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COMMENTARY

United we stand: Double targeting of CD79B and CD20 in diffuse large B-cell lymphoma

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Summary

Polatuzumab vedotin is antibody-drug conjugate (ADC) targeting CD79B approved for the treatment of patients with relapsed/refractory diffuse large B-cell lymphoma when given in combination with bendamustine and rituximab. The report by Kawasaki et al. provide hints on what might be happening in lymphoma cells exposed to polatuzumab vedotin and to rituximab and on potential mechanism of resistance to the ADC.

Commentary on: Kawasaki et al. The molecular rationale for the combination of polatuzumab vedotin plus rituximab in diffuse large B-cell lymphoma. Br J Haematol 2022;199:245-255.

KEYWORDS
antibody-drug conjugate, lymphoma, MMAE, polatuzumab vedotin, resistance, rituximab

In their paper, Kawasaki et al.[1] report on the molecular mechanisms potentially sustaining the benefit of adding the anti-CD20 monoclonal antibody rituximab to polatuzumab vedotin, increasing the anti-tumour activity of the latter in diffuse large B-cell lymphoma (DLBCL) cells.

Polatuzumab vedotin is an antibody-drug conjugate targeting CD79B based on a humanised immunoglobulin G1 monoclonal antibody, a maleimidocaproyl-valine-citrulline-*p*-aminobenzyloxycarbonyl (mc-vc-PABC) protease-cleavable peptide as linker, and the microtubule-disrupting anti-mitotic agent monomethyl auristatin E (MMAE), belonging to the class of auristatins, as payload.[2]

Based on a phase IB/II trial evaluating the combination of the antibody–drug conjugate with bendamustine and rituximab for patients with relapsed or refractory follicular lymphoma or DLBCL,[3] multiple regulatory agencies (including the United States Food and Drug Administration, the European Medicines Agency, the British National Institute for Health and Care Excellence and SwissMedic) have approved or recommended polatuzumab vedotin for the treatment of adult patients with relapsed/refractory DLBCL, not otherwise specified, after at least two prior therapies. With a median follow-up of 4 years, compared to bendamustine/rituximab, polatuzumab vedotin/bendamustine/rituximab achieved higher overall response rate (63% vs. 25%), higher complete response (53% vs. 23%), longer median progression-free survival (9.2 vs. 3.7 months) and longer median overall survival (12.4 vs. 4.7 months).[3]

The CD79B targeting antibody-drug conjugate has entered phase III trials for various patients' populations. Results have already been published for the POLARIX study, a phase III trial that compared the standard R-CHOP regimen (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) against the pola-R-CHP regimen (polatuzumab vedotin instead of the tubulin-targeting agent vincristine) in 879 treatment-naïve patients with DLBCL.[4] Patients treated with pola-R-CHP showed improved 2-year progression-free survival (study primary end-point) versus those treated with the standard R-CHOP (77% vs. 70% for a hazard ratio of 0.73).[4] To date, no improvement on overall survival has been observed (89% at 2 years for both groups).[4]

Kawasaki et al.[1] explored possible mechanisms of resistance to polatuzumab vedotin in a panel of DLBCL cell lines.[1] The mechanism of action of antibody-drug conjugates requires different steps to reach an anti-tumour effect: binding to its target on the cell surface, internalisation of the compound, release of the payload and engagement of the latter with its intracellular target and the cellular response to it (e.g., G2/M arrest and apoptosis for anti-mitotic agents like MMAE). Thus, not surprisingly, Kawasaki et al.[1] identified three factors that can affect the sensitivity of lymphoma cells toward the CD79B targeting antibody-drug conjugate and that could be active in the clinical context as well: low CD79B surface expression, high expression of ATP binding C cassette (ABC) transporters (multidrug resistance pumps), and high expression of the anti-apoptotic protein Bcl-xL (BCL2L1).[1] More importantly, the Authors noticed that, when exposed to polatuzumab vedotin, some DLBCL cell lines resistant to the antibody-drug conjugate upregulate CD20 expression levels with an increased sensitivity to rituximab, in terms of complement mediated cytotoxicity and antibody-dependent cellular cytotoxicity.[1] Involving both AKT and ERK signalling, this phenomenon, to be confirmed also in polatuzumab vedotin sensitive cell lines, can lead to benefit when adding polatuzumab vedotin to an anti-CD20 monoclonal antibody.[1] These results at least partially sustain the clinical activity seen in the phase II trial exploring the combination of polatuzumab vedotin with rituximab in relapsed or refractory patients with B-cell lymphoma,[5] although the lack of control arms with the single agent polatuzumab vedotin makes difficult to extrapolate the exact clinical advantage given by the addition of the anti-CD20 monoclonal antibody.

Upregulation of CD20 expression after exposure to antibody-drug conjugates, with potential benefit of the combination, has been observed for compounds other than polatuzumab vedotin, suggesting that the mechanism described here might not be specific of CD79B.[6] Anti-CD20 monoclonal antibodies are part of almost any regimen for B-cell lymphomas, and trials exploring antibody-drug conjugates are not an exception.[7–10] As the anti-tumour activity of antibody-drug conjugates requires different steps and as the anti-CD20 monoclonal antibodies have potential mechanism of actions, the data presented by Kawasaki et al.[1] provide hints on the potential mechanisms of resistance to polatuzumab vedotin as single agent and also on what might be happening in polatuzumab vedotin-resistant lymphoma cells when exposed to compounds belonging to these two classes of agents.

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CONFLICT OF INTEREST

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