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Original Research

European cost-effectiveness study of uPA/PAI-1 biomarkers to guide adjuvant chemotherapy decisions in breast cancer

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Abstract ***Background:*** This study investigated the cost effectiveness of guideline-recommended (American Society of Clinical Oncology, European Society of Medical Oncology) urokinase plasminogen activator (uPA)/plasminogen activator inhibitor-1 (PAI-1) biomarkers to guide adjuvant chemotherapy decisions for hormone receptor-positive, node-negative early breast cancer patients at intermediate risk of relapse, in France, Germany, and The Netherlands.

Methods: uPA/PAI-1 testing was compared to chemotherapy for all patients and to no chemotherapy in two age-related subgroups (35–49 and 50–75 years). A partitioned survival analysis was performed using patient-level data for survival outcomes and secondary sources. Mean quality-adjusted life years (QALYs) and costs were estimated over a lifetime horizon to calculate the incremental net monetary benefit (INMB) at a willingness-to-pay of

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€50,000/QALY. Uncertainty was explored through bootstrap and probabilistic sensitivity analysis using 5000 replicates.
Results: In the 35–49 year age group, INMBs were negative when uPA/PAI-1 testing was compared to chemotherapy for all patients but positive when it was compared to no chemotherapy for the three countries. In the 50–75 year age group, INMBs of uPA/PAI-1 testing compared to both reference strategies were positive in the three countries, with cost-effectiveness probabilities for the uPA/PAI-1 strategy of 65%, 70%, and 59% for France, Germany, and the Netherlands, respectively, compared with chemotherapy for all patients, and 64%, 58%, and 65%, respectively, compared with no chemotherapy.
Conclusions: uPA/PAI-1 testing could allow the selection of patients older than 50 years requiring chemotherapy in this population, but the cost effectiveness of this strategy is uncertain. Chemotherapy for all patients is the most cost-effective strategy for patients younger than 50 years.

1. Introduction

Patients with oestrogen and/or progesterone receptor-positive (ER+, PR+), node-negative (N0) early breast cancer (EBC) enjoy a relatively good prognosis, especially when treated with adjuvant hormonal therapy (10-year breast cancer mortality rate of 12% [1]). Adjuvant chemotherapy reduces recurrence and mortality rates but is associated with adverse effects. Among patients considered at intermediate risk of relapse based on clinicopathologic factors (N0, ER+ and/or PR+, older than 35 years, grade 2) de-escalating therapy by omitting chemotherapy is under discussion for those patients with a sufficiently good prognosis. The absolute long-term survival benefit of adding chemotherapy to hormonal therapy is indeed small and must be weighed against potential side-effects. The interest in decision-making tools to identify patients in whom chemotherapy can be omitted without compromising long-term outcome is therefore gaining momentum.

The invasion factors, urokinase plasminogen activator (uPA) and its main inhibitor, plasminogen activator inhibitor-1 (PAI-1), have a prognostic value in EBC that is independent of conventional factors, as demonstrated in many studies [2] including a randomized trial [3] and a pooled analysis [4]. Elevated levels of these biomarkers are associated with a poor prognosis and validated cutoffs were established to guide the indication for adjuvant chemotherapy [5]. Measurement of uPA/PAI-1 in EBC is recommended by several expert panels [2] and the test is used in Germany in clinical practice and to a lesser extent in France [2]. Other tools exist to guide the use of adjuvant chemotherapy in EBC. Several multigene tests have been developed, but the expensive costs they incur raise the question of reimbursement by health care systems [6–18].

Only one cost-effectiveness study of the use of uPA/PAI-1 has been performed from a German perspective [19]. That study concluded that uPA/PAI-1 testing was cost effective to guide decision-making regarding adjuvant chemotherapy compared to chemotherapy for all patients or no chemotherapy. However, quality of life was not considered in the health outcomes. The objective of our study was to investigate the cost effectiveness of uPA/PAI-1 testing to identify women with a sufficiently good prognosis not requiring adjuvant chemotherapy among EBC patients at intermediate risk of relapse. A meta-analysis of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) [1] established that there is a trend towards greater benefits of chemotherapy among younger patients and presented its results for two age-related groups with a cutoff at 50 years. Likewise, we performed separate analyses for women younger and older than 50 years at surgery. We considered the perspective of three countries: France, Germany, and The Netherlands.

2. Methods

The recommendations of the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) were followed to report this study [20].

2.1. Study design

This cost-effectiveness analysis used patient-level data to estimate survival outcomes and secondary sources for the efficacy of treatments, quality of life, and costs. The strategy under evaluation was the use of uPA/PAI-1 to select EBC patients at intermediate risk of relapse (defined as aged 35–75 years, with the following tumour characteristics: N0, ER+ and/or PR+, grade 2) for adjuvant chemotherapy. In this strategy, patients with high uPA and/or PAI-1 levels are selected for adjuvant chemotherapy whereas patients with low levels of both biomarkers do not receive this therapy. As the current