



ARTÍCULO DE OPINIÓN

Trastuzumab emtansine in locally advanced or metastatic HER2 positive breast cancer; GENESIS-SEFH drug evaluation report^a

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Abstract

Trastuzumab emtansina (T-DM1) is an antibody-drug conjugate directed against the HER2 for the treatment of HER2+ metastatic breast cancer (MBC), who has previously received trastuzumab plus a taxane. According to the results of the EMILIA trial versus lapatinib plus capecitabine T-DM1 shows an improvement in progression-free survival (PFS) and the overall survival (OS). It has a favorable profile reducing the incidence of grade 3-4 adverse reactions such as hand-foot syndrome and diarrhea. On the contrary increases significantly severe thrombocytopenia; bleeding risk and liver function should also be monitored.

With the current import price T-DM1 has a cost per QALY of over 120,000 €. The price of the drug for the Spanish NHS has not yet been established. Drug cost would be the key factor in the sensitivity analysis and a 50% reduction in the price of the drug would place it close to the threshold of cost-effectiveness usually considered in our midst. According to the budget impact model used, a maximum of 1,218 patients / year and the budgetary impact throughout the Spanish state would be at € 70,490,850.

In the initial analysis no advantage was found for T-DM1 in those patients without visceral involvement. Although a subsequent re-analysis of the results of PFS in which the definition of visceral involvement was specified a significant benefit was shown in this subgroup. We believe that this approach introduces a high degree of uncertainty, which does not guarantee the benefit achieved for this subgroup of patients.

Trastuzumab emtansina en cáncer de mama her2 positivo metastásico o localmente avanzado; informe de evaluación genesis-sefh

Resumen

T-DM1 es un conjugado anticuerpo-fármaco dirigido contra el HER2 para el tratamiento del cáncer de mama metastásico (CMM) HER2 +, que ha recibido previamente trastuzumab más un taxano. De acuerdo con los resultados del ensayo EMILIA frente a lapatinib más capecitabina T-DM1 muestra una mejora en la supervivencia libre de progresión (SLP) y la supervivencia global (SG). Tiene un perfil favorable reducir la incidencia de reacciones adversas grado 3-4 tales como el síndrome mano-pie y la diarrea. Sin embargo, aumenta significativamente el riesgo de trombocitopenia grave y debe monitorizarse el riesgo de hemorragia y la función hepática.

Con el precio de importación actual T-DM1 tiene un coste por AVAC de más de 120.000 €. El precio del fármaco para el Sistema Nacional de Salud en España aún no ha sido establecido. El precio del fármaco sería el factor clave en el análisis de sensibilidad y una reducción del 50% en el precio lo situaría cerca del umbral de coste-efectividad generalmente considerada en nuestro medio como aceptable. De acuerdo con el modelo de impacto presupuestario utilizado, se trataría un máximo de 1.218 pacientes / año y el impacto presupuestario de todo el estado español estaría entorno a 70.490.850 € para este volumen de pacientes.

En el análisis inicial no se encontró ninguna ventaja para T-DM1 en aquellos pacientes sin afectación visceral. Aunque un re-análisis posterior de los resultados de SLP en el que se especifica la definición de la afectación visceral se muestra un beneficio significativo en este subgrupo. Creemos que este enfoque presenta un alto grado de incertidumbre, y no garantiza el beneficio logrado para este subgrupo de pacientes.

^a This paper is an abstract of T-DM1 drug evaluation report GENESIS-SEFH, that could be retrieved in his entire form from GENESIS web. This evaluation has been made with the aid of MADRE 4.0 application1.
http://gruposdetrabajo.sefh.es/genesis/genesis/Documents/GENESIS_SEFH/Trastuzumab-emtansina_Ca_mama_def_GENESIS-SEFH_11_2014.doc

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KEYWORDS

Breast Cancer; Trastuzumab emtansine; Cost-effectiveness; Lapatinib

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Introduction

Metastatic breast cancer (MBC) is described as an invasive breast cancer that has spread beyond the breast and nearby lymph nodes to other organs such as the lungs, distant lymph nodes, skin, bone, liver or brain. The HER2+ breast cancer is characterized by the presence of elevated levels of the HER2 protein on the surface of tumor cells, and affects 15-25% of women with breast cancer. This subtype is a particularly aggressive form that evolves in the absence of specific treatment, prone to early progression and visceral metastases.

The incidence of breast cancer increased by 20% between 2008 and 2012, when 1.67 million new cases were diagnosed, making it the second most common cancer in the world and the most common cancer among women. The mortality of breast cancer increased in those four years by 14%, with a total of 522,000 deaths in 2012, becoming the fifth leading cause of death. In developed countries, most cases are diagnosed in a localized stage or disseminated to regional lymph nodes so that can be treated with curative intent. Breast cancer is one of the areas of oncology where most advances have been achieved in treatment, although for the MBC together the median survival is approximately 24-36 months, and only a quarter of patients live more than five years from diagnosis.

In patients with HER2+ MBC, pertuzumab plus trastuzumab plus docetaxel scheme is recommended as the preferred first-line option. In second line different options appear in treatment guidelines, such as trastuzumab emtansine (T-DM1) or combinations of trastuzumab plus capecitabine, trastuzumab plus lapatinib or trastuzumab plus chemotherapy (e.g. vinorelbine)^{2,3}.

T-DM1 is an antibody-drug conjugate directed against the HER2 receptor containing trastuzumab, a microtubule inhibitor DM1 and linker MCC intended to limit systemic delivery and enhance the transport of DM1 toward specific targets. The recommended dose is 3.6 mg / kg of body weight administered by intravenous infusion every 3 weeks. It was approved by EMA in December 2013 for the treatment of HER2+ MBC, who has previously received trastuzumab plus a taxane, according to the results of the EMILIA trial versus lapatinib plus capecitabine showing an improvement in progression-free survival (PFS) and the overall survival (OS)⁴.

PALABRAS CLAVE

Cáncer de mama; Trastuzumab emtansina; Coste-efectividad; Lapatinib

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Efficacy

Two phase II clinical trials were located (TDM4450g and TDM4374g) but none of these studies were analyzed in the report because they were either performed in patients who had not received prior chemotherapy or used time to response as primary efficacy variable. The study considered for the evaluation report of T-DM1 was the TDM4370g / BO2197 trial (EMILIA) a phase III randomized, open label study conducted in 991 patients with HER2+ MBC. Patients were stratified by geographic location, previous number of chemotherapy (CT) lines, stage, and presence or absence of visceral disease. In the active treatment T-DM1 was administered and the control group received the scheme lapatinib + capecitabine until disease progression or unacceptable toxicity. Analysis was by intention to treat for effectiveness and confirmation of progression and efficacy data through an Independent Review Committee (IRC) table 1 shows the main efficacy results included.

T-DM1 significantly improved PFS and this benefit was consistently observed in clinically relevant subgroups, with less benefit for patients over 65 and those with non visceral or non measurable disease. In the subgroup of patients with non measurable disease (n = 205), the HR (hazard ratio) for PFS and OS, based on assessments of IRC, were 0.91 (95% CI 0.59 to 1.42) and 0.96 (95% CI 0.54 to 1.68), respectively. In the reanalysis with 2 different definitions of visceral disease, the effect in patients with non visceral disease appeared consistent with the overall treatment effect⁵.

Two interim analyses of OS were made. In the second one, a significant increase of OS was observed in the T-DM1 arm compared to lapatinib plus capecitabine (Table 1). The estimated survival rate in the first year was 85.2% (95% CI, 82.0 to 85.5) in the T-DM1 and 78.4% (95% CI, 74.6 to 82.3) in lapatinib plus capecitabine group. The rate at two years was 64.7% (95% CI, 59.3 to 70.2) in the T-DM1 and 51.8% (95% CI, 45.9 to 57.7) in lapatinib plus capecitabine group.

The general applicability of this trial in practice is acceptable because the comparator arm is one of the recommended combinations; trial has mostly included patients with prior treatment for advanced disease (40% more than 1 line of previous CT); two thirds of the patients had visceral involvement and more than a half had hormone receptor positive (HR +). However, only patients with ECOG 0-1 were included when a third of the population in clinical practice has

Table 1. TDM4370g/BO21977

Outcome	T-DM1 N (495)	Lapatinib + Capecitabine N (496)	HR or ARR (CI 95%)	p
Primary outcome				
– PFS IRC (median).	9.6 mo	6.4 mo	0.65 (0.55-0.77)	< 0.0001
– OS (median)	30.9 mo	25.1 mo	0.682 (0.548-0.849)	0.0006
Secondary outcomes				
– PFS investigator (median).	9.4 mo	5.8 mo	0.658 (0.560-0.774)	< 0.0001
– TTP (median).	7.9 mo	5.8 mo	0.703 (0.602-0.820)	< 0.0001
– Time to - 5 pts FACT-B TOI	7.1 mo	4.6 mo	0.796 (0.667-0.951)	0.0121
– ORR (%)	43.6% (38.6%-48.6%)	30.8% (26.3%-35.7%)	12.7% (6.0%-19.4%)	0.0001
– DoR (median. IC95%)	12.6 mo (8.38 – 20.7)	6.5 mo (5.45 – 7.16)		

PFS: Progression free survival. OS: Overall survival. TTP: Time to progression. ORR: Overall response rate. DoR: Duration of response. HR: Hazard ratio. ARR: Absolute risk reduction

ECOG ≥ 2 and only 25 patients were over 75 years at baseline.

One issue that may generate controversy in the analysis of this paper is the use of lapatinib plus capecitabine combination in patients who have not received previously anthracyclines; this subpopulation is outside of the approved indications for lapatinib. This has led the German IQWiG conclude that there is no evidence of added benefit to the population that has not previously received anthracyclines (inappropriate comparator)⁶.

At present, the use of double block anti-HER2 with pertuzumab plus trastuzumab is the recommended treatment in 1st line for patients with metastatic HER2+. So, we should be cautious applying efficacy results of T-DM1 to patients with previous exposure to pertuzumab before its widespread use (data not exist for other treatment options after pertuzumab due to the recent addition in the practice of this drug).

Safety

Serious adverse events occurred in 88 patients (18%) with lapatinib plus capecitabine and in 76 patients (15.5%) of T-DM1 group. The rate of grade 3-4 adverse events was higher in the group of lapatinib plus capecitabine (57.0% vs 40.8%). Diarrhea and palmoplantar erythrodysesthesia were the

grade 3-4 events that occurred more frequently in the lapatinib plus capecitabine arm, and thrombocytopenia and elevated transaminases occurred to a greater extent in the T-DM1 arm. Most grade 3-4 adverse events occurred in the first two cycles of treatment with T-DM1. Data in patients previously treated with pertuzumab do not reveal problems of greater cardiotoxicity although a higher incidence of hypersensitivity reactions was found in this group. In both arms, these grade 3-4 adverse events were resolved by reducing the dose. Most deaths occurred in the study were attributed to disease progression (123 in the lapatinib plus capecitabine arm and 91 in the T-DM1)⁵.

Economic assessment

T-DM1 has a cost per QALY of over 120,000 € (Table 2). Even fulfilling the End of Life criteria established by NICE, the inclusion of this drug would not be considered cost-effective, according to the most used international references⁷. The price of the drug for the Spanish NHS has not yet been established and the import price has been used in calculating the ICER. Drug cost would be the key factor in the sensitivity analysis and a 50% reduction in the price of the drug would place it close to the threshold of cost-effectiveness usually considered in our midst.

Table 2. ICER

Reference	Outcome	VARIABLE	Efficacy T-DM1	Efficacy Lap+Cap	Difference (IC95%)	Incremental cost	ICER (CI95%)
Sunil Verma. MD et. Al.	Primary	OS (median)	30.9 mo	25.1 mo	5.8 mo	56.575.95 €	117.053.7 €/LYG
Sunil Verma. MD et. Al.	Primary	QALY*	18.2 mo	14.1 mo	4.1 mo	56.575.95 €	165.588.1 €/QALY

OS: Overall survival. QALY: Quality adjusted life year. LYG: life of year gained. Note: these results must be recalculated once the price is listed for the NHS

* Utilities pre and post-progression for both arms taken from NICE report on transtuzumab emtansine. See more details in full GENESIS report

Breast cancer is the most common cancer in women, with an incidence of 25,215 cases per year in Spain. We can assume therefore an incidence in our country than 25,000 new cases annually. Approximately 5% of cases are diagnosed in the metastatic phase⁸, and globally is estimated that approximately 20% of patients receiving adjuvant therapy will progress to MBC each year, adding to the population with an initial diagnosis of metastases⁹. We also have patients who undergo rapid relapse (<6 months) and which are subsidiaries of treatment with T-DM1, 3.5%¹⁰.

The decision to treat the MBC criteria included presence of expression of HER2, ER (estrogen receptor) and PR (progesterone receptor). Referring to HER2, is estimated to be expressed in approximately 15-20% of patients with breast cancer but a higher percentage of positivity in patients diagnosed metastatic stage is observed. In a report provided by the manufacturer is estimated that patients diagnosed metastatic stage show 29% of HER2 +. Of these patients, we can assume that two thirds can reach a 2nd line anti-HER2 treatment with good performance status.

According to the budget impact model used, a maximum of 1,218 patients / year and the budgetary impact throughout the Spanish state would be at € 70,490,850. These calculations are based on an assumption of 100% treatment of patients considered as candidates for treatment with T-DM1 in Spain. The actual impact will depend on market penetration and treatment of patients with other options (e.g. clinical trial).

Additional considerations

A major limitation of the trial is re-analysis of efficacy data done by revising the definition of visceral / non-visceral disease since it is one of the key data in the subgroup analysis and also one of the features used in the stratification of patients (T-DM1 showed no benefit in patients with non-visceral disease in the first analysis). The manufacturer provided additional analysis of PFS and OS in patients with visceral disease based on tumor assessments done by IRC (instead of the initial evaluations done at the centers) and by applying different definitions of visceral disease. This same effect was observed in subgroup analysis of the pivotal trial for pertuzumab.

In the initial analysis no advantage was found for T-DM1 in those patients without visceral involvement (n = 322). Although a subsequent re-analysis of the results of PFS in which the definition of visceral involvement was specified a significant benefit was shown in this subgroup. We believe that this approach introduces a high degree of uncertainty, which does not guarantee the benefit achieved for this subgroup of patients, for the following reasons:

A) The definition of visceral / non-visceral disease is one of the key data in the subgroup analysis and also one of the features used in the stratification of patients. If we change post-hoc one of the characteristics used for stratification of patients this can introduce significant imbalances in population subgroups compared, so that the result of the re-analysis may be due to the differences arising on the reallocation of patients and not the feature to be analyzed

To be certain that this re-analysis is acceptable we must show that the baseline characteristics of the new subgroups analyzed are comparable, since the homogeneous distribution guaranteed by stratified randomization is lost. These characteristics are not shown in the EPAR report nor indicate which have been shown to EMA.

B) The initial assessment of visceral and non-visceral involvement was at the discretion of the clinician. If there had been a clear bias classification would have produced an effect of regression to the mean that would not have generated differences in subgroup analysis. We think, though less orthodox from the methodological point of view, initial assessment is closer to what may occur in clinical practice and therefore gives us an indication of effectiveness rather than efficacy, which adds value.

C) The definition of visceral involvement is not clearly defined (in fact several re-analyses with different definitions are made) and has changed considerably in recent years so that, even accepting that the definition used in the re-analysis by the manufacturer is considered "gold standard", it is unlikely that this definition is applied directly and accurately in routine practice.

Conclusion - Therapeutic Positioning and conditions of use

Treatment of adult patients with unresectable locally advanced or metastatic HER2+ breast cancer who have previously received a taxane and trastuzumab separately or in combination. Patients must have received prior treatment for locally advanced or metastatic disease, or have expressed recurrence during adjuvant treatment or within six months of its completion. They must also meet the following criteria:

- ECOG 0-1
- HER2 + status defined as amplification IHC3+ or FISH \geq 2
- LVEF \geq 50%
- Visceral disease

Not showing any of the following:

- Significant cardiac disease
- Neuropathy grade 3 or higher
- Symptomatic brain metastases or treated in the previous two months

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^b This is a summary of the most relevant references, the full list can be retrieved from the original drug evaluation report GENESIS-SEFH (Spanish): http://gruposdetrabajo.sefh.es/genesis/genesis/Documents/GENESIS_SEFH/Trastuzumab-emtansina_Ca_mama_def_GENESIS-SEFH_11_2014.doc