NICE National Institute for Health and Care Excellence

NICE guidance

Guidance on the use of trastuzumab for the treatment of advanced breast cancer

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Trastuzumab in combination with paclitaxel (combination trastuzumab is currently only licensed for use with paclitaxel) is recommended as an option for people with tumours expressing human epidermal growth factor receptor 2 (HER2) scored at levels of 3 or more who have not received chemotherapy for metastatic breast cancer and in whom anthracycline treatment is inappropriate.

1.2 Trastuzumab monotherapy is recommended as an option for people with tumours expressing HER2 scored at levels of 3 or more who have received at least 2 chemotherapy regimens for metastatic breast cancer. Prior chemotherapy must have included at least an anthracycline and a taxane where these treatments are appropriate. It should also have included hormonal therapy in suitable oestrogen receptor-positive patients.

1.3 HER2 levels should be scored using validated immunohistochemical techniques and in accordance with published guidelines. Laboratories offering tissue sample immunocytochemical or other predictive tests for therapy response should use validated standardised assay methods and participate in and demonstrate satisfactory performance in a recognised external quality assurance scheme.

2 Clinical need and practice

2.1 Approximately 32,000 new cases of breast cancer were reported in England and Wales in 1996. In 1998, breast cancer caused over 11,000 deaths in England and Wales and was the leading cause of death in women aged 35 to 54 years.

2.2 Advanced and metastatic breast cancer (MBC) are defined by clinical staging based on the tumour, node and metastasis staging system (stage III denotes locally advanced disease and stage IV indicates metastatic breast cancer).

2.3 Between 16% and 20% of women initially presenting with breast cancer have advanced disease with distant metastases and around 50% of those presenting with early or localised breast cancer will eventually develop MBC.

2.4 Some breast tumours contain an amplification of the human epidermal growth factor receptor (HER2), which causes overexpression of the HER2 protein and is associated with a poorer prognosis. Approximately 15% to 20% of people with MBC overexpress HER2 at level 3 or more, measured by immunohistochemical techniques. The average period of survival after diagnosis of MBC is 18 to 24 months, but this is reduced by up to 50% for patients overexpressing HER2.

2.5 First-line systemic therapy for advanced or metastatic breast cancer is chemotherapy for oestrogen receptor-negative patients (usually an anthracycline-containing regimen or sometimes a combination of cyclophosphamide, methotrexate and fluorouracil), and hormone manipulation therapy for oestrogen receptor-positive patients. However, the choice of therapy is influenced by the rate of progression and distribution of disease and by whether the drugs have already been administered as adjuvant therapies.

2.6 Current NICE guidance states that docetaxel and paclitaxel should be available for the treatment of advanced breast cancer where initial cytotoxic chemotherapy (including an anthracycline) has failed or is inappropriate.

3 The technology

3.1 Trastuzumab is a recombinant humanised monoclonal antibody that specifically targets the HER2 protein. It is licensed for 2 indications for the treatment of MBC overexpressing HER2 at level 3 or more. Firstly, it is licensed in combination with paclitaxel for patients with MBC who have not received chemotherapy for metastatic disease and in whom an anthracycline is unsuitable. Secondly, it is licensed as a monotherapy for patients who have received at least 2 chemotherapy regimens for MBC; prior chemotherapy must have included at least an anthracycline and a taxane, unless these treatments are inappropriate; patients who are oestrogen receptor-positive must also have failed to respond to appropriate hormonal therapy.

3.2 Trastuzumab is administered intravenously. Following an initial loading dose of 4 mg per kg body weight, patients receive a weekly dose of 2 mg per kg body weight until disease progression. Side-effects associated with trastuzumab have been noted to include cardiotoxicity and infusion-related reactions.

3.3 The basic NHS price according to the British National Formulary (September 2001) for trastuzumab is £407 per 150 mg vial. For a typical patient, a 38-week course of combination therapy costs approximately £15,500 for trastuzumab and £9,600 for paclitaxel. The cost of a 12-week course of treatment with trastuzumab monotherapy is approximately £5,300.

3.4 There are costs of testing a woman's suitability for treatment and of monitoring in addition to the cost of administering treatment. HER2 levels must be assessed in patients who are potentially eligible for treatment with trastuzumab, and patients receiving trastuzumab should have left ventricular ejection fraction measured before and during treatment.

4 Evidence

4.1 Clinical effectiveness

Combination therapy

4.1.1 One randomised controlled trial (RCT) (n=469) of first-line trastuzumab combination therapy was available. All individuals had HER2 overexpression at least at level 2 or more. Patients who had not previously received anthracyclines were randomised to an anthracycline in combination with cyclophosphamide with or without trastuzumab. Patients who had previously received an anthracycline as adjuvant therapy (n=188) were randomised to paclitaxel (n=96) or paclitaxel plus trastuzumab (n=92). The primary endpoint was time to progression and the median duration of follow-up was 30 (range 30 to 51) months. Patients in all arms of the trial were given the option of receiving trastuzumab monotherapy at the time of disease progression, meaning that allocation to this further treatment was non-random.

4.1.2 When only the 2 relevant treatment arms involving paclitaxel were considered, there was no significant difference in overall survival between the group treated with trastuzumab plus paclitaxel and the group treated with paclitaxel alone (22 vs 18 months, p=0.17). However, the addition of trastuzumab resulted in longer median times to disease progression (7 vs 3 months, p<0.001), duration of response (11 vs 5 months, p<0.01) and time to treatment failure (6 vs 3 months, p<0.001). There was no statistically significant difference between the 2 treatments in terms of complete response (relative risk [RR] 3.65, 95% CI 0.89 to 15.22), but overall tumour response (RR 2.48, 95% CI 1.49 to 4.12), disease progression (RR 0.38, 95% CI 0.27 to 0.53) and treatment failure (RR 0.46, 95% CI 0.33 to 0.63) favoured treatment with trastuzumab. For patients with HER2 level 3 or more, trastuzumab and paclitaxel was associated with a longer median survival than paclitaxel alone (25 vs 18 months, no p-value provided).

4.1.3 Quality of life, assessed using the pain and dyspnoea domains and the breast cancer module of the EORTC QLQ-C30 questionnaire, was higher in the group

receiving trastuzumab plus chemotherapy than in the group receiving chemotherapy alone.

4.1.4 The most important adverse event seen in the trial was cardiac dysfunction, which occurred in 27% of the group given an anthracycline, cyclophosphamide and trastuzumab, 8% of the group given an anthracycline and cyclophosphamide alone, 13% of the group given paclitaxel and trastuzumab, and 1% of the group given paclitaxel alone. The cardiotoxicity was potentially severe, and in some cases life threatening, but the symptoms were reported generally to improve with standard medical management.

4.1.5 Although not originally observed during clinical trials, serious infusion-related reactions have been reported in 74 from a total of approximately 25,000 patients who received trastuzumab, with the reactions leading to the death of 15 patients. These reactions, which include anaphylaxis and severe dyspnoea, usually occur within 24 hours of the infusion, although delayed reactions have also been reported. Allergic or hypersensitivity reactions, haematological toxicity, hepatic and renal toxicity, diarrhoea and an increased risk of infections have also been noted.

Monotherapy

4.1.6 No comparative RCTs of trastuzumab monotherapy (versus systemic therapy without trastuzumab) were available. Of the studies that were identified, 2 were case-series of trastuzumab (H0551g, n=46; H0649g, n=222) and 1 was an RCT of trastuzumab monotherapy, which was concerned with an unlicensed indication and was essentially a dose ranging study (H0650g, n=113). Women in H0650g received first-line monotherapy with trastuzumab, which is an unlicensed indication.

4.1.7 In H0649g, 4% of women experienced a complete response to treatment and 12% experienced a partial response. The overall response rate was 15%. Smaller proportions of women responded to treatment in study H0551g.

4.1.8 The median duration of survival in H0649g was 13 months for all women and 16 months in a sub-group analysis of women overexpressing HER2 at levels of 3 or

more. In the manufacturer's submission, survival reported in H0649g was indirectly compared with survival reported in 2 RCTs of vinorelbine monotherapy. Both RCTs contained a treatment arm consisting of vinorelbine monotherapy as second-line or salvage therapy for MBC. In 1 of these RCTs, 91% of participants had received prior treatment with anthracyclines for advanced breast cancer. The median duration of survival for people receiving vinorelbine monotherapy was 8 months. The reported median duration of survival in the other study was 10 months. Participants in these 2 RCTs were not selected on the basis of their HER2 status, which may suggest that their prognosis was better than those in H0649g.

4.1.9 The manufacturer also submitted evidence from the Imperial Cancer Research Fund database at Guy's and St Thomas' Hospital NHS Trust on patients who had received third-line chemotherapy for MBC and who were not treated on the basis of their HER2 expression status. Analysis of these data showed that the median survival for these patients was 6.3 months.

4.1.10 Trastuzumab monotherapy appeared to have a relatively low toxicity level. For study H0649g, the common adverse events (occurring in approximately 40% of people) were infusion-related fever and/or chills that usually occurred only during the first infusion. The most clinically significant adverse event was cardiac dysfunction, which occurred in 10 people (5%). However, only 1% of participants in this study discontinued treatment because of treatment-related adverse events. In study H0551g, toxicity was reported as minimal, although 2 patients died as a result of cardiac dysfunction. In study H0650g, the adverse events recorded were mainly mild to moderate in nature and were mostly associated with the higher dose regimen; only 1 person experienced cardiac dysfunction.

4.2 Cost-effectiveness

Combination therapy

4.2.1 The manufacturer evaluated the cost-effectiveness of trastuzumab in combination with paclitaxel versus paclitaxel alone for patients with HER2 level 3 or more, based on results from the RCT. Estimates of direct medical and social

care costs were included in the evaluation, including the costs of HER2 testing (£21 for a single test) and cardiac testing (£520 to £640 for 4 tests).

4.2.2 The manufacturer estimated the incremental cost-effectiveness ratio to be £37,500 per quality-adjusted life-year (QALY) gained (and substantially less per life-year gained). This survival benefit used to estimate the QALY gain was based on a weighting of case-mix reflecting the selection of patients in the pivotal trial who, after the trial, crossed over to trastuzumab monotherapy. After extrapolating the trial results for this selection of patients, approximately 10 months' mean survival advantage was imputed into the economic evaluation. A number of other sources, in particular 2 non-controlled studies that examined the use of taxane monotherapy as first-line treatment for metastatic breast cancer, suggest a survival advantage of combination therapy compatible, or even better, than this.

Monotherapy

4.2.3 One economic evaluation of monotherapy comparing trastuzumab with vinorelbine monotherapy was available to the committee. Direct information relating to clinical effectiveness was unavailable (as there were no RCTs of trastuzumab other than a dose ranging study). Health outcomes were expressed in terms of life years and QALY by extrapolating survival from non-controlled studies. Direct medical and social care costs were included in the evaluation. Information on clinical effectiveness was imputed from H0649g and an RCT of vinorelbine versus melphalan that contained patients who were at an earlier stage of the disease and who were not selected on the basis of HER2 expression status. Patients who received vinorelbine in the RCT survived for approximately a median of 8 months. The manufacturer referenced 2 other non-controlled studies in an attempt to validate this period of survival for patients receiving vinorelbine. One of these studies examined median survival in patients at a similar disease stage who received vinorelbine monotherapy; in this study, median survival was approximately 6 months.

4.2.4 The estimated incremental cost-effectiveness ratio was approximately £7,500 per life-year gained if trastuzumab was used instead of vinorelbine, when it was assumed that the additional survival attributable to trastuzumab monotherapy

was 8 months. The manufacturers also provided a cost per QALY of approximately £19,000 by assuming that the 8 months of additional survival was equivalent to 2.6 quality-adjusted months.

4.3 Considerations

Combination therapy

4.3.1 The appraisal committee considered that a survival gain of approximately 10 months used in the economic evaluation was likely to be an underestimate of the true survival gain attributable to combination therapy given that patients in the non-controlled studies of taxane monotherapy were not HER2 selected. The appraisal committee also concluded that the utility weights used to adjust survival for changes in quality of life were low.

4.3.2 Based on these factors, the appraisal committee believed that trastuzumab combination therapy was likely to be lower than the estimate of £37,500 per QALY gained provided by the manufacturer.

4.3.3 The appraisal committee also noted that improvements in survival of this magnitude due to therapeutic intervention have rarely been recorded in women with metastatic breast cancer.

Monotherapy

4.3.4 The evidence for the effectiveness of trastuzumab monotherapy was limited to 2 case-series and 1 RCT, which was concerned with an unlicensed indication and was essentially a dose ranging study. The report for the first case-series (H0551g) did not state the line of therapy being assessed or the length of follow-up. The second case-series (H0649g), which was relatively well reported, suggested that in terms of response rate trastuzumab monotherapy was an effective treatment in patients with MBC and HER2 overexpression at levels 3 or more.

4.3.5 Although the appraisal committee had some reservations about the quality and robustness of the economic evaluation for trastuzumab monotherapy, as survival was not based on results from controlled studies, it was believed that these misgivings would not increase the ratio sufficiently to suggest that it is not cost-effective.

5 Implications for the NHS

5.1 Patients who receive treatment with trastuzumab should be monitored for the possibility of cardiotoxicity.

5.2 The manufacturer estimated the gross impact of providing trastuzumab plus paclitaxel instead of paclitaxel alone and trastuzumab monotherapy to be approximately £17 million per annum. This estimate is based on the following assumptions: HER2 status is assessed in 20,000 patients with metastatic disease at a cost of £21 per test; 1,600 patients receive monotherapy at a cost of £5,300 per person; 450 patients receive combination therapy costing an additional £15,500 to provide trastuzumab and paclitaxel instead of paclitaxel alone; each person receives 4 cardiac tests at a cost of £580 for each set of 4 tests. (Overall calculation: [20,000 multiplied by £21] plus [1,600 multiplied by £5,300] plus [450 multiplied by £15,500] plus [1,600 multiplied by £580].)

6 Further research

6.1 Information linking side-effects associated with treatments with quality of life would enhance the comprehensiveness of future economic evaluations of treatments for advanced breast cancer.

7 Implementation

7.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

7.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

7.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has advanced breast cancer and the doctor responsible for their care thinks that trastuzumab is the right treatment, it should be available for use, in line with NICE's recommendations.

7.4 Clinicians with responsibility for treating women with breast cancer should review their current practice in the light of the guidance set out in section 1.

7.5 Local clinical guidelines and protocols for the management of women with breast cancer should be reviewed in the light of this guidance.

7.6 It is likely that the rate of HER2 testing will increase as a result of this guidance. The suitability of current service provision for HER2 testing should be reviewed in the light of the guidance set out in section 1.3.

7.7 Prospective clinical audit programmes should record the proportion of treatments adhering to this guidance. Such programmes are likely to be more effective in improving patient care when they form part of the organisation's formal clinical governance arrangements and where they are linked to specific post-graduate activities.

Appendix A: Appraisal committee members

The appraisal committee is a statutory committee whose members sit for 3 years. Two meetings are held per month and the majority of members attend one or the other. Declared interests may also exclude a member from individual technology appraisals. The committee are supplemented by technology specific experts as indicated in appendix B.

Professor R. L. Akehurst
Dean, School of Health Related Research Sheffield University

Professor David Barnett (Chairman)
Professor of Clinical Pharmacology University of Leicester

Professor Sir Colin Berry
Professor of Morbid Anatomy St Bartholomew's and Royal London School of Medicine

Dr Sheila Bird
MRC Biostatistics Unit, Cambridge

Professor Martin Buxton
Director of Health Economics Research Group Brunel University

Dr Karl Claxton
Lecturer in Economics University of York

Professor Sarah Cowley
Professor of Community Practice Development Kings College, London

Professor Nicky Cullum
Reader in Health Studies Department of Health Sciences University of York

Mr Chris Evennett
Chief Executive Mid-Hampshire Primary Care Group

Professor Terry Feest

Clinical Director and Consultant Nephrologist Richard Bright Renal Unit and Chairman of the UK Renal Registry

Ms Jean Gaffin
Formerly Executive Director National Council for Hospice and Specialist Palliative Care Service

Mrs Sue Gallagher
Chief Executive Merton, Sutton and Wandsworth Health Authority

Dr Trevor Gibbs
Head, Global Clinical Safety & Pharmacovigilance GlaxoSmithKline

Mr John Goulston
Director of Finance The Royal Free Hampstead NHS Trust

Professor Philip Home
Professor of Diabetes Medicine University of Newcastle

Dr Terry John
General Practitioner The Firs, London

Dr Diane Ketley
Research into Practice Programme Leader NHS Modernisation Agency

Dr Mayur Lakhani
General Practitioner, Highgate Surgery, Leicester and Lecturer, University of Leicester

Mr M Mughal
Consultant Surgeon Chorley and South Ribble NHS Trust

Mr James Partridge
Chief Executive Changing Faces

Professor Philip Routledge
Professor of Clinical Pharmacology University of Wales

Professor Andrew Stevens (Vice Chairman)

Professor of Public Health University of Birmingham

Dr Cathryn Thomas
General Practitioner Senior Lecturer Department of Primary Care and General Practice University of Birmingham

Appendix B: Sources of evidence

The following documentation and opinion was made available to the appraisal committee:

- Assessment report:
  - Prepared by The NHS Centre for Reviews and Dissemination: A rapid and systematic review of the clinical effectiveness and cost-effectiveness of trastuzumab and vinorelbine for breast cancer, February 2001
  - Prepared by The NHS Centre for Reviews and Dissemination: A rapid and systematic review of the clinical effectiveness and cost-effectiveness of trastuzumab for breast cancer, October 2001
- Manufacturer/sponsor submissions:
  - Roche
- Professional/specialist group submissions from:
  - British Psychosocial Oncology Society
  - Imperial Cancer Research Fund
  - MRC Clinical Trials Unit
  - National Cancer Research Institute
  - Royal College of General Practitioners
  - Royal College of Pathologists
  - Royal College of Physicians
- Patient group submissions from:
  - Breakthrough Breast Cancer, CancerBACUP and the UK Breast Cancer Coalition joint submission
  - Breast Cancer Care
  - Macmillan Cancer Relief

- Other group submissions from:
  - Department of Health
  - National Assembly for Wales
- External expert and patient advocate submissions from:
  - Professor Robert Coleman, Professor of Medical Oncology, Cancer Research Centre,Weston Park Hospital, University of Sheffield
  - Bernie Gardiner, Information Nurse Specialist, Breast Cancer Care
  - Margaret King, Vice Chair, UK Breast Cancer Coalition.

Appendix C: Guidance on the use of trastuzumab for the treatment of advanced breast cancer (patient information)

A summary of this guidance for patients and carers can be found on our website.

Update information

Minor changes since publication

March 2014: The implementation section was updated to clarify that trastuzumab is recommended as an option for treating advanced breast cancer. Additional minor maintenance update was also carried out.

March 2012: Minor maintenance.

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