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Treatment of HER2 positive advanced breast cancer with T-DM1: A review of the literature

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ABSTRACT

Background: Trastuzumab emtansine (T-DM1), a new agent developed for the treatment of HER2-positive breast cancer, is an antibody-drug conjugate with a complex compound obtained by the conjugation of trastuzumab, a stable thioether linker, and the potent cytotoxic drug maytansine-derivate(DM1), which inhibits cell division and induces cell death.
Field of study: PubMed database, ESMO, ASCO, San Antonio Breast Cancer Symposium Meeting abstracts and clinicaltrials.gov were searched using the terms "Anti-HER2 treatment breast cancer and trastuzumab emtansine (T-DM1) "; papers considered relevant for the aim of this review were selected.
Findings/results: The phase I trials have determined the safe dosing range of T-DM1, established at 3.6 mg/kg every 3 weeks. The phase III randomized EMILIA and TR3RESA trials have shown that T-DM1 provides objective tumor responses and significantly improves progression free survival and overall survival in HER2-positive metastatic breast cancer patients previously treated with anti-HER2-based regimens. The ongoing phase III trials KAITLIN and KATHERINE will give us further information about the place T-DM1 should occupy in the treatment of patients with early stage HER2-positive breast cancer.
In this review we analyze the most relevant clinical trials conducted with T-DM1 and the role of this compound in the management of advanced breast cancer.
Conclusion: T-DM1 has shown clinically relevant activity in the treatment of HER2-positive breast cancer patients after progression on trastuzumab and taxane based therapy, both in the second line treatment setting and after early relapse on adjuvant trastuzumab therapy. This is accompanied by a favorable safety and tolerability profile.

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1. Introduction

Approximately 18–20% of invasive breast cancers are HER2-positive. These are characterized by amplification and/or overexpression of HER2, a transmembrane receptor with tyrosine kinase activity (TK), resulting in HER2 gene amplification on chromosome 17. This subtype of invasive breast cancer has a poor prognosis in the absence of specific treatment. Moreover, overexpression of the HER2 oncogene provides predictive information and identifies patients who may benefit from anti-HER2 targeted therapies (Giordano et al., 2014; Figueroa-Magalhaes et al., 2014; Krop and Winer, 2014; Yarden and Sliwkowski, 2001; Dawood et al., 2010; Azim and Azim, 2008; Prat et al., 2010; Perou et al., 2010; Wolff et al., 2007; Ross and Fletcher, 1998; Slamon et al., 2001).

5–10% of the incident cases will be diagnosed in the form of advanced disease. The 5-year overall survival (OS) in these patients reaches 20% (historical median survival 16–29 months), of which 2–5% are long-term survivors (Slamon et al., 1987; Cardoso and Castiglione, 2009). Trastuzumab, a humanized monoclonal antibody that selectively binds to the HER2 receptor on the surface of tumour cells, added to chemotherapy in the first-line treatment of HER2-positive metastatic breast cancer is associated with a significantly reduced risk of progression and death compared to chemotherapy alone (Menard et al., 2000; Sliwkowski, 2003; Arpino et al., 2007; Chang, 2007; Bartsch et al., 2014; Marty et al., 2005).

However, despite these therapeutic advances, the median progression free survival (PFS), and overall survival (OS) of trastuzumab and chemotherapy-based regimens in patients with advanced disease is 7.4 months (vs 4.6 months without trastuzumab) and 25.1 months (vs 20.3 months without trastuzumab) respectively (Slamon et al., 2001, 1987).

T-DM1, an antibody-drug conjugated, represents a new tool for the treatment of HER2-positive breast cancer. It is a complex compound obtained by the conjugation of trastuzumab and the potent maytansine-derived cytotoxic drug DM1, which is able to inhibit cell division and to induce cell death (Lambert and Chari, 2014; Lewis et al., 2008a).

Recently, T-DM1 has been approved by the European Medicines Agency (EMA) and by the Food and Drug Administration (FDA), as a single agent for the treatment of patients with HER2-positive locally advanced and unresectable or metastatic breast cancer, who have previously received taxane- and trastuzumab-based treatment, separately or in combination (Amiri-Kordestani et al., 2014).

In this article, we will analyze the most relevant aspects related to T-DM1 structure and its mechanism of action. Then we will review the most relevant clinical trials performed with T-DM1 in HER2-positive breast cancer and will finally comment on the strategies in HER2 positive breast cancer research with the drug.

2. Molecular structure

T-DM1 is the first antibody-drug conjugate (ADC) developed specifically for the treatment of HER2-positive breast cancer (Lewis et al., 2008b; Peddi and Hurvitz, 2013).

ADCs are biological drugs containing a monoclonal antibody linked by a covalent bond to a cytotoxic drug via a synthetic coupler. The ADC is designed such that when it reaches the target cell it releases the cytotoxic agent inside them, thus sparing non-tumoral cells from damage.

T-DM1 has three components: trastuzumab, DM1 and a non-reducible thioether link set, called *N*-maleimidomethyl cyclohexane-1-carboxylate (MCC), designed to be stable in the circulation before entering HER2-overexpressing cells (See Fig. 1).

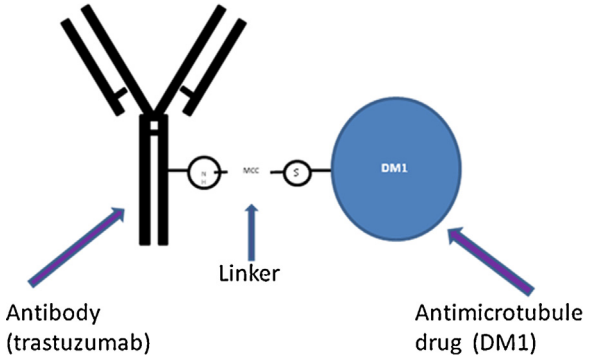

Fig. 1. Structure of T-DM1.

3. Mechanism of action

The binding of T-DM1 to HER2-positive cells allows internalization of this complex by endocytosis and subsequent intralysosomal proteolytic degradation. Its effects depend on two main components: trastuzumab and DM1. Trastuzumab is a humanized monoclonal antibody that selectively binds to subdomain IV of the HER2 receptor at the surface of tumor cells, where it exerts its anti-HER2 activity. Amongst its mechanisms of action includes antibody dependent cell-mediated cellular cytotoxicity which it exerts by binding to HER2-overexpressing target cells and labelling tumor cells for recognition by natural killer lymphocytes (NK), transduction inhibition of ligand-independent intracellular HER2 signalling (PI3K-Akt-mTOR and MAPK pathways), which leads to cell growth arrest and apoptosis, and it prevents proteolytic cleavage of the extracellular domain of HER2 (thereby preventing the lack of response to other treatments) (Scaltriti et al., 2007; Molina et al., 2001). It also causes reduced tumour-associated angiogenesis and HER2 overexpression as well as inhibition of DNA damage repair caused by chemotherapy and radiotherapy (Baselga et al., 1998; Diessner et al., 2014).

DM1, a derivative of the antimitotic drug maytansine, acts as a potent antimicrotubule agent inhibiting the polymerization of tubulin. Although, T-DM1 binds to the β subunit of tubulin at the same place as the vinca alkaloids, DM1 derivatives are 100 fold more cytotoxic than these agents. Unlike trastuzumab, T-DM1 induces cell cycle arrest and significant cell death in HER2-positive cells which is secondary to the DM1 toxin (Junttila et al., 2011; Kovtun et al., 2010).

Therefore, T-DM1 is characterized by an innovative and selective mechanism of action on the HER2-positive tumor cells. Through this mechanism, T-DM1 leads to a double antitumor effect, an anti-HER2 effect mediated by the trastuzumab activity and a selective transport of a powerful antimitotic agent DM1 to the intracytoplasmic area (Fig. 2). This particular mechanism of action increases the effectiveness while it reduces the toxicity (Fig. 3) (Baron et al., 2014; Boyraz et al., 2013).

4. Pharmacokinetics and pharmacodynamics of TDM1

The pharmacokinetics of the ADC is complex due to the difference in molecular weight of the components. Systemic exposure to DM1 is low (usually <10 ng/ml) as a result of a very stable plasma DM1 linker which avoids degradation outside the target cell. A pharmacokinetic study using radio labelled T-DM1 in rats showed that the plasma concentrations of DM1 were low, and evidenced an accumulation of radioactivity in faecal (80%) and a fraction in the urine (<10%) (Shen et al., 2012).

Although interindividual variability in the pharmacokinetics of the drug has been observed depending mainly on the total body