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REVIEW

Bispecific Antibody-Drug Conjugates in Oncology: Design Principles, Clinical Progress, and Challenges

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Abstract

Purpose of Review Bispecific antibody-drug conjugates (bsADCs) are an emerging class of targeted therapeutics that combine dual-antigen recognition with selective cytotoxic payload delivery. By simultaneously targeting two tumor-associated antigens or distinct epitopes, bsADCs aim to improve tumor selectivity, enhance receptor internalization, overcome antigen heterogeneity, and reduce resistance associated with conventional antibody-drug conjugates. This review provides an updated perspective on bsADCs as next-generation cancer therapeutics.

Recent Findings Recent advances in antibody engineering, linker chemistry, site-specific conjugation technologies, and payload diversification have accelerated bsADC development for multiple cancers, including breast cancer, non-small cell lung cancer, ovarian cancer, and gastrointestinal cancers. Several bsADCs have demonstrated encouraging preclinical and clinical efficacy. Emerging immunomodulatory bsADCs targeting PD-L1 and B7-H3 further highlight the therapeutic potential of combining targeted cytotoxicity with enhanced antitumor immunity.

Summary BsADCs have shown significant potential to improve precision oncology through enhanced tumor specificity, improved intracellular payload delivery, and antitumor activity. However, challenges associated with antigen selection, toxicity, manufacturing complexity, tumor heterogeneity, and resistance mechanisms continue to affect clinical translation. Continued improvements in antibody engineering, linker optimization, payload development, computational modeling, and biomarker-guided patient selection are expected to further improve the therapeutic index and translational success of bsADCs in cancer treatment.

Keywords Antibody-drug conjugate · Bispecific ADC · Cancer · Monoclonal antibody · Payload · Linker

Introduction

Cancer remains one of the most pressing global health challenges, imposing an increasing burden on individuals, healthcare systems, and economies worldwide. According to projections from the American Cancer Society, approximately 2.1 million new cases and 0.62 million deaths are expected in the United States in 2026 due to cancer [1]. In 2021, cancer contributed to 14.57% of all global deaths and 8.8% of total disability-adjusted life years (DALYs) across both sexes worldwide, reflecting its pervasive impact on morbidity and mortality [2]. Furthermore, the global cancer incidence is expected to rise substantially, with an estimated 35 million new cases by 2050, representing an increase of nearly 77% compared to the 20 million cases reported in 2022 [3]. Despite advancements, conventional therapeutic modalities, including surgery, radiotherapy, chemotherapy, and hormonal therapy have inherent limitations [4]. Chemotherapeutic drugs exert their cytotoxic effects by targeting rapidly proliferating cells, however, their non-specific mechanism also damages normal tissues, including bone marrow, gastrointestinal epithelium, and hair follicles. The resulting systemic toxicity, including myelosuppression,

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