ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

Section Editor: Susan O'Brien, MD

Loncastuximab Tesirine in Patients With B-Cell Non-Hodgkin Lymphoma

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H&O What type of drug is loncastuximab tesirine?

BK Loncastuximab tesirine is a novel antibody-drug conjugate. Antibody-drug conjugates consist of 3 components: a monoclonal antibody, a linker, and a drug. The monoclonal antibody seeks out a tumor-specific antigen and binds to it. For loncastuximab tesirine, the monoclonal antibody binds to CD19, which is expressed on virtually all mature B-cell malignancies, making it a good target. Upon binding, CD19 is rapidly internalized and pulls the rest of the antibody-drug conjugate inside the cell, where it exerts cytotoxic activities.

The linker connects the monoclonal antibody to the drug, also known as the warhead. The warhead in loncastuximab tesirine is a pyrrolobenzodiazepine (PBD) dimer. PBD dimers are cytotoxic agents that are too potent for administration as a free drug. The hope is that by attaching this potent PBD dimer to a monoclonal antibody and delivering it in a selective targeted way, it will be possible to obtain an antitumor effect without the toxicities associated with intravenous administration of the drug alone.

H&O What was the design of your trial of loncastuximab tesirine?

BK This first-in-human, phase 1 trial enrolled patients with relapsed B-cell lymphoma who did not have good standard treatment options. Loncastuximab tesirine was given as an intravenous infusion over 1 hour every 3 weeks. The trial followed a typical phase 1, 3-by-3 design. The dose started at a very low level of 15 µg/kg and increased to 200 µg/kg.

H&O What were the study results?

BK The phase 1 dose-escalation portion of the study enrolled 138 patients. The patients' average age was 63 years. Their average number of prior treatments was 3, with a range of 1 to 10, and 58% were refractory to their previous line of therapy. This is a difficult population to treat. Most of the patients (68%) had diffuse large B-cell lymphoma. Other subtypes included mantle cell lymphoma, follicular lymphoma, and marginal cell lymphoma. (These other subtypes individually constituted less than 10% of the study's population.) On average,

> In the diffuse large B-cell lymphoma cohort, the overall response rate was 55% in the 49 patients who received loncastuximab tesirine at a dose higher than 120 µg/kg.

Table. Responses to Loncastuximab Tesirine in the Efficacy Analysis of the Dose-Expansion Study

Response, n (%)	Total N=85	Dose ≥120 µg/kg n=68
Complete response	27 (31.8)	24 (35.3)
Partial response	19 (22.4)	17 (25.0)
Stable disease	11 (12.9)	7 (10.3)
Progressive disease	28 (32.9)	20 (29.4)
Overall response (complete response + partial response)	46 (54.2)	41 (60.3)

Data from Kahl BS et al. ASH abstract 187. *Blood*. 2017;130(suppl 1).

patients received 2 cycles of therapy. Treatment was stopped in patients who did not respond after 2 cycles. Some patients received as many as 22 cycles of therapy. Therefore, there was a wide range in the number of cycles administered.

After the phase 1 component of the trial identified 2 doses that appeared effective, there was a dose-expansion portion. The clinical activity of the drug became noticeable when the dose reached 120 µg/kg. Initially, there were dose expansions at 120 µg/kg, 150 µg/kg, and 200 µg/kg. The 200 µg/kg dose was too toxic, so further dose expansion was done at 120 µg/kg and 150 µg/kg.

The investigators were pleasantly surprised by how active loncastuximab tesirine was. Among the patients who received doses higher than 120 µg/kg in the phase 1 dose-escalation portion, the overall response rate was 60% (Table). In the diffuse large B-cell lymphoma cohort, the overall response rate was 55% in the 49 patients who received loncastuximab tesirine at a dose higher than 120 µg/kg. The median duration of response was approximately 5 months. Approximately one-third of the responding patients seemed to derive very durable responses to loncastuximab tesirine. Given the population, this finding was very encouraging. Typically, patients with refractory diffuse large B-cell lymphoma lack good treatment options.

H&O What were the adverse events?

BK The most notable side effects related to a generalized third-spacing of fluid. Some patients experienced significant peripheral edema or even pleural or pericardial effusions. The mechanism for these events is not completely understood. Administration of loncastuximab tesirine might result in some type of vascular injury that can lead to third-spacing.

Increased levels of gamma-glutamyl transferase (GGT) were also seen. Interestingly, this increase was not usually associated with many other liver function test abnormalities. In some patients, elevated GGT levels persisted for weeks or even months. Other adverse events included rash, which tended to develop in areas of skin exposed to the sun and could be problematic for patients. Fatigue was another common adverse event.

H&O Are there any other studies of loncastuximab tesirine?

BK No other studies of loncastuximab tesirine ran concurrently with our phase 1 trial. There are now plans to develop this drug further. Based on the promising signal that was seen in diffuse large B-cell lymphoma, the manufacturer of loncastuximab tesirine initiated a single-arm phase 2 trial in patients with relapsed/refractory disease. The phase 1 trial established a dose and a schedule: 150 µg/kg is given for 2 doses, and then the dose is decreased to 75 µg/kg. Patients can then receive 75 µg/kg every 3 weeks for up to 1 year. The trial is currently enrolling patients.

The manufacturer of loncastuximab tesirine is also developing trials that will evaluate the drug in combination with other therapies. Loncastuximab tesirine will be combined with ibrutinib in patients with mantle cell lymphoma. It will be combined with checkpoint inhibitors in patients with diffuse large B-cell lymphoma.

H&O What other antibody-drug conjugates are under investigation in lymphoma?

BK Several antibody-drug conjugates are being tested in lymphoma. Polatuzumab vedotin is an antibody-drug conjugate that targets the antigen CD79B. The warhead is monomethyl auristatin E (MMAE), similar to brentuximab vedotin (Adcetris, Seattle Genetics), which is already approved by the US Food and Drug Administration (FDA). Polatuzumab vedotin has been studied in diffuse large B-cell lymphoma as a single agent and in combination with rituximab. This combination is being tested in the frontline setting in a large, global, randomized phase 3 trial that is currently enrolling patients. Because polatuzumab vedotin targets the microtubule apparatus inside cells, it may be a superior version of an antitubulin agent and better than vincristine. The randomized clinical trial is comparing rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy, which is the standard in diffuse large B-cell lymphoma, vs rituximab plus cyclophosphamide, doxorubicin, and prednisone (R-CHP) plus polatuzumab vedotin. In other words, vincristine

is removed from the CHOP regimen and replaced by polatuzumab vedotin.

H&O How is the use of antibody-drug conjugates in lymphoma evolving?

BK The only antibody-drug conjugate that is FDA-approved in lymphoma is brentuximab vedotin, which has indications for relapsed/refractory Hodgkin lymphoma, CD30-positive anaplastic large-cell lymphoma, Hodgkin lymphoma after autologous stem cell transplant if the patient has high-risk features, relapsed cutaneous T-cell lymphoma, and CD30-positive mycosis fungoides. In 2018, brentuximab vedotin was approved for frontline use in Hodgkin lymphoma as part of a regimen called AAVD, which combines it with doxorubicin, vinblastine, and dacarbazine, the standard frontline agents in Hodgkin lymphoma. Brentuximab vedotin has a track record of success in lymphoma. We are anxious to see if the next generation of antibody-drug conjugates, such as polatuzumab vedotin and loncastuximab tesirine, can make a similar impact in this setting.

Disclosure

Dr Kahl has performed consulting for Seattle Genetics, Genentech, and ADC Therapeutics.

Suggested Readings

Adcetris [package insert]. Bothell, WA: Seattle Genetics; 2018.

ClinicalTrials.gov. Study to evaluate the efficacy and safety of loncastuximab tesirine in patients with relapsed or refractory diffuse large B-cell lymphoma. https://clinicaltrials.gov/ct2/show/NCT03589469. Identifier: NCT03589469. Accessed September 17, 2018.

Connors JM, Jurczak W, Straus DJ, et al; ECHELON-1 Study Group. Brentuximab vedotin with chemotherapy for stage III or IV Hodgkin's lymphoma. *N Engl J Med*. 2018;378(4):331-344.

Kahl BS, Hamadani M, Caimi P, et al. Encouraging early results from the first-in-human clinical trial of ADCT-402 (loncastuximab tesirine), a novel pyrrolobenzodiazepine-based antibody drug conjugate, in relapsed/refractory B-cell lineage non-Hodgkin lymphoma [ASH abstract 187]. *Blood*. 2017;130 (suppl 1).

Tilly H, Morschhauser F, Bartlett NL, et al. Polatuzumab vedotin combined with rituximab, cyclophosphamide, doxorubicin, and prednisone (R-CHP) for patients with previously untreated diffuse large B-cell lymphoma (DLBCL): updated results of a phase Ib/II study [ASH abstract 1853]. *Blood*. 2016;128(suppl 22).

Zammarchi F, Corbett S, Adams L, et al. ADCT-402, a PBD dimer-containing antibody drug conjugate targeting CD19-expressing malignancies. *Blood*. 2018;131(10):1094-1105.