Review

Predictive Factors of Antibody Drug Conjugates (ADCs) Treatment in Metastatic Breast Cancer: A Narrative Review

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Predictive Factors of Antibody Drug Conjugates (ADCs) Treatment in Metastatic Breast Cancer: A Narrative Review

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Abstract: Antibody-drug conjugates (ADCs) have revolutionized the treatment landscape for metastatic breast cancer (MBC), offering targeted delivery of cytotoxic agents with improved efficacy and tolerability compared to conventional chemotherapy. This narrative review explores key predictive factors influencing the efficacy of ADCs, focusing on HER2-targeted therapies such as trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan (T-DXd), as well as sacituzumab govitecan for triple-negative breast cancer (TNBC). HER2 expression, TROP-2 levels, hormone receptor (HR) status, and the tumor microenvironment emerge as critical biomarkers for patient selection and therapeutic outcomes. Additionally, we discuss resistance mechanisms, such as antigen loss, impaired drug internalization, and the role of circulating tumor DNA (ctDNA) in predicting ADC response. Finally, future perspectives on the sequential use of ADCs and potential combination therapies are highlighted, along with emerging agents targeting alternative antigens like HER3 and LIV-1. Overall, identifying predictive biomarkers and overcoming resistance mechanisms are essential for optimizing the use of ADCs in MBC, thereby improving patient outcomes.

Keywords: Antibody-drug conjugates; metastatic breast cancer; predictive factors; HER2; TROP-2; trastuzumab emtansine; trastuzumab deruxtecan; sacituzumab govitecan

1. Introduction

Antibody-drug conjugates (ADCs) represent a major advance in breast cancer (BC) treatment, combining the specificity of monoclonal antibodies with the cytotoxic power of chemotherapy. By delivering cytotoxic payloads directly to cancer cells, ADCs minimize damage to normal tissues, offering a promising alternative to conventional treatments (Bhardwaj 2023; Chen 2024).

ADCs are composed of three key elements: a monoclonal antibody targeting cancer cell antigens, a linker, and a potent cytotoxic payload (Al Jarroudi 2023; Conte 2024). Some, like trastuzumab deruxetan (T-DXd), exhibit a "bystander effect," where the payload affects neighboring cells lacking the target antigen (Bhardwaj 2023; Chen 2024). This selective delivery enhances tolerability and effectiveness compared to traditional chemotherapy (Grinda 2022).

The first FDA-approved ADC for metastatic breast cancer (MBC), trastuzumab emtansine (T-DM1) remains essential for HER2-positive MBC, particularly in patients progressing after trastuzumab-based therapies (Dieras 2017; Mamounas 2021; Krop 2017; Perez 2017). T-DXd has shown superior efficacy over T-DM1, especially in HER2-low and HER2-positive disease (Modi 2020; Modi 2022; Andrè 2023). Another notable ADC, sacituzumab govitecan, targets TROP-2 and has

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demonstrated substantial benefit in triple-negative breast cancer (TNBC), offering hope for heavily pretreated patients (Bardia 2021).

However, the success of ADCs varies among patients. Predictive factors, such as antigen expression, tumor microenvironment, and genetic mutations, are crucial for optimizing ADC use. Identifying reliable biomarkers and resistance mechanisms is essential for tailoring treatments to individual patients (Chen 2024; Saleh 2024). Emerging biomarkers, such as immune signatures, tumor mutation burden (TMB), and circulating tumor DNA (ctDNA), show potential for predicting ADC response and monitoring treatment resistance in real time (Bhardwaj 2023; Chen 2024; Cai 2024). These advancements hold promise for refining patient selection and improving outcomes in metastatic breast cancer.

This narrative review will explore the predictive factors that influence ADC efficacy in metastatic breast cancer.

2. Key Predictive Biomarkers for ADC Efficacy

2.1. HER2 Expression and Amplification

2.2. Trop-2 Expression in Triple-Negative Breast Cancer

3. Other Predictive Factors (See Table 2)

3.1. Predictive Factors for T-DM1 Efficacy

While T-DM1 has demonstrated efficacy in HER2-positive MBC, response to treatment varies significantly across patients due to several predictive factors. Identifying these factors is crucial for optimizing patient selection and treatment outcomes.

3.1.1. HER2 Expression and Amplification

3.1.2. Circulating Tumor DNA (ctDNA) and Genetic Mutations

3.1.3. Hormone Receptor Status

3.1.4. Pharmacokinetic Factors and Exposure-Response Relationships

3.1.5. Previous Treatment and Resistance Mechanisms

3.2. Predictive Factors for T-DXd Efficacy

Several factors influence the efficacy of T-DXd, and understanding these predictors is critical for optimizing patient outcomes.

3.2.1. HER2 Expression and Amplification

3.2.2. Brain Metastases

3.2.3. Hormone Receptor Status

3.3. Predictive Factors for Sacituzumab Govitecan Efficacy

3.3.1. Previous Therapy

3.3.2. Brain Metastasis

3.3.3. Sequence of Treatment

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4. Future Perspectives and Lines of Research

The future of ADCs in MBC treatment focuses on overcoming challenges related to the tumor microenvironment (TME), resistance mechanisms, and optimizing therapeutic sequencing and combination strategies (Table 3) [Chen 2024; Saleh 2024; Corti 2023; Bosi 2023; Saltamacchia 2024; Nucera 2024]. Emerging ADCs also hold significant promise for expanding treatment options.

4.1. Role of the Tumor Microenvironment

4.2. Resistance to ADCs

4.3. Sequential Treatment of ADCs

4.4. Combination Strategies and Emerging ADCs

5. Concluding Remarks

ADCs represent a significant advancement in the treatment of MBC, particularly in subtypes like HER2-positive, HER2-low, and TNBC. Predictive biomarkers such as HER2 and TROP-2 expression, hormone receptor status, and the tumor microenvironment are crucial in guiding therapy and optimizing treatment outcomes. Novel ADCs like T-DXd and SG have shown promising efficacy, even in heavily pretreated patients, expanding the therapeutic arsenal. However, challenges such as drug resistance, the role of the tumor microenvironment, and optimal sequencing of ADC therapies remain. Future research focusing on predictive factors, resistance mechanisms, and innovative combination strategies will be pivotal in refining patient selection and enhancing the effectiveness of ADCs in MBC. These efforts aim to improve the personalization of care, ultimately benefiting a broader range of patients.

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