CLINICAL INVESTIGATION

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Antibody drug conjugates in lymphoma

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Antibody drug conjugates (ADCs) are comprised of monoclonal antibodies physically linked to cytotoxic molecules. They expressly target cancer cells by delivering cytotoxic agents to cells displaying specific antigens, and minimize damage to normal tissue. The efficacy and tolerability of these agents are primarily determined by the target antigen, the cytotoxic agent and the linker connecting the cytotoxic agent to the monoclonal antibody. Following advances in technology, clinical trials have demonstrated greater efficacy for ADCs compared with the corresponding naked monoclonal antibodies. This review summarizes the features of current clinically active ADCs in lymphoma and emphasizes recent clinical data elucidating the benefit of antibody-directed delivery of cytotoxic agents to tumor cells.

Keywords: antibody drug conjugates • lymphoma • monoclonal antibodies

Lymphoma is the most common hematologic malignancy, and is subdivided into two main types: Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). In the United States, there are an estimated 731,277 people living with or in remission from lymphoma. In 2013, there were an estimated 79,030 new cases of lymphoma diagnosed in the US of which there were 69,740 cases of NHL and 9290 cases of HL and 20,200 people are expected to have died from lymphoma (1180 from HL and 19,020 from NHL).

NHL is comprised of a varied group of malignant neoplasms arising from B-cell progenitors, T-cell progenitors, mature B cells, mature T cells or natural killer cells. The clinical presentation of this diverse group of disorders depends on the type of lymphoma, and involved area. Patients often present with painless lymphadenopathy, although extranodal presentation is common, and may also present with B symptoms (fevers, chills, weight loss and drenching night sweats). Each subtype of NHL has factors that determine prognosis, but, in general, more advanced stage disease, higher age, elevated serum lactate dehydrogenase concentration and poor performance status are adverse prognostic factors. SEER (Surveillance, Epidemiology and End Results) data from the National Cancer Institute, 2013 has revealed a significant improvement in survival rates in this group of diseases in the last four decades.

Diffuse large B-cell lymphoma (DLBCL) is the most common histologic subtype of NHL, and treatment for this disease typically includes multiagent chemotherapy in combination with the anti-CD20 monoclonal antibody, rituximab. This drug was approved by the US FDA in the United States in 1997 and has revolutionized the treatment of lymphomas, laying the foundation for use of antibodies to target malignant cells. Despite this important innovation, patients continue to succumb to their lymphoma, which is the sixth most common cause of cancer death in men and the seventh in women. Most monoclonal antibodies are used along with chemotherapy, and many of them have insufficient clinical activity as single agents. Most cancer therapeutic agents target rapidly dividing cells nonspecifically, and therefore pose a significant risk of toxicity to normal tissue. To

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enhance antitumor activity and specificity, researchers have developed antibody drug conjugates (ADCs) that specifically deliver cytotoxic drugs to tumor cells. ADCs are bioconjugates composed of a monoclonal antibody, linker region and effector molecule, synthesized using a chemical strategy that forms a stable covalent link between the antibody and drug biomolecules. Recent innovations in the ADC field have led to the successful translation of ADCs into clinical use.

Principles of ADC development & mechanism of action

Several key principles are critical to the design of a safe and effective ADC agent.

- The target antigen expression contributes to ADCs specificity. This means that if the target antigen is overexpressed on tumor cells compared with normal tissue, there may be greater ADC selectivity. However, an ADC with very high binding affinity is more likely to attack cells with lower antigen copy numbers;
- Selection of a suitable linker that connects the monoclonal antibody to the drug is a critical factor in this process and minimizes systemic drug release [1]. Cleavable linkers require specific conditions for cleavage, for example, hydrazones are activated in the the acidic pH of the lysosomes. Dipeptide noncleavable linkers are activated by specific lysosomal proteases, and thus, these conditions are found in specific compartments of the cell, and not in plasma, thereby minimizing systemic drug release. Thioethers are noncleavable linkers and here there is intracellular degradation of the attached antibody and subsequent activation of the effector [2];
- The conjugation technology used to link the cytotoxic drug and the monoclonal antibody affects the ADC potency and tolerability. The optimum number of drug molecules per antibody to maximize efficacy and delivery for the majority of ADCs is four [3]. This ratio reduces the amount of unconjugated antibody, limits the circulation half-life to that of the unmodified antibody and does not significantly affect antigen binding [4];
- Potency of the cytotoxic agent is important, as early ADCs were ineffective due to lower potency of cytotoxic drugs [5]. In the era of targeted therapy, bioconjugation enables delivery of toxic agents to cancer cells that are too toxic to use in an untargeted manner. Most of the highly potent cytotoxic agents currently in use are auristatins, maytansinoids or calicheamicins. Both auristatins and maytansinoids lead to inhibition of tubulin polymerization with subsequent cellular apoptosis. Calicheamicin binds to DNA in the minor groove, causing strand scission. Other effector molecules include bacterial-derived agents such as diphtheria or pseudomonas toxins.

After binding the target antigen or receptor, the antibody–antigen complex gets endocytosed and transported to lysosomes. Here the effector molecule is released into the cytoplasm causing cell death.

With these principles in mind, various ADCs have been designed for use in lymphoma patients and we will describe them based on target antigen.

CD30-targeting agents

CD30 is a transmembrane glycoprotein receptor, expressed mostly on activated B cells, T cells and natural killer cells. Expression in normal tissues is minimal. CD30 signaling influences lymphocyte differentiation, proliferation and apopt osis.

Brentuximab Vedotin (BV) is a an ADC consisting of the microtubule-disrupting agent, monomethyl auristatin E (MMAE), linked to a chimeric anti-CD30 monoclonal antibody through a protease-cleavable dipeptide linker. In 2011, BV received accelerated FDA approval for the treatment of patients with classical HL that have relapsed following autologous stem cell transplant (ASCT) or who have failed at least two lines of multiagent chemotherapy in patients ineligible for ASCT. BV also received accelerated approval for the treatment of systemic anaplastic large cell lymphoma (ALCL) after failure of at least one line of multiagent chemotherapy. The approved dose of BV is 1.8 mg/kg intravenously once every 3 weeks for up to 16 cycles.

The mechanism of action of BV is illustrated in Figure 1. The ADC binds to the CD30 antigen on the surface of malignant cells and undergoes rapid internalization and proteolysis with subsequent release of MMAE, and ensuing apoptosis [6].

A Phase I dose-escalation study of 45 patients with relapsed or refractory CD30-positive hematologic malignancies was conducted at four study centers in the United States [7]. The vast majority of these patients had HL (42/45) and had undergone a prior ASCT (73%). The median age was 36 years, and patients had received a median of three prior chemotherapy regimens. The primary objective of the study was to define the maximum tolerated dose (MTD). Accordingly, BV was given intravenously every 3 weeks at doses ranging from 0.1 to 3.6 mg/kg in a conventional dose-escalation design and cohort-expansion. The MTD was established at 1.8 mg/kg after 3 out of

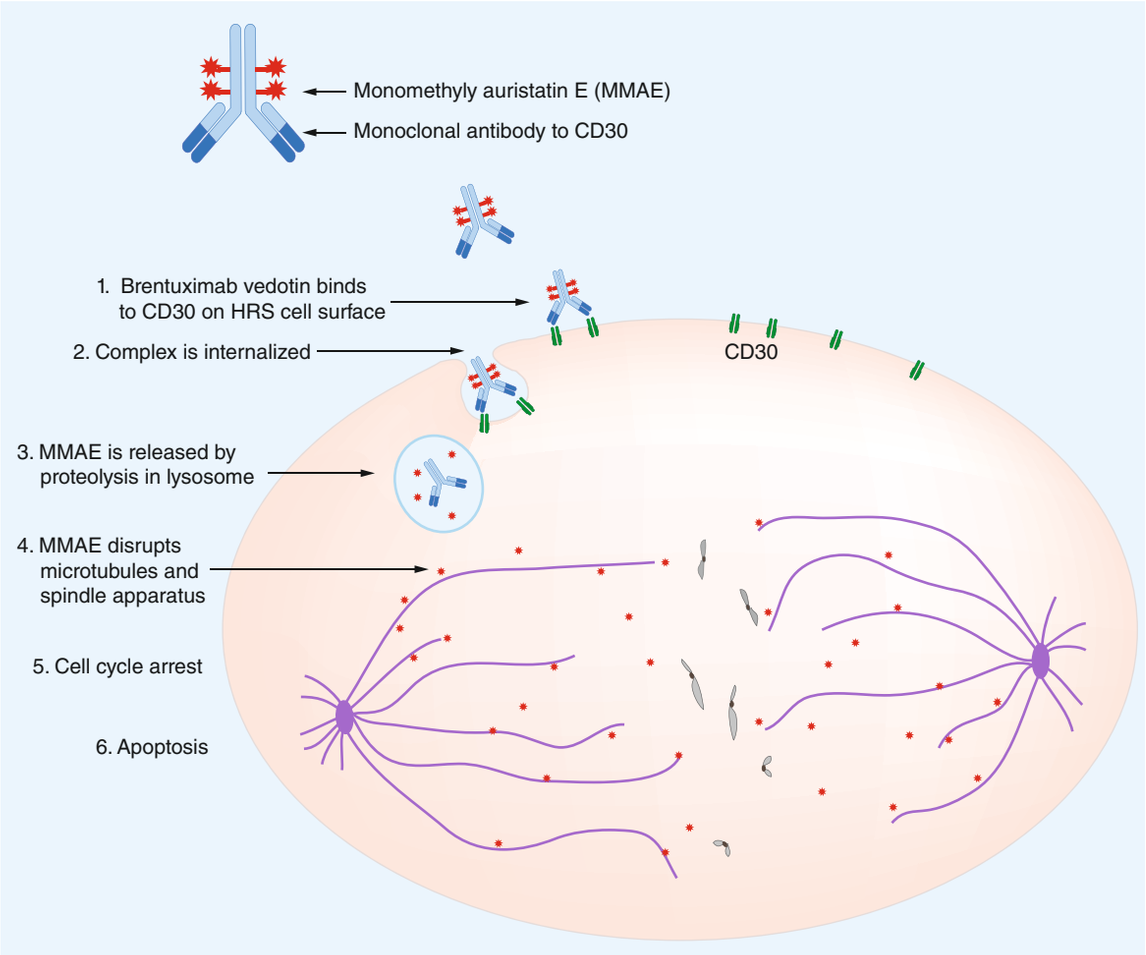

Figure 1. Brentuximab vedotin mechanism of action.
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12 patients receiving the 2.7 mg/kg dose experienced dose-limiting toxicities (DLTs) with grade 2 febrile neutropenia, prostatitis and hyperglycemia. A single patient treated at the highest dose level of 3.6 mg/kg developed febrile neutropenia, sepsis and death. The most common adverse events were generally grade 1 or 2 in severity. They included fatigue (36%), pyrexia (33%), diarrhea, nausea, neutropenia and peripheral neuropathy (10 patients, 22% each). Steady-state pharmacokinetics for both the ADC and MMAE was reached by around 21 days. Objective responses were observed in 17 patients with doses ranging from 0.1 to 3.6 mg/kg, of which 11 were complete remissions. For patients who received the the MTD of 1.8 mg/kg, the response rate was higher (50% objective response rate in 6 out of 12 patients). Radiographic evidence of tumor regression on CT and PET scans was reported in 36 of 42 evaluable patients (86%), and this is correlated with findings from independent reviewers. The median duration of objective response was at least 9.7 months.

Another single-arm, open-label Phase I dose-escalation study [8] was conducted at five study centers in the United States in patients with relapsed or refractory CD30-positive hematologic malignancies. There were a total of 44 patients, the median age was 33 years, 70% were male and the majority had HL (86%). The median number of prior systemic therapies was three, and 68% had received a prior ASCT. BV was given intravenously on days 1, 8 and 15 of each 28-day cycle in a conventional dose-escalation design and cohort-expansion. The starting dose was 0.4 mg/kg, and doses were increased by 0.2 mg/kg until the DLT or the highest dose of 1.8 mg/kg. Patients were enrolled into six cohorts from 0.4 to 1.4 mg/kg. Two patients in the 1.4 mg/kg cohort experienced a DLT (diarrhea and hyperglycemia). The MTD was defined as 1.2 mg/kg. Grade 1–2 infusion reactions occurred in 14% of patients. The most common adverse events were neuropathy (66%), fatigue (52%), nausea (50%), diarrhea (32%), arthralgia (27%), pyrexia (25%) and decreased appetite, myal-

gias, and upper respiratory tract infection (23% each). Most were grades 1–2, but grade 3 peripheral sensory neuropathy (14%), anemia (9%), neutropenia (7%) and peripheral motor neuropathy (7%) were notable. The overall response rate (ORR) was 59% with 34% of patients achieving a complete remission. In this study, BV administered weekly resulted in a similar response rate compared with every 3-week dosing, but with greater peripheral neuropathy. Consequently, the weekly schedule was not pursued in Phase II studies.

Subsequently, an international multicenter, Phase II study was conducted in 102 patients with HL who were relapsed/refractory after ASCT [9]. BV was administered at 1.8 mg/kg intravenously every 3 weeks, up to a maximum of 16 cycles. The median patient age was 31 years, median number of prior chemotherapy regimens was 3.5 and 66% of patients had received prior radiation therapy. All patients had progressed following an ASCT, 71% of patients had primary refractory disease and 42% of patients had disease refractory to the most recent treatment. The median duration of treatment was nine cycles. The ORR was 75% with a complete response (CR) rate of 34%. The median time to response was 5.7 weeks. Among the responders, the median duration of response was 6.7 months and 20.7 months in the patients who attained CR. The median progression-free survival was 5.6 months overall, and 21.7 months in complete responders. The median overall survival was 22.4 months [10].

Another pivotal multinational, open-label Phase II study of BV was conducted, but this time in 58 relapsed refractory ALCL patients [11]. Again, BV was administered at 1.8 mg/kg intravenously every 3 weeks, up to a maximum of 16 cycles. The median number of cycles was seven. The primary end point was the objective response rate. The median age was 52 years, the median number of prior treatment regimens was two and 26% of patients had failed a prior ASCT. Sixty-two percent of patients had primary refractory disease, and 42 patients (72%) were analplastic lymphoma kinase (ALK) negative. Ninety-seven percent of patients attained tumor reduction and most had alleviation of disease-related symptoms. The ORR was 86% with 57% of patients attaining a CR. The median time to objective response was 5.9 weeks and median time to CR was 11.9 weeks. The median progression-free survival (PFS) was 13.3 months and the median overall survival was not reached. Updated results were presented at ASH 2013 after a median observation time of 33.4 months from the first dose of BV. The median PFS for all patients was 14.6 months and the median overall survival has not yet been reached. The estimated 3-year survival rate was 63%. Patients who attained a CR with BV had a longer overall survival than patients who did not attain a CR. Early PET-negative status appeared to correspond with long-term survival [12].

Most BV-associated adverse events are grade 1 or 2, with the most common adverse events being peripheral neuropathy, cytopenias and fatigue. The peripheral neuropathy is mostly sensory and cumulative in nature. In the pivotal Phase II study, the incidence of grade 3 neuropathy was 8%. The median time to onset of neuropathy was 12 weeks for any grade, 27 weeks for grade 2 and 38 weeks for grade 3 with resolution in the majority of patients after holding or dose-reducing BV. The manufacturer recommends discontinuation of BV for grade 4 neuropathy and dose reduction to 1.2 mg/kg every 21 days for new or worsening grade 2 or 3 neuropathy. There has been a recent report of rare but potentially fatal pancreatitis related to BV in eight patients [13].

In the upfront setting in HL patients, BV was being evaluated in combination with ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) chemotherapy in a Phase I trial. Since 44% of patients in a Phase I dose-escalation safety study who received a combination of ABVD + BV developed pulmonary toxicity with two deaths, the combination of BV with bleomycin-containing regimens should be avoided. BV in combination with AVD at 1.2 mg/kg given every 2 weeks was well tolerated [14], and this combination is undergoing a Phase III clinical trial currently. BV has also been studied in relapsed refractory NHL with an ORR of 33%. In DLBCL, 40% of patients responded with a median remission duration exceeding 8 months. There was no correlation between CD30 expression and response [15]. In 35 PTCL patients, the ORR was 41%, and in the angioimmunoblastic T-cell lymphoma subset, the ORR was 54% with a median PFS of 6.7 months. Again, no correlation between CD30 expression by central review and response was noted [16]. BV has also been used as a bridge to allogeneic transplant in responding patients with a 1-year PFS of 92% [17].

There are several ongoing trials to evaluate the efficacy of BV in clinical situations including earlier lines of treatment for HL, systemic ALCL and cutaneous T-cell lymphoma.

- A randomized, double-blind, placebo-controlled multicenter Phase III study is testing post-transplant BV in patients at high risk of residual HL post-ASCT to see if it will prevent progression and improve outcomes (AETHERA trial, NCT01100502);

- A randomized multicenter Phase III trial is comparing the clinical activity of BV versus physician's choice of methotrexate or bexarotene in patients with CD30-positive cutaneous T-cell lymphoma (NCT01578499);
- A randomized double-blind, multicenter Phase III clinical trial to compare the efficacy and safety of BV in combination with CHP (cyclophosphamide, doxorubicin and prednisone) with the standard-of-care CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) in patients with CD30-positive mature T-cell lymphomas (ECHELON 2 trial, NCT01777152);
- A randomized, open-label, two-arm, multicenter Phase III study comparing the modified PFS obtained with BV plus AVD (doxorubicin, vinblastine and dacarbazine) versus ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) for the front-line treatment of advanced classical HL (NCT01712490);
- A randomized Phase II study to assess the safety and efficacy of BV in combination with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) in patients with DLBCL that have never been treated (NCT01925612).

CD22-targeting agents

CD22 plays a role in inhibitory B-cell receptor signaling and avoidance of autoimmunity. It is a sugar-binding transmembrane protein, binding sialic acid with an immunoglobulin domain. It is expressed in almost all B-cell NHLs, and normal lymphocytes. Following binding by anti-CD22 antibodies, CD22 is quickly internalized and undergoes lysosomal degradation, making it an appealing ADC target.

Epratuzumab is a humanized anti-CD22 monoclonal IgG1 antibody. It has been tested in combination with the R-CHOP induction chemotherapy regimen in a Phase II trial of 107 patients with untreated DLBCL, showing it is well tolerated with promising results as combination therapy with an ORR of 96% [18]. It is important to note that these were untreated patients and the role of epratuzumab in this trial is unknown.

Inotuzumab ozogamicin is a humanized anti-CD22 monoclonal antibody conjugated to a calicheamicin derivative. It targets the surface antigen, CD22 expressed on the majority of NHL cells, and is more efficacious than the naked anti-CD22 antibody, epratuzumab. Lymphocyte progenitors and memory B cells do not have significant CD22 expression and this may result in lower chronic immunosuppression. In a Phase I trial of 79 patients, with relapsed refractory B-cell lymphomas the ORR was 39% [19]. The ORR in a Phase II study of 43 patients with relapsed refractory lymphomas was 53% with a higher (66%) response rate in the follicular lymphoma subgroup. In summary, there are multiple ongoing randomized trials evaluating this ADC, which is not yet FDA approved.

DCDT2980S is a humanized anti-CD22 IgG1 attached to MMAE through a valine–citrulline linker, akin to BV. It is currently in Phase I trials. There is an ongoing Phase I, multicenter, open-label, dose-escalation study of DCDT2980S administered intravenously to patients with relapsed or refractory hematologic malignancies (B-cell NHL and chronic lymphocytic leukemia). A recent abstract from an ongoing Phase I/II study of DCDT2980S treated 35 patients with relapsed refractory NHL with encouraging results showing significant reduction in tumor burden in a subset of patients [20]. In addition, at selected sites, DCDT2980S is being studied in combination with rituximab (NCT01209130).

CD19

CD19 is a transmembrane glycoprotein belonging to the immunoglobulin superfamily, and helps regulate B-cell receptor signaling. This part of the B-cell receptor is expressed on the surface of mature B cells, including B lymphocytes, and is quickly internalized following antigen binding, unlike CD20. Another feature that makes it more attractive than CD20 is the ability to reduce initial pathogenic B cell precursors that may escape from CD20-targeted rituximab therapy.

SAR3419 is a humanized anti-CD19 antibody linked to the maytansinoid DM4, a potent anti-mitotic agent. The first-in-human Phase I, open-label, dose-escalation study was performed in 39 patients with relapsed refractory B-cell NHL with CD19 expression [21]. The median age was 66, almost all patients had advanced disease, median number of prior treatment regimens was 4, and 28% had a prior stem cell transplant. SAR3419 was administered as a single agent intravenously every 3 weeks for up to 6 cycles. The MTD was 160 mg/m^2. Seventy-five percent of patients displayed tumor reduction and 47% of patients with rituximab-refractory disease responded, which is promising [22]. The ORR was 23.5% for the 17 evaluable patients at the MTD. The DLTs were reversible severe blurred vision associated with epithelial corneal changes in six patients and neuropathy in one patient [23]. Another Phase I dose-escalation study of the anti-CD19 conjugate SAR3419 was performed in 44 patients with relapsed refractory B-cell NHL. In this trial, a modified dose and schedule were used for 25 patients who received four weekly doses followed by four biweekly doses, resulting in an improved safety

profile, with only 1 out of 25 patients experiencing the characteristic reversible grade I blurred vision. Anti-lymphoma activity was observed in 30% of patients, demonstrating the agent is well tolerated and active [24].

SGN-CD19A is an ADC consisting of a humanized anti-CD19 monoclonal antibody attached to monomethyl auristatin F (MMAF). Following CD19 binding, the ADC is internalized and releases cys-mcMMAF, which binds tubulin and causes cell-cycle arrest in G2/M and subsequent apoptosis. A Phase I, dose escalation study of SGN-CD19A in patients with relapsed or refractory B-cell NHL is currently accruing. So far, 22 patients have been treated [25]. Dose levels range from 0.5 to 6 mg/kg intravenously once every 21 days. No DLTs have been reported so far and the MTD has not yet been identified. Adverse effects in greater than 10% of patients include fatigue, blurred vision, dry eyes, constipation, dyspnea and keratitis. Preliminary data reveal an objective response rate of 40% and CR rate of 30%.

CD79

CD79 is the signaling component of the B-cell receptor that enables response to antigens and is a heterodimer (CD79a and CD79b) expressed on pre-B cells, mature B cells and the bulk of NHL and CLL. Preclinical studies targeting CD79b were conducted in cynomolgus monkeys and the preclinical data suggest that targeting CD79b may provide safe and effective therapies for B-cell malignancies [26,27]. A Phase I study of the anti-CD79b ADC, DCDS4501A, is underway. DCDS4501A is comprised of an anti-CD79b monoclonal antibody conjugated to MMAE through a protease-cleavable peptide linker. In this study, the drug was administered at 0.1–2.4 mg/kg intravenously every 21 days until disease progression or unacceptable toxicity. The most common adverse events occurring in greater than 20% of patients were neutropenia, gastrointestinal toxicity, hyperglycemia, fatigue, peripheral neuropathy, fevers, chills and cough. The recommended Phase II dose (RP2D) was determined to be 2.4 mg/kg. One patient developed a DLT of grade 4 febrile neutropenia and pneumonia. Four serious adverse events were reported in two patients at the RP2D including atrial fibrillation, neutropenia and pneumonia in one patient and cardiac failure in the other patient. In both cases, the serious adverse events resolved and treatment on study was resumed. Preliminary data in 33 patients revealed five patients achieving greater than 50% reduction in tumor burden at the time of the first assessment. Two out of four patients treated at the RP2D had greater than 80% tumor reduction at the time of the first on-treatment tumor assessment. Thus, preliminary data from this heavily pretreated population suggest an acceptable toxicity profile and encouraging anti-tumor activity [28].

Other ADCs

CD74 is an appealing target for ADCs as it internalizes and recycles following antibody binding. CD74 expression occurs in hematologic and solid tumors. ADCs of the humanized anti-CD74 antibody, milatuzumab, are being studied [29]. There is an ongoing Phase I/II trial of milatuzumab–doxorubicin in patients with relapsed CLL and NHL (NCT01585688).

CD37 is a transmembrane protein that is highly expressed on B cells during the pre-B to peripheral mature-B cell stages, but absent on early progenitor cells or terminally differentiated plasma cells. It is expressed in normal lymphoid tissues and highly expressed on malignant B cells in NHL and CLL, and may therefore represent a potential therapeutic target in B-cell malignancies [30]. IMGN529 is an anti-CD37 antibody–maytansinoid ADC which is currently in Phase I studies in relapsed refractory NHL (NCT01534715). Preliminary data from a multicenter Phase I study in 22 patients with relapsed refractory NHL who were given IMGN 529 at dose levels ranging from 0.1 to 0.8 mg/kg intravenously once every 3 weeks was recently reported [31]. DLTs were febrile neutropenia and peripheral neuropathy. There was early evidence of clinical activity in two patients who achieved a partial remission.

Conclusion

The covalent linkage of novel and powerful cytotoxic agents with judiciously selected engineered antibodies is an important advance in the treatment of B cell malignancies as evidenced by the growing number of ADCs moving to clinical trials. Although the clinical data are promising, the field is young, and the durability of responses remains uncertain. Several large studies are underway in lymphoma, testing the ADC, brentuximab vedotin in a variety of clinical settings. Several other ADCs are in clinical development and multiple trials are ongoing, the results of which are eagerly awaited.

Future perspective

With the increasing use of ADCs in both monotherapy and in combination with conventional chemotherapy, the hope is that this treatment modality will be further optimized to reduce toxicity and increase efficacy. With continued improvements in choice of components and in linker and conjugation technology, ultimately, ADCs and other targeted agents have the potential to replace components of multi-agent chemotherapy and

revolutionize treatment of not just B-cell malignancies, but all cancers.

Financial & competing interests disclosure

R Chen has received research funding from Seattle genetics and is a member of their Speakers Bureau. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Executive summary

- Antibody drug conjugates (ADCs) consist of monoclonal antibodies attached to cytotoxic agents.
- ADCs expressly target cancer cells by delivering potent cytotoxic agents to cells bearing specific target antigens, minimizing damage to normal tissue.
- The tumor target, the cytotoxic agent and the linker connecting the cytotoxic agent to the monoclonal antibody primarily influence the efficacy and tolerability of these novel compounds.
- Brentuximab vedotin, an ADC that is comprised of a microtubule-disrupting agent, monomethyl auristatin E linked to a chimeric anti-CD30 monoclonal antibody is an example of an ADC that is transforming the treatment landscape for relapsed refractory Hodgkin's lymphoma.

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