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***Guidance on  
the use of  
topotecan for  
the treatment  
of advanced  
ovarian cancer***

## Technology Appraisal No. 28

Guidance on the use of topotecan for the treatment of advanced ovarian cancer.

**Issue date:** August 2001

**Review date:** June 2002

### Ordering Information

Copies of this guidance can be obtained from the NHS Response Line by telephoning 0870 1555 455 and quoting ref. N0020. A patient version of this document can be obtained by quoting ref. N0022. A bi-lingual patient leaflet is also available ref. N0023.

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### Distribution of Guidelines

This document has been circulated to the following:

- Health Authority Chief Executives in England and Wales
- NHS Trust Chief Executives in England and Wales
- PCG Chief Executives
- Local Health Group General Managers
- Medical and Nursing Directors in England and Wales
- Consultant Oncologists in England and Wales
- Chief Pharmacists, Heads of Drug Purchasing, Heads of Drug Information, Pharmaceutical Advisors, GP Prescribing Advisors and Purchase Advisors in England and Wales
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- Medical Director & Head of NHS Quality – National Assembly for Wales
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- Representative bodies for health services, professional organisations and statutory bodies, Royal Colleges

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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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ISBN: 1-84257-116-8

Published by the National Institute for Clinical Excellence  
August 2001

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# Guidance on the use of topotecan for the treatment of advanced ovarian cancer

## 1. Guidance

- 1.1 It is recommended that topotecan should be considered as one option for the second-line (or subsequent) treatment of women with advanced ovarian cancer where the disease is initially resistant or refractory to first-line platinum based combination therapy or has become resistant after successive courses of platinum based combination therapy (see section 2.5).
- 1.2 Use of topotecan is not recommended in patients with poor performance status (ECOG 3 or worse – defined in Appendix D), sub-acute or established bowel obstruction, or after previous exposure to topotecan or another drug in the same class.
- 1.3 Only oncologists specialising in the chemotherapy of ovarian cancer should undertake supervision of topotecan treatment in advanced ovarian cancer.
- 1.4 The use by oncologists of topotecan in this indication should be accompanied by ongoing audit of its use, with careful documentation of indications for treatment, clinical outcomes and adverse effects.
- 1.5 Treatment response should be monitored by appropriate tumour markers (e.g. CA-125) and/or appropriate radiological techniques. Patients with serological or radiological evidence of disease progression should stop treatment. Deteriorating performance status should also prompt consideration of treatment withdrawal.

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

2 Clinical Need	8 Related Guidance
3 The Technology	9 Review of Guidance
4 Evidence	Appendix A: Appraisal Committee
5 Implications for the NHS	Appendix B: Sources of Evidence
6 Further Research	Appendix C: Information for Patients
7 Implementation	Appendix D: ECOG Performance Status

The full document and a Summary of Evidence are available from our website at [www.nice.org.uk](http://www.nice.org.uk) or by telephoning 0870 1555 455 and quoting the reference number N0021.

Mae'r adran hon (adran 1) hefyd ar gael yn Gymraeg ar ein gwefan neu drwy gysylltu â 0870 1555 455, rhif cyfeirnod N0021.

- 2.1 Ovarian cancer has an incidence of 21.6 cases per 100,000 women per year in England and Wales, making it one of the more common cancers of women. The number of cases diagnosed each year is about 6,000.
- 2.2 The early stages of the disease are often asymptomatic. Most cases are therefore not detected until they are advanced. This gives a poor prognosis for the disease. The five-year survival rate is only about 30%.
- 2.3 A number of potential prognostic factors which may influence survival and response have been suggested, including: the amount of residual disease after 'debulking' surgery, the stage and grade/histology of the tumour, and performance status and age of the patient. Tumour markers (e.g. CA-125) are also potential prognostic indicators, correlating with disease progression. CA-125 along with abdominal CAT scanning is often used to assess both tumour load and response to therapy.
- 2.4 Radiotherapy is usually of limited effectiveness and has side-effects on organs within the abdominal cavity. First-line chemotherapy (given to over 75% patients with ovarian cancer) usually consists of paclitaxel and a platinum-based therapy (cisplatin or carboplatin). While most patients (70 to 80%) initially respond to such therapy, 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 means that malignant disease is not detectable for at least four weeks. A partial response means that tumour size is reduced by at least 50% for more than four weeks).
- 2.5 Patients who respond to platinum-based therapy for more than 6 months are referred to as platinum-sensitive; from 0 to 6 months, as platinum-resistant; and those who do not respond as platinum-refractory. Women whose condition is initially platinum-sensitive are also more likely to respond to second and subsequent courses of platinum-based therapy and to subsequent therapies with other drugs. 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 stage the cancer has reached. Current best practice for women who respond to platinum-based therapy is to give second and possibly subsequent courses of the same treatment.
- 2.6 Six drugs (topotecan, hexamethylmelamine (altretamine), treosulfan, chlorambucil, paclitaxel and liposomal doxorubicin (Caelyx)) are licensed in the UK for therapy after the failure of platinum-based therapy (see section 8.1 on related NICE guidance). Of these, paclitaxel (in combination with cisplatin or carboplatin) is now commonly used as first-line therapy. Etoposide and gemcitabine are unlicensed drugs (for this indication) used as second line therapy. Drugs other than

### 3

#### The Technology

topotecan used in second-line and subsequent therapy have not been formally appraised for this guidance. However, the Committee's understanding is that the effectiveness of chlorambucil and treosulfan, in terms of response, has not been proven; hexamethylmelamine exhibits significant toxicity and is poorly tolerated; and both treosulfan and etoposide are leukaemogenic in a small proportion of cases although this is unlikely to be relevant in the present indication. All of the last three drugs appear from non-randomised trials to have response rates similar to those of paclitaxel, caelyx and topotecan, but the selection of patients differed in studies of their use and, in a number of cases, the patients were not platinum-resistant.

- 3.1 Topotecan (Hycamtin™, produced by GlaxoSmithKline) is derived from the oriental tree *Camptotheca acuminata*. It prevents DNA replication in cancer cells by inhibiting the enzyme topoisomerase I. Launched in 1997, it is licensed for use in ovarian cancer after the failure of first-line or subsequent therapy.
- 3.2 It is administered intravenously for periods of 30 minutes over five consecutive days, with a three-week interval between the start of each course. If well tolerated, treatment may continue until disease progression occurs. An initial dose of 1.5 mg per square metre of body surface per day is recommended (typically, about 2.7 mg per day). Administration can only occur when there are acceptable neutrophil and platelet counts. Treatment is contra-indicated in pregnancy, breast-feeding and in the presence of severe bone-marrow depression and hypersensitivity reactions to the drug. Treatment is not recommended in the presence of severe renal or hepatic impairment. Patients with poor performance status (ECOG 3 or worse – defined in Appendix D) tend to have a lower response rate and an increased incidence of complications such as fever and infection. In addition (based on clinical experience) those with extensive abdominal tumour deposits leading to bowel obstruction are less likely to benefit from treatment.
- 3.3 The drug cost of topotecan depends on both the number of five-day courses the patient undertakes and whether the complete contents of the 4 mg vial is used.
  - If only 2.7 mg of each 4 mg vial is used (the amount required for the average size patient), the cost of the recommended minimum four courses would be £6,250. The cost of 5.92 courses (the average for patients in a recent trial) would be £9,250.
  - If no wastage of the drug occurs, the cost of the recommended minimum four courses would fall to £4,220. The cost of 5.92 courses (the average for patients in a recent trial) would be £6,240.

## 4.1 Clinical effectiveness

- 4.1.1 Three randomised controlled trials (RCT) studying advanced ovarian cancer patients pre-treated with a platinum containing regime as first line therapy are available for the appraisal of topotecan, although none of these compare topotecan against other second-line therapies or best supportive care.
- 4.1.2 The first RCT of topotecan against paclitaxel monotherapy, was a multicentred trial of 235 patients (at the time of the trial, paclitaxel was the main second-line therapy). In this trial interim results have been published, but the final analysis is in abstract only. The results for complete or partial response were: topotecan 21%, paclitaxel 14%, relative risk 1.46 (95% confidence interval 0.83 to 2.61). The differences between the drugs for overall survival, duration of response and time to progression could also have arisen by chance. There was also no statistically significant difference in any subgroup for these outcomes.
- 4.1.3 Topotecan had rather more frequent and severe haematological side-effects than paclitaxel (leukopenia, neutropenia, thrombocytopenia and anaemia), though the reverse was the case for alopecia. The combined effect of outcomes and adverse effects was measured by TWiST (Time Without Symptoms and Toxicity). The results of the analysis using this method favoured paclitaxel, though the difference was not statistically significant.
- 4.1.4 In the second trial of 474 patients (currently published in abstract only), topotecan was compared with Caelyx. For the population of patients as a whole, there were no statistically different outcomes and thus no difference in clinical effectiveness between the two drugs. The two drugs have different side effect profiles.
- 4.1.5 A third (unpublished) trial compared oral topotecan with intravenous topotecan in 266 patients with relapsed ovarian cancer. Patients treated with intravenous topotecan had a median time to progression of around six months. The median survival of 57.6 weeks for patients treated with intravenous topotecan was 6.2 weeks longer than for oral topotecan, which was statistically significant. This was accepted as evidence of a survival advantage of intravenous topotecan in this clinical setting.

## 4.2 Cost effectiveness

- 4.2.1 There have been three cost-effectiveness analyses of topotecan as a second-line therapy for advanced ovarian cancer. One study, from the perspective of US health insurance companies, compared topotecan with paclitaxel, altretamine and etoposide. This study was not based on randomised controlled trial data and was effectively a cost minimisation analysis, based on the assumption that there is no difference in the effectiveness of the four drugs. On this basis, it concluded that altretamine and etoposide were the most cost-effective of the four drugs compared. However, the assumption of equal effectiveness of the four drugs may not be well founded, as it appears to rely on the results of studies where the patients came from different prognostic groups with differing platinum sensitivities.
- 4.2.2 The second analysis (unpublished), conducted by the manufacturers of topotecan, used paclitaxel as a comparator and data from the trial of paclitaxel against topotecan in second line therapy. It assumes that topotecan is more clinically effective than paclitaxel, and is thereby able to conclude that topotecan is cost-effective against paclitaxel. The incremental cost per responder is estimated to be £3,000, the incremental cost per median year of response, £2,400, and the incremental cost per life year gained, £1,000. However, as indicated in section 4.1.2 above, the assumption that topotecan is more effective than paclitaxel is not supported by the trial data (which indicates no statistically significant differences between the two drugs), so the cost-effectiveness analysis consequent upon this assumption is unsound.
- 4.2.3 The third study, a cost-minimisation analysis, was provided (unpublished) by the manufacturers of Caelyx, and was used by them to argue the case in favour of Caelyx over topotecan. However, the fairness of the cost basis for comparison is unclear.
- 4.2.4 Establishing the true cost effectiveness of topotecan against other second line therapies has proved difficult because there are no head-to-head trials of any of these drugs with topotecan, and also the effectiveness data for the comparators are poor and equivocal.
- 4.2.5 While no analysis has been provided for the cost-effectiveness of topotecan as salvage therapy (that is, against best supportive care, rather than against another drug as in 4.2.1.to 4.2.4 above), some results can be inferred from the manufacturer's submission. This is based on a trial in which the median duration of response was 26 weeks, and in which it was estimated

that the cost per patient for any response (complete or partial) was £32,500. Assuming that the duration of response without treatment was zero, the cost per year of response for those with median response would be £65,000. However, the distribution of responses is skewed, with a mean response likely to be more than 26 weeks (possibly as great as 52 weeks). Under the latter circumstances, the cost per year of response would be £32,500. A precise cost per quality-adjusted life-year gained is not reliably calculable. However, some survival gains are deducible from the trial of intravenous versus oral topotecan. These are additional to the quality of life benefits of response to the treatment.

### 4.3 Summary

4.3.1 In terms of clinical effectiveness, topotecan appears to be equivalent to paclitaxel, its main comparator for second line therapy at the time of the trial. Since it is of similar cost, it is therefore appropriate that topotecan is made available for second line treatment now that paclitaxel is indicated for first line treatment. In addition, there is some evidence of an overall survival advantage in patients treated with intravenous topotecan (see 4.2.5.).

## 5

### Implications for the NHS

5.1 About 4,500 women die each year of ovarian cancer in England and Wales of whom approximately 360 already receive topotecan. It is assumed that, on the basis of this guidance, topotecan would be prescribed to an additional 1,500 women following the failure of platinum-based therapy. If the drug cost were about £4,500 per patient (based on the administration of four courses with some wastage) then the costs to the NHS are expected to be in the region of £7 million per annum.

## 6

### Further Research

6.1 Topotecan is one of a number of drugs in use (currently or potentially in the near future) for advanced ovarian cancer when first-line therapy has failed. Research is required into topotecan as a second-line or subsequent therapy, either singly or in combination with other drugs. The comparators should include those second-line treatments with a significant response rate in platinum refractory or resistant patients and best supportive care (in the case of its use in last-line therapy). Data sufficient to allow cost effectiveness analyses should be collected. In common with many new cancer therapies, insufficient evidence of clinical effectiveness has been available to determine the optimal administration and timing of drugs currently in use.

6.2 Studies are needed of the molecular pathological characteristics of tumours that favour the use of topotecan as opposed to that of other drugs.

## 7

### Implementation

- 7.1 Relevant clinical guidelines and protocols for advanced ovarian cancer should be reviewed in the light of this guidance.
- 7.2 Clinicians with responsibility for treating people with advanced ovarian cancer should review their current practice in line with the guidance set out in Section 1.
- 7.3 To enable clinicians to audit their own compliance with this guidance it is recommended that treatment plans be recorded for each patient and incorporated into local audit data recording systems. If not already in place, consideration should be given to the establishment of appropriate categories in routine electronic databases.
- 7.4 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.

## 8

### Related Guidance

- 8.1 The Institute has been commissioned to appraise Caelyx early in 2002.

## 9

### Review of Guidance

- 9.1 This guidance will be reviewed in June 2002. The review will take account of data derived from ongoing audit of the use of topotecan as indicated in sections 1.4 and 7.4.

Andrew Dillon  
Chief Executive

August 2001

## 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.

**Dr Jane Adam**

Radiologist  
St. George's Hospital

**Dr Sunil Angris**

General Practitioner  
Waterhouses Medical Practice

**Professor David Barnett (Chair)**

Professor of Clinical Pharmacology  
University of Leicester

**Professor Carol Black**

Consultant Physician  
Royal Free Hospital & UCL

**Professor John Brazier**

Health Economist  
University of Sheffield

**Professor Bruce Campbell**

Consultant Surgeon  
Royal Devon & Exeter Hospital

**Professor Mike Campbell**

Statistician  
Institute of General Practice &  
Primary Care, Sheffield

**Dr Karl Claxton**

Health Economist  
University of York

**Professor Jack Dowie**

Health Economist  
School of Hygiene & Tropical Medicine

**Dr Paul Ewings**

Statistician  
Taunton & Somerset NHS Trust

**Sally Gooch**

Director of Nursing  
Mid-Essex Hospital Services Trust

**Liz Heyer**

Chief Executive  
Barnet & Chase Farm Hospitals NHS  
Trust

**Dr Diane Ketley**

Clinical Governance Programme  
Leader  
Leicester Royal Infirmary

**Ruth Lesirge**

Patient Representative  
Director, Mental Health Foundation

**Dr George Levvy**

Patient Representative  
Chief Executive, Motor Neurone  
Disease Association

**Dr Gill Morgan**

CEO  
North & East Devon Health Authority

**Professor Miranda Mugford**

Health Economist  
University of East Anglia

**Siân Richards**

General Manager  
Cardiff Local Health Group

**Professor Philip Routledge**

Professor of Clinical Pharmacology  
University of Wales

**Dr Rhiannon Rowsell**

Pharmaceutical Physician  
AstraZeneca UK Ltd

**Dr Stephen Saltissi**

Consultant Cardiologist  
Royal Liverpool University Hospital

**Professor Andrew Stevens**

Professor of Public Health  
University of Birmingham

**Professor Ray Tallis**

Consultant Physician  
Hope Hospital, Salford

**Professor Mary Watkins**

Head of Institute of Health Studies  
University of Plymouth

**Dr Norman Waugh**

Public Health Consultant  
University of Southampton

**Dr Fay Wilson**

General Practitioner  
Birmingham

## APPENDIX B

### Sources of Evidence

1. The following documentation and opinion was made available to the Appraisals Committee:
  - a. Assessment Report:
    - Prepared by the NHS Centre for Reviews and Dissemination, University of York (A rapid and systematic review of the clinical effectiveness and cost effectiveness of topotecan for ovarian cancer, February 2001).
  - b. Manufacturer/sponsor submissions:
    - GlaxoSmithKline
  - c. Professional/specialist group, patient/carer group and trade association submissions:
    - The Joint Collegiate Council for Oncology on behalf of the Royal College of Physicians and the Royal College of Radiologists
    - CancerBACUP and Ovacome (joint submission)
  - d. External expert and patient advocate submissions:
    - Dr Trivadi Ganesan from ICRF Medical Oncology Unit at the Churchill Hospital in Oxford
    - Professor Hilary Calvert, Professor of Medical Oncology at Newcastle General Hospital
    - CancerBACUP
    - Ovacome

## APPENDIX C

### Guidance on the use of topotecan for the treatment of advanced ovarian cancer – Information for Patients

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](http://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 N0022 for the English patient leaflet and N0023 for the bi-lingual patient leaflet.

#### What is NICE Guidance?

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

When the Institute evaluates these things, it is called an appraisal. Each appraisal takes around 12 months to complete and involves the manufacturers of the drug or device, the professional organisations and the groups who represent patients and their carers.

NICE was asked to look at the available evidence on topotecan and provide guidance that would help the NHS in England and Wales decide where it should be used in the management of advanced ovarian cancer.

#### 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. Ovarian cancer is one of the most common cancers in women; about 6000 cases of ovarian cancer are diagnosed in England and Wales each year.

Ovarian cancer can be difficult to detect because it does not produce many symptoms in the early stages. Therefore when it is diagnosed the cancer is often at an advanced stage. Of the women diagnosed with ovarian cancer about 3 in 10 will survive for more than five years.

The type of treatment given for a cancer depends on many factors. These include:

- the type of cancer,
- where in the body it started,
- what the cancer cells look like under the microscope,
- how far they have spread, if at all
- the general health of the patient

Current treatments for ovarian cancer include radiotherapy and chemotherapy (the use of anti-cancer drugs to destroy cancer cells). Radiotherapy is not usually successful and because the ovaries are located in the abdominal cavity and radiation aimed at the ovaries may also affect other organs close by. Therefore more than 7 out of 10 women receive first-line chemotherapy treatment consisting of paclitaxel (Taxol) and a platinum-based therapy (cisplatin or carboplatin). While around 8 out of 10 women respond to this treatment at first, between 5 and 7 out of 10 cancers come back within 2 years. Sometimes women whose cancer comes back will respond when this first-line chemotherapy is repeated for a second and even a third time, although the improvement is not usually as frequent nor does it last as long as the previous treatment.

### What is topotecan?

Topotecan (Hycamtin™) is a drug that inhibits a protein that is required for cancer cells to replicate and therefore it can slow down the progression of the cancer. It is licensed for use in treating ovarian cancer when first-line or subsequent treatments have failed.

Topotecan is given through a drip for 30 minutes a day for five days in a row with three-weeks between the start of each course of treatment. A minimum of four courses is recommended and treatment may continue until the cancer stops responding to the treatment.

### What has NICE recommended about the use of topotecan?

NICE has recommended to the NHS that:

- Topotecan should be considered as one of the treatment options for women with advanced ovarian cancer if first-line chemotherapy has not worked or if the cancer has stopped responding to the platinum based chemotherapy.
- Topotecan is not recommended for women who have an ECOG (Eastern Cooperative Oncology Group) score of 3 or below. ECOG is a scale used by doctors to assess the overall health and ability of the patient:
  - 0 = fully active, the same as before having cancer
  - 1 = unable to do strenuous activities but still able to do tasks such as light housework or office work
  - 2 = able to walk and carry out self care (e.g. washing, dressing) but not able to work
  - 3 = only able to carry out limited self care, mainly confined to bed
  - 4 = completely confined to bed and not able to carry out self care
- Topotecan is also not recommended for women who have an obstruction in their bowel (intestine) which is caused by the cancer or who have already been treated with topotecan or another drug of the same type.

- Only oncologists (doctors) who specialise in the use of chemotherapy for the treatment of ovarian cancer should supervise the use of topotecan treatment.
- A woman's response to the treatment should be monitored carefully. If there is evidence that the cancer has progressed, then treatment with topotecan should be stopped. Also a reduction in the ECOG (described above) may be a reason to stop treatment.

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**What should I do?**

If you, or someone you care for, have ovarian cancer then you can discuss this advice with the doctor or nurse at your next appointment.

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**Will NICE review its guidance?**

Yes. The guidance will be reviewed in June 2002 when new data on the drug is expected.

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**Further Information**

Further information on NICE, and the full guidance issued to the NHS is available on the NICE web site ([www.nice.org.uk](http://www.nice.org.uk)).

The guidance can also be requested from 0870 1555 455, quoting reference N0020.

If you have access to the Internet and would like to find out more about cancer visit the NHS Direct website: [www.nhsdirect.nhs.uk](http://www.nhsdirect.nhs.uk). If you would like to speak to NHS direct please call them on 08 45 46 47.

## APPENDIX D

### ECOG performance status\*

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

\* As published in Am. J. Clin. Oncol.:  
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.