A Case Report of a Patient with HER2-Positive Metastatic Breast Cancer on Dialysis, Who Responded to Ado-Trastuzumab Emtansine

Elia Sais and Sonia Del Barco*

University Hospital Doctor Josep Trueta, The Catalan Institute of Oncology (ICO), Medical Oncology Service, Girona, Spain

Abstract

Introduction: Ado-trastuzumab emtansine (T-DM1) is a human epidermal growth factor receptor 2 (HER2)-targeted drug that comprises trastuzumab, a stable linker, and the potent cytotoxic agent derivative of maytansine (DM1). Once T DM1 binds to the HER2 receptor, it allows intracellular drug delivery specifically to HER2-overexpressing cells, minimizing the exposure of the drug to normal tissue.

Case: We report the case report of a 47-year old woman with HER2-positive metastatic breast cancer (MBC) on dialysis, which was treated with T-DM1. The tolerance of T-DM1 in this patient was predictable and good and the patient achieved a durable response.

Discussion and Conclusions: A previous exploratory analysis has shown that the pharmacokinetic properties of T-DM1 are unaffected by age, race or renal function. However, there are no specific trials for patients with severe renal impairment treated with T-DM1. Only one patient with these characteristics has been treated before with T-DM1, although no dosage recommendation was given.

Keywords: Antibodies; Antineoplastic agents; Breast neoplasms; Monoclonal; Renal dysfunction

Introduction

Breast cancers expressing human epidermal growth factor receptor 2 (HER2+) have higher rates of proliferation and a worse prognosis than non-HER2-expressing tumors without target therapy. This type of breast cancer represents about 15% of all breast cancer types. Despite adjuvant trastuzumab treatment, some of these patients will present a relapse. The arrival of new anti-HER2 therapies such as pertuzumab and ado-trastuzumab emtansine (T-DM1) have provided not only a benefit in terms of progression-free survival (PFS) but also an improvement in overall survival (OS) in patients with HER2+ metastatic breast cancer (MBC) [1]. This has led to the development of a guideline for the management of patients with HER2+ MBC by the American Society of Clinical Oncology (ASCO) [2]. This guideline addresses current knowledge and makes recommendations for the use of such treatments in first-line and beyond.

Case Presentation

A 47-year old Caucasian woman presented to the district hospital in June 2012 with a history of mammography screening with calcifications in the right breast. A breast biopsy reported a grade III ductal carcinoma. She underwent a mastectomy and clearance of axillary nodes on the right side in June 2012. Pathological analysis showed ductal carcinoma pT2 (5 cm) grade III, pN3a involving 9 of 14 nodes with capsular rupture, HER2+ and carcinoma in situ > 25%, hormone receptor negative and 50% Ki-67 index, so an oncology referral was made. The tolerance of T-DM1 in this patient was predictable and good and the patient achieved a durable response.

She had been undergoing hemodialysis and immunosuppressive treatment since 1992 because of kidney transplantation owing to bilateral renal atrophy while she was a teenager. New kidney transplantation was performed in September 2011, as severe chronic glomerulopathy was observed in the original transplanted kidney after a renal biopsy.
Discussion

T-DM1 is a HER2-targeted antibody–drug conjugate comprising trastuzumab, a stable linker, and the potent cytotoxic agent derivative of maytansine (DM1). Once T-DM1 binds to the HER2 receptor, it allows intracellular drug delivery specifically to HER2-overexpressing cells, consequently improving the therapeutic index of the drug and minimizing its exposure to normal tissue [3]. The EMILIA trial is a phase III randomized, multicenter, international, open-label study designed to compare the safety and efficacy of T-DM1 with capecitabine plus lapatinib in HER2+ MBC patients who had previously received trastuzumab and a taxane in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant therapy [1]. In this trial, T-DM1 demonstrated improved median PFS compared with capecitabine and lapatinib (9.6 vs. 6.4 months, respectively; hazard ratio [HR] = 0.65; 95% confidence interval [CI] 0.55-0.77; p < 0.001). Median OS also favored T-DM1 (30.9 vs. 25.1 months, respectively; HR = 0.68; 95% CI 0.55-0.85; p < 0.001). Overall response rate and duration of response were also superior in patients treated with T-DM1 [1]. These results led to the approval of T-DM1 in 2013 by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment as single agent of patients with HER2+ MBC who previously received trastuzumab and a taxane, separately or in combination.

The drug is given as an intravenous infusion every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity occurs. After being administered, T-DM1 undergoes a process of deconjugation and catabolism in cell lysosomes. DM1 is metabolized by CYP3A4 and CYP3A5 in liver microsomes. With a dose of 3.6 mg/kg, the clearance is 12.9 ml/day/kg and the terminal half-life (t1/2) is 3.5 days [4]. It has a linear pharmacokinetic process and preclinical trials show that T-DM1 catabolites are eliminated by the biliary system with minimal participation of the renal system [5].

An exploratory analysis has shown that the pharmacokinetic properties of the drug are unaffected by age, race or renal function [6]. In patients with low to moderate renal impairment, the pharmacokinetic profile was similar to patients with normal creatinine clearance. There are no specific trials for patients with severe renal impairment (creatinine clearance between 15 ml/min-29 ml/min). Only one patient with these characteristics has been treated with T-DM1, but there is no dosage recommendation. We presented here the case report of a 47-year old patient with HER2+ MBC who previously received trastuzumab and a taxane, separately or in combination.

In July 2012, she received trastuzumab and docetaxel as first-line treatment for the breast cancer until December 2012 every Thursday on a three-week cycle because she was receiving hemodialysis on Monday, Wednesday and Friday. She completed 6 cycles of treatment with complete liver response and stable disease in bone. She continued receiving trastuzumab until September 2013.

In September 2013, a CT scan showed disease progression in the liver. She started treatment with capecitabine plus lapatinib as second-line therapy. She showed gastrointestinal toxicity with diarrhea grade 3 and, due to that, lapatinib was substituted by trastuzumab. In January 2014, capecitabine was replaced with vinorelbine due to the appearance of important gastrointestinal toxicity. In April 2014, a new radiological examination showed complete response in liver and stable disease in bone. In July 2014, the patient was referred to our hospital in order to continue the treatment with vinorelbine plus trastuzumab.

In August 2014, a CT scan revealed stable disease in the liver, but new tumors in the peritoneum appeared (Figure 1). She started T-DM1 in September 2014 as third-line treatment. A CT scan was carried out in December 2014 after three months of treatment, which revealed partial response in bone and complete response in peritoneal carcinomatosis (Figure 2). Patient recived TDM1 for two years. Finally in September 2016 she presented progression at SNC with clinical deterioration and she died three months later. During she was receiving T-DM1 she had performance status 0, which allowed her to perform normal life without any toxicity. The last CT performed in September 2016 showed that the partial response in the bone and the complete response in the peritoneum have been maintained (Figure 3).

In July 2012, she received trastuzumab and docetaxel as first-line treatment for the breast cancer until December 2012 every Thursday on a three-week cycle because she was receiving hemodialysis on Monday, Wednesday and Friday. She completed 6 cycles of treatment with complete liver response and stable disease in bone. She continued receiving trastuzumab until September 2013.

In September 2013, a CT scan showed disease progression in the liver. She started treatment with capecitabine plus lapatinib as second-line therapy. She showed gastrointestinal toxicity with diarrhea grade 3 and, due to that, lapatinib was substituted by trastuzumab. In January 2014, capecitabine was replaced with vinorelbine due to the appearance of important gastrointestinal toxicity. In April 2014, a new radiological examination showed complete response in liver and stable disease in bone. In July 2014, the patient was referred to our hospital in order to continue the treatment with vinorelbine plus trastuzumab.

In August 2014, a CT scan revealed stable disease in the liver, but new tumors in the peritoneum appeared (Figure 1). She started T-DM1 in September 2014 as third-line treatment. A CT scan was carried out in December 2014 after three months of treatment, which revealed partial response in bone and complete response in peritoneal carcinomatosis (Figure 2). Patient recived TDM1 for two years. Finally in September 2016 she presented progression at SNC with clinical deterioration and she died three months later. During she was receiving T-DM1 she had performance status 0, which allowed her to perform normal life without any toxicity. The last CT performed in September 2016 showed that the partial response in the bone and the complete response in the peritoneum have been maintained (Figure 3).
References


