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Cost-effectiveness of trastuzumab in metastatic breast cancer: Mainly a matter of price in the EU?

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ABSTRACT

Trastuzumab (TR), a monoclonal antibody approved by EMA in 2000 and one of the first examples of "targeted therapy", is indicated to treat human epidermal growth factor receptor 2 (HER2) positive breast cancer. TR, whose patent will expire in 2015 in Europe, has been judged positively for reimbursement by most public authorities in the EU. Here we critically review the existing evidence on TR in metastatic breast cancer (MBC), in line with the multidisciplinary health technology assessment (HTA) approach, to assess whether the existing evidence supports TR positive reimbursement decisions taken in MBC by EU health authorities. We did a literature search for the main HTA topics (efficacy, quality of life and ethics) on the PubMed international database (2000–2013). Then, we did a specific literature search to select the full economic evaluations (FEEs) conducted in EU countries focused on TR as first-line innovative therapy in MBC. We retrieved scant evidence in the literature to support TR reimbursement in MBC. We found only two clinical trials and their results were unclear because of the large proportion of patients who crossed over. Moreover, the quality of methods was poor in all four European FEEs selected. This example of HTA exercise on a mature monoclonal antibody in a specific indication casts doubts on how often the reimbursement decisions taken by EU health authorities in emotional pathologies like cancer are rational. These decisions should at least be reconsidered periodically on the basis of the latest evidence.

1. Introduction

Breast cancer is the most common female cancer worldwide. Incidence rates in Western Europe vary from 56.5 per 100,000 women in Greece to 145.2 in Belgium [1]. Treatment modalities range from surgery and radiotherapy to systemic therapy, including chemotherapy and biological agents, depending on the cancer stage and histological characteristics [2].

While treatable, metastatic breast cancer (MBC) is rarely curable at present, although some women live with it for many years; the median overall survival (OS) ranges from 18 to 24 months [3]. Around a quarter of patients overexpress human epidermal growth factor receptor 2 (HER2), with a worse outlook in general. Trastuzumab (TR), a monoclonal antibody approved by EMA in 2000 and one of the first examples of "targeted therapy" [4], is indicated to treat HER2 positive breast cancer.

Targeted therapy, aiming at maximizing clinical benefits for selected patients, poses a new challenge to health authorities by adding new tests to expensive drugs [5]. TR, like many other biological anti-cancer agents, has been judged positively for reimbursement by most public authorities in the EU. The patent will expire in 2015 in Europe [6] and its biosimilars are expected to be launched in the next few years [7,8].

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Here we critically review the existing evidence on TR in MBC, in line with the multidisciplinary health technology assessment (HTA) approach [9,10] that decision makers often claim to adopt for evaluating the cost-effectiveness of new drugs, in the attempt to gain efficiency in the allocation of scarce resources. After a systematic literature search, we summarize the main clinical aspects, then analyze the full economic evaluations (FEEs) published in the EU, to assess whether the existing evidence supports TR positive reimbursement decisions in MBC taken by EU health authorities. Finally, we discuss the policy implications of our assessment in a broader perspective, including potential market changes in the near future.

2. Literature search

We did a literature search on the PubMed international database for the main HTA topics (2000–2013), combining "efficacy and clinical trial"/"quality of life"/"ethics" with the terms "trastuzumab" and "metastatic breast cancer". We retrieved 114 articles for efficacy: 112 were discarded because they did not include a clinical trial (CT) on TR as a first-line therapy in MBC, being: (i) CTs with a different design (90); (ii) reviews (12); (iii) pharmacological studies (8) and (iv) observational studies (2). Finally we selected two CTs and identified one meta-analysis on TR adverse events through references. Then, we identified 60 publications for quality of life (QoL): 58 were discarded because they did not include a study on QoL impact of TR in MBC, being: (i) QoL studies on different drugs (4); (ii) reviews and comments (37); (iii) FEEs (3); (iv) studies focused on clinical issues (12); (v) case-studies (2). In the end two studies were selected, the first reporting a review of three small studies and the second analyzing one of them in detail. Finally, we retrieved 14 publications for ethics, but none of them included specific information on TR.

Then, we did a specific literature search to select the FEEs conducted in EU countries, focused on TR as first-line innovative therapy in MBC, published in English from January 2000 until December 2013. The search terms used were "trastuzumab" and "metastatic breast cancer", "cost" or "cost-effectiveness" or "economic evaluation".

We retrieved 45 articles: 34 were discarded because they did not include a FEE on TR as first-line innovative therapy in MBC, being: (i) reviews (16); (ii) partial EEs (10); (iii) FEEs not on TR in MBC (3); (iv) studies focused on clinical issues (3); (v) letters or comments (2). Since seven FEEs did not concern the EU setting, we selected eventually four articles. We screened the selected articles to assess the main methodological features of the FEEs, using a common checklist based on the one used to abstract studies in the EURONHEED database [11].

3. Clinical background

3.1. Bioagent

TR reduces the reappearance of cancer as adjuvant therapy in the early phase, and helps metastatic patients live longer without their cancer getting worse [12]. Before starting treatment, HER2 status should be confirmed. Testing includes immunohistochemical (IHC) assays to detect protein over-expression and fluorescence *in situ* hybridization (FISH) to detect gene amplification. IHC are relatively cheap and easy to conduct and are recommended as primary tests, while the FISH test is more expensive and thus mainly used to confirm positive IHC results [13].

3.2. Efficacy and safety

It is still difficult to estimate the OS increase when TR is used in MBC, because in some CTs patients could cross over from the control arm to TR. Undermining the power of the original CT design, crossover can lead to more or less favorable incremental OS estimates depending on the prognostic factors of patients who switch [14]. One CT [15] estimated that adding TR to chemotherapy could increase median OS by 4.8 months in women with progressive MBC that over-expressed HER2 and were naïve to chemotherapy. However, two thirds of patients who were initially assigned to chemotherapy alone began, after disease progression, to receive open-label TR alone or with chemotherapy. One more recent CT [16] estimated that TR in addition to docetaxel (chemotherapy) led to a gain of 8.5 months in median OS in the same type of patients; in this CT 57% of patients in the docetaxel-alone arm were reported to have crossed over to TR. The median estimated OS was 16.6 months in patients who received docetaxel only and 30.3 months in those who crossed over to TR. However, it is hard to draw firm conclusions since these subgroups were very small and not randomized.

Since TR significantly increases the risk of cardiac dysfunction in patients receiving anthracycline-based chemotherapy, cardiotoxicity is its most important adverse event (AE) [17]. The incidences of left ventricular ejection fraction decrease and congestive heart failure were 7.5% (95% CI 4.2–13.1) and 1.9% (95% CI 1.0–3.8) respectively. Thus patients under TR treatment need continuous monitoring of the cardiac function. Furthermore, TR may induce infusion-related reactions, hematotoxicity (in particular neutropenia), infections and pulmonary adverse reactions [12].

3.3. Quality of life

Three studies were reported to show a positive impact of TR on QoL in a review co-authored by employees of the TR manufacturer [18]. However, the only significant improvement recorded in one of them [19] was a slight decrease in fatigue and this can hardly be important, since TR is an add-on therapy, with AEs likely to induce disutilities [14].

3.4. Ethics

Although ethics is always claimed to be a very important HTA component, its implications on specific technologies are hardly ever reported [20,21], so the lack of ethical studies on TR was not surprising. The only study indirectly concerning TR was a qualitative survey conducted in a Dutch teaching hospital [22] on a few terminal patients (15) with MBC or metastatic colon-rectal cancer. The main conclusion was that, despite AEs, patients perceived