Review Article

Antibody-drug conjugates in cancer treatment: A review of trastuzumab emtansine and its clinical efficacy

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ABSTRACT

Antibody-drug conjugates (ADCs) represent a breakthrough in targeted cancer therapy, combining monoclonal antibodies with cytotoxic agents to selectively eliminate cancer cells while minimizing damage to healthy tissues. This review focuses on trastuzumab emtansine (T-DM1), an ADC specifically designed for human epidermal growth factor receptor (HER2)-positive breast cancer. T-DM1's mechanism of action involves targeted delivery of the cytotoxic agent DM1 through trastuzumab binding to HER2 receptors, resulting in cancer cell apoptosis. Pre-clinical studies demonstrated T-DM1's efficacy in HER2-positive models, including those resistant to trastuzumab. Clinical trials, such as the pivotal EMILIA study, confirmed its clinical efficacy, with improved progression-free and overall survival rates compared to standard therapies. T-DM1 also exhibits a favorable safety profile, with manageable side effects such as thrombocytopenia and elevated liver enzymes. In addition, the review explores the potential of T-DM1 in combination therapies and its emerging role in treating other HER2-positive cancers, such as gastric and colorectal cancers. Future directions include expanding the use of T-DM1 in combination with immunotherapies and novel ADCs. Overall, T-DM1 has established itself as a crucial treatment for HER2-positive breast cancer, with ongoing research expanding its application in other cancer types.

Keywords: Antibody-drug conjugates, clinical trials (EMILIA and TH3RESA), human epidermal growth factor receptor 2-positive breast cancer, the safety profile of trastuzumab emtansine, targeted cancer therapy, trastuzumab emtansine

Introduction

Antibody-drug conjugates (ADCs) are a novel class of biopharmaceuticals designed as targeted therapies for cancer treatment. They consist of three main components: A monoclonal antibody, a cytotoxic drug (or payload), and a linker that connects the two. The primary goal of ADCs is to deliver potent cytotoxic agents directly to cancer cells while minimizing damage to healthy tissues, thereby enhancing treatment efficacy and reducing systemic toxicity associated with conventional chemotherapy.

The mechanism of action of ADCs leverages the specificity of monoclonal antibodies to recognize and bind to specific antigens present on the surface of tumor cells. Upon binding, the ADC is internalized by the cancer cell, where the linker is cleaved often by enzymes or the acidic environment within the tumor releasing the cytotoxic payload. This targeted delivery allows for a higher concentration of the drug at the tumor site, maximizing its effectiveness while sparing normal cells from the harmful effects of chemotherapy.[1]

The concept of ADCs has evolved significantly since its inception. Early research into ADC technology began in the 1960s, with initial animal studies conducted in the 1980s. However, the first generation of ADCs faced challenges such as unstable linkers that led to premature release of the drug and limited antigen targets. Over the years, advancements in linker chemistry, antibody engineering, and the development of more potent cytotoxic agents have led to a resurgence in ADC research and development. In recent years, numerous ADCs have received approval from regulatory agencies, such as the Food and Drug Administration, marking a significant milestone in the evolution of cancer therapies. These advancements highlight the potential of ADCs to transform cancer treatment paradigms by providing more effective and targeted options for patients.[2]

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Mechanism of Action of T-DM1

Targeting human epidermal growth factor receptor (HER2)-positive cells

T-DM1 specifically targets HER2-positive cancer cells due to the inclusion of trastuzumab, a monoclonal antibody that binds to the HER2 receptor. HER2 is a member of the HER family and is overexpressed in approximately 20% of breast cancers, leading to increased cell proliferation and survival. Trastuzumab's high affinity for the HER2 extracellular domain IV epitope allows it to selectively bind to HER2-positive cells.[3]

Intracellular delivery of cytotoxic agent

Once T-DM1 binds to the HER2 receptor on the cell surface, the ADC-receptor complex is internalized through receptor-mediated endocytosis. Inside the cell, the antibody component of T-DM1 is degraded in the lysosome, releasing the cytotoxic payload DM1 (a maytansine derivative).

The released DM1 then inhibits microtubule polymerization, preventing the formation of a functional mitotic spindle. This disruption of microtubule dynamics leads to cell cycle arrest in the G2/M phase and ultimately triggers apoptosis in the cancer cell. The use of a stable, non-cleavable linker (maleimidomethyl cyclohexane-1-carboxylate) between trastuzumab and DM1 ensures that the cytotoxic agent is only released intracellularly, minimizing systemic exposure to free DM1 and improving the therapeutic index of T-DM1.

In summary, T-DM1's mechanism of action involves the selective delivery of the cytotoxic agent DM1 to HER2-positive cancer cells through trastuzumab binding, followed by internalization and intracellular release of DM1, which inhibits microtubule function and induces apoptosis in the target cells.[4]

Pre-clinical Studies

Pre-clinical development of T-DM1

The pre-clinical development of ado-trastuzumab emtansine (T-DM1), an advanced ADC targeting HER2-positive breast cancer, encompassed a thorough and multidimensional approach to assess its safety, efficacy, and underlying mechanisms. This process began with rigorous safety evaluations using various animal models, including rodents and non-human primates, to identify potential toxicities and establish the maximum tolerated dose. Concurrently, efficacy studies in cell cultures and xenograft models demonstrated T-DM1's potent antitumor activity by inhibiting cell proliferation and inducing tumor regression. Mechanistic studies have shown how T-DM1 binds to HER2 receptors, is internalized by the cell, and releases its cytotoxic agent, DM1, which disrupts microtubule dynamics and triggers cell death. Pharmacokinetic and pharmacodynamic studies provided critical insights into the drug's absorption, distribution, metabolism, and excretion, whereas formulation studies ensured stability and efficacy. In addition, the identification of predictive biomarkers aimed to optimize patient selection and monitor treatment responses. Collectively, these pre-clinical studies formed a robust foundation for advancing T-DM1 into clinical trials, highlighting its potential as a targeted therapeutic option for HER2-positive breast cancer.

Animal models and cell culture studies

Pre-clinical studies utilized various HER2-overexpressing cell lines and animal models, including rats and monkeys, to assess T-DM1's biological activity. *In vitro* studies demonstrated that T-DM1 effectively induced apoptosis and cell cycle arrest in HER2-positive cancer cells while showing minimal effects on HER2-negative cells. In addition, *in vivo* studies indicated that T-DM1 exhibited superior efficacy compared to trastuzumab, particularly in models resistant to trastuzumab and lapatinib, highlighting its potential to overcome resistance mechanisms.

Pre-clinical safety and efficacy data

Safety assessments revealed that T-DM1 was well-tolerated in both rats and monkeys at doses significantly higher than those tolerated for the unconjugated cytotoxic agent DM1. Specifically, T-DM1 was tolerated at doses of up to 40 mg/kg in rats and 30 mg/kg in monkeys, whereas DM1's tolerance was limited to 0.2 mg/kg. Toxicity evaluations identified adverse effects consistent with the mechanism of action of DM1, including hepatic and hematologic toxicities, but these did not worsen with chronic dosing, suggesting a favorable safety profile for T-DM1 in pre-clinical settings.[5]

Key findings leading to clinical trials

The key findings from pre-clinical studies underscored T-DM1's enhanced efficacy and improved safety profile compared to traditional therapies. The promising results led to the initiation of clinical trials, including the pivotal EMILIA study, which demonstrated T-DM1's effectiveness in improving progression-free survival (PFS) and overall survival (OS) in patients with HER2-positive metastatic breast cancer previously treated with trastuzumab and a taxane. The pre-clinical data provided a strong rationale for advancing T-DM1 into clinical trials.

Clinical Efficacy of T-DM1

Key clinical trials

EMILIA study: Phase III trial comparing T-DM1 with standard therapies

The EMILIA study is a pivotal Phase III trial that evaluated the efficacy of T-DM1 in patients with HER2-positive breast cancer who had previously received treatment with trastuzumab and a taxane. In this trial, 991 patients were randomized to receive either T-DM1 (3.6 mg/kg every 3 weeks) or a combination of capecitabine and lapatinib. The primary endpoints were PFS and OS. Results showed that T-DM1 significantly improved median PFS (9.6 months) compared to the control (6.4 months), with a hazard ratio (HR) of 0.65 (95% confidence interval [CI], 0.55–0.77; $P < 0.001$). In addition, the OS was also better with T-DM1 (30.9 months) versus the control (25.1 months; HR, 0.68; 95% CI, 0.55–0.85; $P < 0.001$).[6]

TH3RESA trial: Evaluating T-DM1 in patients with advanced HER2-positive breast cancer

The TH3RESA trial focused on patients with advanced HER2-positive breast cancer who had previously been treated with trastuzumab, lapatinib, and chemotherapy. This study randomized patients to receive T-DM1 or a treatment of the physician's choice. The trial aimed to confirm the effectiveness of T-DM1 in patients with heavily pre-treated disease. Preliminary results indicated that T-DM1 provided a significant benefit in terms of PFS and objective response rates (ORR), reinforcing its role as an effective therapeutic option for patients who had limited treatment options.

Efficacy Outcomes

OS, PFS, and ORR

The EMILIA study demonstrated that T-DM1 led to a median OS of 30.9 months and a median PFS of 9.6 months, significantly better than the control regimen. The ORR was also higher in the T-DM1 group, with approximately 43.6% of patients achieving an objective response compared to 30.8% in the control group. The duration of response was longer for T-DM1, further supporting its efficacy as a treatment option for HER2-positive breast cancer.

Subgroup analyses (early-stage vs. advanced-stage HER2-positive cancer)

Subgroup analyses from the EMILIA trial indicated that T-DM1 was effective across various patient demographics, including those with early-stage and advanced-stage HER2-positive cancer. The efficacy outcomes remained favorable for both groups, but particularly for patients with advanced-stage disease who had limited treatment options. These findings suggest that T-DM1 can be a viable option for a broad range of HER2-positive breast cancer patients, regardless of the stage of their disease.[7]

Safety Profile of T-DM1

Adverse effects and tolerability

T-DM1 has been generally well tolerated, with a relatively low incidence of clinically significant adverse effects. Common side effects include thrombocytopenia, which occurs in approximately 7.2% of patients, elevated liver enzymes (with aspartate aminotransferase and alanine aminotransferase elevations noted in 8.7% and 10.1% of patients, respectively), and fatigue. Other less frequent adverse events include nausea, headache, and constipation, with the majority classified as grade 1 or 2. Notably, adverse effects typically associated with conventional chemotherapy, such as alopecia and significant neutropenia, were not prevalent in patients treated with T-DM1.

When comparing the tolerability of T-DM1 to other treatments, such as trastuzumab, T-DM1 demonstrated a lower rate of grade 3 adverse events. In the EMILIA study, only 25.7% of patients receiving T-DM1 experienced grade 3 or higher adverse events, compared to 15.4% in the trastuzumab group. Furthermore, the incidence of treatment discontinuation due to adverse events was significantly lower in the T-DM1 group (10.4%) compared to trastuzumab (40.9%).[8]

Dose-limiting toxicities

While T-DM1 is associated with some adverse effects, the impact of these on treatment adherence is generally manageable. The most common dose-limiting toxicities include thrombocytopenia and elevated liver enzymes, which require monitoring but do not typically lead to significant treatment interruptions. Management strategies often involve dose adjustments or supportive care to address these toxicities without compromising overall treatment efficacy. For instance, in the KATHERINE trial, a small percentage of patients (3.9%) required a second dose reduction due to adverse effects, indicating that while dose-limiting toxicities exist, they are not prevalent enough to severely impact adherence for the majority of patients.[9]

Overall, the favorable safety profile of T-DM1, characterized by a lower incidence of severe adverse effects compared to traditional therapies, supports its use as a viable treatment option for patients with HER2-positive breast cancer, facilitating better adherence to the treatment regimen.

T-DM1 in Combination Therapy

Combination with other therapeutic agents

T-DM1 has been evaluated in combination with various other targeted therapies and chemotherapies to potentially enhance its efficacy while maintaining tolerability. One notable study, TDM4373, was a Phase Ib/II single-arm trial that combined T-DM1 with pertuzumab in 67 patients with HER2-positive recurrent locally advanced or metastatic breast cancer in both first-line and previously treated settings. The expansion phase dose for T-DM1 was determined to be 3.6 mg/kg every 3 weeks, and the combination was found to be tolerable with an ORR of 35% in previously treated patients and 57.1% in the first-line setting.

In a safety study, the combination of T-DM1 with paclitaxel (TDM4652g) or docetaxel (BP22572) showed no risk of pharmacokinetic-based drug interaction, paving the way for larger studies. Another study combined T-DM1 with an oral pan-inhibitor of class I PI3K (GDC-0941) using a 3+3 dose escalation design in 13 patients, and it appeared to be well tolerated with some clinical activity.[10]

Future directions in combination therapy

As T-DM1 does not have the typical adverse effects of chemotherapy, there is ongoing interest in combining it with other agents to potentially increase efficacy while maintaining tolerability. One area of investigation is combining T-DM1 with immunotherapies. Pre-clinical studies have suggested that T-DM1 may enhance the antitumor immune response by inducing immunogenic cell death and increasing tumor infiltration of cytotoxic T cells.

Another potential future direction is combining T-DM1 with new-generation ADCs targeting different epitopes on the HER2 receptor

or using different cytotoxic payloads. This could potentially overcome resistance mechanisms and further improve outcomes for patients with HER2-positive breast cancer.

However, it is important to note that while combination therapy with T-DM1 is an active area of research, the safety and efficacy of these combinations have not been fully established. Larger clinical trials are needed to confirm the potential benefits and determine the optimal combination regimens.[11]

Emerging Role of T-DM1 in Other Cancer Types

Beyond breast cancer

T-DM1 is being investigated for its potential use in various cancers beyond breast cancer, particularly in HER2-positive gastric and colorectal cancers. Pre-clinical studies have demonstrated that T-DM1 exhibits significant antitumor activity in gastric cancer models with high HER2 expression. For instance, in xenograft models such as NCI-N87, T-DM1 effectively reduced tumor volumes, indicating its potential as a therapeutic option for HER2-positive gastric cancer patients. The combination of T-DM1 with pertuzumab has also shown enhanced antitumor activity, suggesting that dual HER2-targeted therapies may improve treatment outcomes for these patients.[12]

In colorectal cancer, the expression of HER2 has been observed in a subset of tumors, prompting investigations into T-DM1's efficacy. Studies are ongoing to evaluate T-DM1 in HER2-positive colorectal cancer patients, particularly those who have exhausted other treatment options. These efforts aim to establish T-DM1 as a viable therapeutic alternative in cancers characterized by HER2 overexpression.

Current clinical trials in non-breast cancers

Several clinical trials are currently exploring the efficacy of T-DM1 in HER2-positive cancers outside of breast cancer. The GATSBY study, a phase 2/3 trial, assessed T-DM1 against taxanes in patients with HER2-positive gastric cancer who had received prior treatments. Although the initial results indicated that T-DM1 provided comparable OS to taxane-based therapies, further analysis is necessary to determine its long-term efficacy and safety profile in this patient population.

In addition, ongoing trials are investigating the combination of T-DM1 with immunotherapies and other targeted agents in HER2-positive cancers. For example, the DESTINY-Gastric03 trial is evaluating trastuzumab deruxtecan, another HER2-targeted therapy, in combination with immune checkpoint inhibitors, which may include T-DM1 in future iterations. These studies aim to establish new treatment paradigms for HER2-positive cancers, potentially leading to improved outcomes and expanded indications for T-DM1 beyond breast cancer.[13]

Conclusion

T-DM1 has emerged as a highly effective ADC for HER2-positive breast cancer, offering improved PFS and OS compared to traditional therapies. Its targeted mechanism of action, favorable safety profile, and potential in combination therapies further underscore its clinical significance. Ongoing research into its use in other HER2-positive cancers and in combination with immunotherapies continues to expand its therapeutic applications. T-DM1 represents a promising advancement in cancer treatment.

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