
A. This protocol is provisional and subject to change

B. Details of review team

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C. Full title of research question
A rapid and systematic review of the clinical effectiveness and cost effectiveness of capecitabine (Xeloda® Roche) for metastatic breast cancer.

D. Clarification of research question and scope
This review will examine the clinical effectiveness and cost effectiveness of oral capecitabine (Xeloda® Roche) for metastatic breast cancer in relation to its licensed indications. At the time of preparing this protocol the use of capecitabine for the treatment of advanced breast cancer is awaiting approval from the Medicines Control Agency. This protocol is based on licensing information received from Roche, therefore, any changes to the licensing information may have consequences for this protocol. All studies where capecitabine is used alone or in combination with docetaxel, to treat patients who have failed anthracycline-containing regimens will be included. Only studies comparing capecitabine, used alone or in combination with docetaxel, to taxane monotherapy (paclitaxel or docetaxel), vinorelbine or best supportive care, will be considered in the assessment of clinical effectiveness. The assessment of cost-effectiveness will include consideration of all available full economic evaluations.

E. Report Methods
Search strategy
The following databases will be searched for relevant published literature (details of the search strategy are given in Appendix 1):

- BIOSIS
- CancerLit
- CCTR (Cochrane Controlled Trials Register)
- CDSR (Cochrane Database of Systematic Reviews)
- CINAHL (Cumulative Index for Nursing and Allied Health Literature)
- DARE (Database of Abstracts of Reviews of Effectiveness)
- EMBASE
- Health Technology Assessment (HTA) database
- HealthStar
- ISTP (Index to Scientific & Technical Proceedings)
- MEDLINE
- NHS EED (NHS Economic Evaluation Database)
- Science Citation Index
- OHE Health Economic Evaluations Database

Research groups identified through searches of the registers listed below will be contacted for information about ongoing trials:

- National Research Register
- Cochrane Library CD-ROM
- UKCCCR Register (http://www.cto.mrc.ac.uk/ukcccr/text_only/search.html)
- National Cancer Institute (http://cancernet.nci.nih.gov/trialsrch.shtml)
- National Institute of Health (http://clinicaltrials.gov/ct/gui/c/r)
- CenterWatch Clinical Trials Listing Service (http://www.centerwatch.com/main.htm)
- Current Controlled Trials (CCT) (http://www.controlled-trials.com/)
- American Society of Clinical Oncology (ASCO) (http://www.asco.org/)
- National Cancer Institute of Canada (NCIC) (http://www.ctg.queensu.ca/)
Inclusion and exclusion criteria

Two reviewers will independently screen all titles and abstracts. Full paper manuscripts of any titles/abstracts, which may be relevant, will be obtained where possible and the relevance of each study assessed according to the criteria below. Studies, which do not meet all of the criteria, will be excluded and their bibliographic details listed with the reason for exclusion. Any discrepancies will be resolved by consensus and if necessary a third reviewer will be consulted.

a. Study design

The following study designs will be included:

- Randomised controlled trials (RCTs) comparing capecitabine in combination with docetaxel, or capecitabine as monotherapy, to taxane monotherapy (paclitaxel or docetaxel), vinorelbine or best supportive care. The review will assess the best available evidence about the benefits and harms of capecitabine for making an informed decision about its use in the NHS. In the first instance this will involve randomised controlled trials, but if it is felt that studies using other designs, such as well-performed comparative observational studies, would add usable information these will be included. This process of including studies of ever-weaker designs will be followed through until it has been demonstrated that going further does not add any usable information.

- Full economic evaluations that compare two or more options and consider both costs and consequences; including cost-effectiveness, cost-utility and cost-benefit analyses.

b. Interventions

Oral capecitabine (Xeloda® Roche) as second or subsequent line therapy used alone or in combination with docetaxel as part of the following stages of treatment will be included:

- In combination with docetaxel for patients who have failed anthracycline-containing chemotherapy regimens.

- As monotherapy for patients who have failed taxanes and anthracycline-containing chemotherapy regimens or for whom further anthracycline therapy is not indicated, e.g. patients who have received cumulative doses of 400 mg/m² of doxorubicin or doxorubicin equivalents.

c. Participants

Women with metastatic breast cancer will be included. According to the UICC (International Union Against Cancer) staging system, metastatic breast cancer refers to stage IV (see Appendix 4).

d. Outcomes

Data on the following outcomes will be included:

- Overall survival

- Progression-free survival
• Tumour response (complete and partial)
• Time to treatment failure
• Adverse events/toxicity (diarrhoea, abdominal pain, nausea, vomiting, stomatitis, hand-foot syndrome (also known as hand-foot skin reaction or palmar-plantar erythrodysaesthesia), hyperbilirubinaemia, fatigue, anaemia, thrombocytopenia, dermatitis and any other adverse effects judged to be appropriate.)
• Quality of life
• Costs from all reported perspectives

If possible, patient preference and impact of using oral instead of intravenous treatment will also be assessed.

Data extraction strategy
Data relating to both study design and quality (see Appendix 2) will be extracted by one reviewer into an Access database and independently checked for accuracy by a second reviewer. Disagreements will be resolved through consensus and if necessary a third reviewer will be consulted. If time constraints allow attempts will be made to contact authors for missing data. Data from studies with multiple publications will be extracted and reported as a single study. Only data from English language studies will be included in the report. The bibliographic details of non-English language studies will be tabulated.

Quality assessment strategy
The quality of the individual studies will be assessed by one reviewer, and independently checked by a second, into an Access database. Disagreements will be resolved through consensus and if necessary a third reviewer will be consulted.

The quality of the clinical effectiveness studies will be assessed according to criteria based on NHS CRD Report No. 4\(^1\) (see Appendix 3A). The quality of the cost effectiveness studies will be assessed by one reviewer and checked by a second according to a checklist updated from that developed by Drummond et al\(^2\) (see Appendix 3B). This checklist will reflect the criteria for economic evaluation detailed in the methodological guidance developed by the National Institute for Clinical Excellence.\(^3\) This information will be tabulated and summarised within the text of the report.

Methods of analysis/synthesis
The results of the data extraction and quality assessment for each study of clinical effectiveness will be presented in structured tables and as a narrative summary. The possible effects of study quality on the effectiveness data and review findings will be discussed. Where sufficient data are available, treatment effects will be presented as relative risks (RR) for dichotomous data, weighted mean differences for continuous data or as hazard ratios where appropriate. Relative risks will be presented as Forest plots but only pooled when this is statistically and clinically meaningful. Heterogeneity between the included studies will be assessed by considering differences in (a) the study population, (b) intervention, (c) outcome measures, and (d) study quality. Studies will be grouped according to the comparator used. In addition, where pooling seems appropriate, \(\chi^2\) tests of heterogeneity will be performed. Where feasible, the possibility of publication bias will be investigated using funnel plots and Egger’s test.

Methods of analysis for economic studies
Details of each published economic evaluation, together with an assessment of study quality will be presented in structured tables.
As part of the assessment process the results of each study will be assigned, according to estimates of the incremental costs and effectiveness, to one of four categories corresponding to the quadrants of the cost-effectiveness plane (shown in Figure 1 below):

**Figure 1. Cost-effectiveness plane and quadrants**

- **Quadrant I.** Intervention increases costs and effectiveness. Incremental analysis required to assess cost-effectiveness compared with other interventions.
- **Quadrant II.** Intervention is dominated as it increases costs and reduces effectiveness.
- **Quadrant III.** Intervention reduces costs and effectiveness. Incremental analysis required.
- **Quadrant IV.** Intervention is dominant as costs are reduced and effectiveness increased.

This analysis does not address the uncertainty surrounding these estimates. To further aid the interpretation of the included studies, where appropriate and sufficient data are available, the underlying uncertainty will be assessed and presented by appropriate methods such as confidence intervals around incremental cost-effectiveness ratios or cost-effectiveness acceptability curves. These will be produced from either published analyses, Monte Carlo simulation, or per patient data on total costs and effects.

**F. Handling the company submission(s)**
All data submitted by the drug manufacturers will be considered if received by the review team no later than 12th July 2002. Data arriving after this date will only be considered if time constraints allow. If the data meet the inclusion criteria for the review then they will be extracted and quality assessed in accordance with the procedures outlined in this protocol. Any confidential information will be clearly underlined in the final report.

Any economic evaluations included in the company submission will be assessed. This will include a detailed analysis of the appropriateness of the parametric and structural assumptions involved in any models in the submission and an assessment of how robust the models are to changes in key assumptions. Following this analysis, if the original models are not sufficient modified versions of any models may be developed. Clarification on specific aspects of the model may be sought from the drug manufacturer.
G. Project Management
   a. Timetable/milestones
   Submission of draft protocol to NCCHTA: 15th April 2002
   Submission of final protocol to NCCHTA: 6th May 2002
   Receipt of company submissions: 12th July 2002
   Submission of progress report to NCCHTA: 19th July 2002
   Submission of draft final report to NCCHTA: 23rd September 2002

   b. Competing Interests
   None of the research team has any competing interests to declare. Any competing interests relating to the external reviewers will be declared in the final report.

   c. External reviewers
   The rapid review will be subject to external peer review by at least two experts. These reviewers will be chosen according to academic seniority and content expertise and will be agreed with NCCHTA. We recognise that methodological review will be undertaken by the NICE secretariat and Appraisal Committee, but if the rapid review encounters particularly challenging methodological issues we will organise independent methodological reviews. External expert reviewers will see a complete and near final draft of the rapid review and will understand that their role is part of external quality assurance. We will require peer reviewers to sign a copy of the NICE Confidentiality Acknowledgement and Undertaking form. We will return peer reviewers’ signed copies to NCCHTA. Comments from external reviewers and our responses to these will be made available to NCCHTA in strict confidence for editorial review and approval.

H. References


I. Appendices

Appendix 1: Details of the search strategy

The following search strategy will be used in MEDLINE and combined, where necessary, with search filters to identify appropriate study types. It will be adapted for use in the other databases searched.

capecitabine in ti,ab
xeloda in ti,ab
#1 or #2
"Breast-Neoplasms"/ all subheadings
(breast* near4 (cancer* or tum*r* or malignan*)) in ti,ab
(breast* near4 (oncolog* or carcinoma* or neoplas*)) in ti,ab
#4 or #5 or #6
#3 and #7

Full details of the searching process will be recorded.
Appendix 2 Details about data extraction
A. Clinical effectiveness data will be extracted and entered into an Access database under the following headings:

[ ] indicates a list of options included in a pull down box
( ) indicates a click on/off button, where on represents ‘yes’ and off ‘no’
{ } indicates free text entered in a box

Study Details
- Name of trial {trial name, I.D. or ‘not stated’}
- Endnote reference {endnote reference number}
- Primary source [database, handsearching, company submission]
- Author {i.e. Jones et al}
- Date {i.e. year of publication or date of interim data collection}
- Type of report [abstract, full manuscript, interim report]
- Type of study phase [phase II, phase III….., not stated]
- Comparison group included [placebo, alternative drug, unclear, not stated]
- Intervention 1 {i.e. drug(s) name(s)}
- Dose of intervention 1 {dose}
- Number of cycles of intervention 1 {number}
- Length per cycle of intervention 1 {length}
- Intervention 2 {i.e. drug(s) name(s)}
- Dose of intervention 2 {dose}
- Number of cycles of intervention 2 {number}
- Length per cycle of intervention 2 {length}
- Comments about interventions {summary of comments or ‘none’}

Participants
- Inclusion/exclusion criteria {summary of trial inclusion/exclusion criteria}
- Previous treatment {summary of drugs or other treatments such as debulking, radiotherapy etc…}
- Refractory disease present after first treatment [yes, no, unclear, not stated, not applicable]
- Dominant site of metastatic disease {state whether visceral or non-visceral, summary of numbers and specific site such as lung, liver etc…}
- Age or age range of participants {age(s)}
- Other participant characteristics {summary of characteristics including: treatment free interval, disease bulk, number of previous regimens, histology and performance status}
- Comments about participants {summary of comments or ‘none’}

Numbers in conditions
- Number recruited or accrued {summary or ‘not stated’}
- Length of follow-up after treatment finishes {summary or ‘not stated’}
- Number and times of follow-up measurements {summary or ‘not stated’}
- Attrition intervention 1 {summary of number involved and reasons for loss}
- Attrition intervention 2 {summary of number involved and reasons for loss}
- Per protocol analysis performed [yes, no, not stated, unclear]
- Comments {summary of comments or state ‘none’}
Results (data for all outcomes specified in the protocol will be entered in the following format)

- Outcome 1 {description of outcome measure}
- Intervention 1 baseline data {data for outcome 1}
- Intervention 2 baseline data {data for outcome 1}
- Intervention 1 follow-up data {data for outcome 1}
- Intervention 2 follow-up data {data for outcome 1}
- Comments on outcome 1 {summary of comments}
- Overall comments {summary of comments}

B. Economic evaluation data will be extracted and entered into an Access form under the following headings:

[] indicates a list of options included in a pull down box
( ) indicates a click on/off button, where on represents ‘yes’ and off ‘no’
{} indicates free text entered in a box

- Endnote reference {in the form of xyz, no ‘#’}
- Primary source [database, handsearching, company submission]
- Author {i.e. Jones et al}
- Date {i.e. year of publication or date of interim data collection}
- Type of economic evaluation [cost effectiveness analysis, cost utility analysis, cost benefit analysis]
- Currency used [$US, $AS, £Sterling …., not stated]
- Year to which costs apply {enter year or not stated}
- Perspective used [health service, societal, hospital, third party payer, patient, unclear]
- Study population {describe the population characteristics}
- Intervention 1 {description of intervention 1}
- Intervention 2 {description of intervention 2}
- Source of effectiveness data [single study, review/synthesis of previous studies, expert opinion, not stated]
- Source of unit cost data [literature, data from actual source, not stated]
- Link between cost and effectiveness data [prospective/concurrent, retrospective/disconnected…]
- Clinical outcomes measured and methods of valuation used {summary of outcomes and valuation methods used}
- Cost data handled appropriately {summary of methods used to e.g. discount, inflate}
- Modelling {summary of models used, type of model, purpose of model, components of model, key input parameters and model outputs}
- Outcome measures used in economic evaluations {summary of outcome measures used in economic evaluations e.g. incremental cost-effectiveness ratio, net benefit, cost-effectiveness acceptability curve}
- Direction of result with appropriate quadrant location
- Statistical analysis for patient-level stochastic data {summary of analyses used}
- Appropriateness of statistical analysis {comment on appropriateness}
- Uncertainty around cost-effectiveness expressed
- Appropriateness of method of dealing with uncertainty around cost-effectiveness
- Sensitivity analysis {list summary of analysis}
- Appropriateness of sensitivity analysis {comment on appropriateness}
- Modelling inputs and techniques appropriate
• Author’s conclusions {list as in publication}
• Implications for practice {summary of implications}
• Comments {summary of comments}
Appendix 3: Details about quality assessment

A. Studies of clinical effectiveness will be assessed using the following criteria, based on CRD Report No.4:

1. Was the method used to assign participants to the treatment groups really random? (Computer generated random numbers and random number tables will be accepted as adequate, while inadequate approaches will include the use of alternation, case record numbers, birth dates or days of the week).

2. Was the allocation of treatment concealed (Concealment will be deemed adequate where randomisation is centralised or pharmacy-controlled, or where the following are used: serially numbered containers, on-site computer-based systems where assignment is unreadable until after allocation, other methods with robust methods to prevent foreknowledge of the allocation sequence to clinicians and patients. Inadequate approaches will include: the use of alternation, case record numbers, days of the week, open random number lists and serially numbered envelopes even if opaque).

3. Was the number of participants who were randomised stated?

4. Were details of baseline comparability presented in terms treatment free interval, disease bulk, number of previous regimens, age, histology and performance status?

5. Was baseline comparability achieved for treatment free interval, disease bulk, number of previous regimens, age, histology and WHO performance status?

6. Were the eligibility criteria for study entry specified?

7. Were any co-interventions identified that may influence the outcomes for each group?

8. Were the outcome assessors blinded to the treatment allocation?

9. Were the individuals who were administered the intervention blinded to the treatment allocation?

10. Were the participants who received the intervention blinded to the treatment allocation?

11. Was the success of the blinding procedure assessed?

12. Were at least 80% of the participants originally included in the randomisation process followed up in the final analysis?

13. Were the reasons for any withdrawals stated?

14. Was an intention to treat analysis included?

Items will be graded in terms of ✅ yes (item properly addressed), ❌ no (item not properly addressed), ✓/❌ partially (item partially addressed), ? unclear or not enough information, or NA not applicable.

B. Studies of cost effectiveness will be assessed using the following criteria, based on an updated version of the checklist developed by Drummond et al.:

1. Was a well-defined question posed in answerable form?

   1.1 Did the study examine both costs and effects of the service(s) or programme(s)?

   1.2 Did the study involve a comparison of alternatives?

   1.3 Was a viewpoint for the analysis stated and was the study placed in any particular decision-making context?

2. Was a comprehensive description of the competing alternatives given? (i.e. can you tell who? did what? to whom? where? and how often?)

   2.1 Were any important alternatives omitted?

   2.2 Was (Should) a do-nothing alternative (be) considered?

3. Was the effectiveness of the programmes or services established?

   3.1 Was this done through a randomised, controlled clinical trial? If so, did the trial protocol reflect what would happen in regular practice?

   3.2 Was effectiveness established through an overview of clinical studies?
3.3 Were observational data or assumptions used to established effectiveness? If so, what are the potential biases in results?

4. Were all the important and relevant costs and consequences for each alternative identified?
4.1 Was the range wide enough for the research question at hand?
4.2 Did it cover all relevant viewpoints? (Possible viewpoints include the community or social viewpoint, and those of patients and third-party payers. Other viewpoints may also be relevant depending upon the particular analysis.)
4.3 Were capital costs, as well as operating costs, included?

5. Were costs and consequences measured accurately in appropriate physical units? (e.g. hours of nursing time, number of physician visits, lost work-days, gained life-years)
5.1 Were any of the identified items omitted from measurement? If so, does this mean that they carried no weight in the subsequent analysis?
5.2 Were there any special circumstances (e.g. joint use of resources) that made measurement difficult? Were these circumstances handled appropriately?

6. Were costs and consequences valued credibly?
6.1 Were the sources of all values clearly identified? (Possible sources include market values, patient or client preferences and views, policy-makers' views and health professionals' judgements.)
6.2 Were market values employed for changes involving resources gained or depleted?
6.3 Where market values were absent (e.g. volunteer labour), or market values did not reflect actual values (such as clinic space donated at a reduced rate), were adjustments made to approximate market values?
6.4 Was the valuation of consequences appropriate for the question posed? (i.e. Has the appropriate type or types of analysis - cost-effectiveness, cost-benefit, cost-utility - been selected?)

7. Were costs and consequences adjusted for differential timing?
7.1 Were costs and consequences which occur in the future 'discounted' to their present values?
7.2 Was any justification given for the discount rate used?

8. Was an incremental analysis of costs and consequences of alternatives performed?
8.1 Were the additional (incremental) costs generated by one alternative over another compared to the additional effects, benefits or utilities generated?

9. Was allowance made for uncertainty in the estimates of costs and consequences?
9.1 If data on costs or consequences were stochastic, were appropriate statistical analyses performed?
9.2 If a sensitivity analysis was employed, was justification provided for the ranges of values (for key study parameters)?
9.3 Were study results sensitive to changes in the values (within the assumed range for sensitivity analysis, or within the confidence interval around the ratio of costs to consequences)?

10. Did the presentation and discussion of study results include all issues of concern to users?
10.1 Were the conclusions of the analysis based on some overall index or ratio of costs to consequences (e.g. cost-effectiveness ratio)? If so, was the index interpreted intelligently or in a mechanistic fashion?

10.2 Were the results compared with those of others who have investigated the same question? If so, were allowances made for potential differences in study methodology?

10.3 Did the study discuss the generalisability of the results to other settings and patient/client groups?

10.4 Did the study allude to, or take account of, other important factors in the choice or decision under consideration (e.g. distribution of costs and consequences, or relevant ethical issues)?

10.5 Did the study discuss issues of implementation, such as the feasibility of adopting the 'preferred' programme given existing financial or other constraints, and whether any freed resources could be redeployed to other worthwhile programmes?
Appendix 4: Details about staging system for cancer of the breast (adapted from Harris and colleagues, 1992\textsuperscript{13})

The TNM system is an internationally recognised staging system for cancer of the breast. The system is based on the extent of the tumour, the involvement of the lymph nodes, and the presence of metastases.

**TNM staging system for breast cancer**

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<tr>
<th>T</th>
<th></th>
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<tbody>
<tr>
<td>TX</td>
<td>Primary tumour cannot be assessed</td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumour</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>Tumour &lt; 2 cm</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>Tumour 2-5 cm</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>Tumour &gt; 5 cm</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>Tumour of any size with direct extension to chest wall or skin</td>
<td></td>
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</tbody>
</table>

<table>
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<tr>
<th>N</th>
<th></th>
<th></th>
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<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph-node metastases</td>
<td></td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis to movable ipsilateral axillary nodes</td>
<td></td>
</tr>
<tr>
<td>N2</td>
<td>Metastases to fixed ipsilateral axillary nodes fixed or to other structures</td>
<td></td>
</tr>
<tr>
<td>N3</td>
<td>Metastases to ipsilateral internal mammary lymph nodes</td>
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<tr>
<th>M</th>
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<tbody>
<tr>
<td>M0</td>
<td>No evidence of distant metastasis</td>
<td></td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastases</td>
<td></td>
</tr>
</tbody>
</table>

**Clinical Staging**

*Early breast cancer*

Stage I  Small tumour (< 2 cm)

Stage IIA  No evidence of primary tumour, lymph-node positive, no evidence of distant metastasis

Stage IIB  Tumour 2-5 cm, lymph-node positive, no evidence of distant metastasis

*Advanced breast cancer*

Stage IIIA  No evidence of primary tumour or tumour < 2 cm, fixed lymph-node positive, no evidence of distant metastasis

Stage IIIB  Tumour of any size with direct extension to chest wall or skin, lymph-node negative or positive, no evidence of distant metastasis

Stage IV  Any tumour size, lymph-node negative or positive, distant metastases
Appendix 5: Background Information

Breast cancer is the most common cancer affecting women in the UK, accounting for nearly 30% of all cancers in women. It is the second leading cause of cancer deaths in women, in 1998 there were over 13,000 deaths from breast cancer in the UK.

Although the aetiology of breast cancer is largely unknown, a number of risk factors have been identified. These factors include early menarche, late first pregnancy, low parity, and late menopause. The endogenous hormones, both oestrogen and androgens, may also play an important role.

At least 50% of women diagnosed with primary breast cancer eventually relapse and develop advanced metastatic cancer. Metastatic breast cancer is defined by the presence of disease at distant sites such as the bone, liver or lung. The risk of metastatic disease relates to known prognostic factors in the original primary tumour. These factors include oestrogen receptor status negative disease, primary tumour > 3 cm and axillary node involvement. Metastatic breast cancer is currently considered incurable and ultimately most women will die of the disease. Prognosis depends on age, extent of disease, and oestrogen receptor status.

Current service provision

The choice of first line treatment, whether hormonal therapy or chemotherapy for metastatic breast cancer is based on a variety of clinical factors. The choice of a specific drug or regimen is based on what drugs have already been given as adjuvant treatment, together with the likelihood of benefit balanced against a given drug’s adverse effects and tolerability profile. There is strong evidence to suggest that polychemotherapy decreases mortality compared to single agent, but otherwise there appears to be no evidence that any particular treatment regimen is more effective than any other.

First-line chemotherapy regimens available for metastatic breast cancer include CMF (cyclophosphamide, methotrexate and 5-fluorouracil) and anthracycline-containing regimens. A short disease free interval (less than 1 year) between surgery for early breast cancer and developing metastases suggests that the recurrent disease is likely to be resistant to the drug used for adjuvant therapy. Current guidance from the National Institute for Clinical Excellence (NICE) recommends taxanes (docetaxel and paclitaxel) ‘as an option for the treatment of advanced breast cancer where initial cytotoxic chemotherapy has failed or is inappropriate’. The Institute has also issued guidance on trastuzumab, recommending the drug in combination with paclitaxel and as monotherapy for patients with tumours expressing human epidermal growth factor receptor 2 (HER2). NICE guidance on the use of vinorelbine for metastatic breast cancer is expected in July 2002.

No recommendations or guidance have been issued in the UK, about the role of capecitabine in the treatment of metastatic breast cancer.

Description of technology (based on Summary of Product Characteristics)

Capecitabine (Xeloda® Roche) is a non-cytotoxic fluoropyrimidine carbamate, which functions as a precursor of the cytotoxic moiety, 5-fluorouracil (5-FU). Capecitabine is an antimetabolite and is activated via several enzymatic steps. The enzyme involved in the final conversion to 5-FU, thymidine phosphorylase, is found in tumour tissues at higher levels than in normal tissue. The metabolism of 5-FU is thought to block the methylation reaction of deoxyuridylic acid to thymidylic acid, thereby interfering with the synthesis of deoxyribonucleic acid (DNA). The incorporation of 5-FU also leads to inhibition of RNA and protein synthesis. The effect of 5-FU is thought to create a thymidine deficiency that causes unbalanced growth and cell death. The effects of DNA and RNA deprivation are most marked in those cells which proliferate more rapidly and which metabolise 5-FU at a more rapid rate.
Licensed indications, contra-indications and warnings
Capecitabine (Xeloda® Roche) is currently licensed in the UK for first-line monotherapy of metastatic colorectal cancer. At the time of preparing this protocol use of capecitabine in the treatment of breast cancer is awaiting approval from the Medicines Control Agency.

The following draft SmPC have been provided by Roche and is used as the basis for this protocol: Xeloda in combination with docetaxel is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy. Previous therapy should have included an anthracycline. Xeloda is also indicated as monotherapy for the treatment of patients with locally advanced or metastatic breast cancer after failure of taxanes and an anthracycline-containing chemotherapy regimen or for whom further anthracycline therapy is not indicated.
Appendix 6: Expert panel

Dr Ian Manifold                  Professor Hilary Calvert
Weston Park Hospital            Cancer Research Unit
Whitham Road                    The Medical School
Sheffield  S10 2SJ               University of Newcastle upon Tyne
Email: Ian.manifold@wph.trent.nhs.uk     Newcastle upon Tyne  NE2 4HH
                                           Email: Hilary.Calvert@ncl.ac.uk

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