

COMMENTARY

Antibody-Drug Conjugates in Cancer

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Dear Colleagues,

Despite new therapeutic options, cancer remains a significant health burden in our society, with one in two patients being incurable. Therefore, there is an urgent and unmet need for novel therapeutic strategies in cancer treatment. Since the introduction of chemotherapy more than 70 years ago, several new therapeutic strategies have come to the patient including targeted therapy, high-dose chemotherapy with transplantation and immunotherapy, including T-cell-directed therapy. Antibody-drug conjugates (ADCs) are a newer form of therapy with high potential for improving outcomes in the therapeutic landscape.¹

An ADC consists of a cancer-directed antibody against a cancer-expressed antigen, such as human epidermal growth factor receptor 2 (HER2) or trophoblast cell-surface antigen 2 (TROP2), a cleavable linker and a cytotoxic payload that is directly attached to the antibody *via* the linker.¹ The design of the chemical structure of the linker is of paramount importance since it directly determines the location where chemotherapeutic agents are released and deposited, either within the tumor cell or in close proximity to it. Another important question in the development of ADCs is the problem of tumor resistance to the substance. This resistance can be directly influenced by the linker, chemotherapy payload and the antibody. In some cases, changing the linker or antibody may enable the same chemotherapeutic agents to remain effective. Currently, more than 100 ADCs are in clinical development to target cancer in different ways. The most commonly used targets on tumor cells include HER2 and TROP-2. Three ADCs are approved for breast cancer treatment: trastuzumab emtansine (TDM-1),^{2,3} trastuzumab deruxtecan (T-DXd)^{4,5} and sacituzumab govitecan (SG)⁶⁻⁸; more are expected to come. All three ADCs are approved in the metastatic setting. TDM-1 is also approved for adjuvant therapy in patients with HER2-positive early breast cancer who did not completely respond to neoadjuvant chemotherapy and surgery.^{2,3} TDM-1 has a longer development history than T-DXd, which has a different/higher drug-to-antibody ratio and a stronger bystander effect.⁹ In contrast to TDM-1, T-DXd is also effective in patients with HER2-low expressing tumors¹⁰ and is approved for HER2-low expressing hormone receptor-positive (HR+) metastatic breast cancer.

Importantly, ADCs have a different safety profile compared with standard chemotherapy, potentially exhibiting severe toxicities. Recently, interstitial lung disease (ILD) has been identified as a novel and severe toxicity that affects approximately 10% of all patients treated with T-DXd.¹¹ Clinical trials have taught clinicians that rigorous management of side effects is crucial, underscoring the need for early diagnostic interventions and steroid use.

Recently, combinations of ADCs and Immunotherapeutic agents, such as immune checkpoint inhibitors (ICIs) have been assessed in clinical trials with success. The combination of enfortumab vedotin, an ADC directed against nectin-4, and pembrolizumab, a programmed death-ligand 1 (PD-L1) inhibitor, showed very promising results in metastatic urothelial cancer,¹² and the combination has been meanwhile approved by the United States Food and Drug Administration (FDA).¹³ The primary endpoint was progression-free survival (PFS), which was doubled in the combination group versus the standard chemotherapy group (median PFS: 12.5 months vs 6.3 months; HR for disease progression or death: 0.45 [95% CI: 0.38–0.54]; $p < 0.001$). The secondary endpoint of overall survival (OS) was also significantly improved (median OS: 31.5 months vs 16.1 months; HR for death: 0.47 [95% CI: 0.38–0.58]; $p < 0.001$). In triple-negative breast cancer (TNBC), data from the phase Ib/II BEGONIA study also demonstrated a synergistic benefit of the ADC and ICI drug combination.¹⁴ In this study, datopotamab deruxtecan (Dato-DXd) plus durvalumab was assessed as the first-line treatment for unresectable locally advanced or metastatic TNBC.

In conclusion, ADCs represent a novel form of targeted chemotherapy that has shown superior efficacy and a robust response compared with standard chemotherapy. However, a new safety profile must be considered, such as the risk of ILD associated with T-DXd exposure. There is a high medical need in metastatic cancer, and ADCs might help overcome treatment resistance and improve outcomes in cancer. Currently, more than 100 ADCs are in development, and some of them are likely to improve patient outcomes in cancer care.

Best wishes,



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Conflict of interest

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Author contributions

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