

Lapatinib and trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormone receptor-positive breast cancer which over-expresses human epidermal growth factor 2 (HER2): a systematic review and economic analysis

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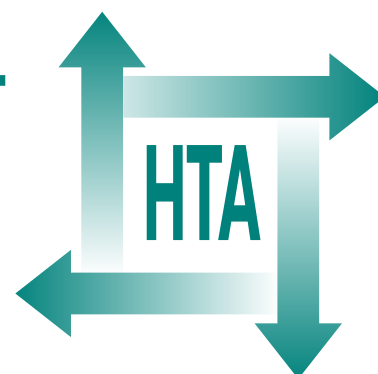


Executive summary

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Executive summary

Background

Breast cancer is the uncontrolled, abnormal growth of malignant breast tissue affecting predominantly women. Metastatic breast cancer (mBC) is an advanced stage of the disease when the disease has spread beyond the original organ.

Hormone receptor status and human epidermal growth factor 2 (HER2) status are two predictive factors that are taken into consideration when estimating the prognosis of patients with breast cancer. Tumours that express either oestrogen receptor-positive (ER+) or progesterone receptor-positive (PgR+) are commonly referred to as being hormone receptor positive (HR+), and patients with HR+ breast cancer generally have an improved prognosis compared with those who are hormone receptor negative (HR-). More recently, it has been discovered that over-expression of ErbB2 protein (also known as HER2), which is a member of the epidermal growth factor receptor family, and/or amplification of the *HER2* gene results in an abnormally high number of *HER2* genes per cancer cell, which results in cancer cells growing and dividing more quickly. Thus, human epidermal growth factor 2-positive (HER2+) breast cancer is considered to be an aggressive disease and there is growing evidence that the prognosis of HER2+ patients is generally poor, whether or not they are HR+ or HR-.

The aim of current treatments for mBC is to palliate symptoms, prolong survival and maintain a good quality of life with minimal adverse events (AEs). Trastuzumab (TRA) (Herceptin®, Roche) is commonly given in combination with chemotherapy [paclitaxel or docetaxel (Taxotere®, Sanofi-Aventis)] for patients with HR+/HER2+ mBC. Data on the number of women with HR+/HER2+ mBC are not routinely collected, but the number of patients estimated to be suitable for treatment with either lapatinib (LAP) (Tyverb®, GlaxoSmithKline) or TRA in combination with an aromatase inhibitor (AI) has been estimated to be relatively small (under 200 patients per year).

Objectives

The remit of this appraisal is to review the clinical effectiveness and cost-effectiveness evidence base for LAP in combination with an AI (LAP + AI) and TRA in combination with an AI (TRA + AI) within their licensed indications for the first-line treatment of patients who have HR+/HER2+ mBC.

Methods

Evidence for clinical effectiveness of LAP + AI and TRA + AI for the first-line treatment of HR+/HER2+ mBC was assessed by conducting a systematic review of published research evidence. The review was undertaken following the general principles published by the Centre for Reviews and Dissemination's (CRD's) guidance for undertaking reviews in health care.

Randomised controlled trials (RCTs) were identified by searching major electronic medical databases including MEDLINE, EMBASE and the Cochrane Library. Two reviewers independently screened all titles and abstracts. Data were extracted by one reviewer using a standardised data extraction form and checked independently by a second reviewer. The quality

of the individual clinical effectiveness studies was assessed independently by two reviewers according to criteria based on the CRD's guidance for undertaking reviews in health care.

It was intended by the Assessment Group (AG) that meta-analyses would be conducted in which direct evidence would be pooled using a standard meta-analysis and, where a direct comparison between LAP + AI and TRA + AI was not possible, by indirect comparisons. However, the AG considered it inappropriate to conduct either of the analyses, as discussed further below.

Results

Assessment of clinical effectiveness

Quantity and quality of research available

A total of 2069 references were identified, of which two trials [the efficacy and safety of lapatinib combined with letrozole (EGF30008) trial and the efficacy and safety of trastuzumab combined with anastrozole (TAnDEM) trial] met the inclusion criteria. A further trial [efficacy and safety of letrozole combined with trastuzumab (eLEcTRA) trial], which was halted prematurely and reported only as a conference abstract, was also included following information passed on to the AG by Roche at the National Institute for Health and Clinical Excellence (NICE) consultation meeting in February 2010.

Overall, the risk of bias assessment conducted by the AG found the EGF30008 and the TAnDEM to be of a good standard. The eLEcTRA was deemed to be of poorer quality, which may be a reflection of poor-quality reporting rather than trial design as this trial was published as an abstract.

A much greater proportion of patients in the EGF30008 trial received second-line chemotherapy than in the TAnDEM trial. The EGF30008 trial also explicitly excluded patients with extensive symptomatic visceral disease and patients in which the disease was considered by the investigator to be rapidly progressing or life-threatening; this was not an explicit exclusion criteria of the other two trials.

Assessment of effectiveness

All of the three main trials examining the efficacy of LAP + letrozole (LET) (Femara[®], Novartis) (EGF30008 trial), TRA + anastrozole (ANA) (Arimidex[®], AstraZeneca) (TAnDEM trial) and TRA + LET (eLEcTRA trial) suggest that LAP + AI or TRA + AI result in improved outcomes when compared with AIs alone (LET, ANA and LET, respectively). Although these differences were not significant for overall survival (OS), significantly different outcomes were reported for progression-free survival (PFS)/time-to-treatment progression (TTP) in the EGF30008 and the TAnDEM trials. Large differences were also reported in the eLEcTRA trial. Both overall response rate and clinical benefit rate appeared to be improved for patients taking LAP + AI or TRA + AI in all three trials. An interesting finding from EGF30008 and eLEcTRA was that AIs alone appeared to be less effective in the HR+/HER2+ population than in the HR+/HER2- population.

Although both AEs and SAEs were more common in the LAP + LET and TRA + AI groups than in those treated with AIs alone, no new safety concerns were identified from the trials. For LAP + LET, the most significant AE was diarrhoea, experienced by around two-thirds of all patients. The majority of cases of AEs (including diarrhoea) were of grade 1 or 2 severity. For TRA + ANA patients, the most frequently reported AEs were fatigue, diarrhoea and vomiting, experienced by around one-fifth of all patients, of which the majority were grade 1 or 2 severity. Fatigue was also a problem for around one-quarter of patients who received TRA + LET, but

infections, gastrointestinal disorders and musculoskeletal and connective tissue disorders were even more common.

As direct comparison across trials would be too crude and simplistic, both manufacturers conducted adjusted indirect comparisons. However, the AG believed indirect comparisons were not appropriate because the patient populations were not sufficiently similar in the EGF30008 and the TAnDEM trials. The AG reached this conclusion when examining median OS in the AI arms, which was reported to be ≤ 23.9 months (unadjusted intention-to-treat population) or 28.6 months (centrally confirmed hormone receptor status) in the TAnDEM trial compared with 32.3 months in the EGF30008 trial. If it is assumed that LET and ANA are equally effective (as NICE guidance on early breast cancer suggests), then a similar median OS would be expected in the LET and ANA arms if the populations were sufficiently similar. Thus, it was felt that any comparisons made across trials would not be reliable and, hence, the AG focused on within-trial comparisons.

Assessment of cost-effectiveness

Cost-effectiveness review

The AG did not identify any relevant papers for inclusion in the cost-effectiveness review. A poster presented at the American Society of Clinical Oncology 2010 conference, comparing LAP + LET versus TRA + ANA based on an indirect comparisons analysis, was identified by Roche. Aside from the concerns with conducting indirect comparisons highlighted by the AG above, it is difficult to comment on the reliability of the cost-effectiveness results presented in this poster without access to more detailed information on costs.

Submitted economic evaluations by manufacturers

The two economic evaluations submitted by the manufacturers appear to meet the NICE reference case criteria. However, the AG is critical of the projective modelling approaches used by the manufacturers in this group of patients, which it believes can lead to substantial bias in OS estimates. In addition, the AG also identified several costing inaccuracies and inconsistencies in both of the economic evaluations submitted.

For the direct comparisons, GlaxoSmithKline demonstrated that LAP + LET is not cost-effective compared with LET and Roche demonstrated that TRA + ANA is not cost-effective compared with ANA.

Both of the manufacturers undertook indirect comparisons analyses in order to be able to compare LAP + LET versus TRA + ANA. For reasons outlined above, the AG believes that the indirect comparisons analyses conducted by the manufacturers are unreliable.

Roche makes the case for TRA + ANA to be considered as an end-of-life treatment for women with HR+/HER2+ mBC. The AG does not have sufficient information to verify whether or not all three NICE criteria for consideration of end-of-life treatments are met.

Assessment Group's cost-effectiveness results and sensitivity analysis

The AG reports the results of two separate de novo cost-effectiveness analyses using a common framework and common parameter values, but employing effectiveness data drawn only from a single RCT (either the EGF30008 or the TAnDEM trial). The AG model has employed outcome data derived from the relevant clinical trial in the form of Kaplan–Meier estimated survival values augmented by projected survival estimates calibrated against the observed data. The AG used PFS and post-progression survival estimates directly as the basis for calculating expected OS in each group of the RCT.

As the AG is of the opinion that the evidence base is too unstable to allow meaningful comparison of LAP + LET versus TRA + ANA, the only questions that may be addressed legitimately are:

- Can LAP + LET be considered a cost-effective treatment compared with LET alone?
- Can TRA + ANA be considered a cost-effective treatment compared with ANA alone?

Base-case result: lapatinib in combination with letrozole versus letrozole alone

The AG concludes that in HR+/HER2+ women with mBC, LAP + LET compared with LET is not cost-effective. Using a time horizon of 20 years, the AG estimates an incremental cost-effectiveness ratio (ICER) that exceeds £225,000 per quality-adjusted life-year (QALY) gained for the comparison of LAP + LET versus LET; the incremental total costs and QALYs per patient treated are estimated as £26,150 and 0.116, respectively.

Base-case result: trastuzumab in combination with anastrozole versus anastrozole alone

The AG concludes that in HR+/HER2+ women with mBC, TRA + ANA compared with ANA is not cost-effective. Using a time horizon of 20 years, the AG estimates an ICER that exceeds £69,000 per QALY gained for the comparison of TRA + ANA versus ANA; the incremental total costs and QALYs per patient treated are estimated as £37,899 and 0.545, respectively.

Lapatinib in combination with aromatase inhibitor versus trastuzumab in combination with aromatase inhibitor

The AG emphasises, again, that the currently available clinical evidence base is too unstable to allow meaningful comparison of LAP + AI versus TRA + AI.

Sensitivity analyses undertaken by the Assessment Group

For the comparison of LAP + LET versus LET, the univariate sensitivity analysis shows that the ICER is most sensitive to the choice of health-state utility parameter values, the cost of LAP and is insensitive to most of the other variables. In all cases, the ICER remains >£148,000 per QALY gained. The probabilistic sensitivity analysis (PSA) shows that the probability of LAP + LET being cost-effective is 0.1% at a willingness-to-pay threshold of £50,000 per QALY gained; to achieve a 50% probability of LAP + LET being cost-effective, the willingness-to-pay threshold needs to increase to around £231,000 per QALY gained.

For the comparison of TRA + ANA versus ANA, the univariate sensitivity analysis shows that the ICER is most sensitive to the choice of health-state utility parameter values, the cost of TRA and discounting rates only. In all cases, the ICER exceeds £58,000 per QALY gained. The PSA shows that there is no measurable probability of TRA + ANA being cost-effective compared with ANA at a willingness-to-pay threshold of £40,000.

Discussion

Strengths and limitations of the analyses and uncertainties

Only three RCTs have been identified, which present head-to-head comparisons of the interventions of interest to this appraisal. It was not possible to compare the data across the trials because of differences in the patient populations. However, each individual trial suggests a benefit in terms of PFS/TTP for LAP + LET, TRA + ANA and TRA + LET compared with LET, ANA and LET alone, respectively. Furthermore, the EGF30008 and the eLEcTRA trials suggest that LET alone is less effective in the HR+/HER2+ population than in the HR+/HER2- population.

From a health economics perspective, the AG agrees with both manufacturers that LAP + LET and TRA + ANA are not cost-effective compared with AIs alone for women with HR+/HER2+mBC. The ICERs estimated by the AG for LAP + LET versus LET and TRA + ANA versus ANA are higher than those estimated by the manufacturers. The AG did not address the cost-effectiveness of LAP + LET versus TRA + ANA as there were insufficient comparative clinical data available to allow estimation of meaningful ICERs.

Generalisability of the findings

None of the patients in the EGF30008 or the TAnDEM trial received prior treatment with TRA. This is not surprising as, at the time the trials were recruiting, the use of TRA for patients with early or advanced breast cancer was relatively rare. This contrasts greatly with what is increasingly happening in clinical practice today for a patient diagnosed with early HER2+ breast cancer, where TRA is the standard treatment of choice. Thus, in reality, typically only de novo patients with HR+/HER2+ mBC will be eligible for TRA + AI, as per the wording of the recently awarded European Medicines Agency licence. Patients who have been treated with TRA previously are eligible for treatment with LAP + AI; however, it is uncertain whether or not the clinical effectiveness of LAP + AI is the same for patients who are and who are not TRA naive.

Conclusions and research recommendations

Clinical effectiveness evidence demonstrates that LAP + LET, TRA + ANA or TRA + LET improves median PFS/TTP compared with AI monotherapy in patients with HR+/HER2+ mBC; LET also appears to be less effective in patients with HR+/HER2+ mBC than in those with HR+/HER2- mBC. To date, the trials do not show a statistically significant benefit in terms of OS for patients taking LAP + LET versus AI monotherapy or TRA + ANA versus AI monotherapy. However, the OS data in the HR+/HER2+ population of the EGF30008 trial had yet to reach maturity and no OS data were presented for eLEcTRA, presumably because this trial was halted prematurely. The results of the economic evaluations conducted by the manufacturers, and confirmed by the AG, demonstrate that LAP + LET is not cost-effective compared with AI monotherapy, nor is TRA + ANA cost-effective compared with AI monotherapy.

As a result of differences in the patient populations of the EGF30008 and the TAnDEM trials, the AG believes the indirect comparisons analyses conducted by the manufacturers are inappropriate and for the same reason chooses not to compare LAP + LET with TRA + ANA in an economic evaluation.

Given the uncertainties in the evidence base, the AG suggests that the following research priorities should be addressed (in order of priority).

1. Given that most patients who present for HR+/HER2+ mBC are now likely to have been previously treated with TRA for early breast cancer, further research may be required into treating mBC in the HR+/HER2+ population who are not TRA (or LAP) naive. It is noted by the AG that such a study (EGF114299) is planned by GlaxoSmithKline.
2. As trials are increasingly allowing patients to cross over following disease progression, attempts should be made to consider how to adjust for crossover at the trial design stage.
3. As the EGF30008 reports, there were large differences in PFS for HER2+ and HER2- patients receiving both LAP + LET and, in particular, LET. Further research may be warranted comparing the clinical effectiveness of AIs as monotherapy in patients with HER2+ and HER2- breast cancer.

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Publication

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NIHR Health Technology Assessment programme

The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

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Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

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