WORKING GROUP ON ACUTE PURCHASING

Supplementary Document: The Use of Paclitaxel in the First Line Treatment of Ovarian Cancer

October 1998

GUIDANCE NOTE FOR PURCHASERS 98/10

Supplement to 97/05

Series Editor: Nick Payne

InterDEC Report No: 20/1998

Trent Development and Evaluation Committee

The purpose of the Trent Development and Evaluation Committee is to help health authorities and other purchasers within the Trent Region by commenting on expert reports which evaluate changes in health service provision. The Committee is comprised of members appointed on the basis of their individual knowledge and expertise. It is chaired by Professor Sir David Hull.

The Committee recommends, on the basis of evidence provided, priorities for:

- the direct development of innovative services on a pilot basis;
- service developments to be secured by health authorities.

The statement that follows was produced by the Development and Evaluation Committee at its meeting on 20 October 1998 at which this Guidance Note for Purchasers (in a draft form) was considered.

SUPPLEMENTARY DOCUMENT: THE USE OF PACLITAXEL IN THE FIRST LINE TREATMENT OF OVARIAN CANCER

AUTHORS: Beard S M, Coleman R E, Radford J and Tidy J A. Sheffield: Trent Institute for Health Services Research, Universities of Leicester, Nottingham and Sheffield 1998. Guidance Note for Purchasers: 98/10.

EXPERT ADVISORS TO TRENT DEC: Mr S M Beard, Senior Operational Research Analyst, ScHARR. Dr J Radford, Director of Public Health, Doncaster Health Authority. Mr J A Tidy, Senior Lecturer in Gynaecology, Northern General Hospital, Sheffield.

(The recommendations made by the Committee may not necessarily match the personal opinions expressed by the experts.)

DECISION: The Committee considered that the evidence in the supplementary document supported its initial decision that Paclitaxel should be available for patients within nationally controlled trials, and for other patients at the discretion of the clinicians. This decision was in line with the recent clinical consensus document and a Joint Council for Clinical Oncology (JCCO) statement.

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S M Beard
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Trent Institute for Health Services Research
Universities of Leicester, Nottingham and Sheffield

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Conflict of Interest None of the authors of this document has any financial interests in the drug or product being evaluated here.

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ABOUT THE TRENT INSTITUTE FOR HEALTH SERVICES RESEARCH

The Trent Institute for Health Services Research is a collaborative venture between the Universities of Leicester, Nottingham and Sheffield with support from NHS Executive Trent.

The Trent Institute:

- undertakes Health Services Research (HSR), adding value to the research through the networks created by the Institute;
- provides advice and support to NHS staff on undertaking HSR;
- provides a consultancy service to NHS bodies on service problems;
- provides training in HSR for career researchers and for health service professionals;
- provides educational support to NHS staff in the application of the results of research;
- disseminates the results of research to influence the provision of health care.

The Directors of the Institute are: Professor R L Akehurst (Sheffield);
Professor C E D Chilvers (Nottingham); and
Professor M Clarke (Leicester).

Professor Clarke currently undertakes the role of Institute Co-ordinator.

A Core Unit, which provides central administrative and co-ordinating services, is located in Regent Court within The University of Sheffield in conjunction with The School of Health and Related Research (ScHARR).

FOREWORD

The Trent Working Group on Acute Purchasing was set up to enable purchasers to share research knowledge about the effectiveness and cost-effectiveness of acute service interventions and determine collectively their purchasing policy. The Group is facilitated by The School of Health and Related Research (ScHARR), part of the Trent Institute for Health Services Research, the ScHARR Support Team being led by Professor Ron Akehurst and Dr Nick Payne, Consultant Senior Lecturer in Public Health Medicine.

The process employed operates as follows. A list of topics for consideration by the Group is recommended by the purchasing authorities in Trent and approved by Health Authority and Trust Chief Executives (HATCH) and the Trent Development and Evaluation Committee (DEC). A public health consultant from a purchasing authority leads on each topic assisted by a support team from ScHARR, which provides help including literature searching, health economics and modelling. A seminar is led by the public health consultant on the particular intervention where purchasers and provider clinicians consider research evidence and agree provisional recommendations on purchasing policy. The guidance emanating from the seminars is reflected in this series of Guidance Notes which have been reviewed by the Trent DEC, chaired by Professor Sir David Hull.

In order to share this work on reviewing the effectiveness and cost-effectiveness of clinical interventions, The Trent Institute's Working Group on Acute Purchasing has joined a wider collaboration, InterDEC, with units in other regions. These are: The Wessex Institute for Health Research and Development, The Scottish Health Purchasing Information Centre (SHPIC) and The University of Birmingham Department of Public Health and Epidemiology.

Professor R L Akehurst
Chairman, Trent Working Group on Acute Purchasing

LIST OF ABBREVIATIONS

AOC	Advanced Ovarian Cancer
ASCO	American Society of Clinical Oncology
AUC	Area Under the Curve
CAP	Cyclophosphamide/cisplatin/doxorubicin
CP	Cyclophosphamide/cisplatin
CR	Clinical Response
DoH	Department of Health
ECOCIT	European-Canadian Ovarian Cancer Intergroup Trial
EORTC	European Organisation for Research and Treatment of Cancer
FIGO	International Federation of Obstetricians and Gynaecologists
GOG	Gynecologic Oncology Group
IDS	Interval Debulking Surgery
JCCO	Joint Council for Clinical Oncology
LYS	Life Year Saved
NCIC	Canadian National Cancer Institute
NOCOVA	Scandinavian Gynaecological Cancer Study Group
ONS	Office for National Statistics
PFYG	Progression-free Year Gained
QALY	Quality Adjusted Life Year
QoL	Quality of Life
RCT	Randomised Controlled Trial
SMAC	Standing Medical Advisory Committee
TP	Paclitaxel/cisplatin
Trent WGAP	Trent Working Group on Acute Purchasing
WHO	World Health Organisation

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EXECUTIVE SUMMARY

Carcinoma of the ovary is the commonest gynaecological malignancy and the fourth most common cause of cancer death in women. Around 70-80% of diagnosed patients are at stages III/IV with five year survival rates at less than 30% for those patients in advanced disease states. Based on data from the Office for National Statistics, it is estimated that ovarian cancer is responsible for between 4,500-5,000 deaths in the UK every year.

In the last few years the drug paclitaxel has been introduced in treatment regimens, in combination with platinum drugs. In the US the combination paclitaxel/cisplatin is now considered to be the gold standard first-line therapy for advanced ovarian cancer. An internationally based inter-group trial, led by the European-Canadian Ovarian Cancer Inter-group Trial (ECOCIT), was presented at the American Society of Clinical Oncology (ASCO) annual meeting in Los Angeles in May 1998. This trial follows the earlier GOG-111 trial, which originally indicated the potential overall survival and progression-free survival benefits of paclitaxel in first-line therapy.

Including more than 1,000 patients with advanced disease, the two trials appear to have considered similar groups of patients, in terms of prognostic factors and general patient characteristics. The ECOCIT covered a slightly wider scope of severity with the inclusion of lower stage II disease. However, this represented only a small proportion of all recruited patients. Both trials randomised patients in a balanced way across the two treatment arms.

Taken together, the trials report clear and significant clinical advantages for paclitaxel/cisplatin over cyclophosphamide/cisplatin based first-line therapy in terms of both progression-free survival (4-5 months/0.3-0.4 life years saved) and overall survival (10-14 months/0.8-1.2 life years saved). These advantages appear to hold firm irrespective of patient prognostic factors and severity of disease.

Clear, significant advantages in terms of clinical response were also noted in both trials, with that in the paclitaxel-based arms reported at 73-77% compared with a 60-66% clinical response in control arm patients.

Using UK based estimates of treatment cost, the marginal cost per patient of paclitaxel/cisplatin therapy is £8,000. This represents a marginal cost of approximately £260,000 for a ‘typical’ district, assuming that 35% of patients would not be suitable for cisplatin-based treatment.

Comparing these marginal costs with the benefits predicted from the randomised trial evidence, it is estimated that the cost per life year saved lies in the range £7-11,000. This is based on a prediction of benefits comparing single-point median survival times. A similar comparison of progression-free survival indicates a cost per progression-free year of between £20-22,000.

A sensitivity analysis was also conducted to explore the overall impact of potential reduction in hospitalisation costs due to shorter infusion times, but higher drug costs of dosage escalation, implied by the ECOCIT. This analysis indicates that the cost per life year range could be expected to be relatively little changed at around £7-12,000, given this form of higher dose regimen.

The analysis also considered the potential range of the ratio of the trial median survival times of paclitaxel/cisplatin against cyclophosphamide/cisplatin. This confirmed the median survival time ratio as 1.4 (1.1 - 1.8 C.I. 95%) in favour of paclitaxel/cisplatin. Based on these figures the marginal survival benefit could fall anywhere between 0.3-1.6 life year gained.

Since the publication of the Trent Institute Working Group on Acute Purchasing Guidance Note No. 97/05, in 1997, there have been eight separate cost-effectiveness studies published in peer reviewed journals. Although the studies are set within the context of different health care systems, and measure benefits in a number of different units, it is interesting to note that the cost-effectiveness ratios remain within a range of £5-15,000 per life year saved. These studies have been based on a mixture of modelled analysis and retrospective case-series reporting.

The other major on-going trial which would also inform the first line paclitaxel debate is ICON 3, currently being conducted by the MRC within the UK. The trial aims to compare paclitaxel in combination with carboplatin against control arms of either single agent carboplatin or cyclophosphamide/cisplatin/doxorubicin (CAP). This trial has currently finished its recruitment phase, targeting around 2,000 patients, and is generally expected to begin producing interim results around the year 2000, but with full reporting some 2-3 years away.

The key messages of the ECOCIT appear positive, confirming the clinical benefits achieved in the original GOG-111 trial. The results have been presented and debated in the context of local and national gynaecology group meetings, with positive clinical statements produced in the form of a recent clinical consensus document and a Joint Council for Clinical Oncology (JCCO) statement. The JCCO statement is widely expected to be endorsed by the NHS

Standing Medical Advisory Committee (SMAC). However, it is important to note also that the results of the ECOCIT have been communicated to date in abstract and presentation forms only, and have not been subject to any peer review process.

Final publication and dissemination of the ECOCIT results are expected to re-enforce this clinical view. The eventual completion and publication of the ICON 3 results, in about two years' time, will allow these conclusions to be revisited with regard to a carboplatin/ paclitaxel rather than a cisplatin/paclitaxel combination.

It is concluded that the quality of newly available evidence further supports the use of paclitaxel, in combination with platinum compounds, in the first-line treatment of advanced ovarian cancer.

1. INTRODUCTION

Carcinoma of the ovary is the commonest gynaecological malignancy and the fourth most common cause of cancer death in women.[1]

Within a 'typical' district there are expected to be around 100 newly reported cases of ovarian cancer every year. The reported annual incidence rate for the Trent region is around 19 per 100,000 women.[2] The Trent figures also indicate that approximately 50% of these cases are in women over the age of 65. With presentation of disease often delayed, due to the insidious nature of the illness, patients are often found to have advanced stages of disease at final diagnosis. International Federation of Obstetricians and Gynaecologists (FIGO) data suggest that around 70-80% of diagnosed patients are in stages III/IV at initial presentation.[3] Long-term prognosis is also generally poor, with five year survival rates for patients in advanced disease states quoted at less than 25-30%.[1] Based on figures from the Office for National Statistics (ONS) it is estimated that ovarian cancer is responsible for between 4,500-5,000 deaths in the UK every year.

To date, chemotherapy-based treatments for advanced ovarian cancer (AOC) have been based around platinum compounds, after analysis of early trial data suggested clear advantages over non-platinum-based therapy. The two key platinum drugs are cisplatin and carboplatin, which have been generally accepted to be of equal efficacy when used as single agent therapy.[4,5,6]

More recently, platinum combination therapy has been promoted as a new alternative, the two most commonly used regimens being cyclophosphamide/cisplatin/doxorubicin (CAP) and cyclophosphamide/cisplatin (CP).[7,8] Over the last few years the drug paclitaxel has also been introduced in treatment regimens, again in combination with platinum drugs. In the USA, paclitaxel/cisplatin (TP) is now considered the gold standard first-line therapy for AOC. This followed the publication in 1996 of a single randomised controlled trial (RCT) GOG-111, which compared TP to the then USA conventional approach based on CP therapy.[9]

In 1997, the Trent Working Group on Acute Purchasing (Trent WGAP) produced a Guidance Note for Purchasers considering the evidence of effectiveness for paclitaxel in the first-line treatment of patients with AOC.[10] The report was produced to support purchasing authorities in their decision-making processes as they came under increasing pressure to consider providing financial support for new paclitaxel-based therapies.

In identifying a suitable comparator, the Trent WGAP paper selected single agent carboplatin as the current UK standard therapy. The marginal cost of TP treatment was estimated to be around £8,500, representing the extra treatment costs above those already indicated for UK conventional treatment, based on single-agent carboplatin. As the control arm of the GOG-111 trial was not based around UK standard therapy, conservative clinical assumptions were taken to allow the original trial outcome data to be used directly as a proxy for carboplatin. On this basis the TP arm was predicted to provide a 1.1 life year gain (LYG) per patient. Cost per LYG figures lay in the range £7-8,000, and these remained under £20,000 even after exploring wide confidence intervals to both costs and benefits through sensitivity analysis. The estimated marginal cost to an average health authority was estimated to be approximately £260,000, based on an uptake of therapy in around 65% of ovarian cancer patients. This represents those patients in advanced stage disease who are expected to have a functional status, measured as European Clinical Oncology Group (ECOG) performance status 0-2, sufficient to allow them to undergo TP based treatment.

The Trent WGAP report concluded that, although based on only a single RCT, the evidence of clinical effectiveness was of a good quality, having been conducted by a well respected clinical group with adequate controls and a solid trial design. The cost-effectiveness ratios suggested by the available evidence indicated that TP therapy was comparable with existing supported therapies for ovarian cancer.

As part of its recommendations, the Trent WGAP also suggested that the evidence should be reviewed further at some future date. This future review was deemed necessary because:

- The clinical evidence was still based on a single trial only;
- The control arm used represented a conventional therapy not commonly used in the UK (requiring some clinical assumptions in the calculation of benefits);
- A large confirmative RCT trial was expected to complete within 18 months of publication;
- Other ongoing RCTs were considering the use of paclitaxel in other combinations (i.e. with carboplatin, at different infusion rates etc.).

The European-Canadian Ovarian Cancer Inter-group Trial (ECOCIT) was presented at the American Society of Clinical Oncology (ASCO) annual meeting in Los Angeles in May 1998. This trial represents an internationally-based study and was conducted through the European Organisation for Research and Treatment of Cancer (EORTC), the Canadian National Cancer Institute (NCIC), the Scottish Gynaecological Study Group (GCSG) and Scandinavian Gynaecological Cancer Study Group (NOCOVA). The rationale behind the

trial design was to provide an opportunity to provide independent consideration to the results of the original Gynecologic Oncology Group (GOG) trial. Data from the ECOCIT have been released in abstract form, with a full publication in a peer-reviewed journal expected later.[11] Moreover, the EOCIT results have been subject to critical consideration through the development of a recent statement by the Joint Council for Clinical Oncology (JCCO) and the publication of a clinical consensus document, as well as the ASCO process itself.

The recently published clinical consensus document cites the results of both the ECOCIT and the earlier GOG-111 trial and strongly advocates the introduction of TP as a recommended first-line therapy for AOC.[12] The consensus document also points towards the outcome advantage of managing patients though specialist multidisciplinary teams, an issue further recognised and supported by the Royal College of Obstetricians and Gynaecologists and the British Gynaecological Cancer Society.[13] The consensus panel covered a wide range of UK clinicians and was co-ordinated under the guidance of Dr Martin Gore of The Royal Marsden Hospital.

The published statement from the JCCO recommends that a combination of paclitaxel and a platinum compound is the most effective first-line therapy for ovarian cancer patients, and that the majority of patients should be considered for this treatment. The statement also calls for regular audits of treatment for ovarian cancer.[14]

Wider commissioning guidelines, covering all gynaecological cancers, are planned for release in early 1999. These guidelines, forming part of the implementation process of the Calman/Hine recommendations, are intended to provide guidance on the organisation and management of services for all gynaecological cancers including AOC.[15] However, as a result of the recent movement in the AOC evidence-base, and with the expected increase in pressure on health authorities to provide new treatments for AOC, the Department of Health (DoH) has now made a direct request for a follow-up evidence review document. The purpose of this supplementary document to the Trent WGAP report is to support the DoH in its dissemination of evidence, through the Standing Medical Advisory Committee (SMAC), to health authorities throughout the UK, prior to the release of these wider gynaecological guidelines.

This supplementary document considers the latest evidence of clinical effectiveness and should be read alongside the original Trent WGAP document.[10]

2. USE OF PACLITAXEL IN THE FIRST LINE TREATMENT OF OVARIAN CANCER: SUMMARY OF EVIDENCE OF EFFECTIVENESS

To date, the published evidence of clinical effectiveness for the use of TP as a first-line treatment in AOC has come exclusively from a single RCT conducted by the Gynecologic Oncology Group (GOG), the GOG-111 trial.[9] This trial was considered in some detail within the original Trent WGAP report and formed the basis of the economic analysis presented. The trial was well supported and welcomed by clinicians, although there was a general view that confirmatory data would add further weight to the evidence-base.[16]

The GOG-111 trial was published in the New England Journal of Medicine in 1996 and was the first large randomised trial to consider the role of paclitaxel as a first line therapy. The trial was based on 400 women with advanced staged disease and showed clear advantages in terms of both progression-free survival and overall survival, although only the latter was a primary end-point of the trial. The following tables summarise the clinical benefits suggested by the trial. A fuller consideration of the trial design and outcomes can be found in the Trent WGAP report.[10]

GOG-111 Trial Results

Table 1 GOG-111 Median Survival

Regime	Median Survival	95% CI Interval
Paclitaxel/Cisplatin (TP)	38 months	32 - 44 months
Cyclophosphamide/Cisplatin (CP)	24 months	21 - 30 months
Marginal Benefit	14 months($p < 0.001$)	

Table 2 GOG-111 Median Progression-free Survival

Regime	Median Progression-free Survival	95% CI Interval
Paclitaxel/Cisplatin (TP)	18 months	16 - 21 months
Cyclophosphamide/Cisplatin (CP)	13 months	11 - 15 months
Marginal Benefit	5 months($p < 0.001$)	

The differences in both progression-free and survival benefits were both significant ($p < 0.001$) and favoured the TP group over the CP group.

More recently, a second RCT has reached completion, which again considers the role of TP in the first-line treatment of AOC. This multicentre international trial, co-ordinated by the ECOCIT, reported at the May 1998 meeting of the ASCO.[11] The results from the trial are expected to be published in full.

The overall rationale for the ECOCIT was to provide an independent body of evidence either to confirm or refute the results of the GOG-111 trial. This confirmatory trial is generally seen as providing further support to the results of the GOG-111 trial, and the general clinical opinion within the UK is that it will prove to be the catalyst for a world-wide movement towards TP being introduced as a recommended first-line treatment.[12]

Currently, the only publicly available evidence upon which any judgements of the ECOCIT can be made are:

- abstract published for the ASCO 1997 meeting;[17]
- copies of interim results slides presented at ASCO 1997;[18]
- abstract published for the ASCO 1998 meeting;[11]
- copies of final results slides presented at ASCO 1998;[19]

The remainder of this chapter provides a summary of the abstract published ECOCIT data, making direct comparisons to the GOG-111 trial, where appropriate, and drawing together an up-dated picture of the current state of the evidence for the clinical effectiveness of TP.

2.1 ECOCIT Design

2.1.1 Trial End-points

The primary end-point of the trial was progression-free survival, with secondary end-points targeted at: overall survival; clinical response rate; and quality of life. Cost-effectiveness was also cited as a secondary outcome, although no data are provided. The key reason for this secondary consideration of survival was the fact that the trial allowed cross-over to paclitaxel for control-group patients with disease progression. The expected effects of approved cross-over are a reduction in the likelihood of any significant survival difference being detected. This contrasts with the GOG-111 trial, which was primarily focused on overall survival as a trial end-point; cross-over was far more limited in this case as paclitaxel was not generally available. This fact is an important one, as the GOG-111 survival data are likely to be unique in the fact that they are influenced by limited patient cross-overs.

2.1.2 Treatment Arms

The ECOCIT was conducted on 680 ovarian cancer patients, who were randomised in roughly equal numbers over two treatment groups using CP as a control arm, as in the GOG-111 trial. This represents a much larger group of patients than covered by the GOG-111 trial, which was based on 410 similarly randomised patients.

The following summarises the specific treatment regimens used in the two treatment arms.

Table 3 ECOCIT Treatment Arms

Arm A (Control Arm)	Arm B (Treatment Arm)
• Cyclophosphamide 750 mg/m^2 • Cisplatin 75 mg/m^2 • Repeated every three weeks • Up to nine cycles • IDS allowed • Number of patients = 330	• Paclitaxel 175-200 mg/m^2 • 3 hour infusion • Cisplatin 75 mg/m^2 • Repeated every three weeks • Up to nine cycles • IDS allowed • Number of patients = 338

IDS = Interval Debulking Surgery *Source : Proc ASCO Vol 17 1998*

As with the GOG-111 trial, the control arm used is based on CP. This is not typical of the UK where conventional treatment is generally based on either single agent carboplatin or CAP.[7]

Importantly, the dosage of cisplatin in the control arm represents optimum treatment as, beyond this level, renal toxicity would cause significant side-effects.

2.1.3 Patient Characteristics

The severity of disease was much broader in the ECOCIT, with optimally debulked patients at stage II accepted. The earlier GOG-111 trial had been more restrictive in terms of patient disease severity, limiting entry to those with surgically sub-optimally debulked stage III/IV disease. However, patient characteristics show that in both trial arms roughly 93-94% of patients were at either stage III or stage IV of advanced disease. The World Health Organisation (WHO) performance status was also similar across both groups, with comparable age ranges and overall median ages of 58 in both arms. This compares with median ages of 59-60 in the GOG-111 trial, and similar ranges from around 20-80. The

distribution of cell-type between the patient groups was virtually identical in the two ECOCIT arms, and was also very similar to those reported in the GOG-111 trial.

Optimal residual disease was defined as none, microscopic or <1cm maximum dimension.

Interval debulking surgery (IDS) was permitted in ECOCIT with 8-9% of patients in both arms operated on after the first three courses of chemotherapy. Second-look surgery was optional in the trial and was conducted in 17% and 21% of the CP and TP arms respectively.

Table 4 ECOCIT Patient Characteristics

	Control Arm: CP		**Treatment Arm: TP**	
Number	330		338	
Median Age & Range	58 (22-85)		58 (23-79)	
	Number	**%**	**Number**	**%**
WHO Performance Status				
0	168	51%	157	46%
1	119	36%	135	40%
2	39	12%	40	12%
3 or missing	4	1%	6	2%
FIGO[a] Stage				
II	24	7%	21	6%
III	235	71%	253	75%
IV	71	22%	64	19%
Tumour Grade				
1	26	8%	27	8%
2	82	25%	91	27%
3	190	58%	193	57%
Missing or Not Applicable	32	10%	27	8%
Cell Type				
Serous adenocarcinoma	208	63%	234	69%
Endometrioid adenocarcinoma	44	13%	31	9%
Mucinous adenocarcinoma	17	5%	12	4%
Clear-cell adenocarcinoma	17	5%	15	4%
Other	44	14%	46	14%

Source : Proc ASCO Vol 17 1997

[a] FIGO - International Federation of Obstetricians and Gynaecologists

The following shows the rough split of patients over the treatment arms based on levels of debulking:

Table 5 Residual Disease Presence in the ECOCIT

	Control Arm : CP		Treatment Arm : TP	
Optimal Residual Disease	111	33%	138	38%
Suboptimal Residual Disease	216	65%	209	62%
Presence Of Measurable Disease	151	46%	149	44%

Source : Proc ASCO Vol 17 1998

2.1.4 Summary of Trial Characteristics

The key differences between the ECOCIT and the GOG-111 trials are summarised as:

1. the ECOCIT allowed entry for optimally debulked patients (i.e. less severe prognosis group);
2. TP treatment was based on a 3-hour infusion and a slightly higher dosage of paclitaxel;
3. the primary end-point was progression-free survival;
4. paclitaxel was available as salvage for control arm patients with disease progression.

The following table compares and summarises further the designs of the two main trials.

Table 6 Comparison of the GOG-111 and ECOCIT Randomised Trials

Design Aspect	ECOCIT	GOG-111
Patient Groupings	Sub-optimal & Optimal Residual Disease FIGO IIB IIC III IV	Sub-optimal Residual Disease FIGO III IV
Cisplatin Dosage	75mg/m^2	75mg/m^2
Paclitaxel Dosage	175-200 mg/m^2	135 mg/m^2
Paclitaxel Infusion	3 hours	24 hours
Number of Cycles	Up to a maximum of 9 (repeated every 3 weeks)	6 (repeated every 3 weeks)
Interval Debulking Surgery	Optional	No
Second Look Surgery	Optional	Yes
Patient Numbers	680 randomised 668 patients eligible	410 randomised 386 patients eligible
Median Follow-up	30 months	37 months
Recruitment/Study Period	4/1994 to 8/1995 (18 months)	Not known

The two trials appear to have considered similar groups of patients in terms of prognostic factors and general patient characteristics. The ECOCIT covered a much wider scope of disease severity with the inclusion of lower stage II disease and well debulked stage III disease. This represented around a third of all recruited patients. The trial protocol provides some detail on method of patient randomisation and cites the minimisation technique detailed by Pocock et al.[20] The reported patient characteristics appear to suggest an acceptable randomisation of patients between the two treatment arms.

2.2 ECOCIT End-point Data

The only published outcome data from the ECOCIT results come from abstracts published and presented at the ASCO 1997 and 1998 meetings. The first abstract and presentation form an interim analysis and, together, claimed a higher clinical response rate (77%

compared to 66%) for the TP arm over the CP arm. This advantage was statistically significant with a p-value of 0.02. The presentation also referred to a longer progression-free survival (16 months compared to 12 months) again in favour of the TP arm. Importantly, this difference in progression-free survival was noted in patients with either sub-optimal or optimal disease.

Table 7 ECOCIT Abstract - Primary Outcome Progression-free Data

Source : Proc ASCO Vol 17 1998

	CP	TP	p-value
Median Progression-free Survival (months)	12	16	p=0.0001

Presenting an up-dated analysis, the 1998 abstract reports on a median trial follow-up period of 28 months. This appears to confirm both the differences in clinical response rate and progression-free survival as presented at the 1997 ASCO meeting. The abstract goes further in presenting the following table, highlighting statistically significant differences in the secondary trial end-point of overall survival.

Table 8 ECOCIT Abstract - Secondary Outcome Survival Data

	CP	TP
Events/Patients	168/337 (49.9%)	131/342 (38.3%)
Median Overall Survival (months)	25	35
Logrank p-value	p<0.001	

Source : Proc ASCO Vol 17 1998

Further trial details and outcomes, outside the scope of the original published abstract data, have been presented at the ASCO 1998 meeting. These data help to provide a more in-depth view of the significance of clinical outcomes and also begin to allow for the effects of case-mix to be taken into consideration. Therefore, the remainder of the review of trial outcome data has been based on the content of the original presentation slides, which remains unpublished in any peer reviewed journal. These data have also been reviewed by the UK clinical consensus group and the JCCO.[14]

In terms of the general principles adopted by the trial group, the outcome data have been analysed under the following conditions:

- Outcome analysis from the trial is based on an intention-to-treat basis;
- Kaplan-Meier techniques have been used to analyse the outcome data using 2-sided logrank tests to identify the level of statistical significance;
- A Cox-regression analysis has been conducted to adjust outcomes for a range of prognostic factors;
- The presented data are based on a 30 month median patient follow-up.

2.2.1 Progression-free Survival

The primary end-point of the trial was progression-free survival. The following table presents the results both with and without adjustments for prognostic factors. The median progression-free survival was 16.6 months in the TP arm, compared with 12 months in the CP control arm. This difference of over four months was statistically significant ($p<0.001$) and remained so after prognostic adjustment. The confidence intervals remain somewhat tight around the relative risks and do not approach unity. The risk ratio has been calculated using Kaplan- Meier survival curve techniques over the whole of the trial period.

Table 9 Progression-free Survival Unadjusted/Adjusted for Prognostic Factors

	Risk Ratio	**95% C.I.**	**p-value**
Unadjusted	0.68	0.57 to 0.81	<0.001
Adjusted for Prognostic Factors	0.66	0.54 to 0.79	<0.003

Source : Proc ASCO Vol 17 1998

median follow-up 30 mths

2.2.2 Overall Survival

Although only intended as a secondary outcome, significant differences were also found in overall survival ($p < 0.001$). Importantly, this is despite the allowed cross-over to Paclitaxel for control arm patients at onset of disease progression, coupled with the intention-to-treat basis of the analysis. Again, adjustment for prognostic factors did not alter this difference greatly.

Table 10 Survival Unadjusted/Adjusted for Prognostic Factors

	Risk Ratio	95% C.I.	p-value
Unadjusted	0.70	0.56 to 0.87	<0.001
Adjusted for Prognostic Factors	0.71	0.57 to 0.89	<0.003

Source : Proc ASCO Vol 17 1998

median follow-up 30 mths

Taken together, the data presented at the ASCO meeting appear to confirm that both the survival and progression-free advantages of TP remain significant in both sub-optimal and optimal residual disease. This is an interesting result as it appears to suggest that, even in patients with less advanced disease, an advantage is clear.

The fact that survival data remain significantly different, despite the allowance for wide cross-over on disease progression, would appear to suggest the advantage of TP as a first-line therapy is clear; that is, aside from its use as second and third line salvage therapy. In general, it would be expected that any large scale patient cross-over to salvage therapy within trial would reduce the difference between the overall survival results. However, it is also true that, where patients are in relapse, the advantage of any salvage therapy would be expected to be greatly reduced.

2.2.3 Pooled Survival Data

The recently issued consensus document suggests the following pooled data for the overall relative risk of survival.[12] The relative risk is assumed to be calculated from the Kaplan-Meier data plots over the period of follow-up for both trials.

Table 11 Consensus - Pooled Survival Data

Trial	n	Median Survival (months)		Relative Risk	C.I. 95%	p-value
		CP	TP			
GOG-111	386	24	38	0.6	(0.5-0.8)	<0.001
ECOCIT	686	25	35	0.71	(0.57-0.87)	0.003
Pooled	1,054	-	-	0.66	(0.56-0.77)	<0.000001

Source : Consensus Document

The approach is based on a simple meta-analysis of the two trials using the log transformations of relative risks, with weightings based on the inverse of the variances. A similar pooling analysis has been conducted by the Trent WGAP authors using the same overall relative risk data. It follows the general variance with confidence intervals methodology as supported and suggested by Petitti et al. 1994.[21] This approach assumes a fixed-effects basis to the meta-analysis and enables the pooled risk ratio to be calculated, along with variance and confidence intervals, using only published trial estimates of relative risk. The validity of the test relies on the trial data passing a test of heterogeneity. The results of the Trent WGAP analysis are virtually identical to those presented in the consensus document.

Table 12 Trent - Pooled Survival Data

Pooled Trial Data	Relative Risk	C.I. 95%	p-value
Trent Approximation	0.64	(0.56-0.77)	<0.000001
Consensus Approximation	0.64	(0.56-0.74)	<0.000001

This small meta-analysis of the two trials confirms a real clinical difference in terms of survival, with a narrowing of the confidence intervals when pooling the trial data.

2.2.4 Confidence Interval on Median Survival Times

It is possible, from the data presented in abstract form, to calculate a confidence interval around the ratio of median survival times. The purpose of this is to explore the range within which the difference in the medians could realistically be expected to lie.

The method for calculating the confidence interval of the ratio is covered by Altman and is based on an approximation of variance based on the number of observed events.[22] An assumption of exponentially distributed survival times is required and, although easily checked, the raw data are required. Based on this approach, and assuming that exponential survival times hold, the following results are suggested.

Table 13 Confidence Interval of Median Survival Difference

Median Survival (months)		Difference in Median Survival	Ratio of Median Survival	C.I. 95% (months)	
CP	TP	(months)	(TP/CP)	Lower	Upper
25	35	10	1.40	1.11	1.76

The 95% confidence interval does not cross unity, again providing support to the strength of survival benefit towards TP. This calculation is obviously closely related to the risk ratio calculations presented at the ASCO meeting.

This information is also very useful in implying the range of confidence that should be adopted in using the difference in median survival outcome in the calculation of cost-effectiveness ratios. This issue is expanded in Chapter 3.

2.2.5 Prognosis Factors

The following table highlights the range of prognostic factors used in the Cox-regression analysis. These factors cover issues of severity of disease and patient morbidity and again are similar to the patient classification data used in the analysis of the GOG-111 data.

Table 14 Prognostic Factors

Prognostic Factor	Range
Age	<=58 years, >58 years
WHO performance status	0,1,2,3
FIGO stage	II,III,IV
Histology	serous, other
Grade	1,2,3,UK
Measurability	Yes, No, NED
Residual Disease	No, <=1cm, >1cm

Source : Proc ASCO Vol 17 1998

2.2.6 Clinical Response

The ECOCIT reports rates of clinical response (CR) to treatment in those with measurable disease after debulking surgery. These rates show a significant difference in the level of CR (p=0.02); however, the strict definitions of CR are not provided in the presentation slides.

Table 15 ECOCIT Clinical Response Rates

Treatment Arm	Complete Response	Partial Response	Clinical Response	Surgical Response
TP	50%	27%	77%	47%
CP	36%	30%	66%	24%
Difference	14%	-3%	11% (p=0.02)	23%

Source : Proc ASCO Vol 17 1997

This level of difference is also reflected in the results of the original GOG-111 trial where the levels of response were observed in 216 patients with measurable disease after debulking surgery.

Table 16 GOG-111 Clinical Response Rates

Treatment Arm	Complete Response	Partial Response	Clinical Response
TP	51%	22%	73%
CP	31%	29%	60%
Difference	20% (p=0.01)	-7%	13%

Source : Proc ASCO Vol 17 1998

2.2.7 Patient Drop-outs

The GOG-111 trial reports a total 160 out of 184 patients successfully completing the TP regimen, representing an 87% completion rate. This compares with 158 of 202 patients, or 78%, completing the conventional CP treatment. When considering those drop-outs for reasons other than clinical disease progression or death, the apparent difference between treatment arms reduces with only an 8% drop-out rate in the TP arm compared to 10% in the CP arm.

The ASCO presented data do not allow us to make any real judgement about the levels of patient drop-out during the trial. If accessible, this could be compared to the results of the GOG-111 trial, which appear to show no real difference in terms of drop-outs related to the levels of toxicity.

What is provided is a breakdown of reasons for ineligibility following the initial randomisation or trial entry of patients. In total, 12 patients were excluded from the ECOCIT due to: wrong histology(6); second malignancy(4); wrong stage(1); and poor medical condition(1). This compares with 24 patients ruled out of the GOG-111 trial due to: inappropriate staging(3); histology(13); cell type(3); history of cancer(4); and wrong surgery type(1).

2.2.8 Observed Toxicity

In a review of the toxicity events noted during the ECOCIT, the following areas were identified as being associated with significantly higher rates in the TP arm:

- alopecia;
- hypersensitivity;
- neurotoxicity;
- severe arthralgia;
- myalgia.

It was also noted that grade 3 and 4 nausea and vomiting was less common in the TP arm. Both arms were noted to have comparable grade 3 and 4 neuropenia.

The GOG 111 trial reported significant differences in toxicity with TP being associated with higher rates in the following areas, $p<0.05$:

- alopecia;
- neutropenia;
- febrile neutropenia;
- peripheral neurotoxicity.

The interim report comments on the comparatively higher rates of severe neurotoxicity in the ECOCIT compared to the GOG-111 trial. This is speculated to be due to the higher doses and shorter infusion times used. Without further data behind the rates of toxic events, it is difficult to draw any further conclusions from the trial comparisons. These data would be particularly useful in establishing patient quality of life estimates.

2.2.9 Patient Cross-Over

As previously stated, patients in the control arm were allowed to switch treatment to salvage TP therapy on the onset of disease progression. The final analysis reports that 52% of patients from the control arm crossed over to a paclitaxel-based therapy at some point in the trial.

Following the 6th cycle of therapy, patients who remained disease-free were allowed to move to different combinations of their existing therapy. However, control arm patients were not allowed to receive paclitaxel.

The following table is taken from the interim analysis in 1997 and shows the levels of dose escalation of paclitaxel-treated patients. The table also highlights the number of patients who had their cisplatin component substituted by carboplatin. This change of platinum component was only allowed after six cycles of therapy and only in cases where patients were experiencing renal- neuro- or ototoxicity related to the cisplatin.

Table 17 ECOCIT Patient Switching

	Control Arm : CP		Treatment Arm : TP	
No. of patients where carboplatin was substituted for cisplatin (after 6 courses of therapy)	30	9%	43	12%
No. of patients increasing their paclitaxel dosage	-	-	233	70%

It is interesting to note that a large proportion of the paclitaxel-treated patients experienced dose escalation, i.e. 200 mg/m^2. The trial protocol allowed TP treated patients to move to this higher dosage of paclitaxel if they experienced no toxic effects after the first cycle. If problems were then experienced, patients returned to the original dosage for the remaining cycles.

Cisplatin dosage was reduced by 20% of the original dosage if febrile neutropenia was evident after the first or subsequent treatment cycles.

2.2.10 Quality of Life Indicators

A limited amount of quality of life analysis has been conducted by the trial group. This has been based on patient views taken via questionnaire. Changes in these patient views were compared to 210 baseline patients. This questionnaire covered areas such as:

- fatigue;
- constipation;
- appetite loss;
- pain;
- insomnia;
- cognitive functioning;
- global Quality of Life.

The exact tools used to measure these quality of life (QoL) score changes are not detailed. Early reports suggest that the QoL in the two treatment arms is roughly comparable, with some significant differences in favour of both CP and TP, but only at specific time-points. There are plans, however, for further longitudinal analysis. This is likely to appear in greater detail in the final published paper.

2.3 Remaining Evidence of Effectiveness

Besides the GOG-111 trial and the ECOCIT, there are two further trials which have been reported in abstract form. These trials help to add to the body of knowledge regarding the use of paclitaxel.

du Bois

The du Bois[23] trial compared TP with a treatment of carboplatin/paclitaxel in a group of 798 patients. As in the GOG-111 trial, cisplatin was used at a dosage of 75mg/m^2 and the paclitaxel was infused over a three hour period. However, the dosage of paclitaxel was increased to 185 mg/m^2. This set of interim results indicates a median progression-free survival of 16.6 months for the patient group as a whole, with no significant difference between the treatment arms. A 74% CR rate is also reported, again similar to the findings of the GOG-111 trial and the ECOCIT. Apart from alopecia, non-haematological toxicity occurred more frequently in the cisplatin arm. QoL measurement pointed towards a much inferior patient experience ($p<0.008$) in the cisplatin arm.

GOG-132

The GOG-132 trial[24], conducted in over 600 patients, compared three treatment regimens:

- Combination therapy - paclitaxel infused over a 24 hour period at a dosage of 135 mg/m^2, cisplatin was set at a dosage of 75mg/m^2;
- Single agent therapy - cisplatin dosage was higher at 100 mg/m^2;
- Single agent therapy - paclitaxel was infused over a 24 hour period at a dosage of 200 mg/m^2.

Table 18 GOG-132 Trial Results

GOG132	Number of Patients	Median Progression-free Survival (months)	Median Overall Survival (months)
Paclitaxel/cisplatin (TP)	201	14	26
Cisplatin	200	16	30
Paclitaxel	213	11	26

The results of this trial appear to contradict the earlier findings of the GOG-111 trial and the ECOCIT. The results point towards no significant differences between high dose (100mg/m^2) cisplatin and the TP treatments. Importantly, paclitaxel, as a single agent, was proven to be significantly inferior in terms of both outcome measures.

However, the study design of this trial has been widely debated, particularly in respect of the amount of patient cross-over permitted in the early stages of treatment. A proportion of patients treated with single agent cisplatin did cross-over to the TP arm without showing any sign of clinical progression. The precise numbers of such patients remain unknown. This coincided with the abstract release of early positive results from the GOG-111 trial and it is felt that this could explain the possible shift in clinical practice. The majority clinical opinion appears to be that this trial remains very difficult to interpret as a result of this early, unquantified cross-over issue.[25]

2.4 Summary of Clinical Evidence

There now exist four independent RCTs which have considered the role of TP as a first-line treatment for AOC. All trials have been based in relatively large populations, (of at least 380 patients) and represent a broad mix of patients with advanced disease in stages IIB, IIC, III and IV. Three of these trials appear to suggest that paclitaxel, in combination with cisplatin, should be expected to provide definite patient benefits, in terms of both progression-free survival and overall survival. One trial suggests that no real difference exists, when using high dose (100mg/m^2) single agent platinum therapy. However, its study design has been questioned.

The two major trials, GOG-111 and ECOCIT, are similar in their comparison to a standard therapy based on CP. Although both trials use conventional therapies not commonly used in the UK, it is possible to make methodologically sound clinical links with the UK standard of single agent carboplatin. Previous trial data suggest that carboplatin should be expected to have very similar efficacy and outcomes to either of the control arms used.[8] Therefore, equating the control arm benefits with those expected from carboplatin should represent a fair estimate of paclitaxel's benefits.

Both trials report clinical advantages for TP over CP based first-line therapy in terms of both progression-free survival (4-5 months) and overall survival (10-14 months). These advantages appear to hold firm irrespective of patient prognostic factors and severity of disease. The trial data and analysis do not allow any patient sub-groups to be explored to identify those who would benefit more or less from treatment.

The survival differences of the ECOCIT were achieved, despite a high rate of patient cross-over to TP on eventual disease progression. This fact has been claimed by some as support to the real first-line advantage of TP, following a logical argument that, if TP were as effective in second-line therapy, we would have expected to see much closer survival results.

The ECOCIT results also point towards the efficacy of a shorter time-period of infusion for paclitaxel (three hours). This could have potential impact in terms of movement towards reducing the amount of overnight admissions, representing a potential cost saving. It is not possible, from abstract results alone, to identify the actual hospital resource usage of the TP arm. Within our cost calculations we assumed that each course would require a single night in-patient stay, although this could be arguably less depending on treatment duration.

Both trials clearly demonstrate that there is a range of toxic effects which are associated with TP; however, these do not appear to be detrimental to the overall clinical advantages of the therapy. The shorter infusion time will raise the level of some toxic effects; however, other neurological effects are reduced. It is difficult to make any further conclusions without access to more detailed data.

The other major on-going trial, which will also inform the first line paclitaxel debate, is ICON 3, currently being conducted by the MRC within the UK and Italy.[7] This trial will, for the first

time, provide data on the first line use of paclitaxel-based treatment strictly within a UK setting. The trial aims to compare paclitaxel in combination with carboplatin against control arms of either single agent carboplatin or CAP. This trial has currently finished its recruitment phase, targeting around 2,000 patients, and is generally expected to start producing interim results around the year 2000, with full reporting some 2-3 years away.

Currently, internationally-based trials are looking at direct comparisons of TP versus paclitaxel-carboplatin therapy with the expectation that a carboplatin-based combination would be less toxic.[23, 26,27] Whilst these trials are still some way off any full publication of survival outcomes, they do begin to suggest equal efficacy between the treatments in terms of both progression-free survival and CR rates. Interestingly, one trial reports progression-free survival rates of 16 months for both arms, which are again very close to those identified in both the GOG-111 trial and ECOCIT. They also suggest lower rates of neurotoxicity in the paclitaxel/carboplatin arm. In measures of patient QoL, using the ECOCIT Quality of Life Questionnaire, a significant advantage was found for the carboplatin-based arm (p=0.008). However, no firm conclusions can be drawn effectively before further publication.

The ECOCIT and GOG-111 trial appear to provide confirmation of paclitaxel's potential clinical benefits in the first-line treatment of AOC. Although not presented as yet in a peer-reviewed journal, it is likely that full publication of the ECOCIT will consolidate the data already presented to the ASCO. Given the comparative nature of cisplatin and carboplatin, it is also likely that ongoing explorations of paclitaxel in combination with carboplatin will produce similar trial results. The advantages of carboplatin may become more apparent with its reduced toxicity.

Whilst it is important to stress that the ECOCIT has only been published in abstract form, following presentation at the ASCO 1997 and 1998 meetings, this process will have involved some degree of peer review. A full published paper is anticipated and this should provide further data and more details of the actual methodology used. The paper will also allow considerations of this evidence to be discussed in the public domain. The JCCO statement and clinical consensus document also provide a considered opinion of the trial outcomes.[14]

3. COST AND BENEFIT IMPLICATIONS OF ADOPTING INTERVENTION

3.1 Revised Cost Analysis

In the original primary cost-analysis, the published median survival and progression-free statistics from the GOG-111 trial were used to bring together a picture of cost-effectiveness. It was necessary, in the absence of any published trial cost data, to base the predicted costs of TP and carboplatin therapy using UK regional costings. The range of costs used included drugs, the management of adverse effects and hospitalisation. More details of the costings used can be found in the Trent WGAP report.[10]

Table 19 Cost of Treatment

Regime	Cost Per Patient	Average District Cost	Trent Regional Cost
Paclitaxel/Cisplatin (TP)	£10,427	£321,932	£3,108,574
Carboplatin	£2,059	£63,564	£613,774
Marginal Cost Difference	£8,368	£258,368	£2,494,800

The extra or marginal cost per patient between the two treatments is estimated at £8,368.

The following table presents the original cost per life year gained (LYG) analysis and repeats the calculations using ECOCIT outcome measures. In building this cost-effectiveness analysis we have used treatment costs based on our original estimates. However, we then consider the potential impact of any reduction in hospitalisation (i.e. a move to out-patient treatment) and also a possible increase in drug dosage (175 mg) as suggested by the ECOCIT.

The economic analysis of TP varies very little irrespective of which trial results are used. The ECOCIT survival benefits show slightly less difference from those suggested by the GOG-111 trial, despite the fact that patients with a wider scope of disease severity were recruited into the study. However, they remain clearly significant.

Table 20 Revised Cost-effectiveness Analysis

		Overall Survival		Progression-Free Survival	
		GOG-111	**ECOCIT**	**GOG-111**	**ECOCIT**
(A)	Marginal LYG per person	1.17 (14 months)	0.83 (10 months)	0.42 (5 months)	0.38 (4 months)
(B)	Marginal Treatment Cost per person	£8,368	£8,368	£8,368	£8,368
(B/A)	Cost per LYG	£7,173	£10,081	£20,084	£22,021

3.2 Sensitivity Analysis

The original sensitivity analysis indicated that the cost-effectiveness argument was robust to changes in drug costs, hospitalisation costs and clinical benefits. In the case of the ECOCIT data, the reduction to a three hour infusion of TP would reduce the need for any in-patient stay to a single overnight stop. This would have the effect of reducing the potential marginal cost of the new treatment. If the three hour infusion reduced the need for in-patient stay from two days to one day per course, then the total cost of treatment for TP would fall by around £1,200. This would in turn reduce the marginal cost to around £7,000. On this basis, the cost per LYG could range between £6,000 - £8,500 depending on the trial data used. However, this would only be possible realistically if the dosage of paclitaxel were to increase.

The following table explores the cost per LYG ratio using the ECOCIT data as its basis. The analysis considers three scenarios around possible variations in terms of hospitalisation rates and dosages of paclitaxel.

Table 21 Potential Change in Cost per Life Year Gained

	Paclitaxel at 135 mg/m^2 2 days' in-patient stay (24 hr infusion)	**Paclitaxel at 175 mg/m^2 1 day in-patient stay (3 hr infusion)**	**Paclitaxel at 200 mg/m^2 1 day in-patient stay (3 hr infusion)**
Cost of TP	£10,427	£11,045	£12,365
Marginal Cost	£8,368	£8,980	£10,306
LYG	0.83	0.83	0.83
Cost per LYG	£10,081	£10,827	£12,417

As a high proportion of the TP treated patients experienced a dosage increase during the period, consideration has been given to the cost per LYG incorporating this potential increase in drug cost. Calculating 100% of the paclitaxel costs at a 200 mg/m^2 dosage, the cost of TP therapy is estimated at £10-14,000 based on six treatment courses. It is important to note that there is still no clinical evidence to indicate that 200 mg/m^2 is any better than 175 mg/m^2.

Overall, the cost-effectiveness analysis remains steady irrespective of possible movement in costs which variations in treatment regimens could bring.

3.3 Secondary Analysis

Confidence intervals on median survival

As a secondary analysis a further look has been taken at the survival event data presented in the ASCO abstract 1998. Using the methodology detailed by Altman,[22] it is possible to make approximations to the confidence range around the ratio of median survival times (see Chapter 2).

This analysis gives the range 1.11 to 1.76 years as the 95% confidence interval for the difference between the median survival times. A more accurate estimate would be possible using the actual trial data, although this calculation does at least allow the magnitude of the

range to be considered. Using this approximated confidence range, the difference between treatment could range from three months (0.3 LYG) to 19 months (1.6 LYG). On this basis the cost per LYG could vary between £5,255 - £28,000 due to a sampling error in estimating the median survival times.

An interesting analysis would be to consider further the variance of median survival from the combined trial data. This would potentially narrow the width of the confidence interval, as was seen with the pooled relative risk, or hazard ratio.

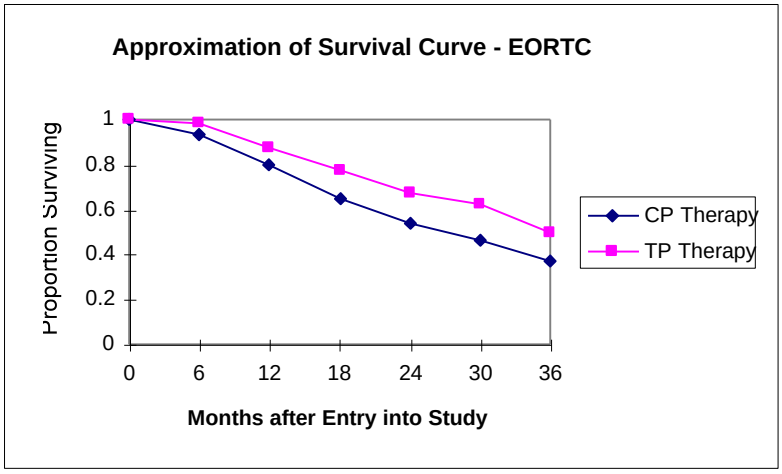
Area Under the Curve Analysis

Whilst the comparison of median survival statistics is a common approach in comparing trial arms, it is still very much a single point estimate of any real difference between the treatment effects. It may be that at other times the relative outcome differences vary. In cases where there are longer-term benefits to a treatment, as in a potential plateau state, or where early mortalities are experienced with more aggressive treatments, as in high dose therapy, median point estimates may mask the true impact of a treatment

One approach to counter this potential bias is to consider the actual area under the curve (AUC) for the two separate trial arms. A comparison of these two AUC estimates suggests an alternative estimate of benefit difference.

The following graph shows an approximation of the survival curve for the TP and CP arms of the ECOCIT. The 6-monthly data points have been taken from the presented slides and therefore, represent estimates only.

Figure 1 Area Under the Curve Estimate of Benefit



Based on these data, the AUC estimates for the TP and CP trial arms are 28 and 24 months respectively. Therefore, the implied marginal benefit of TP is four months, representing 0.33 LYG. However, in this case the patient numbers at the end of the trial remain low and long-term cure is not achieved. For this reason our main analysis is based upon median point statistics.

3.4 Published Cost-effectiveness Analysis

Since the publication of the original Trent WGAP Report there have been a number of subsequently published cost-analyses, focusing specifically on the role of TP as a first line therapy for AOC.

A follow-up literature search has been conducted to identify studies dealing specifically with the cost-effectiveness of paclitaxel. Search terms included 'paclitaxel', 'taxol', 'ovarian neoplasms', 'ovarian cancer', 'meta analysis', 'health care planning', 'economic aspects', 'costs and cost analysis', 'economics' and 'practice guidelines'. The search was conducted over the period 1994-1998.

As a result, eight key economic analyses were identified, including the original Trent based UK study, covering a variety of different health care settings including the UK, USA, Italy and Canada. Whilst all the studies necessarily have the same evidence-base, the GOG-111 trial, they use a range of different economic analyses and modelling techniques, applied in a variety of different health care contexts.

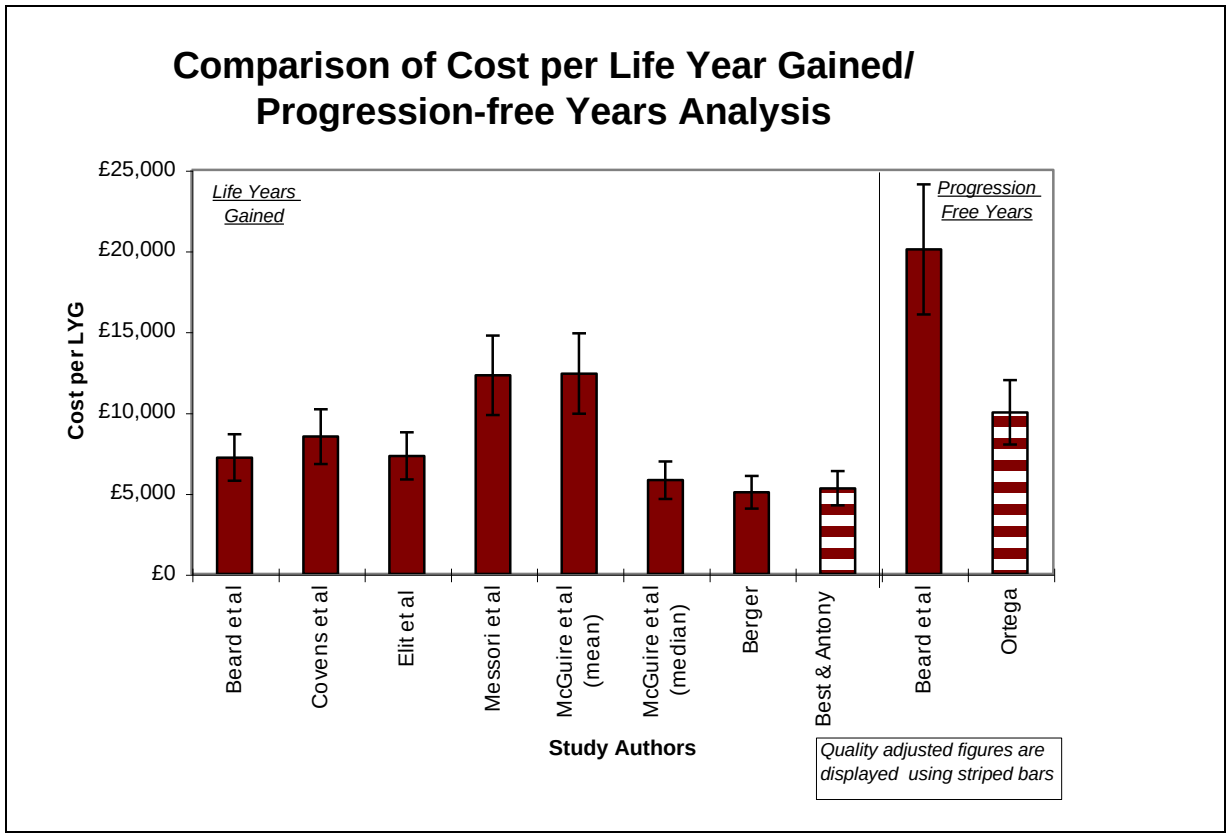
The majority of the studies used LYG as the currency of clinical benefit, although two studies quote data using progression-free years, one of which was the Trent WGAP report. The use of progression-free years is an attempt to account for benefits in terms of years spent in relative good health. However, it is entirely possible for patients to lead a reasonable quality of life even in early disease progression. Therefore, LYG is still a good measure of benefit. Two studies also make adjustments to clinical benefit to account for quality of life, in terms of quality adjusted life years (QALY)s.

Some of the studies include the costs of first-line therapy only, whilst others base their cost calculations on a more life-time treatment basis (i.e. including the cost of subsequent phases of salvage therapy).

All the studies point clearly towards the relative cost-effectiveness of TP. Costs have been included on a mix of first-line only and lifetime costs basis.

The following graph compares the published cost-effectiveness ratios of these studies.

Figure 2 Comparison of Published Cost-Analyses



Whilst each study is set within the context of its own health care system, it is interesting to see that, in general, the figures tend to lie within a very similar range of cost-effectiveness. Again, this is not surprising given the limitation of the trial data. However, the studies cost treatment on very different bases, some using bottom-up costings from retrospective patient studies whilst others make general modelled assumptions around average cost figures.

The following table provides a summary view of the basic approach and conclusions of these reports and further highlights the type of sensitivity analysis performed.

Table 22 Economic Modelling to Determine the Cost-effectiveness of Paclitaxel in the Treatment of Ovarian Cancer

Authors	Country	Treatments Compared	Method	Benefit/CE Measures	Sensitivity Analysis	Authors Conclusions
Beard et al.[10]	UK (1997)	*1st-line therapy* TP vs Carboplatin.	Survival analysis based on published trial median statistics, with supporting survival curve analysis. Area under survival curve using Weibull curve fitted to survival data.	• cost per LYG • cost per progression-free year gained (PFYG)	• hospital costs • adverse effects, costs • cost of paclitaxel • clinical benefits	• LYG : 1.17 & PFYG : 0.42 • cost per LYG : £7,200 • cost per PFYG : £20,084 • LYG : 0.53 (based on AUC estimates of benefit) • cost per LYG : £15,788 (based on AUC estimates of benefit) • marginal cost of £8,000 per patient • marginal cost of £260,000 for a typical UK health authority
Best & Anthony[27]	UK (1996)	*1st-line therapy* TP vs Carboplatin vs CAP vs no treatment.	TP benefits taken from GOG111 median survival times. CAP and CARB benefits derived by combining several small RCTs.	• QALYs	• survival benefits of no treatment • dosage of Carboplatin	• 1.1 QALYs per patient on TP c.f. Carboplatin • cost per QALY = £5,297 c.f. Carboplatin • extra 110 QALYs per 100 patients when c.f. Carboplatin • marginal cost of £580,000 per 100 patients c.f. Carboplatin
Ortega[28]	CANADA (1997)	1st-line therapy TP vs CP also included variations in 2nd and 3rd line therapies.	Cost utility analysis based on a decision-tree model. Localised costings combined with patient record tracking of resource usage. Treatment preference study to identify utility of health states.	Quality adjusted PFYG	• variety of 2nd and 3rd line therapies • healthy volunteers utility scores • 95% CI of benefits and costs	• cost per quality adjusted PFYG lay between £5,000 (Can$11,000) to £10,000 (Can$24,000)

Authors	Country	Treatments Compared	Method	Benefit/CE Measures	Sensitivity Analysis	Authors Conclusions
Covens et al.[29]	CANADA (1996)	1st-line therapy TP vs CP. Also included costs of 2nd and 3rd line therapy	Linear modelling based cost-benefit analysis designed to combine costs and expected benefits. Based on four stages of patient treatment defined as: • surgery/chemotherapy/relapse/ terminal care. • time/proportion in stages determined from retrospective chart analysis. • assume a 50% increase in survival for paclitaxel.	• average life time cost per patient • cost per LYG	• drug costs • longer TP infusion • survival benefits (25%,50% ,75%)	• average life time cost per patient : ⇒ TP at £20,800 (Can$50,054) ⇒ CP at £15,400 (Can$36,837) • cost per LYG cost for TP was £8,500 (Can$20,355) • sensitivity analysis indicates a cost per LYG range of £6,400 - £11,200
Elit et al.[30]	CANADA (1997)	1st-line therapy TP vs CP	Standard cost-effectiveness study using mean data derived directly from the GOG-111 survival curves.	• cost per LYG	• drug costs • benefits	• cost per LYG for TP was £7,300 (Can$17,500)
Messori et al.[31]	ITALY (1996)	1st-line therapy TP vs CP	Incremental cost-effectiveness analysis. Survival curve fitting of trial data using weighted least squares procedure, best fit Gompertz curve. Extrapolation beyond trial data to life benefits.	• LYG • cost per LYG	• drug costs • hospitalisation costs • benefits limited to trial period	• 46 LYG per 100 patients. • extra cost of £563,500 (US$901,723) per 100 patients • cost per LYG for TP was: £12,300 (US$19,603) • sensitivity analysis presents a cost per LYG range of £10,000-£14,250 (US$15,960-$22,793).

Authors	Country	Treatments Compared	Method	Benefit/CE Measures	Sensitivity Analysis	Authors Conclusions
McGuire et al.[32]	USA (1997)	1st-line therapy TP vs CP	Cost-effectiveness study based on the GOG-111 trial. Treatment cost data applied to resource utilisation data. Median survival data and equivalent mean survival data used to determine benefits. Estimates of cumulative proportion surviving in the trial were based on Kaplan-Meier procedures. No account taken of patient utility and QoL.	• LYG • cost per LYG	• Monte Carlo analysis of clinical benefits • Use of different estimates of benefits based on median survival and mean survival data	• cost per LYG: ⇒ mean survival data to present time: £6,500 (US$10,454) ⇒ mean survival data to end of trial: £12,400 (US$19,820) ⇒ median trial survival data: £5,800 (US$9,323) • expected distribution from multivariate Monte Carlo analysis: £12,400±£680 (US$19,868±US$1087) per LYG.
Berger K, Szucs T[33] (abstract only)	Europe (1997)	1st-line therapy TP vs CP	Face-face interviews with oncologists. Costs built from local telephone interviews with health providers. Calculations made for 6 individual European countries (D,E,F,I,NL,UK). Benefits based on GOG-111. Declining exponential approximation of life expectancy (DEALE) used in calculating LYS.	• LYG • cost per LYG	• Sensitivity analysis conducted but not detailed in abstract	• Range of LYG estimated at: 1.27-1.3 LYG • Marginal treatment cost for UK: £5,062 (US$ 8,100) • Cost per LYG of UK : £4,000 (US$6,400) • Improved ratio using a 3 hour infusion (reduced hospitalisation costs)

4. DISCUSSION AND CONCLUSIONS

The presentation of the results from the ECOCIT provides further support to the clinical efficacy of TP in the first line treatment of AOC. The trial data indicate:

- a confirmation of the magnitude of benefits, in terms of both overall survival and progression-free survival, as reported in the GOG-111 trial;
- a similar range of side-effect profiles to those observed in the GOG-111 trial (more data may be needed to confirm this comparison);
- indications of significant benefit to a wider patient group, including stage IIB and IIC patients;
- confirmation of the efficacy of shorter infusions of paclitaxel (3 hour intravenous infusion);
- the potential to deliver therapy on an out-patient basis.

Importantly, the survival and progression-free advantages still remained significant when using an intention-to-treat basis, with cross-over allowed for salvage therapy after disease progression. It is likely that full publication of the trial results will provide even more detail confirming these results.

The next major trial data to take into account will be the interim results and final publication of mature data from the ICON 3 trial. This will represent the first major trial of paclitaxel to make a direct comparison to UK conventional therapy., results are not due for another two years. However

All published economic studies to date have been based on the GOG-111 RCT. Although each economic analysis approaches the problems of cost-effectiveness modelling from a slightly different perspective and using a different methodology, they appear to arrive at the same conclusion, namely, that TP as a first line therapy provides cost-effectiveness ratios comparable to other interventions currently supported by the NHS.

Many unanswered questions remain regarding the treatment of AOC with paclitaxel, such as, the place of using more cycles of treatment. The effects of intra-peritoneal delivery of chemotherapy, high dose consolidation therapy and IDS are also not known. Research currently being undertaken in the treatment of AOC using paclitaxel will clarify many of the unanswered questions with regard to clinical and cost-effectiveness.

Whilst the economics of paclitaxel remain relatively favourable on a patient-by-patient basis, the overall budgetary impact remains unquestionably substantial. Over the next few years there is likely to be much more debate and consideration of the relative merits of other new treatments for ovarian and other gynaecological cancers, with pressure to target resources effectively.

The key messages of the ECOCIT appear positive, confirming the clinical benefits achieved in the original GOG-111 trial. The results have been presented and debated in the context of local and national gynaecology group meetings, with positive clinical statements produced in the form of a recent clinical consensus document and a JCCO statement. Clinical opinion suggests that paclitaxel in combination with cisplatin or (probably) carboplatin would be the treatment of choice for the majority of women with ovarian cancer.

The JCCO statement has been endorsed by the NHS SMAC. Final publication and dissemination of the ECOCIT results is due and is expected to re-enforce this clinical view. The eventual completion and publication of the ICON 3 results, in around two years' time, will allow these clinical views to be revisited.

Pre-publication note (10/02/99)

Since the original considerations of the Trent DEC, there has been further publication of final overall survival data from the ICON 2 trial.[28] ICON 2 makes a direct comparison between single agent carboplatin and platinum combination CAP and, importantly, confirms equity in terms of overall survival. However, the median survival (33mths), is notably much higher than either the control arms of the two international paclitaxel comparison studies (CP 24-25mths) or the Wessex report (CARB 20mths / CAP 24mths).[9,11,27] Although ICON 2 does not present comparative data with paclitaxel, if such results were repeated in a direct carboplatin/CAP/paclitaxel study, they may imply potentially smaller marginal survival benefits for paclitaxel over conventional therapy.

APPENDIX POOLED ANALYSIS OF TRIAL DATA

The following presents a step-by-step pooled analysis of the relative risks suggested by the data from the two trials. The methodology used is based on the general variance-based method using confidence intervals.

Study 1 = GOG-111 trial

Study 2 = ECOCIT

RR_i = relative risk of the i^{th} trial

RR_p = relative risk of the pooled data

$Weight_i$ = weight assigned to the i^{th} trial

Log-transformation of RR

Study 1 ln(RR1) = ln(0.6) = -0.5118

Study 2 ln(RR2) = ln(0.71) = -0.3425

Estimated Variance

$$Vari = \left[\frac{\ln(RRi \,/\, RRil)}{1.96}\right]^2$$

Study 1 Var1 = [ln(RR1/RR1L)/1.96]^2 = [ln(0.6/0.5)/1.96]^2 = 0.0087

Study 2 Var2 = [ln(RR2/RR1L)/1.96]^2 = [ln(0.6/0.5)/1.96]^2 = 0.0126

Estimated Weights

$$Weighti = \frac{1}{Vari}$$

Study 1 Weight1 = 1 / Var1 = 1/0.0087 = 115.5676

Study 2 Weight2 = 1 /Var2 = 1/0.0126 = 79.6406

Sum of Weights = Weight1 + Weight2 = 115.5676 + 79.6406 = 195.2082

Products

Study 1 Product1 = Weight1 * ln(RR1) = 115.5676 X -0.5118 = -59.0349

Study 2 Product2 = Weight2 * ln(RR2) = 79.6406 X -0.3425 = -27.2761

Sum of the Products = Product1 + Product2 = -59.0349 -27.2761 = -86.3110

Estimate of Pooled Relative Risk

$$RRp = e^{\left[\frac{Sum\sim of\ \sim Pducts}{Sum\sim of\ \sim Weights}\right]}$$

RRp = e^(Sum of Products/Sum of Weights) = e^(-86.3110/195.2082) = e^(-0.4421) = **0.64**

Estimate of 95% C.I.

$$CI = e^{\left[\ln(RR)+\left\{1.96\,X\,\sqrt{\text{var}\,iance}\right\}\right]}$$

Upper bound = e^(ln(RRp) +(1.96 X SQRT(1/195.2082)) = e^(-0.4421 + 0.1403) = **0.74**

Lower bound = e^(ln(RRp) -(1.96 X SQRT(1/195.2082)) = e^(-0.4421 - 0.1403) = **0.56**

Estimate of Significance

It is possible to construct a test of significance for the RRp by standardising it to a standard normal distribution.

RRp/SQRT(1/variance) = 0.64/SQRT(1/195.2082) = 8.9419

Using the standard normal distribution p(Z<8.9419) <= 0.0000001

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