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Original Research

An exploratory analysis of the factors leading to delays in cancer drug reimbursement in the European Union: The trastuzumab case

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Abstract ***Background:*** The European Union (EU) has adopted a common procedure for granting marketing authorisation for cancer drugs. Nevertheless, pricing and reimbursement decisions are a competency of EU national governments, and their policies are diverse. We aimed to evaluate the time for trastuzumab reimbursement approval and its association to health expenditure, to health policy performance, to the availability of cost-effectiveness studies and to breast cancer outcome.

Methods: Breast cancer outcome was estimated by the mortality/incidence (M/I) ratio. Trastuzumab reimbursement approval dates were provided by Roche. Spearman's rank correlation and Wilcoxon rank-sum test were used to evaluate associations and/or differences between the variables studied. Additional analyses were made by grouping countries according to compliance to the 180 day timeframe stipulated in the EU 89/105/EEC Directive for drug pricing and reimbursement.

Results: A statistically significant inverse and strong correlation between breast cancer M/I ratio and health expenditure ($r_s = -0.730$, $p < 0.001$) and health policy performance ($r_s = -0.711$, $p < 0.001$) was found, meaning the better the score and the higher the expenditure, the fewer patients died after a breast cancer diagnosis. Factors associated with

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trastuzumab faster reimbursement and compliance to the 89/105/EEC Directive were better health policy score, higher health expenditure and availability of cost-effectiveness studies.
Conclusion: Higher health policy scores and health expenditure are associated with faster reimbursement of trastuzumab and better breast cancer outcome. Although the study design does not allow inference of causal associations, a marked difference is observed between Eastern and Western Europe, with long delays and increased breast cancer mortality identified in Eastern European countries.

1. Introduction

Cancer is a major public health issue in Europe, with almost 3.5 million new cases of cancer diagnosed in 2008 [1]. These numbers are likely to increase because of environmental factors, demographic changes and an ageing population [2]. Despite the increasing incidence of breast cancer, mortality from the disease is declining in Europe [3], a fact thought to be related to improvements in breast cancer screening and multidisciplinary treatment [4].

One important factor contributing to improved patient survival and longevity is the uptake of innovation. Econometric approaches estimate that around 40% of the increase of life expectancy in recent decades is due to the launch of new drugs [5].

For drugs to be publicly accessible in clinical practice, marketing authorisation and pricing and reimbursement approval are necessary. Since 1995 the European Union (EU), through the European Medicines Agency (EMA), has adopted the 'Centralised Procedure' to evaluate medicinal products (Regulation (EC) No 726/2004) [6] and grant a unique marketing authorisation valid in all EU members states [7]. Despite this, managing and funding national health systems is a responsibility of each national government, and reimbursement decisions are individually taken by each member state [8]. In this context, cost-effectiveness analysis of any new health technology is an important tool for health policy decision-making [9].

For historical reasons, policies for health resource allocation in Europe are heterogeneous [10,11]. A clear division is noticeable between Western and Eastern European countries, with the former allocating higher budgets to health than the latter [12]. This translates into better survival after a cancer diagnosis in Western Europe, which is particularly marked in breast cancer [13]. The reduction in breast cancer mortality observed in recent decades for Europe as a whole is also not homogeneous, being more significant in Western European countries [14].

In recent years, one of the greatest improvements in breast cancer treatment was the development of anti-HER2 agents, in particular trastuzumab. Trastuzumab is a humanised monoclonal antibody targeting the extracellular domain of the HER2 receptor. Around 20% of breast cancers show amplification of the HER2 gene [15], which defines a molecular subtype with aggressive biological behaviour and worse clinical prognosis. Trastuzumab has changed the natural history of this disease, dramatically improving the survival of patients with HER2-positive breast cancer in both the metastatic [16] and in the adjuvant settings [17–21]. Nevertheless, despite the great benefit of trastuzumab treatment for HER2-positive breast cancer, because of the diversity in health resource allocation, the drug has not become available across the EU at equal speeds, and in some cases has been considerably delayed.

This study therefore aims to evaluate the time periods between trastuzumab marketing authorisation and reimbursement approval in the EU member states, and the association of these processes to health expenditure, wealth indicators, health policy performance, availability of cost-effectiveness studies and breast cancer outcome. We hypothesised that two factors are related to the speed of drug reimbursement after its efficacy has been proven: the efficiency of a country's health policies and the allocation of resources to health care.

2. Material and methods

2.1. Data extraction

Health expenditure and wealth indicators were extracted from the publicly available online database of the World Bank (reference years 2000 and 2006, corresponding to the years of trastuzumab approval in the metastatic and adjuvant setting, respectively) [22]. The total expenditure on breast cancer and breast cancer drug expenditure were extracted from the Luengo-Fernandez et al. publication [12]. In this study the authors used drug expenditure data from IMS Health and applied a framework already validated in previous studies to be able to make comparisons between countries. Breast cancer indicators were extracted from the World Health Organisation database (GLOBOCAN 2008) [23]. The mortality/incidence (M/I) ratio was established by dividing the values for mortality by those of incidence; this provides an estimate of the fraction of patients dying after a breast cancer diagnosis, being a good approximation of 5-year relative survival [24].