival was higher with brentuximab vedotin than with the prior therapy (Figure 1).

Brentuximab vedotin was generally well tolerated, with few grade 3 or 4 events reported. The main adverse event observed with brentuximab vedotin was peripheral neuropathy, which developed in 55% of patients (9% grade 3). Peripheral neuropathy was cumulative, occurring after at least 2 doses, and was managed with dose delays and reductions. The toxicity was often reversible, improving to at least some degree in 80% of patients and fully resolving in 50%. It is important to keep in mind that patients may have had existing neuropathy from prior therapies. Grade 3/4 neutropenia developed in 20% of patients and was grade 4 in approximately 6%. Other adverse events, including nausea, vomiting, and thrombocytopenia, were minimal.

The phase II trial of brentuximab vedotin in systemic ALCL enrolled 58 patients with relapsed or refractory systemic ALCL.[11] The objective response rate in this study was 86%, including 59% complete remissions. The median response duration was 13.2 months overall and was not reached after a median follow-up of 15 months in patients in complete remission. Thus, the activity of brentuximab vedotin was similar in both disease states.

Future Directions for Brentuximab Vedotin

Ongoing and planned studies are evaluating other uses of brentuximab vedotin. Multiple studies are evaluating combination strategies in the frontline setting of Hodgkin lymphoma. The use of brentuximab vedotin in the frontline setting should yield response rates even higher than the 75% ORR observed in the relapsed/refractory setting.

A phase I study was designed to evaluate brentuximab vedotin in combination with adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) or adriamycin, vinblastine, and dacarbazine without bleomycin (AVD) in the first-line treatment of Hodgkin lymphoma. Interim results suggested the activity of this approach, with all patients in the study attaining complete remission.[12] However, the combination of brentuximab vedotin plus ABVD was associated with pulmonary toxicity in approximately 40% of patients. Subsequently, the bleomycin was eliminated, and patients are continuing to receive brentuximab vedotin plus AVD. The FDA has added a contraindication for brentuximab vedotin, warning against the concomitant use of bleomycin.[13] The omission of bleomycin should not present a major challenge, as bleomycin may be considered the weakest component of the ABVD regimen.

The investigators also conducted interim positron emission tomography (PET) analyses of disease activity. The clinical significance of interim PET results in the context of novel combinations such as AVD plus brentuximab vedotin is unknown. However, the ABVD experience predicts that patients with detectable disease by PET scan at the interim analysis typically have poor outcomes and require additional therapy.

The ongoing AETHERA (Antibody-Drug Conjugate [ADC] Empowered Trial for Hodgkin to Evaluate Progression After ASCT) trial is a randomized, double-blind, placebo-controlled phase III study comparing brentuximab vedotin and placebo in approximately 325 patients at high risk of developing residual Hodgkin lymphoma following autologous stem cell transplant.[14] Patients in this high risk category include those with a history of refractory Hodgkin lymphoma, those who relapsed or progressed within 1 year after receiving frontline chemotherapy, and those who had disease outside of the lymph nodes at the time of relapse before autologous stem cell transplant. The primary endpoint of the AETHERA trial is progression-free survival. Secondary endpoints include overall survival, safety, and tolerability.

Another strategy being evaluated in the pretransplant setting is the addition of brentuximab vedotin to platinum-based regimens such as ifosfamide, carboplatin, and etoposide (ICE) or dexamethasone, high-dose cytarabine, and cisplatinum (DHAP). At least 2 trials will evaluate whether brentuximab vedotin can increase the likelihood of attaining complete remission prior to ASCT and decrease the toxicity of these regimens.

Finally, there is also interest in evaluating brentuximab vedotin–based combination strategies in patients with relapsed or refractory Hodgkin lymphoma after ASCT, in an attempt to improve upon the 34% CR rate observed with single-agent brentuximab vedotin. Although no trials evaluating combination strategies are under way, several combinations will likely be evaluated in this setting to improve on the quality and duration of response.
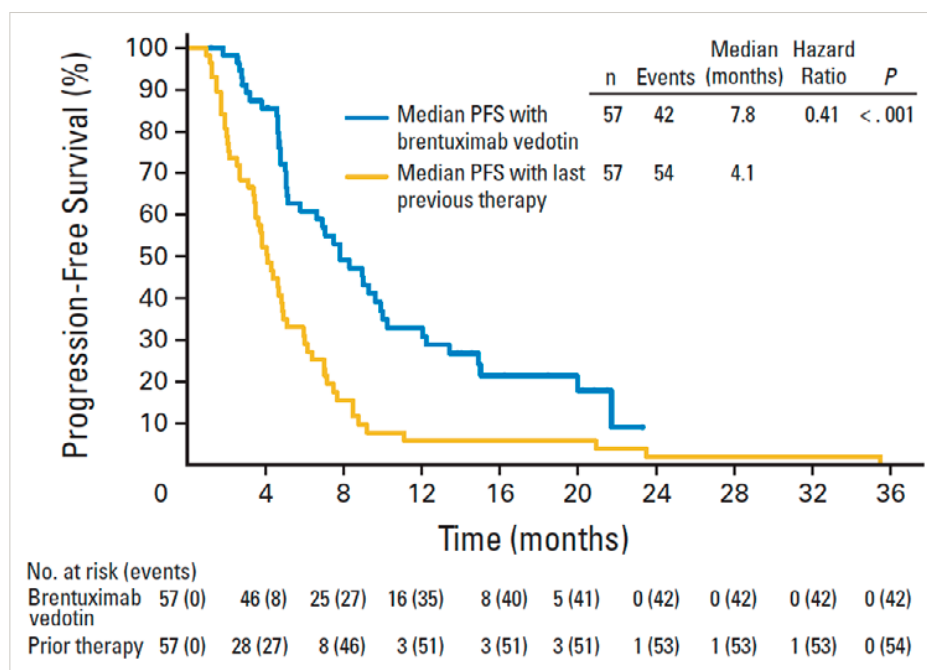
Figure 1. Median progression-free survival with brentuximab vedotin compared with that achieved with the patients' last prior therapy. Patients had received systemic therapy after autologous stem-cell transplantation before receiving brentuximab vedotin. Adapted from Younes A et al. *J Clin Oncol.* 2012;30:2183-2189.[10]

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Antibody-Drug Conjugate Technology Development for Hematologic Disorders: Discussion

Myron S. Czuczman, MD, and Anas Younes, MD

Myron S. Czuczman, MD It has been very exciting to see the progression of these agents from theory to laboratory studies to the positive clinical trial results described here. For example, in Hodgkin lymphoma, we sometimes forget that although the majority of patients are cured with standard therapy, a significant proportion of patients, typically younger patients, die from the disease because they cannot undergo autologous stem cell transplantation (ASCT) or are not cured by ASCT.

With brentuximab vedotin, we have an agent that is well tolerated and is extending life in patients who failed transplant, and is potentially opening the door for transplantation in previously ineligible patients with resistant disease.

As an example, I have been caring for a 30-year-old man with primary refractory nodular sclerosing Hodgkin lymphoma. Despite having no poor prognostic factors, he did not attain a complete response after initial therapy with adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD). A subsequent course of 2 cycles of ifosfamide, carboplatin, and etoposide (ICE) yielded less than a 50% reduction in tumor size. We then switched to dexamethasone, high-dose cytarabine, and cisplatinum (DHAP) therapy, which only led to disease progression. At that point, there were few options, as he was not a candidate for ASCT. Perhaps we could have used radiotherapy in an attempt to attain sufficient disease control to proceed to ASCT, though this approach depends on the ability of high-dose chemotherapy to overcome any drug resistance, and is thus not very likely.

However, this patient was able to start brentuximab vedotin. After only 2 doses, he had approximately 95% regression of what we believe was right mid-lobe lung disease by computed tomography and positron-emission tomography. He subsequently received additional doses of brentuximab vedotin and is now being screened for ASCT. A year ago, I do not know if we would be as optimistic as we are right now for this patient.

To discuss an example in systemic ALCL, I have been caring for an older man in his late 60s or early 70s with ALK-negative systemic anaplastic large cell lymphoma (ALCL). This subtype of ALCL is associated with much worse outcomes than ALK-positive ALCL.[1] Induction therapy with 6 cycles of CHOP appeared to induce a CR. However, within 2 weeks, he began to develop suspicious skin lesions that were biopsy-positive for disease. He is still a candidate for ASCT. However, just last week, I started him on brentuximab vedotin. It is great to have this agent available, and it will be very exciting to see what develops in the next few years in the field of targeted drug conjugates.

Anas Younes, MD I agree that it will be exciting to see what the future will hold. In my view, today we are seeing the tip of the iceberg in regard to antibody-drug conjugates (ADCs). The ability to precisely deliver anti-cancer drugs to tumor cells will continue to evolve. In the future, we will likely see even more effective agents that can be linked to antibodies to deliver the cytotoxic agent with precision to tumor cells.

Myron S. Czuczman, MD That is a good point. Today, there are only 2 major classes of cytotoxic agents being conjugated to antibodies. I am sure that in the near future, studies will be evaluating a much wider variety of potent cytotoxic agents that will be incorporated into ADCs. So yes, the future looks bright.

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Antibody-Drug Conjugates (ADCs)

- Arose as an effort to combine cytotoxic chemotherapy and antibody specificity in order to obtain the benefit of their complementarity
- The antibody can be used to direct the cytotoxic agent to the tumor cell and thereby accomplish 2 objectives:
  - Diminish the side effect profile of the cytotoxic agent
  - Enable delivery of a more potent therapeutic because of the ability to control the target and the side effects

Components of an ADC

- The cancer, or target, antigen
- The antibody to that target
- The linker that connects the drug to the antibody
- The drug itself

The Target Antigen

- Should have high expression on a tumor
- Should have little or no expression in normal tissue
- Should be present on the cell surface
- Should be an internalizing antigen

The Linker: Cleavable vs Noncleavable

- The linker of an ADC should be stable in the circulation so that the cytotoxic agent is not released systemically where it can be internalized into normal, nontarget cells. The linker should also maintain attachment of the cytotoxic agent (the conjugate to the antibody) until the ADC reaches the tumor and is internalized[1]
- The early, cleavable linkers were too labile,[2] which led to release of free drug in the circulation and consequent off-target toxicity
- Approximately 10 years ago, a non-cleavable linker was developed. This type of linker is extremely stable in the circulation, and it prevents premature release of the cytotoxic agent into the circulation[2]

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Cytotoxic Agents

- The most common cytotoxic agents currently used in ADCs—maytansinoids and monomethyl auristatin E—have IC50s that are 100-1,000–fold more potent than those of conventional chemotherapeutic agents from the same or a similar class
- Most current ADCs use a ratio of cytotoxic drug to antibody in the range of 2:1 to 4:1

Current ADC Technology: Brentuximab Vedotin

- Approved by the FDA for the treatment of patients with Hodgkin lymphoma after failure of autologous stem cell transplant or at least 2 prior multiagent chemotherapy regimens, and the treatment of patients with systemic anaplastic large cell lymphoma after failure of at least 1 prior multiagent chemotherapy regimen
- In clinical trials, brentuximab vedotin has shown significant antitumor activity at well-tolerated doses

Brentuximab Vedotin: Clinical Trials

Study	Design	Population	Outcome
Younes 2010[1]	Phase I	Hodgkin lymphoma (n=42), systemic ALCL (n=2), and CD30-positive AITL (n=1)	Objective response in 50% of patients who received brentuximab vedotin at 1.8 mg/kg. Median duration of response, at least 9.7 months. Tumor regression, 86%
Younes 2012[2]	Phase II	Relapsed or refractory Hodgkin lymphoma who had failed a prior ASCT (N=102)	Overall response rate, 75%, including 34% complete responses. Median duration of response, 6.7 months overall and 20.5 months among patients in complete remission. Tumor regression, 94%
Advani 2011[3]	Phase II	Relapsed or refractory systemic ALCL (N=58)	Objective response rate, 86%, including 59% complete remissions. Median response duration, 13.2 months overall and not reached after a median follow-up of 15 months in patients in complete remission

AITL=angioimmunoblastic T-cell lymphoma; ALCL=anaplastic large cell lymphoma; ASCT=autologous stem cell transplant.
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The AETHERA Trial

- Randomized, double-blind, placebo-controlled phase III study comparing brentuximab vedotin and placebo in approximately 325 patients at high risk of developing residual Hodgkin lymphoma following autologous stem cell transplant

- Primary endpoint: progression-free survival

- Secondary endpoints: overall survival, safety, tolerability

AETHERA=Antibody-Drug Conjugate (ADC) Empowered Trial for Hodgkin to Evaluate Progression After ASCT. ClinicalTrials.gov. A phase 3 study of brentuximab vedotin (SGN-35) in patients at high risk of residual Hodgkin lymphoma following stem cell transplant (the AETHERA trial). http://clinicaltrials.gov/ct2/show/NCT01100502?term=AETHERA&rank=1. Identifier: NCT01100502.

Current ADC Technology: Trastuzumab-DM1 (T-DM1)

- Uses a noncleavable linker to attach the maytansinoid DM-1 to trastuzumab, an anti-HER2 antibody1

- Well tolerated

- Has demonstrated significant antitumor activity in patients with HER2-positive metastatic breast cancer, including patients who had progressed on trastuzumab plus chemotherapy2

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ADCs in Clinical Trials for Hematologic Malignancies

- Inotuzumab ozogamicin (CMC-544), a humanized anti-CD22 antibody conjugated to calicheamicin, a potent DNA-binding antibiotic

- SAR3419, a humanized IgG1 anti-CD19 monoclonal antibody conjugated to the maytansinoid derivative DM4

- Gemtuzumab ozogamicin, an ADC conjugating anti-CD33 to calecheamicin

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