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Antibody Drug Conjugates and their Place in Lymphoma Treatment

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Abstract

Most of the available cancer chemotherapeutic agents show low therapeutic index, and severe side effects attributed to the non-specific exposure of the drug to off target tissues. Antibody drug conjugates (ADC) are novel cancer therapeutics with higher targeting ability. Brentuximab vedotin, polatuzumab vedotin, and loncastuximab tesirine, are three ADCs that have been approved by the Food and Drug Administration (FDA) in clinical applications and exert favorable effects in various types of lymphoma.

Abbreviations: ADCs: Antibody Drug Conjugates; BV: Brentuximab Vedotin; Pola: Polatuzumab; mAb: Monoclonal Antibody; MMAE: Monomethyl Auristatin; PBD: Pyrrolobenzodiazepines; DLBCL: Diffuse Large B-cell lymphoma

Introduction

Antibody drug conjugate (ADC) is a novel class of promising immunotherapy that is used in the treatment of cancer. It is composed of monoclonal antibody (mAb) connected to a small molecule of cytotoxic agent (payload) via a covalent linker [1]. ADC could be subdivided into three generations according to drug composition and technology characteristics. The third generation of ADC has lower toxicity and higher anticancer activity, as well as higher stability, than other generations allowing patients to receive better anticancer therapeutics [2].

The target antigens of the approved ADC drugs are typically specific proteins overexpressed in cancer cells, including HER2, trop2, nectin4 and EGFR in solid tumors and CD19, CD22, CD33, CD30, BCMA and CD79b in hematological malignancies. The selection of ADC target antigen has extended from conventional tumor cell antigens to targets in the tumor microenvironment, e.g., in the stroma and vasculature [2]. The ADC is internalized once attached to the corresponding cell-surface antigen of cancer cells, and the cytotoxic payload is released, causing cell cycle termination and cell apoptosis. The drug can also diffuse into the adjacent cells resulting in cell death termed "bystander killing" even if these cells are target negative. This effect occurs possibly independent of internalization [1]. Multiple factors hampered the application of ADCs, in clinical practice, including the selection of the corresponding antibodies, the stability of the linkers, the internalization rate of the payloads and the narrow therapeutic index [1].

The most common severe side effect (grade 3 or higher) among the 14 ADCs receiving market approval is hematotoxicity including anemia, thrombocytopenia, leukopenia, and neutropenia. The reported hematotoxicity, hepatotoxicity and gastrointestinal reaction are consistent with conventional chemotherapy drugs that mainly affect rapidly proliferating healthy cells. It is probably related to premature release of cytotoxic payloads into blood circulation. Moreover, the immune response induced by the antibody part of ADC may cause secondary injuries, resulting in nephrotoxicity [2].

At present, brentuximab vedotin (BV), polatuzumab vedotin (Pola), and loncastuximab tesirine, are three ADCs that exert favorable effects in various types of lymphoma. They have been approved by the Food and Drug Administration (FDA) in clinical applications [1]. BV is an example of a second-generation ADCs [3] while Pola is an example of a third generation ADC [2]. The payload used in Pola and BV is monomethyl auristatin (MMAE), the synthetic derivative of the natural product dolastatin 10 that is also widely used in several ADCs. It functions as an ultrapotent antimitotic agent that induces cell cycle arrest by blocking tubulin polymerization [2]. Loncastuximab tesirine is currently the only ADC in clinical use that employs pyrrolobenzodiazepines (PBD) as

the payload. PBD dimer does not depend on the cell division cycle and shows better cytotoxicity [2].

Brentuximab vedotin (BV)

BV is a compound of CD30 targeting chimeric IgG1 mAb linked to the cytotoxic moiety MMAE via valine–citrulline linker. CD30 is rapidly internalized after binding to mAb. The linker is cleaved after internalization into the cell to release MMAE payload which disrupts the microtubules leading to apoptosis mainly of proliferating lymphoid neoplastic cells. Patients with CD30 expression less than 10% also showed response to BV. This response may be explained by the by standing effect of BV on neighboring tumor cells possibly by traveling of the cytotoxic moiety through cell membranes to other cells that do not express the surface target [3].

BV was approved by FDA in 2011 for the treatment of r/r CD30 positive Hodgkin lymphoma (HL) and systemic anaplastic large cell lymphoma. In November 2017, BV received additional approval for the treatment of primary cutaneous anaplastic large cell lymphoma or CD30-expressing mycosis fungoides who have received prior systemic therapy. In 2018, BV in combination with chemotherapy was approved for the treatment of certain types of peripheral T-cell lymphoma and newly diagnosed stage III or IV classical Hodgkin lymphoma (cHL) [2]. BV is also approved for use as a consolidative treatment after ASCT in high-risk cHL patients. Up to 25% of diffuse large B-cell lymphoma (DLBCL) patients express CD30. In DLBCL, its use as monotherapy is mostly limited to patients who have CD30 expression in the r/r setting or in patients who are unfit for chemotherapy [3]. The most common side effects related to the drug were peripheral neuropathy, nausea, fatigue, neutropenia, and diarrhea [1].

Loncastuximab tesirine

Loncastuximab tesirine consists of a humanized mAb targeting CD19 conjugated to pyrrolobenzodiazepines (PBD) dimer via a cleavable (valine-alanine dipeptide) maleimide type linker. PBD irreversibly binds to DNA and cause strong inter strand cross-linking that prevents DNA strand separation, thus destroying the necessary DNA metabolic processes leading to cell death. The damage is not easy to restore. Loncastuximab tesirine is the first and so far, the only CD19 targeted ADC that approved for patients with r/r DLBCL as a single agent. In April 2021, it received accelerated FDA approval for treatment of adult r/r large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL not otherwise specified (NOS), DLBCL arising from low grade lymphoma and high-grade B-cell lymphoma. The most common adverse effects (grade≥3) were neutropenia (26%), thrombocytopenia (18%), and increased gamma-glutamyltransferase (17%) [2].

Polatuzumab (Pola)

Polatuzumab is an anti-CD79b mAb linked to MMAE via a protease-sensitive dipeptide valine–citrulline linker. CD79b along with CD79a initiates the signal transduction cascade activated by BCR leading to internalization of the complex, trafficking to late endosomes and antigen presentation [3]. In July 2019, Pola in combination with bendamustine plus rituximab (BR) was approved by the FDA for the treatment of r/r diffuse DLBCL in patients who are ineligible for ASCT and have received at least two prior therapies [2]. Response was seen regardless of the cell of origin subtype, degree of CD79b expression, and MYC/BCL2 double expression. Pola plus BR may be given as a bridge to CAR T cell therapy or allo-SCT [3]. Main side effects of Pola plus BR include dose and duration dependent peripheral neuropathy and cytopenias. It is recommended to hold pola in those who develop high grade neuropathy until improvement to grade 1 or total resolution with subsequent dose reduction [3]. Pola led to positive outcomes in r/r DLBCL patients when combined with mAbs including rituximab and obinutuzumab. Pola is likely active in r/r DLBCL patients who failed prior CAR T cell therapy [3].

Conclusion

Further efforts are needed to overcome the factors that hampered the application of ADCs, in clinical practice, such as identification of new antigen overexpressed in cancer cells, new payloads with optimal toxicity, and new linkers that balance between stability and payload release. These factors are critical to improve the efficacy of the next generation ADCs.

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