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A CD205-directed antibody drug conjugate – lymphoma precision oncology or sophisticated chemotherapy?

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doi:10.3324/haematol.2020.261073

Precision oncology is expected to improve outcome of patients with malignant diseases by taking into account individual variability.¹ This approach is strictly linked to the availability of a targeted treatment the efficacy of which depends on the presence of a molecular alteration, i.e., a predictive biomarker. This concept has been shown to be highly successful in well-defined subgroups of patients and has led to the histology-agnostic approval of drugs in solid tumors.² Biomarker-stratified treatment has become first-line treatment in several solid tumors, such as non-small cell lung cancer. In many hematopoietic malignancies, including B-cell lymphomas, comparably higher cure rates and more treatment options have led to a more prognosis-oriented stratification of treatment. Here, prognostic biomarkers help to adjust treatment intensity to a cohort risk assessment.³ Together with improved prognostication of patients, a more refined diagnosis also helps with better treatment allocation.

Therefore, diagnostic biomarkers will help with the identification of defined disease subgroups.⁴ This might also correspond to differential outcome and/or response to treatment, and can therefore overlap with predictive and/or prognostic markers.

However, despite numerous advances in the understanding of cancer heterogeneity, not all diagnostic or prognostic stratifications will ultimately impact treatment and a number of patients will eventually have disease recurrence or progression. Therefore, the identification of novel treatment strategies is urgently required. The development of additional predictive biomarkers and corresponding drugs promises to improve outcome and limit toxicity. This advancement of precision oncology can be achieved in at least two ways: (i) the identification of the right treatment for given patients (as often tried in umbrella or unstratified precision oncology trials);⁵ or (ii) the identification of the right patient for a given treatment (as

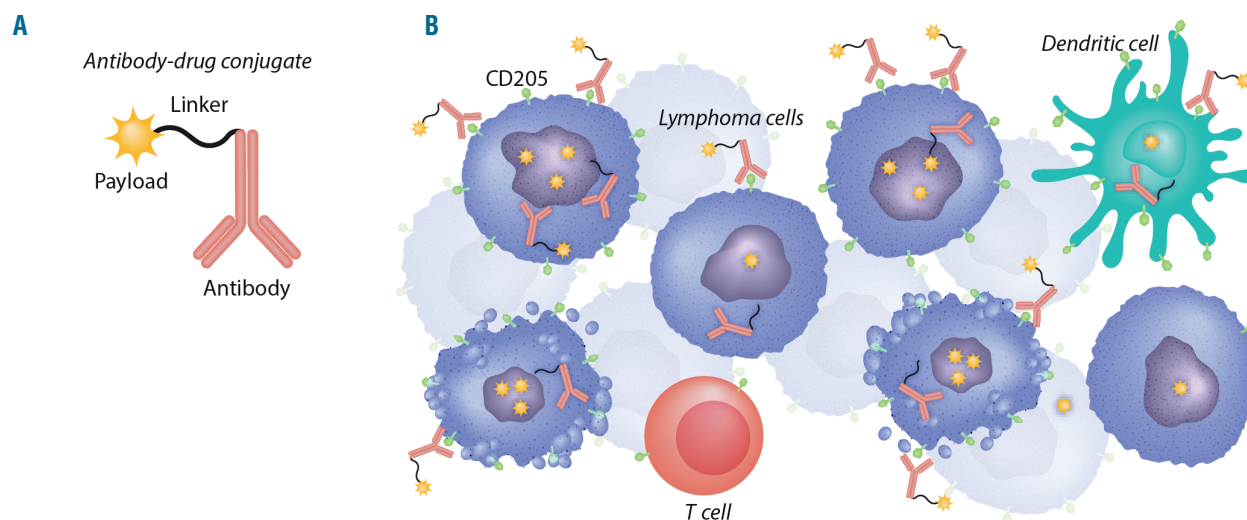


Figure 1. On- and off-target toxicities from antibody-drug conjugates (ADC) within the lymphoma microenvironment. (A) Schematic ADC, consisting of an antibody, a linker and the cytotoxic payload. Endocytosis of the ADC and linker cleavage will release the payload, resulting in cytotoxic effects. (B) On- and off-target cytotoxic effects from payload release with or without ADC internalization in a tumor microenvironment with abundant but heterogeneous expression of the target antigen. Payloads might be cleaved without endocytosis and/or permeate cell membranes to be taken up by bystander cells, thus facilitating drug efficacy even in tumor cells without adequate antigen expression. Toxic effects from microtubule-targeted compounds like maytansine on non-proliferating cells are typically reduced as compared to highly proliferating malignant cells (blue) with activated cell cycle checkpoints.

usually tried in basket trials).²

In this issue of *Haematologica*, Gaudio *et al.* show the efficacy of an antibody drug conjugate (ADC) targeting CD205 in lymphoma models.⁶ Importantly, the efficacy of this new drug, MEN1309/OBT076, was significantly associated with cell surface expression of the target CD205 in B-cell lymphoma cell lines. Furthermore, cytotoxicity of MEN1309/OBT076 was reduced with the introduction of a competitive CD205 antibody. These findings underline the dependence of drug efficacy on target availability, suggesting the potential of CD205 expression as a predictive biomarker. In an *in vitro* screen, MEN1309/OBT076 efficacy did not depend on B-cell lymphoma subtype. Together with previous preclinical results in CD205-positive triple-negative breast, pancreatic and bladder cancer cell lines and xenografts,⁷ this creates a virtual preclinical basket trial which now awaits clinical validation.

However, several questions remain to be answered for the clinical development of MEN1309/OBT076 in lymphoma. In addition to its predictive significance in preclinical models (that, as we have said, still needs to be validated in clinical trials), the biological function of CD205 is surprisingly unclear. Previous reports show that CD205 is expressed on leukocytes, mainly dendritic cells and monocytes^{8,9} with a role in endocytosis and the recognition of apoptotic and necrotic cells.^{10,11} The role in lymphomagenesis remains even less understood. A fusion protein involving CD205 was identified in Hodgkin lymphoma¹² but also in normal dendritic cell maturation.¹⁰ However, improved characterization of the biological role of this protein remains vital to understanding its implications in the clinic (as a prognostic biomarker in the identification of adequate clinical settings for the introduction of a novel drug) as well as a diagnostic biomarker. If CD205 helps in defining a biologically distinct subgroup within lymphomas, this would be particularly relevant for the identi-

fication of rational combination partners, of which two, venetoclax and rituximab, showed promising signals in the study by Gaudio *et al.*⁶ However, the broad expression of the antigen with a moderate to intense CD205 expression in 20-50% of tested lymphoma samples, and an overall expression of the antigen in more than 70% of samples, makes it unlikely that CD205 adequately reflects lymphoma heterogeneity, and stability of CD205 protein expression needs to be validated. Stable expression of the antigen is probably linked to continued efficacy of the drug, following the successful examples of other ADC such as brentuximab vedotin (targeting CD30),¹³ polatuzumab vedotin (targeting CD79b),¹⁴ or trastuzumab emtansine (targeting HER2).¹⁵ Efficacy of trastuzumab emtansine could still be demonstrated despite previous HER2-directed therapies and retreatment with brentuximab vedotin showed responses in the majority of patients that had relapsed after initial response to the same drug.¹⁶ In the work by Gaudio *et al.*,⁶ a rechallenge with MEN1309/OBT076 was also sufficient to induce remission in the only xenograft model with tumor regrowth after a first dose of the ADC. These and other data support the further development of ADC as powerful tools for the targeted delivery of cytotoxic drugs. Interestingly, neither resistance to CD30-directed ADC or to HER2-directed ADC seems to be mediated by a loss of target antigen expression but rather by dysfunctional intracellular metabolism of the payload.^{17,18} Again, the continued expression of CD205 even under therapeutic pressure remains to be determined and is probably linked to its biological role. Expression of the antigen is also important to predict toxicities in human trials. Even though previous work has not identified relevant toxicities in cynomolgus monkeys,⁷ potential risks to humans will also depend on disease characteristics and are still to be determined in ongoing clinical trials.

Since CD205 is broadly expressed in lymphoma cells and leukocytes, target antigen expression can be expected in most tumors and/or their microenvironment. Since MEN1309/OBT076 is designed with a cleavable linker, payload release does not necessarily depend on ADC endocytosis, thus facilitating bystander killing and off-target toxicity.¹⁹ In the case of a broadly CD205 expressing tumor microenvironment, an adequate on-tumor efficacy could therefore be expected even without adequate on-target effects and ubiquitous antigen expression on lymphoma cells (Figure 1). In this case, the novel ADC could rather act as a more sophisticated chemotherapy-delivery system and CD205 expression will not allow adequate patient selection. Even in this case, the drug might still prove useful in lymphoma therapy alone or in combination. However, the integration of this novel agent into current treatment schedules might become more difficult.

In conclusion, the work by Gaudio *et al.*⁶ shows the activity of the anti-CD205 ADC MEN1309/OBT076 in preclinical CD205-positive lymphoma models that warrants further clinical investigation. The development of a biomarker-drug combination allows for a targeted application of this drug in clinical trials. However, additional pre-clinical and translational work is required to shed light on the role of CD205 in lymphomagenesis. This is important for the rational development of this treatment as monotherapy, but also, and in particular, as a part of combination therapy. ADC continue to be important components of tumor therapy that could sometimes find a place between precision oncology and refined chemotherapy.

Funding

UK is supported by Deutsche Forschungsgemeinschaft, Deutsche Krebshilfe, Stiftung Charité, Wilhelm Sander-Stiftung and the Berlin Institute of Health.

Acknowledgments

DTR is a participant in the Berlin Institute of Health – Charité Clinical Scientist Program funded by the Charité – Universitätsmedizin Berlin and the Berlin Institute of Health.

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