

**Guidance on
the use of
paclitaxel in the
treatment of
ovarian cancer**

Technology Appraisal No. 55

Guidance on the use of paclitaxel in the treatment of ovarian cancer.

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This guidance is written in the following context:

This guidance represents the view of the Institute which was arrived at after careful consideration of the available evidence. Health professionals are expected to take it fully into account when exercising their clinical judgement. This guidance does not, however, override the individual responsibility of health professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

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Guidance on the use of paclitaxel in the treatment of ovarian cancer

Issue date
Note

January 2003

This guidance replaces Technology Appraisal Guidance No 3 issued in May 2000.

The Institute reviews each piece of guidance it issues.

The review and re-appraisal of the use of paclitaxel in the treatment of ovarian cancer has resulted in a change in the guidance. Specifically there has been:

- a change in recommendations on the alternative treatments offered for first-line therapy (section 1.1);
- an emphasis that women should be involved in making choices about their treatment (section 1.2);
- clarification of the distinction between re-challenge and second-line treatment (section 1.3);

There has been no significant change in the guidance on the use of paclitaxel in the second-line (or subsequent) treatment (section 1.4).

Guidance on the use of paclitaxel in the treatment of ovarian cancer

This document replaces the previous guidance on the use of paclitaxel in the treatment of ovarian cancer (Guidance on the use of Taxanes for Ovarian Cancer: National Institute for Clinical Excellence Technology Appraisal Guidance No 3. London: NICE, www.nice.org.uk, May 2000).

1. Guidance

- 1.1 It is recommended that paclitaxel in combination with a platinum-based compound or platinum-based therapy alone (cisplatin or carboplatin) are offered as alternatives for first-line chemotherapy (usually following surgery) in the treatment of ovarian cancer.
- 1.2 The choice of treatment for first-line chemotherapy for ovarian cancer should be made after discussion between the responsible clinician and the patient about the risks and benefits of the options available. In choosing between treatment with a platinum-based compound alone or paclitaxel in combination with a platinum-based compound, this discussion should cover the side-effect profiles of the alternative therapies, the stage of the woman's disease, the extent of surgical treatment of the tumour, and disease-related performance status.
- 1.3 When relapse occurs after an initial (or subsequent) course of first-line chemotherapy, additional courses of treatment with the chosen chemotherapy regimen (re-challenge therapy) should be considered if the initial (or previous) response has been adequate in extent and duration. Once the tumour fails to respond adequately to the chosen first-line regimen, different treatment options should be considered as part of second-line therapy (see 1.4).
- 1.4 Paclitaxel is not recommended as second-line (or subsequent) therapy in women with ovarian cancer who have received the drug as part of their first-line treatment. For women who have not received paclitaxel as part of first-line treatment, it should be considered as one option alongside other drugs licensed for second-line treatment of ovarian cancer.
- 1.5 Only oncologists specialising in ovarian cancer should supervise the provision of chemotherapy in ovarian cancer.

This section (Section 1) constitutes the Institute's guidance on the use of paclitaxel in the treatment of ovarian cancer. The remainder of the document is structured in the following way:

| | | |
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| 2 | Clinical need and practice | Appendix A: Appraisal Committee |
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| 5 | Implications for the NHS | Appendix D: Detail on criteria for audit of the use of paclitaxel in the treatment of women with ovarian cancer |
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- 2.1 Ovarian cancer is a significant cause of early death, resulting in approximately 5000 deaths in the UK each year.
- 2.2 Early stages of the disease are often asymptomatic, and as a result most women are diagnosed with advanced disease. This gives a relatively poor prognosis, and 5-year survival rates are reported to be around 30% in the UK and up to 40% in some European countries.
- 2.3 Surgery is usually the first intervention used to treat the disease. However, in most women it is not possible to remove the tumour completely. Radiotherapy is usually of limited effectiveness and has side-effects on other abdominal organs.
- 2.4 Platinum-based chemotherapy has been the established therapy in ovarian cancer for some time. However, as research evidence emerged, paclitaxel (Taxol) was added in combination with platinum. It is estimated that 75% of women with ovarian cancer currently receive a paclitaxel/platinum combination as first-line therapy.
- 2.5 Although most patients (70% to 80%) initially respond to first-line chemotherapy, most responders eventually relapse (55% to 75% within 2 years). Responses can occur when first-line chemotherapy is repeated for a second and sometimes a third time, although they occur proportionately less frequently and do not last as long. A complete response is defined as malignant disease not detectable for at least 4 weeks, and a partial response is defined as tumour size reduced by at least 50% for more than 4 weeks.
- 2.6 Women who initially respond to first-line therapy are also more likely to respond to second and subsequent courses of therapy. The two factors shown to be predictive of second and subsequent response to first-line therapy are the length of the progression-free interval and the extent of the relapse (that is the number of tumour sites involved and their volume). Current best practice for women who initially respond to first-line therapy is to give second and possibly subsequent courses of the same treatment at some point.
- 2.7 Once re-treatment with first-line therapies has failed, second-line therapies can be offered. These may alleviate symptoms, but may also prolong survival. At the same time, however, they are likely to have a different range of adverse effects.
- 2.8 Seven chemotherapy agents are licensed for second-line treatment of ovarian cancer: paclitaxel, carboplatin, chlorambucil, treosulfan, hexamethylmelamine (altretamine), topotecan, and pegylated liposomal doxorubicin hydrochloride (PLDH).

2.9 Choice of second-line therapy is influenced by the effectiveness of the different agents and the patient's response to first-line therapy regimens.

2.10 In May 2000, the National Institute for Clinical Excellence issued the following guidance.

- Paclitaxel in combination with a platinum-based therapy (cisplatin or carboplatin) should be the standard initial therapy for patients with ovarian cancer following surgery.
- The use of paclitaxel/platinum combination therapy in the treatment of recurrent (or resistant) ovarian cancer is recommended if the patient has not previously received this drug combination. If the patient has already received both drugs, the combination of paclitaxel and platinum-based therapy in recurrent (or resistant) ovarian cancer is not recommended, outside the context of clinical trials.

It was recommended that the NICE guidance should be reviewed once full results from a further study (ICON3) were available. The present document has been prepared as part of that review.

3

The technology

3.1 Paclitaxel (Taxol) is a cytotoxic anticancer drug and belongs to the taxane group of drugs. It has the following licensed indications for ovarian cancer in the UK:

- primary ovarian cancer in combination with cisplatin (a platinum drug) in patients with advanced disease or residual disease after initial surgical treatment
- metastatic ovarian cancer where standard platinum-containing therapy (cisplatin or carboplatin) has failed (that is, paclitaxel as monotherapy).

3.2 Paclitaxel is usually administered at a dose of 175 mg per m² body surface area, in a 3-hour intravenous infusion, followed by a platinum compound, at 3-weekly intervals. The paclitaxel infusion is usually undertaken on an outpatient basis, with drug costs of approximately £1100 per cycle. Patients normally receive six cycles, with a total drug cost of approximately £6600, excluding costs of platinum drugs, pre-medication, wider outpatient or inpatient care, the cost of treating side effects, and value added tax (VAT).

3.3 While paclitaxel is licensed in combination with cisplatin for first-line therapy, both carboplatin and cisplatin are licensed for monotherapy in ovarian cancer and there is good evidence of their equivalent efficacy. However, carboplatin is recognised as being less toxic and resulting in fewer side effects. Consequently in UK clinical practice, paclitaxel is usually provided in combination with carboplatin.

The Appraisal Committee reviewed the evidence from a number of sources (Appendix B).

4.1 Clinical effectiveness

First-line treatment

- 4.1.1 Four randomised controlled trials (RCTs) provide the main evidence base for the consideration of paclitaxel as first-line therapy in ovarian cancer. Full results from the ICON3 trial and updated results from two others (GOG111, OV10) have become available since NICE issued its last guidance on the use of paclitaxel in the treatment of ovarian cancer.
- 4.1.2 The GOG111 trial compared combination treatments of paclitaxel (135 mg/m²)/cisplatin (75 mg/m²) and cisplatin (75 mg/m²)/cyclophosphamide (750 mg/m²) in 410 women. All had severe disease (as defined by the International Federation of Gynaecology staging system, FIGO stage III or IV) and sub-optimal tumour reduction following surgery. No statistically significant difference in overall tumour response (that is, complete and partial response) was found (relative risk = 1.19, 95% CI = 0.95 to 1.5). However, median progression-free survival was statistically significantly longer for patients receiving the paclitaxel/cisplatin combination (18 months vs 13 months, relative risk = 0.7, 95% confidence interval [CI] = 0.5 to 0.8, p value < 0.001). Overall survival was also statistically significantly longer in these patients (38 months vs 24 months, relative risk = 0.6, 95% CI = 0.5 to 0.8, p < 0.001). Estimates from updated longer-term study results suggest that the death rate is 30% less among those treated with the paclitaxel-containing regimen (relative hazard: 0.7, 95% CI = 0.57 to 0.87). No statistically significant difference in performance scores was found between the two groups.
- 4.1.3 The OV10 trial also compared the combinations of paclitaxel (175 mg/m²)/cisplatin (75 mg/m²) and cisplatin (75 mg/m²)/cyclophosphamide (750 mg/m²). The 680 women had optimal or sub-optimal tumour reduction following surgery, and 93% had FIGO stage III or IV disease. A statistically significant difference in overall tumour response (that is, complete and partial response) in favour of the paclitaxel combination was found (relative risk = 1.92, 95% CI = 1.52 to 2.42). Like GOG111, the study also found statistically significantly longer median progression-free survival for the paclitaxel combination (15.3 months vs 11.5 months, hazard ratio = 0.74, 95% CI = 0.63 to 0.88, p value = 0.0005). Overall survival was also statistically significantly higher in this group (35.6 months vs 25.8 months, hazard ratio = 0.73, 95% CI = 0.60 to 0.89, p value = 0.0016).

4.1.4 The GOG132 trial included comparison of combination paclitaxel (135 mg/m²)/cisplatin (75 mg/m²) with cisplatin (100 mg/m²) alone. All 424 women had FIGO stage III or IV disease and sub-optimal tumour reduction following surgery. No statistically significant difference in overall tumour response (that is, complete and partial response) was found between the group receiving cisplatin alone and those receiving the paclitaxel/cisplatin combination (relative risk = 0.97, 95% CI = 0.86 to 1.09). However, unlike GOG111 and OV10, no statistically significant differences were found in progression-free survival (14.1 months vs 16.4 months, hazard ratio = 1.06, 95% CI = 0.86 to 1.30), and overall survival (26.6 months vs 30.2 months, hazard ratio = 0.99, 95% CI = 0.80 to 1.23). The difference between the findings of the trial and those reported for the GOG111 and OV10 studies may be explained by the extent of patient cross-over between treatments before the disease progressed. However it is unlikely that this is sufficient to explain such markedly different findings.

4.1.5 The most recent trial, ICON3, compared a different combination of paclitaxel (175 mg/m²)/carboplatin (5 AUC) with either carboplatin (5 AUC) alone or a combination of cyclophosphamide (750 mg/m²)/doxorubicin (75 mg/m²)/cisplatin (75 mg/m²) (CAP). The trial differs from the others, in that patients had a wider range of residual tumour following surgery (54% had optimally reduced tumours), and a smaller proportion (80%) had FIGO stage III and IV disease. Of the total 2074 women recruited, 1421 were randomised to receive the paclitaxel/carboplatin combination or carboplatin alone. The findings of the ICON3 trial after more than 3 years' follow-up also differ from those of the GOG111 and OV10 studies. No statistically significant difference was found between the groups receiving the paclitaxel/platinum combination or carboplatin alone, in terms of progression-free survival (17.1 months vs 16.1 months, hazard ratio = 0.94, 95% CI = 0.84 to 1.05, p value = 0.24) or overall survival (37.6 months vs 36.1 months, hazard ratio = 0.96, 95% CI = 0.84 to 1.09, p value = 0.53). Also, no statistically significant differences were found in anxiety and depression scores. It is possible that the recruitment of more patients with less severe disease could have diluted the effect of paclitaxel treatment, but sub-group analyses by FIGO stage and extent of residual tumour did not show any trend supporting this. The trial design allowed choice of the control arm before randomisation, and although some suggest that this could also have diluted any treatment effect, it may be that this may better reflect clinical practice in some respects.

- 4.1.6 The four trials showed consistently that treatment with paclitaxel in combination with platinum leads to more side effects. Over the four trials statistically significantly higher rates of neutropenia, allergic reactions, cardiovascular problems, hypersensitivity, neuromotor and neurosensory problems, fever and alopecia were reported in patients receiving the paclitaxel/carboplatin combination compared with the control treatments.
- 4.1.7 While design differences between the four trials, in terms of severity of disease of included patients, differences in treatment and control drugs and doses, length of follow-up, and the extent of cross-over (before and after disease progression), may hamper statistical pooling of results, meta-analyses have been undertaken by the Medical Research Council (MRC) and Bristol-Myers Squibb (BMS). These take account of statistical heterogeneity as far as possible, and their results appear consistent, reporting that the findings for progression-free survival (hazard ratios = 0.84, 95% CI = 0.70 to 1.02 [MRC] and 0.87, 95% CI 0.72 to 1.05 [BMS]) and overall survival (hazard ratios = 0.82, 95% CI 0.66 to 1.01 [MRC] and 0.82, 95% CI 0.68 to 1.00 [BMS]) across the trials do not show statistically significant differences between paclitaxel/platinum and the alternatives.

Second-line treatment

- 4.1.8 Four published RCTs on the second-line use of paclitaxel (monotherapy) in the treatment of ovarian cancer were identified. However, two of these studies compared paclitaxel with unlicensed treatments, and one compared different dosing schedules of paclitaxel itself.
- 4.1.9 In the remaining RCT, paclitaxel was compared with topotecan in 235 women who had been previously treated with a platinum-based compound (they had not been previously treated with paclitaxel). The trial found no statistically significant differences in overall tumour response, progression-free survival or overall survival. The incidence of neutropenia, anaemia, thrombocytopenia, leukopenia, nausea and vomiting was significantly lower among patients receiving paclitaxel than among those receiving topotecan. However, there was a significantly higher incidence of alopecia among the paclitaxel-treated group.

4.2 Cost effectiveness

- 4.2.1 Eleven cost-effectiveness analyses and three cost–utility analyses were available as evidence on the first-line use of paclitaxel. All were based on trials favouring paclitaxel (that is, GOG111 or OV10), and therefore found the paclitaxel/platinum combination to be more costly and more effective than control treatments. Three of the analyses could be directly applied to the UK.
- 4.2.2 Two published UK cost-effectiveness analyses found that the incremental cost per life-year gained for paclitaxel/platinum ranged between £7173 and £12,417, depending on the effectiveness trial results and drug doses applied. One of the studies reported the incremental cost per progression-free life-year gained to be between £20,084 and £22,021, again depending on the trial results applied.
- 4.2.3 One published UK cost–utility analysis was available, but its methods were not well reported, and its results need to be interpreted with caution. An incremental cost–utility estimate based on this analysis, for paclitaxel/platinum compared with carboplatin alone, showed the incremental cost per quality-adjusted life year to be £5273.
- 4.2.4 A cost-effectiveness analysis undertaken by the manufacturer of paclitaxel was also available. The analysis was based on resource use and outcomes from GOG111, though carboplatin was substituted as the control treatment, as this better reflects UK practice. Consequently the analysis assumed equivalent efficacy between carboplatin and cisplatin in combination with paclitaxel. UK unit costs were incorporated from routine sources, and included: chemotherapy drugs, pre-medication, drug administration, management of febrile neutropenia, and other inpatient and outpatient care. For the paclitaxel/carboplatin combination vs carboplatin alone, the analysis reported an incremental cost of £7074 per life-year gained and £10,808 per progression-free life-year gained.
- 4.2.5 Given that this analysis was based on the survival in the most favourable survival findings available (that is, a hazard ratio of 0.61 in favour of paclitaxel/platinum combination for overall survival), sensitivity analyses were undertaken by NICE to indicate the likely magnitude of effect on the cost-effectiveness ratio of changing the survival gains attributed to paclitaxel/platinum. Simply adjusting the manufacturer's analysis to the survival difference reported by ICON3 (hazard ratio of 0.96) suggests an incremental cost per life-year gained in the region of £45,000. However, other

analyses undertaken by NICE suggest that the cost per life-year gained could be much higher.

4.3 Consideration of the evidence

- 4.3.1 Having carefully considered the design and full findings of ICON3 in conjunction with the three other published (updated) RCTs, the Committee concluded that all of the trials contribute to the understanding of the clinical effectiveness of paclitaxel in the first-line treatment of ovarian cancer.
- 4.3.2 The Committee noted that the availability of the full ICON3 evidence meant that two of the four published trials favoured paclitaxel in combination with a platinum-based compound, whereas two trials failed to show a significant difference in survival between the combination and a platinum-based compound alone. The combination of these findings in meta-analyses suggested that there was no statistically significant survival advantage for one of these therapeutic approaches over the other. In addition, cost-effectiveness estimates varied considerably with the assumed magnitude of the survival difference.
- 4.3.3 The Committee took account of this range of trial evidence as well as other factors that would differentiate between the two regimens including the side-effect profiles of the treatments, and the broad range of cost-effectiveness estimates presented. On this basis the Committee considered that paclitaxel/platinum combination treatment should no longer be recommended exclusively as standard therapy for women receiving first-line chemotherapy for ovarian cancer. As a consequence the Committee considered that both platinum therapy alone and a combination of paclitaxel and a platinum compound were appropriate first-line treatments for women with ovarian cancer.
- 4.3.4 The Committee discussed pathways of care for women with ovarian cancer. It was recognised that women with a good initial response to first-line therapy will be offered additional courses of the chosen treatment, and will be offered second-line treatment options once the tumour fails to respond to the chosen first-line regimen.
- 4.3.5 In view of the limited evidence available on the clinical effectiveness of paclitaxel in second-line treatment, the Committee concluded that paclitaxel should be considered as an option for second-line treatment only for women who do not receive it as part of their first-line therapy. For such women, it should be offered as one option alongside other drugs that are licensed for second-line treatment of ovarian cancer.

5

Implications for the NHS

- 5.1 In May 2000 the Institute's guidance indicated that the total annual cost of adding paclitaxel to platinum therapy in England and Wales was approximately £28 million (assuming that 4000 patients were treated at a cost of £7000 each).
- 5.2 Given that the guidance set out in Section 1 promotes informed choice between the available treatments, it is difficult to estimate the likely current resource impact on the NHS. However it appears unlikely that the guidance will result in an increase in the resources required to treat ovarian cancer. In fact, since women who do not receive paclitaxel in combination as first-line chemotherapy may receive the drug later as second-line therapy, the total number receiving paclitaxel at some point in their treatment may remain approximately unchanged, as may the total cost of chemotherapy for ovarian cancer.

6

Further research

- 6.1 Research would be beneficial to examine the following aspects of effectiveness and cost effectiveness of paclitaxel:
 - whether paclitaxel/platinum combination therapy is of particular benefit to identifiable clinical sub-groups
 - the optimal sequencing of paclitaxel therapy with other ovarian chemotherapy compounds – that is paclitaxel/platinum combination vs platinum followed by paclitaxel in sequence.

7

Implementation

- 7.1 Clinicians with responsibility for treating women with ovarian cancer should review their current practice in line with the guidance set out in Section 1.
- 7.2 Local guidelines, protocols or care pathways on the care of women with ovarian cancer should incorporate the guidance set out in Section 1.
- 7.3 To measure compliance locally with the guidance, the following criteria can be used. Further details on audit criteria are presented in Appendix D.
 - 7.3.1 First-line chemotherapy (usually following surgery) in the treatment of ovarian cancer includes the options of paclitaxel in combination with a platinum-based compound or platinum-based therapy alone.
 - 7.3.2 The choice of treatment for first-line chemotherapy for an individual woman with ovarian cancer is based on discussion between the woman and the responsible clinician regarding the risks and benefits of the options available. The following issues should be discussed: side-effect profiles of the alternative therapies, the stage of the woman's disease, the extent of surgical treatment of the tumour, and disease-related performance status.

7.3.3 Additional courses of treatment with the chosen chemotherapy regimen are offered to women following relapse after the initial (or subsequent) course of first-line treatment, if the extent and duration of the initial (or previous) response is adequate.

7.3.4 Paclitaxel is considered as second-line (or subsequent) treatment for women with ovarian cancer only if they have not received the drug previously as part of first-line treatment.

7.3.5 Only oncologists specialising in ovarian cancer supervise the provision of chemotherapy in ovarian cancer.

7.4 Local clinical audits on the management of ovarian cancer also could include measurement of compliance with accepted clinical guidelines or protocols or with the measures for the treatment of ovarian cancer that are suggested in *Improving Outcomes in Gynaecological Cancers, Guidance on Commissioning Cancer Services*.

8

Related guidance

8.1 In August 2001, NICE issued the guidance on topotecan: National Institute for Clinical Excellence (2001), *Guidance on the use of topotecan for the treatment of ovarian cancer. NICE Technology Appraisal Guidance No.28*. London: National Institute for Clinical Excellence. Available from www.nice.org.uk

8.2 In July 2002, NICE issued guidance on the use of PLDH in ovarian cancer: National Institute for Clinical Excellence (2002), *Guidance on the use of pegylated liposomal doxorubicin hydrochloride in the treatment of advanced ovarian cancer. NICE Technology Appraisal Guidance No. 45*. London: National Institute for Clinical Excellence. Available from www.nice.org.uk.

9

Review of guidance

9.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider any new evidence on the technology, in the form of an updated assessment report, and decide whether the technology should be referred to the Appraisal Committee for review.

9.2 It is planned that a review of this technology, along with topotecan and PLDH, will start in July 2003 and will take into account all new evidence.

Andrew Dillon
Chief Executive

January 2003

Appendix A

Appraisal Committee members

NOTE The Appraisal Committee is a standing advisory committee of the Institute. Its members are appointed for a 3-year term. A list of the Committee members appears below. The Appraisal Committee meets twice a month other than in December, when there are no meetings. The Committee membership is split into two branches, with the chair, vice-chair and a number of other members attending meetings of both branches. Each branch considers its own list of technologies and topics are not moved between the branches.

Committee members are asked to declare any interests in the technology to be appraised. If there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declaration of interests, are posted on the NICE website.

Professor R L Akehurst

Dean, School of Health Related
Research, Sheffield University

Professor David Barnett (Chair)

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

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

Professor Gary Ford

Professor of Pharmacology of Old Age
/ Consultant Physician
Wolfson Unit of Clinical Pharmacology
University of Newcastle

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
Barts & the London 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 considered by the Committee

The following documentation and opinion were made available to the Committee:

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| <p>A. Assessment Report prepared by the NHS Centre for Reviews and Dissemination, University of York <i>An update of a rapid and systematic review of the effectiveness and cost-effectiveness of the taxanes used in the treatment of advanced ovarian cancer</i>, March 2002.</p> <p>B. Manufacturer/sponsor submissions:</p> <ul style="list-style-type: none">• Bristol-Myers Squibb <p>C. Professional/specialist and patient group submissions:</p> <ul style="list-style-type: none">• CancerBACUP• Ovacome• Marie Curie Cancer Care• MRC Clinical Trials• National Cancer Research Institute (formerly UKCCCR)• Royal College of Obstetricians and Gynaecologists | <p>D. External expert and patient advocate submissions:</p> <ul style="list-style-type: none">• Dr Martin Gore, Consultant Oncologist, Royal Marsden Hospital, London• Dr Ganesan, Consultant Medical Oncologist, ICRF Medical Oncology Unit, Oxford Radcliffe Hospital, Oxford• Louise Bayne, Chair, Ovacome• Martin Ledwick, Senior Cancer Information Specialist, CancerBACUP• Joanne Rule, Chief Executive, CancerBACUP |
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Appendix C

Patient information

Guidance on the use of paclitaxel in the treatment of ovarian cancer

The patient information in this appendix has been designed to support the production of your own information leaflets. You can download it from our website at www.nice.org.uk where it is available in English and Welsh. If you would like printed copies of the leaflets please ring the NHS Response Line on 0870 1555 455 and quote reference number N0187 for the English patient leaflet and N0188 for the bi-lingual patient leaflet.

What is NICE guidance?

The National Institute for Clinical Excellence (NICE) is part of the NHS. It produces guidance for both the NHS and patients on the use of medicines, medical equipment, diagnostic tests and clinical and surgical procedures and under what circumstances they should be used.

To produce this guidance, NICE looks at how well the medicine, equipment or procedure works and also how well it works in relation to how much it costs. This process is called an appraisal. The appraisal process involves the manufacturer of the medicine or equipment for which guidance is being produced and the organisations that represent the healthcare professionals, patients and carers who will be affected by the guidance. Each appraisal takes about 12 months to complete.

In May 2000, NICE issued guidance to the NHS in England and Wales on the use of paclitaxel for the treatment of ovarian cancer. NICE always reviews its guidance taking into account any new evidence. Following a review, NICE has updated its guidance on paclitaxel for the treatment of ovarian cancer. This new guidance was published in January 2003.

What is ovarian cancer?

Cancer is a disease of the body's cells. Normally, all cells divide and reproduce themselves in an orderly and controlled manner. In cancer, the cells multiply without proper control. Cancer of the ovaries ('ovarian cancer') is one of the most common cancers in women; in England and Wales, about 6000 cases of ovarian cancer are diagnosed each year.

Women who have ovarian cancer usually have surgery to remove as much of the tumour (the mass of cancer cells) as possible and then have 'chemotherapy', which means treatment with drugs that destroy cancer cells. The type of drug used depends on the stage of the disease.

What is paclitaxel?

Paclitaxel is one of a group of anticancer ('cytotoxic') drugs known as taxanes. Cytotoxic drugs are used to destroy cancer cells.

The most common initial ('first-line') chemotherapy treatment for ovarian cancer is a combination of a platinum-containing drug (cisplatin or carboplatin) and another drug known as paclitaxel (Taxol). It's estimated that currently more than 7 out of 10 women with ovarian cancer receive this initial treatment.

NICE carried out an appraisal of the use of paclitaxel for the treatment of ovarian cancer and issued recommendations in May 2000. It has now carried out a review of that guidance, taking into account both the evidence that was available for the previous appraisal and new evidence. In particular, it has considered the full results of a clinical study that were not available for the previous appraisal.

What has NICE recommended?

NICE has made the following recommendations about the use of paclitaxel to treat ovarian cancer.

- Either paclitaxel in combination with a platinum-based therapy (cisplatin or carboplatin) **or** platinum-based treatment alone should be offered for initial (first-line) chemotherapy (usually after surgery). The choice of treatment should be made after the woman and her doctor have discussed the potential risks and benefits of the treatment options available. This discussion should cover the side effects of the treatments, the stage of the woman's disease, how much of the tumour has been removed by surgery, and how much the disease has affected the woman's overall health and function.
- If the cancer returns, further courses of the first-line chemotherapy used previously should be considered, provided that the response to the previous treatment was adequate in terms of how well it worked and how long it lasted. (This is called 're-challenge therapy'.) When there is not an adequate response to the chosen first-line treatment, different treatment options should be considered as part of second-line chemotherapy.
- Paclitaxel is not recommended as second-line (or subsequent) therapy for a woman with ovarian cancer who has been treated with paclitaxel as part of her first-line treatment. For a woman who has not received paclitaxel as part of first-line treatment, it should be considered as one option alongside other drugs licensed for second-line treatment of ovarian cancer.
- When chemotherapy is used to treat ovarian cancer, the treatment should be supervised by a doctor who specialises in the treatment of ovarian cancer.

Are these recommendations different from the ones NICE issued previously?

Yes. When all the evidence now available is considered together, it suggests that there is no clear advantage of the combination of paclitaxel and a platinum-based drug over a platinum-based drug on its own for first-line treatment of ovarian cancer. So NICE now recommends that both treatments should be offered as options and that the choice of treatment should be made after the woman has discussed the potential risks and benefits with her doctor. The new guidance emphasises that women should be involved in making choices about their treatment.

The new guidance also makes clear the distinction between re-challenge therapy and second-line treatment. There has been no significant change in the guidance on the use of paclitaxel in the second-line (or subsequent) treatment.

What should I do next?

If you or someone you care for has ovarian cancer, you should discuss this guidance with your hospital doctor at your next appointment.

Will NICE review its guidance?

Yes. The review of this guidance will begin in July 2003. The review will cover the use of paclitaxel and two other drugs – topotecan and pegylated liposomal doxorubicin hydrochloride (PLDH) – in the treatment of ovarian cancer.

Further information

The NICE website (www.nice.org.uk) has further information on NICE and the full guidance on the use of paclitaxel in the treatment of advanced ovarian cancer that has been issued to the NHS. The guidance can also be requested from the NHS Response Line by phoning 0870 1555 455 and quoting reference N0185. The recommendations NICE has made on the use of topotecan and PLDH in the treatment of ovarian cancer are also available from the NICE website or from the NHS Response Line (for topotecan, quote N0020 for the full guidance and N0022 for information for patients; for PLDH, quote N0114 for the full guidance and N0116 for the information for patients).

If you have access to the Internet, you can find more information about ovarian cancer on the NHS Direct website (www.nhsdirect.nhs.uk). You can also phone NHS Direct on 08 45 46 47.

Appendix D

Detail on criteria for audit of the use of paclitaxel in the treatment of women with ovarian cancer

Possible objectives for an audit

An audit on the treatment of ovarian cancer could be carried out to ensure that:

- paclitaxel is used appropriately
- women with ovarian cancer participate in making the choice concerning their therapy
- chemotherapy for women with ovarian cancer is supervised by an appropriate specialist.

Patients to be included in an audit

All women undergoing treatment for ovarian cancer over a reasonable time period, for example, 1 year. For measures 3 and 4 below, it may be useful to include women who were diagnosed and begun on chemotherapy sufficiently long ago that relapses and second-line therapy may have occurred.

Measure that can be used as a basis for audit

The measures that can be used in an audit are as follows:

| Criterion | Standard |
|---|---|
| 1. Paclitaxel in combination with a platinum-based compound or platinum-based therapy alone is offered for first-line chemotherapy | 100% of women with ovarian cancer |
| 2. The choice of treatment for first-line chemotherapy is based on discussion between the patient and the responsible clinician | 100% of women with ovarian cancer |
| 3. Additional courses of treatment with the chosen chemotherapy regimen are offered to women following relapse after initial (or subsequent) courses of first-line chemotherapy, if the extent and duration of the initial response is adequate | 100% of women with ovarian cancer who received first-line chemotherapy and who have experienced a relapse |
| 4. Paclitaxel is considered as second-line (or subsequent) treatment | 0% of women with ovarian cancer |
| 5. The provision of chemotherapy is supervised by an oncologist specialising in ovarian cancer | 100% of women with ovarian cancer |

Calculation of compliance with the measures

Compliance with the measure described in the table is calculated as follows.

$$\frac{\text{Number of patients whose care is consistent with the criterion plus the number meeting any applicable exceptions}}{\text{Number of patients in the audit to which the Criterion and Exception(s), where applicable, apply}} \times 100$$

Clinicians should review the findings of measurement, identify if practice can be improved, agree on a plan to achieve any desired improvement and repeat the measurement of actual practice to confirm that desired improvement is being achieved.

| Exception | Definition of Terms |
|---|--|
| A. None | First-line = usually following surgery. Platinum-based compound = cisplatin or carboplatin |
| None | Local specialists should agree on how discussion with the woman about the risks and benefits of the options available is documented, for audit purposes. Reference should be made to side-effect profiles of the alternative therapies, the stage of the woman's disease, the extent of surgical treatment of the tumour, and disease-related performance status |
| <p>A. Inadequate or too short a duration of initial response</p> <p>B. The woman declines treatment following discussion with the responsible clinician</p> | Local specialists should agree on how to judge the adequacy and duration of initial response, for audit purposes |
| A. The woman has not received paclitaxel previously as part of first-line treatment | |
| None | Local specialists should agree on what constitutes supervision, for audit purposes |



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