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When to HER2 test? A cost perspective

S. Lane[1], G. Coast[1], A.M. Hanby[1], A. Moss[2]. [1]*Leeds General Infirmary, Algernon Firth Institute, Leeds, UK;* [2]*Roche Products Limited, HealthCare Management, Welwyn Garden City, UK*

Background: Metastatic breast cancer patients with HER2 overexpression should be identified and given the option to be treated with trastuzumab. One approach, defined as prospective testing, establishes whether breast tumours overexpress HER2 at time of tumour diagnosis. Whereas retrospective testing examines retrieved archival tissue for HER2 overexpression, once patients are diagnosed with metastatic disease.

The objective was to assess the difference in the cost burden for the Yorkshire cancer network with a population of 2.5 million and for an average cancer network with a population of 1.4 million to perform HER2 testing using the prospective or retrospective approach.

Material and Methods: We developed a simulation model to look at the total cost attributed to both prospective and retrospective testing. The number of patients in the prospective arm equalled the number of breast cancer patients presenting in the network. For the retrospective testing this number equalled the number of patients diagnosed with metastatic disease eligible for further treatment. The cost of the testing kit is included. The retrospective strategy included the cost of retrieving patients' samples, the cost of an additional consultation to inform the patient of their HER2 status and eligibility for treatment with Herceptin. We also looked at the total cost of each strategy excluding the consultation costs.

Results: For the Yorkshire cancer network (Table 1), despite an increased number of patients requiring prospective testing, the overall cost of testing was shown to be less compared to retrospective testing by £11,928 per annum. This result was driven by the time expended to find and retrieve the samples of patients diagnosed with metastases, as well as the need for additional consultations. If there were no additional consultations prospective analysis would be more costly, however this additional cost would be negligible. Note the analysis did not take into account the potential benefits of not delaying treatment for patients progressing to metastatic breast cancer, which would make the prospective testing strategy even more attractive.

Table 1. Yorkshire cancer network

	Prospective	Retrospective	Variation
Number of patients	1420	710	+710
Total testing cost	£35,500	£17,750	+£17,750
Total cost of each strategy	£56,800	£68,728	−£11,928
Total cost excluding consultations	£56,800	£53,250	+£3550

Conclusions: We conclude that earlier prospective testing will be, as a whole, less costly than later retrospective testing. According to these findings, all patients should be HER2 tested at diagnosis of breast cancer rather than waiting for metastases to appear.

394 POSTER HIGHLIGHT

HER-2 as an independent prognostic factor in node negative cases

R. Rampaul[1], S. Pinder[2], J. Robertson[1], L. Ellis[3], R. Blamey[1]. [1]*Breast Unit, Surgery, Nottingham, UK;* [2]*Breast Unit, Pathology, Nottingham, Uk;* [3]*Breast Unit, Pathology, Nottingham, Uk*

Many studies have claimed individual prognostic significance for HER-2 but are often too small, too short follow-up (FU) and lack multivariate (MVA) analysis.

A previous study from NCH (Lovekin et al 1991) failed to show overall independent significance, HER-2 over-expression being in any case associated with poor prognostic factors. The use of adjuvant therapies has also been a confounding factor since HER-2 may relate to therapeutic response.

Patients and; Methods n=674 LN negative cases. Median FU 20 years (14–30). No adjuvant therapies. DAKO antibody used with semiquantitative scoring.

Results: In LN negative cases c-erbB2 showed independent significance for survival in multivariate analysis with Size, Stage, Grade, LVI and the Nottingham Prognostic Index (NPI). Survivals in LN negative cases in the NPI Good and Moderate groups were significantly worse for c-erbB2 over-expression.

References

[1] Lovekin, C, Ellis, IO, Locker, A, Robertson, J, Bell, J, Nicholson, R, Gullick, WJ, Elston, CW, Blamey, RW. CerbB2 oncoprotein expression in primary and advanced breast cancer Br J Cancer 1991: 63: 439–443.

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HER-2/neu gene copy quantified by real-time PCR and serum HER-2/neu by Elisa assay: comparison with fluorescence in situ hybridization and immunohistochemistry

C. Tse[1], D. Brault[1], J. Gligorov[2], M. Antoine[3], K. Lelay[4], J.P. Lotz[2]. *HER.ME.S trialist's group, Délégation Recherche Clinique.* [1]*Hôpital Tenon, Biochemistry, Paris, France;* [2]*Hôpital Tenon, Oncology, Paris, France;* [3]*Hôpital Tenon, Pathology, Paris, France;* [4]*REES, Paris, France*

Background: HER2 transmembranous receptor expression is commonly evaluated at the timepoint of surgery on the biopsy material by Immuno Histo Chemistry (IHC) with a good correlation to FISH testing (considered the 'gold standard'). HER2 overexpression is not only a prognostic factor in breast cancer but also a predictive factor of anti HER2 targeted therapy. HER2 extra-cellular domain (ECD) can be shedded into the blood and therefore measured during the whole timeperiod of the disease. A high level of ECD appears to be correlated to HER2 expression and may be interesting in the follow-up of treated patients. ECD level and quantification of HER-2 gene amplification by real time PCR is a new approach not yet compared together with FISH and IHC.

HERMES study is a multicentric French pharmacoeconomic study evaluating impact of trastuzumab treatment in metastatic HER2 overexpressed breast cancer and evaluating different method of early prediction of clinical response to this treatment. All patients included on this study had initial IHC, FISH, ECD and HER2 gene amplification by real time PCR. We compare the results of these different techniques.

Methods: The population (n=60) is represented by the patients included in HERMES study.

Amplification of HER-2 gene was analysed in situ by FISH. FISH was performed with the *Ventana Benchmark ISH system*. In situ protein overexpression was determined by IHC. IHC was performed on paraffin embedded samples with *Ventana Nexes* automates and the A485 antibody (*Dako, Glostrup, Denmark*). Immunostaining was scored according to the Herceptest scoring system. Amplification after DNA extraction tissue sample from embedded paraffin block was performed by real time PCR on *Light Cycler®* engine with LC-HER/neu quantification kit (*ref 3113922 Roche*). IHC and FISH are centralized and carried out by 2 pathologists from paraffin embedded tissue sample.

To measure ECD, sera were collected within one day before initiation of treatment and performed by an enzyme-linked immunosorbent assay (*Human HER-2/neu Quantitative Elisa – Oncogene Science/Bayer ref OSDI-10*).

Results: Preliminary results show a statistically strong correlation between the 4 techniques evaluating HER2 expression (IHC, FISH, Elisa assay and HER2 realtimePCR). These results are under validation considering the overall population of the HERMES study.

Conclusions: Considering these results, HER2 status could be evaluated by different techniques presenting different advantages. In a daily practice, techniques on primary tumour (IHC, FISH or realtimePCR) could represent a 'standard'. The realtimePCR could be an alternative technique to FISH considering specificity results, simplicity of the technique, rapidity of the results and economical point of view (cheaper technique).

ECD explore not only the HER2 status at metastatic time but also could help for predicting the impact of antiHER2 therapies during the treatment.

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The number of resected axillary lymph nodes (ALN) influences the risk for axillary recurrences in node-positive, but not in node-negative patients

W. Thieleke, W. Janni, B. Rack, B. Strobl, D. Riosk, H. Sommer, B. Gerber, K. Friese. *University Hospital, Ludwig-Maximilians University, Department of Gynecology and Obstetrics, Munic, Germany*

Background: Based on broad evidence, the 'International Consensus Conference, Primary Therapy of Early Breast Cancer' St. Gallen 2003 established sentinel lymph node excision as sufficient surgical procedure in the axilla of node-negative breast cancer patients. However, there is little data available, whether the excision of a low number of ALN increases the risk for axillary recurrences, compared to systematic axillary dissection.

Material and Methods: By multivariate analysis of 3800 pts. treated for early breast cancer UICC stage I–III, we investigated the prognostic relevance of the number of resected ALN for axillary recurrences in patients with and without evidence of axillary lymph node metastases. Pts. with carcinoma in situ, distant metastases at time of presentation, primary systemic therapy, unknown hormone receptor status or histopathological grading were excluded. Data were contemporaneously collected and pts. were followed for a mean of 72 months.

Results: Axillary recurrences as sole manifestation site of recurrence occurred in 67 pts (1.7%). In node negative patients (n=2667), multivariate analysis, allowing for number of removed ALN, histopathological grading, tumor size and hormone receptor status, revealed only grading (P=0.04,