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Epcoritamab, a Promising Therapy for Richter Syndrome?

Arnon Kater, MD, PhD
Professor of Hematology
Deputy Head of Department
Department of Hematology
Lymphoma and Myeloma Research Amsterdam
Amsterdam UMC
Amsterdam, The Netherlands

H&O What defines Richter syndrome?

AK Richter syndrome (RS), also known as Richter transformation, refers to the development of an aggressive lymphoma in the setting of an underlying low-grade lymphoma such as chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). It occurs in approximately 2% to 10% of patients with CLL/SLL.[1] This aggressive lymphoma often originates from the same cell as the low-grade lymphoma, and most commonly is the transformation to a CD20-positive (CD20+) OR B-cell lymphoma (DLBCL). However, there are also much less common transformations into Hodgkin lymphoma. RS is mostly due to the direct transformation of the CLL clone, as documented by the same immunoglobulin heavy-chain variable region (IGHV) rearrangement in both CLL and RS cells. If this is the case, the term clonally related RS is used. In rare cases the RS clone harbors a different IGHV rearrangement compared with the CLL phase. In such a case, the RS is called clonally unrelated. Clonally unrelated RS is considered to have an overall better outcome.

H&O What is epcoritamab, and how does it work?

AK Epcoritamab (Epkinly, Genmab/AbbVie) is a bispecific antibody administered subcutaneously. It binds to CD3 on T cells on one side to activate the T-cell receptor, and it binds to CD20 on B cells on the other side.[2,3] This dual binding mechanism induces a T-cell–mediated killing of CD20+ malignant B cells. It is approved by the US Food and Drug Administration for the treatment of adults with relapsed or refractory DLBCL, not otherwise specified, including DLBCL arising from indolent lymphoma, as well as high-grade B-cell lymphoma after 2 or more lines of systemic therapy.

> With the data we have with bispecific antibodies, epcoritamab as a monotherapy is a very promising agent to further explore.

H&O What have studies of epcoritamab in RS shown?

AK The EPCORE CLL-1 study was the first stand-alone trial on a bispecific antibody for CLL.[4] Within this broader phase 1/2 study, a cohort of CLL and RS patients were treated with epcoritamab monotherapy.

Patients in the RS cohort must of had a biopsy-confirmed transformation to CD20+ RS-DLBCL, a prior clinical history of CLL/SLL, be ineligible for chemotherapy, and a maximum of 1 prior line of therapy. The primary endpoint was overall response rate (ORR). Epcoritamab was administered weekly in cycles 1 to 3, every 2 weeks in cycles 4 to 9, and every 4 weeks in cycles 10 and above (28 days per cycle) until disease progression or unacceptable toxicity. In cycle 1, step-up dosing and corticosteroid prophylaxis were required to mitigate cytokine release syndrome (CRS). The results show that monotherapy with epcoritamab in this very difficult-to-treat patient population, which almost all had received state-of-the-art CLL treatment before their Richter's transformation, showed an ORR of 60%, with a 50% complete metabolic response confirmed by positron emission tomography/computed tomography scan.

Drugs that activate T cells, similar to chimeric antigen receptor (CAR) T cells, have a specific type of side effects related to T-cell activation. In this case, it was predominantly CRS. This occurred in the majority of patients, but all cases were low-grade (grade 1 and grade 2) and resolved after treatment with corticosteroids. No cases of CRS led to treatment discontinuation.

H&O What makes epcoritamab a promising therapy for RS?

AK RS is associated with very poor outcomes, and the current standard treatment, chemoimmunotherapy, has an overall survival of only a few months to approximately 1 year. Therefore, we need new tools to treat these patients. This study demonstrates for the first time that bispecific antibodies are a mechanism to activate autologous T cells and are beneficial and effective in this disease. Whether epcoritamab works best as a monotherapy or in smart combinations, such as with Bruton tyrosine kinase (BTK) inhibitors or checkpoint inhibitors, is yet to be defined. However, what we have shown is a very promising monotherapy activity.

H&O How does epcoritamab compare with other existing treatments for RS?

AK For RS, we have previously discussed chemoimmunotherapy. This works very well for some patients but the effects are temporary, and it does not work at all in most patients. There are ongoing trials that show the efficacy of BTK inhibitors as monotherapy.[5] A recent study published by the German CLL study group in *Nature Medicine* explored programmed death 1 inhibition in combination with BTK inhibition, showing an overall response rate of 58%, including a 19% complete remission rate.[6] Each of these treatments has its own merits and disadvantages. Moving forward, we have to strive for new combinations. Based on the data we have seen so far with epcoritamab, these combinations should include a bispecific antibody.

H&O What impact might epcoritamab's success have on the future landscape of RS therapies?

AK With the data we have with bispecific antibodies, epcoritamab as monotherapy is a very promising agent to further explore. What we have shown is already promising enough to consider trying this on your patients. However, to achieve long-lasting remissions and hopefully a cure, I strongly believe that a combination approach is necessary, and this combination should include a bispecific antibody. Additionally, combinations of epcoritamab with lenalidomide in chemo-ineligible patients, or with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), which is also part of this trial, will also be explored in the next couple of months.

Disclosures

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