

Brentuximab vedotin for relapsed or refractory Hodgkin's lymphoma

Runzhe Chen
Baoan Chen

Department of Hematology and Oncology (Key Department of Jiangsu Medicine), Zhongda Hospital, Medical School, Southeast University, Nanjing, Jiangsu Province, People's Republic of China

Abstract: Brentuximab vedotin is a promising antibody–drug conjugate (ADC) targeting CD30 of tumor cells. It selectively delivers monomethyl auristatin E (MMAE) into CD30-expressing cells and induces tumor cell apoptosis. Various clinical trials have provided evidence that it is effective in relapsed or refractory Hodgkin's lymphoma (HL), and it has also shown its advantages in other CD30-positive lymphomas. In this review, we focus on the structure, mechanisms, and pharmacokinetics of brentuximab vedotin. We also summarize clinical trials with brentuximab vedotin and make recommendations for brentuximab vedotin in the treatment of relapsed or refractory HL.

Keywords: lymphoma, CD30-positive, clinical trials, tumor cells, antitumor effects, monoclonal antibody

Introduction

Hodgkin's lymphoma (HL) accounts for approximately 30% of all lymphomas.¹ On the basis of current clinical advances, due to the development of highly active chemotherapy protocols and the optimization of radiotherapy, patients with newly diagnosed HL have an excellent prognosis after frontline therapy, and their 5 year progression-free survival rate can be as high as 75%–80%.² However, curing HL patients who are refractory after salvage chemotherapy and who relapse after autologous hematopoietic stem cell transplantation (auto-SCT) or allogeneic hematopoietic stem cell transplantation (allo-SCT) remains a clinical challenge in view of limited effective treatment, and such patients are rarely cured, having a median overall survival of only 2–3 years.^{2–5}

Brentuximab vedotin (SGN-35), a promising antibody–drug conjugate (ADC) that selectively delivers a toxic microtubule-disrupting agent monomethyl auristatin E (MMAE) into CD30-expressing cells,⁶ was approved by the US Food and Drug Administration (FDA) in 2011.^{7–10} In various clinical trials, brentuximab vedotin has demonstrated efficacy and safety in patients with HL after failure of auto-SCT, or after failure of at least two prior multidrug regimens in HL patients who are not candidates for auto-SCT, and in patients with systemic anaplastic large-cell lymphoma (SALCL) after failure of at least one prior multiagent chemotherapy regimen.^{11–15} In this review, we address the structure, mechanisms, and pharmacokinetics of brentuximab vedotin. We also summarize clinical experiences with brentuximab vedotin and recommend critical strategies of brentuximab vedotin in the treatment of relapsed or refractory HL.

Mechanism, structure, and pharmacokinetics

Mechanism

CD30 is an important therapeutic target for the treatment of malignant lymphomas.^{16–18} It is a member of the tumor necrosis factor (TNF) cell receptor superfamily and is highly

Correspondence: Baoan Chen
Department of Hematology and Oncology (Key Department of Jiangsu Medicine), Zhongda Hospital, Medical School, Southeast University, Dingjiaqiao 87, Gulou District, Nanjing 210009, Jiangsu Province, People's Republic of China
Tel +86 25 8327 2006
Fax +86 25 8327 2011
Email cba8888@hotmail.com

expressed in a variety of lymphoma subsets, including HL and SALCL. The initial design plan of brentuximab vedotin is just developing a monoclonal antibody targeting CD30. In order to enhance the antitumor effects, a tubulin inhibitor was added to the monoclonal antibody,¹⁹ and it produced high response rates with an excellent safety profile.²⁰ These results led to the approval of brentuximab vedotin for the treatment of patients with CD30-expressing malignancies such as relapsed HL and ALCL.^{21,22} The mechanism of brentuximab vedotin is that binding of the ADC to CD30 on tumor cells initiates internalization of the ADC-CD30 complex with subsequent release of MMAE into the lysosomal compartment, after which MMAE binds to tubulin, thus disrupting the microtubule network and inducing cell cycle arrest and apoptosis.^{20,23,24}

Structure

Brentuximab vedotin is an ADC consisting of the monoclonal antibody cAC10 and the cytotoxic agent MMAE.²⁵ cAC10 (SGN-30) is a chimeric anti-CD30 monoclonal antibody that is derived from the fusion of the variable heavy and light region of the murine anti-CD30 antibody AC10, with the constant γ 1-heavy and κ -light region of the human immunoglobulin.²⁶ MMAE is a synthetic derivative of dolastatin 10, a cytostatic pseudopeptide isolated from the marine shell-less mollusk *Dorabella auricularia*. MMAE has the effect of cytostasis, tubulin-dependent GTP hydrolysis, and polymerization. As a result, MMAE has shown significant activity against various hematopoietic tumors by inhibiting the G2/M phases of the cell cycle.^{19,25,27} The points of MMAE attachment on cAC10 scaffold are $-SH$ groups of cysteine residues produced by reduction of the inter-chain disulfide bonds. The linker includes a thiolreactive maleimidocaproyl spacer, the dipeptide valine-citrulline linker, and a self-immolative *p*-aminobenzylcarbamate spacer. The peptide-based linker provides a highly stable bond between the antibody and the cytotoxic compound under physiologic conditions while it facilitates the rapid and efficient drug cleavage on internalization of the ADC by the target tumor cell.²⁵

Pharmacokinetics

According to research, the area under the concentration–time curve (AUC) of brentuximab vedotin can be increased relative to its dosage and will not accumulate with repeated dosing. Preclinical research showed that the elimination half-life of brentuximab vedotin in mice was approximately 5 days and the maximum tolerated dose was >30 mg/kg.²⁸

Preclinical studies

In models of HL, the chimeric monoclonal antibody cAC10 has been shown to promote arrest of tumor cell growth and cause DNA fragmentation. Cross-linking cAC10 suppressed proliferation in a variety of Hodgkin and ALCL cell lines. When combined with chemotherapy agents, brentuximab vedotin could enhance the efficacy of these agents.²⁶

Clinical studies

The efficacy of brentuximab vedotin in the treatment of relapsed and refractory HL has been investigated in several clinical trials on register (Table 1).

Phase I

In a Phase I, open-label, multicenter dose-escalation study, Younes et al²⁹ administered brentuximab vedotin at a dose of 0.1–3.6 mg/kg of body weight every 3 weeks to 45 patients with relapsed or refractory CD30-positive hematologic cancers, including HL; the results showed that the maximum tolerated dose (MTD) was 1.8 mg/kg, administered every 3 weeks. However, another Phase I study conducted by Fanale et al³⁰ demonstrated that the MTD for patients with relapsed or refractory HL and SALCL was 1.2 mg/kg. In a Phase I/II study carried out in Japan, brentuximab vedotin was given intravenously on day 1 of each 21-day cycle up to 16 cycles. In the Phase I part of a dose-escalation design, three patients per cohort were treated at doses of 1.2 and 1.8 mg/kg, and the study confirmed that brentuximab vedotin has an acceptable safety profile and promising antitumor activity in the Japanese population.⁶

Phase II

There have been three Phase II clinical trials of brentuximab vedotin in the treatment of relapsed/refractory HL. Gopal et al³¹ evaluated brentuximab vedotin in 25 HL patients, and patients received 1.2 or 1.8 mg/kg of brentuximab vedotin intravenously every 3 weeks. Among 24 evaluable patients, overall and complete response rates were 50% and 38%, respectively. Median time to response was 8.1 weeks, median progression-free survival was 7.8 months, and the median overall survival was not reached. Their results supported the potential efficacy of brentuximab vedotin for patients with HL relapsing after allo-SCT.

In another multinational, open-label, Phase II study, the efficacy and safety of brentuximab vedotin were evaluated in 102 patients with relapsed or refractory HL after auto-SCT, and the patients were treated with brentuximab vedotin 1.8 mg/kg by intravenous infusion every 3 weeks. The results

Table 1 Characteristics of the clinical studies of brentuximab vedotin in relapsed/refractory HL

Study (yr)	Number (median age, range)	Design	Disease characteristics	Dosage and cycle of brentuximab vedotin
Younes et al ²⁹	45 (36, 20–87)	Phase I	Relapsed or refractory CD30-positive HL and ALCL after chemotherapy or auto-SCT.	At a dose of 0.1–3.6 mg/kg of body weight every 3 weeks.
Fanale et al ³⁰	44 (33, 18–82)	Phase I	Relapsed/refractory CD30-positive hematologic malignancies, including HL, SALCL, peripheral T-cell lymphoma.	Brentuximab vedotin was administered intravenously on Days 1, 8, and 15, of each 28-day cycle at doses ranging from 0.4 to 1.4 mg/kg.
Ogura et al ⁶	20 (41, 22–88)	Phase I/II	Relapsed or refractory CD30-positive HL or SALCL.	1.8 mg/kg was given to 14 patients (nine with HL and five with SALCL). The median number of treatment cycles was 16 (range, 4–16).
Gopal et al ³¹	25 (32, 20–56)	Phase II	> 100 days after allo-SCT, had no active GVHD, and received a median of 9 (range, 5–19) prior regimens.	1.2 (n=6) or 1.8 (n=19) mg/kg every 3 weeks (median, 8 cycles; range, 1–16).
Younes et al ³² and Gopal et al ³³	102 (31, 15–77)	Phase II	Relapsed/refractory HL after auto-SCT.	1.8 mg/kg intravenously once every 3 weeks over 30 minutes on an outpatient basis for up to 16 infusions.

Abbreviations: allo-SCT, allogeneic stem cell transplantation; auto-SCT, autologous stem cell transplantation; GVHD, graft-versus-host disease; HL, Hodgkin's lymphoma; SALCL, systemic anaplastic large-cell lymphoma.

demonstrated that the overall response rate (ORR) was 75% with complete remission (CR) in 34% of patients. The median progression-free survival time for all patients was 5.6 months, and the median duration of response for those in CR was 20.5 months. The study also indicated that younger age, good performance status, and lower disease burden at baseline were characteristic of patients who achieved a CR and were favorable prognostic factors for overall survival.^{32,33}

In the Phase II part of the study conducted by Ogura et al⁶ in Japan, a dose of 1.8 mg/kg was given to nine patients with HL. The median number of treatment cycles was 16 (range, 4–16). Six patients (67%) achieved an objective response with 56% of complete response rate, so these results indicated that brentuximab vedotin has a promising antitumor activity in the Japanese population.

Use in other diseases

Several clinical trials have also been conducted to investigate the role of brentuximab vedotin in other diseases in addition to HL.

In a Phase II trial conducted by Pro et al,³⁴ 58 patients with SALCL and recurrent disease after at least one prior therapy received brentuximab vedotin 1.8 mg/kg intravenously every 3 weeks over 30 minutes as an outpatient infusion. Fifty patients (86%) achieved an objective response, 33 patients (57%) achieved CR, and 17 patients (29%) achieved a partial remission (PR). The median durations of overall response and CR were 12.6 and 13.2 months, respectively.

Another Phase II study evaluated the efficacy and safety of brentuximab vedotin in relapsed/refractory CD30+ non-Hodgkin's lymphomas (NHL). The analysis included patients with peripheral T-cell lymphomas (PTCLs; n=35), specifically angioimmunoblastic T-cell lymphoma (AITL; n=13) and PTCL not otherwise specified (n=22), and in this study brentuximab vedotin showed antitumor activity in patients with relapsed PTCL, particularly AITL.³⁵

Jacobsen et al³⁶ studied the role of brentuximab vedotin in 78 patients, including 49 diffuse large B-cell lymphoma (DLBCL) patients and 19 with other B-cell NHLs, and ORR was 44% for DLBCL, and patients with other B-cell lymphomas also responded: one CR, two PRs of six with gray zone, one CR of six with primary mediastinal B-cell, and one CR of three with posttransplant lymphoproliferative disorder.

Adverse effect

Brentuximab vedotin is reported to have been generally well tolerated by patients,^{6,31–36} however, adverse effects also occurred, according to reports, but they were considered

manageable.^{37,38} Common adverse effects included peripheral neuropathy, fatigue, nausea, arthralgia, and pyrexia.^{39–41} Neutropenia, thrombocytopenia, diarrhea, hyperglycemia, cytomegalovirus infection, peripheral sensory neuropathy, tumor lysis syndrome, Stevens–Johnson syndrome, and progressive multifocal leukoencephalopathy have also been reported with its use.^{3,31,32,38,39,41}

Conclusion and future directions

Brentuximab vedotin is an effective therapy for patients with relapsed or refractory HL. Binding of the ADC to CD30 on tumor cells induces tumor cell cycle arrest, and apoptosis is its main mechanism. In clinical trials, brentuximab vedotin shows its advantages, and it is a very promising agent in the treatment of relapsed or refractory HL, though some side effects still occurred in patients, according to clinical studies. In the future, brentuximab vedotin may become first line in dealing with relapsed/refractory CD30 positive malignancies; however, clinical trials with larger samples need further investigations; the efficacy of brentuximab vedotin combined with chemotherapy or radiotherapy should also be evaluated in clinical trials, and methods of decreasing the toxicity of brentuximab vedotin need further study.

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Disclosure

The authors report no conflicts of interest in this work.

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