Karolinska Institutet

DEPARTMENT OF ONCOLOGY-PATHOLOGY

Studies of targeted therapy in breast cancer using trastuzumab: HER2 testing and trastuzumab treatment – clinical and economic evaluation.

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av
Ulla Wilking
legitimerad sjuksköterska

Huvudhandledare:
Professor Jonas Bergh
Karolinska Institutet
Institutionen för onkologi-patologi,

Bihandledare:
Professor Emeritus Bengt Jönsson
Handelshögskolan Stockholm
Nationalekonomiska Institutionen
Center för hälsoekonomi,

Fakultetsopponent:
Professor Scott Ramsey
Fred Hutchinson Cancer Research Center
Seattle, USA

Betygsnämnd:
Professor Kristian Bolin
Lunds Universitet
Nationalekonomiska institutionen

Professor Carsten Rose
Lunds Universitet
Medicinska fakulteten

Professor Emeritus Ulrik Ringborg
Karolinska Institutet
Institutionen för onkologi-patologi,

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ABSTRACT

The incidence in breast cancer has more than tripled in Sweden since the 1960-ies. During the same time period the 5-year survival rate has increase from around 65% to almost 90%. The survival increase is mainly related to medical treatments (endocrine treatments, chemotherapy in different combinations), radiotherapy and breast cancer screening. Two thirds of costs for breast cancer are not related to these therapies, but to costs outside of the health care system (e.g. early retirement and premature death). Continued improvements in therapies would therefore be of great gain for the outcome and overall cost of breast cancer. One of these improvements has been the discovery of the Human Epidermal Growth Factor Receptor 2 (HER2) in the nineteen eighties and the development of the monoclonal antibody directed against HER2 (trastuzumab) in the nineteen nineties. Trastuzumab is registered for treatment of HER2 positive early and metastatic breast cancer. HER2 diagnosis and trastuzumab treatment are dependent on each other, as diagnosis is meaningless without the treatment and treatment is meaningless without diagnosis. This relationship is usually called co-dependent technologies.

The aim of this thesis was to determine how a targeted patient population is optimally managed in terms of co-dependent technologies.

The results demonstrate that HER2 testing is not optimally carried out in all situations. In 151 patients we found a 10% change in HER2 status between primary tumours and relapses (19% from HER2+ to HER2– and 6% from HER2– to HER2+). Patients with a change in HER2 status had a significant 5.47 (95% CI 2.01–14.91) increased risk of dying compared to patient with stable positive HER2 status (86% of these patients received trastuzumab treatment). In another study, there was a 32% change in 459 patients in Oestrogen Receptor (ER) status (ER+ to ER- 24.6% ER– to ER+ 7.8%). Also ER change is related to worse prognosis and patients with ER negative systemic relapses had a significant twofold (95% CI 1.39-2.87) increased risk of dying compared to patients with ER positive relapses. This shows that it is clinically relevant to re-test relapses for tumour marker status, and changes may offer additional treatment options. To be able to follow-up and monitor usage and outcome in clinical practice (clinical effectiveness as opposed to use in clinical trials: clinical efficacy) treatment with trastuzumab should be used according to guidelines, although we found large differences in usage between Health Care Regions (HCRs) in Sweden (years 2000-2004 300% difference between North HCR and South HCR, years 2006-2008 40% difference between Stockholm-Gotland and South-East and West HCRs). Another important aspect is that re-testing of HER2 status before trastuzumab treatment in the metastatic setting is cost-effective (USD 56,000 - USD 67,000 per Quality Adjusted Life Year and USD 39,000 – USD 46,000) and should therefore always be done.

Diagnosis of HER2 status and treatment with trastuzumab is a challenge and this thesis points to the complexity of co-dependent technologies. The knowledge created could be used for the introduction of future co-dependent technologies in order to gain the most benefit, both to patients and to society.

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