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WORKING GROUP ON ACUTE PURCHASING

The Use of Cisplatin and Paclitaxel as a First Line Treatment in Ovarian Cancer

June 1997

GUIDANCE NOTE FOR PURCHASERS 97/05
Series Editor: Nick Payne

Trent Development and Evaluation Committee

The purpose of the Trent Development and Evaluation Committee is to help health authority 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, and includes non-clinically qualified scientists and lay members. It is chaired by Professor Sir David Hull.

The committee recommends, on the basis of appropriate evidence, 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 22 July 1997 at which this Guidance Note for Purchasers (in a draft form) was considered.

THE USE OF CISPLATIN AND PACLITAXEL AS A FIRST LINE TREATMENT IN OVARIAN CANCER

AUTHORS: Beard SM, Coleman R, Radford J and Tidy J. Sheffield: Trent Institute for Health Services Research, Universities of Leicester, Nottingham and Sheffield, 1997. Guidance Note for Purchasers: 97/05

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SUMMARY:
Carcinoma of the ovary is the commonest gynaecological malignancy and the fourth most common cause of cancer death in women. There are approximately 450 cases of ovarian cancer reported annually in the Trent region, giving an annual incidence rate of around 19 per 100,000 women. Chemotherapy combinations that include an alkylating agent and a platinum analogue (i.e. cisplatin, carboplatin) have been demonstrated to have high response rates in women with advanced ovarian cancer. Single agent carboplatin is the most widely used regime in the UK. A single phase III RCT has reported a median survival of 38 months for paclitaxel/cisplatin and 24 months for the cisplatin/cyclophosphamide (US baseline treatment).

An economic analysis of the treatment calculated that the introduction of paclitaxel/cisplatin treatment programme for an average district (500,000) population would cost £258,368 per year. The treatment is expected to give each patient an average of 1.17 years extra survival at a cost of £7,200 per life year gained.

DECISION: **The Committee recommended that Paclitaxel should be available for patients within national controlled trials. Some members felt it should be limited only to those in clinical trials, but a majority agreed that in limited circumstances Paclitaxel should be available for other patients at the discretion of the clinicians. This decision should be reviewed when more evidence is made available from the trials in hand.**

June 1997

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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 Institute:

- provides advice and support to NHS staff on undertaking Health Services Research (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 Akehurst 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

A network exists in the Trent Region where purchasers can share research knowledge about the effectiveness and cost-effectiveness of acute service interventions and determine collectively their purchasing policy.

ScHARR, which houses the Sheffield Unit of the Trent Institute for Health Services Research, facilitates a Working Group on Acute Purchasing. A list of interventions for consideration is recommended by the purchasing authorities in Trent and approved by the Purchasing Authorities Chief Executives (PACE) and the Trent Development and Evaluation Committee (DEC). A public health consultant from a purchasing authority leads on each topic and is assisted by a support team from ScHARR, led by Dr Nick Payne, Senior Lecturer in Public Health Medicine, which provides help including literature searching, health economics and modelling. A seminar is then led by the 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 ratified by the Trent DEC which is chaired by Professor Sir David Hull.

The Trent Institute's Working Group on Acute Purchasing is part of a wider collaboration working with three units in other regions (The Wessex Institute for Health Research and Development, The Scottish Health Purchasing Information Centre (SHPIC) and The Birmingham University Institute for Public and Environmental Health) to share this work on reviewing the effectiveness and cost-effectiveness of clinical interventions. This group, InterDEC, will share this work, avoid duplication and improve the peer reviewing and quality control of these reports.

Professor R L Akehurst,

Chairman, Trent Working Group on Acute Purchasing.

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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 half of cases occur in women aged 65 or over. Whilst many clinical trials have been published previously concerning the treatment of advanced ovarian cancer, only one randomised controlled trial (RCT) exists which has fully reported on the use of cisplatin in combination with paclitaxel, specifically as a first line treatment.

There are approximately 450 cases of ovarian cancer reported annually in the Trent region, giving an annual incidence rate of around 19 per 100,000 women. Trent figures indicate that 49% of cases are in women over the age of 65.

Chemotherapy combinations that include an alkylating agent and a platinum analogue have been demonstrated to have high response rates in women with advanced ovarian cancer. Single agent carboplatin is the most widely used regime in the UK.[1]

Thesaurus searches of Medline (using MeSH terms 'paclitaxel' and 'ovarian neoplasms') and Embase (using terms 'paclitaxel' and 'ovary cancer'), limited to identify randomised controlled trials, reveal only one RCT comparing paclitaxel with a standard treatment regime **-** the Gynecologic Oncology Group (GOG) trial.[2]

On the basis of our analysis, based on the GOG trial, there appears to be a definite clinical benefit from the use of paclitaxel/cisplatin (TP) combination therapy in the first line treatment of ovarian cancer, although this is still very much based on the results of a single phase III RCT. Median survival statistics as published indicate 38 months for paclitaxel/cisplatin and 24 months for the cisplatin/cyclophosphamide US baseline treatment.

Put into the context of the Trent region prevalence rates and female population, an economic analysis of the treatment implies an increase in total treatment costs of just under £2.5 million per annum. For an average district of 250,000 females this equates to an increase of around £258,368.

In terms of extra life years gained (LYG) the treatment is expected to give each patient an average of 1.17 years extra survival. This equates to a cost per extra LYG of approximately £7,200, which compares favourably with similar cost per life year gained figures for other

treatments and falls below the threshold of £20,000 per LYG which is often used and referred to.

A recent Wessex DEC Report[3] has also independently recommended the use of paclitaxel/cisplatin as a first line treatment option, along with the current standard treatments of carboplatin and cyclophosphamide/doxorubicin/cisplatin. However, a review of this recommendation was also advised after the publication of further trial evidence.

Supportive evidence from an economic evaluation conducted by the GOG trial produced comparable results when costing treatment benefits in the context of the US marketplace.

A number of RCTs are currently ongoing exploring further the use of first line paclitaxel and considering uses in combination with carboplatin and with dosage variation.

In terms of options for purchasers, it is concluded that there is certainly a strong enough body of evidence for the continued support of ongoing RCTs into paclitaxel, via the ICON 3[1] trial recruitment (although this is limited to 2,000 patients). It is also felt that given further supporting evidence, from the interim results of the EORTC Inter-Group trial[4] the first line use of paclitaxel should be funded in conjunction with other existing standard treatments.

1. INTRODUCTION

Carcinoma of the ovary is the commonest gynaecological malignancy and the fourth most common cause of cancer death in women. Around half of cases occur in women aged 65 or over. Whilst many clinical trials evaluating cytotoxic treatment regimes for ovarian cancer have been published, only one Randomised Controlled Trial (RCT) exists which has fully reported on the use of paclitaxel as a first line treatment. This trial was conducted by the Gynecologic Oncology Group (GOG)[2] and focused in particular on the therapy of cisplatin in combination with paclitaxel. This paper examines the clinical evidence for the effectiveness of the paclitaxel/cisplatin (TP) platinum combination and relates this to the expected costs of such a treatment.

1.1 Incidence and Pathology

There are approximately 450 cases of ovarian cancer reported annually in the Trent region, giving an annual incidence rate of around 19 per 100,000 women. Trent figures indicate that 49% of cases are in women over the age of 65, based on average values 1990-93. The mean and modal age at presentation lie between 60 and 64 years.

The natural history of the disease is characterised by an insidious onset with vague non-specific symptoms, and a high, although often transient, response to surgery and chemotherapy. As ovarian cancer is often asymptomatic in its early stages, most patients have widespread disease at the time of diagnosis.

Table 1: Disease Stage at Diagnosis[2]

	STAGE I(%)	STAGE II(%)	STAGE III(%)	STAGE IV(%)
OVARY	10	8	60	17

Ovarian cancer spreads via local shedding into the peritoneal cavity followed by implantation on the peritoneum, via local invasion of bowel and bladder, or via the abdominal lymphatics.

1.2 Prognosis and Mortality

In Trent, between 1989 and 1993, 42% of patients died in the first year after diagnosis. Overall 32% of patients survived into their third year after diagnosis.[5]

International Federation of Obstetricians and Gynaecologists (FIGO) data provide information on survival by disease stage at presentation. [6]

Table 2: Five Year Survival Rates[2]

	STAGE I(%)	STAGE II(%)	STAGE III(%)	STAGE IV(%)	OVERALL
FIGO STAGE	85	50	25	5	32.7

Prognosis is influenced by several factors. Good prognostic factors include younger age, good performance or functional status, cell type other than mucinous and clear cell, early stage at presentation, well differentiated tumour, small disease volume prior to any surgical debulking and the absence of ascites.[7]

Early-stage ovarian cancer is readily controlled by resection and chemotherapy. Extensive debulking surgery and multi-agent chemotherapy, show significant, although still modest, improvements in the survival of advanced-stage cancer. The incidence of positive nodes at primary surgery has been reported as high as 24% in stage I, 50% in stage II, 74% in stage III, and 73% in stage IV.[8]

Chemotherapy combinations that include an alkylating agent and a platinum analogue have demonstrated high response rates in women with advanced ovarian cancer. However, these combinations provide long-term control of the disease in only a small number of patients.[9] After two influential meta-analyses found no difference in survival between cisplatin and carboplatin, treatment for women focused on single agent carboplatin in the UK. Although carboplatin is substantially more expensive than cisplatin it is much better tolerated, with less renal, gastro-intestinal and neurological toxicity, and is suitable for out-patient administration.[10,11] The main dose limiting toxicity of carboplatin is myelosuppression, and this may make its use in combination with other myelosuppressive agents more difficult.[12]

The disease will recur in approximately 30%-50% of patients with a pathologically confirmed complete response to chemotherapy.[13] The risk of recurrence in patients treated with

platinum-based combination chemotherapy is directly related to stage, histological grade, and amount of tumour remaining after first operation.[14]

1.3 Current Standard Treatment Options

The following section details the current treatment options for ovarian cancer organised by disease stage.

1.3.1 Stage I

Surgery alone is usually considered adequate for stages IA and IB (total abdominal hysterectomy and bilateral salpingo-oophorectomy with omentectomy) if tumour is well or moderately well differentiated.

Patients with poorly differentiated stage 1A or 1B may be treated with chemotherapy in addition to surgery.

1.3.2 Stages Ic, II, III and IV

Therapy for these stages of ovarian cancer is largely palliative. Treatment is based initially on surgery (total abdominal hysterectomy and bilateral salpingo-oophorectomy and tumour debulking and omentectomy) to remove all or most of the tumour. Surgery is followed by adjuvant chemotherapy for those patients with good performance status.

Single agent carboplatin is the most widely used regime in the UK.[1]

<u>Alternative regimes include :-</u>

- cyclophosphamide/cisplatin (CP)
- cyclophosphamide/doxorubicin/cisplatin (CAP)
- cyclophosphamide/carboplatin

However, in the USA the current first line treatment is now firmly established as paclitaxel/cisplatin. This follows the recent results from the GOG 111 trial.

1.4 Scale of Problem in a 'Typical' District

In a typical district of 500,000 people (250,000 females), approximately 47 newly reported cases of ovarian cancer would be expected each year.

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

2.1 Summary of Evidence for the Effectiveness of Paclitaxel

2.1.1 Mechanism of Action

Paclitaxel is a mitotic inhibitor with a novel mechanism of action. It promotes polymerisation of tubulin dimers to form microtubules and also stabilises microtubules by preventing depolymerisation. The drug is unique amongst chemotherapeutic agents in having a specific binding point on the microtubule.[15]

Paclitaxel microtubules are stable in conditions that usually promote tubule disassembly. Prolonged infusion produces distinct changes in cell morphology which adversely affect microtubule function during both interphase and mitosis. The precise reasons for cell death are unclear.[16]

The entire mechanism of systemic clearance is not known. Hepatic metabolism is significant and biliary deposition accounts for 20% (paclitaxel) and 40% (metabolites) of drug administered. Urinary excretion is 5-10%.

The most significant complications of the drug include allergic reactions, neutropenia and peripheral neuropathy.[17]

2.1.2 Paclitaxel as an Adjuvant Primary Therapy for Stages III and IV Ovarian Cancer

Thesaurus searches of Medline (using MeSH terms ‘paclitaxel’ and ‘ovarian neoplasms’) and Embase (using terms ‘paclitaxel’ and ‘ovary cancer’), limited to identify randomised controlled trials, reveal only one RCT comparing paclitaxel with a standard treatment regime - the GOG trial.[2] It is unlikely that such a trial will be repeated in the USA. Combination therapy with paclitaxel is now seen as standard therapy there. In addition, as the authors point out, this trial was carried out when supplies of paclitaxel were difficult to obtain, and this was felt to minimise the crossover effect common in US trials when patients actively seek new and promising therapies and drop out of a trial, or receive the test agent on relapse. In the UK the MRC established the ICON 3[1] trial to compare paclitaxel/carboplatin,

carboplatin alone and combination cyclophosphamide/doxorubicin/cisplatin. This trial continues to recruit patients.

2.1.3 The Gynecologic Oncology Group Trial

The GOG in the USA established a multi-centre randomised phase 3 trial to compare two combinations of chemotherapy, cisplatin and cyclophosphamide versus cisplatin and paclitaxel, in women with incompletely resected stage III or any stage IV ovarian cancer. It began recruiting in April 1990. 410 women with advanced ovarian cancer and residual masses larger than 1 cm after initial surgery were randomised to receive cisplatin (75 mg per square metres of body-surface area) with either cyclophosphamide (CP) (750 mg per square metre) or paclitaxel (TP) (135 mg per square metre over 24 hours). The trial authors concluded that incorporating paclitaxel into first-line therapy improved the duration of progression-free survival and of overall survival in women with incompletely resected stage III and stage IV ovarian cancer.

2.1.4 Eligibility

Only women with incompletely resected stage III (>1cm residual mass) or any stage IV ovarian cancer were recruited i.e. those in the worst prognostic group. Trial eligibility criteria were: no previous chemotherapy, good performance status, normal renal and liver function and a white cell count of at least 3,000 per cubic millimetre. Women with a history of cardiac arrhythmias were excluded. Trial entry was within six weeks of surgery.

No study power calculation is referred to. The trial recruited only 400 women. However, given the relatively low incidence of the disease, this represents a major achievement. Women were randomised with equal probability after stratification by institution and for the extent of clinical disease.

If a woman's white cell count fell below 3,000 per cubic millimetre or platelet count below 100,000 per cubic millimetre, treatment was delayed. If the delay exceeded three weeks, these women were withdrawn from the study. Severe neurological, otic or renal toxicity and cardiac toxic events were grounds for ceasing therapy but with continued trial follow-up. No reduction in cisplatin dose was allowed. Dose reduction for paclitaxel and cyclophosphamide was based on white blood cell count or platelet counts.

2.1.5 Outcome Measures

The main outcome measure of the study was a reduction in measurable disease extent. Assessment was not blinded. Clinical response was measured in accordance with WHO guidance.[18] This included a re-assessment laparotomy for those women without clinically measurable disease.

Progression free survival was measured from randomisation. Survival was measured up to date of death or last contact.

2.1.6 Population

Three hundred and eighty-six women met all the eligibility criteria. The oldest woman in the trial was 84. There was an imbalance in prognostic factors between the two arms of the trial. In any randomisation process this is to be expected and none of the differences was statistically significant. In the CP arm there were 12 per cent fewer patients with serous adenocarcinoma, 64% as against 76% . Conversely, there was almost double the proportion of grade 1 tumours, 7% as against 4%. Stage tended to be more advanced and extent of disease (as measurable disease) worse in the CP group.

2.1.7 Withdrawals

21 (10%) women in the standard regime and 15 (8%) in the paclitaxel group failed to complete six cycles of therapy because of choice or toxicity. In total 201 women received CP and 184 TP.

Interestingly, 23 (11%) women failed to complete the standard regime because of disease progression or death compared to 9 (5%) in the paclitaxel group.

Alopecia, neutropenia, fever, and allergic reactions were significantly greater in the TP group although the clinical significance of this is difficult to gauge from the published tables. There were 10 treatment related deaths (6 CP and 4 TP).

2.1.8 Major End-point

Among the cohort of 216 women with measurable disease, 73% in the paclitaxel/cisplatin group responded to therapy, compared with 60% in the cisplatin/cyclophosphamide group (P = 0.01). The frequency of surgically verified complete response was similar in the two groups (20% for CP and 26% for TP).

Table 3: Median Progression-Free Survival

REGIME	MEDIAN PROGRESSION FREE SURVIVAL	95% CI INTERVAL
Paclitaxel/Cisplatin (TP)	18 months	16 - 21 months
Cisplatin/Cyclophosphamide (CP)	13 months	11 - 15 months

Progression-free survival was significantly longer (P < 0.001) in the paclitaxel/cisplatin (TP) group than in the cisplatin/cyclophosphamide (CP) group (median, 18 vs. 13 months).

Table 4: Median Survival

REGIME	MEDIAN SURVIVAL	95% CI INTERVAL
Paclitaxel/Cisplatin (TP)	38 months	32 - 44 months
Cisplatin/Cyclophosphamide (CP)	24 months	21 - 30 months

Survival was also significantly longer (P < 0.001) in the paclitaxel/cisplatin group (median, 38 vs. 24 months).

The improvement in median progression-free survival is less than half the observed improvement in median overall survival. This is an apparent discrepancy. Is the better survival due to chance? It has been suggested that this is due to the unique mode of action of the paclitaxel altering the biology of the disease. Alternatively, it may be due to responsiveness to second line therapy.

2.2 Conclusion on Direction of Evidence and its Quality

The lack of a blinded assessment of response is the only major methodological weakness of this study. There are a number of small technical deficiencies. Nevertheless, although it is

dangerous to base therapy on a single trial, the results of this trial are impressive, and although similar studies are progressing, this particular trial is unlikely to be repeated.

The results are not out of line with the preliminary results and investigations on the drug in a number of other solid tumours[19] and as second line therapy for cisplatin resistant ovarian cancer.[20]

3. COST AND BENEFIT IMPLICATIONS OF ADOPTING INTERVENTION

3.1 Selection of Appropriate Baseline

Since there has been only one RCT focusing on paclitaxel as a first line treatment for ovarian cancer, this must form the basis of the clinical evidence for the cost-effectiveness analysis.

In performing an economic analysis of paclitaxel it is important to select a suitable baseline treatment from which both the increase in clinical benefit due to the proposed new treatment and the economic consequences of such a move can be measured.

Based on clinical advice, and the ICON 3 protocol,[1] the current UK standard treatment of single agent carboplatin has been selected for the purposes of this Guidance Note as the baseline for our comparisons with the paclitaxel/cisplatin platinum combination.

3.2 Patient Cohort

In order to calculate the overall potential cost to the Trent region due to TP treatment for advanced ovarian cancer it is necessary to consider the number of patients likely to be challenged with this regimen.

For the purpose of the cost-effectiveness analysis it has been assumed that 35% of patients who present with ovarian cancer will not be challenged with TP.

This estimate is based on expected levels of health status using the ECOG (European Clinical Oncology Group) performance status 0 - 2 and good general medical condition, rather than age, and is been based on clinical opinion. It has been assumed that this group of patients will continue to use the standard single agent therapy. The estimate also takes into account a proportion of patients who would be expected to present with Stage 1, surgery only, disease, based on FIGO data.

These factors combine to imply an expected patient cohort of 299 patients per annum within Trent.

3.3 Treatment Details and Costs

In calculating the cost of treatment the analysis has focused on two specific areas of cost:

1. ***Direct Treatment*** - which includes the chemotherapy drugs and supporting treatments administered in each of the individual treatment courses; and

2. ***Adverse Effects*** - where extra costs are incurred in managing the adverse effects caused by the treatments e.g. alopecia, fever etc.

The analysis has been limited to the costs incurred in the first line treatment of ovarian cancer. The treatment regimes have been analysed primarily using local Trent drug costs in order to provide costings based very much in the 'local' context. Also, standard Trent costs for in-patient, out-patient and day case activity have been used.

In deriving the treatment costs it has been assumed that each treatment regime is repeated an average of six times for each patient.

A standard body surface area of $1.8m^2$ has also been assumed in order to calculate the correct drug dosages.

The paclitaxel/cisplatin treatment was varied slightly from the original trial regime as a number of the supporting drugs would be prescribed and administered slightly differently within Trent. However, this has very little effect on total cost as the actual costs of the drugs concerned are small when compared to the cost of the chemotherapy drugs cisplatin, carboplatin and paclitaxel.

The following tables detail the treatment regimes used for the economic analysis.

Table 5: Treatment Details - Paclitaxel/Cisplatin

DRUG	DOSE
Cisplatin	75 mg/m2 (iv)
Paclitaxel	135 mg/m2 (iv) - 24hr -
Chlorpheniramine	10 mg (iv)
Cimetidine	300 mg (iv)
Granisetron	3 mg (iv)
Dexamethasone	8 mg (iv)
Dexamethasone	40 X 2mg tabs
Average Treatment Cycles = 6	
In-patient Requirement = 2 days	

Table 6: Treatment Details - Carboplatin

DRUG	DOSE
Carboplatin	400 mg/m2 (iv)
Granisetron	3 mg (iv)
Dexamethasone	8 mg (iv)
Dexamethasone	20 X 2mg tabs
Average Treatment Cycles = 6	
Out-patient Attendance	

Details of the specific treatment costings can be found in the Appendix.

3.4 Adverse Effects

As well as the drug costs, it has also been necessary to examine the potential differences between treatments of the costs involved in the management of side-effects.

The GOG trial identified a number of potential adverse effects for the paclitaxel/cisplatin combination. Of these, two were identified as having potential cost implications which would not be expected with single agent carboplatin treatment.

These effects were identified as :-

Alopecia - requiring a wig as treatment

Fever - requiring antibiotics and a degree of in-patient stay.

Using the trial data combined with clinical opinion, a percentage risk per patient has been derived for each of the effects and a standard Trent cost has been applied.

The following table details the adverse effect data used in the study.

Table 7: Adverse Effects

EFFECT	TREATMENT	CARBOPLATIN	PACLITAXEL/ CISPLATIN
		Probability	Probability
Alopecia	Wig	0%	100%
Fever	Antibiotics + In-Patient Admission (3 days)	1%	19%

3.5 Expected Costs

Using the cohort data and the costing information, an overall cost picture for the Trent region as a whole and also on a per patient basis can be developed.

Table 8: Total Expected Costs per Annum

REGIME	COST PER PATIENT	AVERAGE DISTRICT COST	TRENT REGIONAL COST
Paclitaxel/Cisplatin	£10,427	£321,932	£3,108,574
Carboplatin	£2,059	£63,564	£613,774
Cost Difference	£8,368	£258,368	£2,494,800

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

Put into the context of the Trent region's prevalence rates and female population, this implies an increase in total treatment costs of just under £2.5 million per annum. For an average district of 250,000 females this equates to an increase of around £258,368.

3.6 Treatment Benefits

In terms of treatment benefits, this Guidance Note has concentrated on the two particular output measures linked to the detailed outcomes from the GOG trial.

- Life Years Gained (LYG) - A measure, in years, of the expected increase in survival time from randomisation.

- Progression Free Years Gained (PFYG) - A measure, in years, of the expected increase in the period of time from randomisation to the beginning of clinical progression. This is in effect a measure of life years gained which implies a quality health state. (Although it is noted that patients in clinical progression can still have a period of disease which brings little disruption to their daily lives).

The benefits for the paclitaxel/cisplatin treatment have been taken directly from the median point values published in the GOG trial results.

Unfortunately, no direct RCT trial comparison of carboplatin to paclitaxel/cisplatin exists. Therefore, in order to derive suitable data on clinical benefits for carboplatin, two options present themselves:

Option 1. To use supporting data collated and derived from a number of smaller independent RCT trials which have focused on carboplatin versus a number of other alternative treatment regimes. This approach has a risk in that the existing trial data on carboplatin are not always directly comparable due to differences in trial design and entry criteria. Therefore, any calculation of data would be pragmatic. This is the approach taken by the Wessex DEC report[3] to be discussed later.

Option 2. To use clinical judgement of comparative trial data, ICON 2, to enable the control arm benefits in the GOG trial to be used as a proxy for those of carboplatin. This has the benefit of keeping the comparison data within the same trial structure, but carries the possible danger of over-estimating the benefits of carboplatin.

Within the main analysis Option 2 has been used, as it was felt that any acceptance of paclitaxel under these conditions would be based on a strong assumption of carboplatin's benefits. However, sensitivity results using Option 1 have also been considered.

The clinical benefits for carboplatin were derived based on the interim findings of the ICON 2[21] trial, originally designed to compare carboplatin against the platinum combination CAP, and the results of available trial evidence comparing CAP with CP treatment.

The interim trial results of ICON 2[21] have pointed towards a possible survival and progression free benefit in using the platinum combination CAP rather than single agent carboplatin. However, there is no definite statistical proof of this effect and, importantly, confidence intervals at this stage are still wide and cross unity. Indeed, as more data become available from the ICON 2[21] trial, the strength of this evidence for CAP appears to be diminishing. Therefore, until ICON 2[21] reports in full on this issue the working assumption is that carboplatin should be considered to be as effective as CAP or any other standard platinum combination therapy.

Evidence comparing CAP with CP directly is limited and inconclusive. While evidence from the original GOG 52 trial and the Ovarian Cancer Project meta-analysis[9] did suggest CAP as being more beneficial, the scale and strength of this evidence is limited. It is currently felt that the difference here is marginal and must be considered in the light of the increased toxicity of the CAP treatment. Therefore, in our analysis we have considered CAP as having a similar efficacy to CP.

In summary, by using the CP arm benefits from the GOG 111 trial as an indication of carboplatin's potential benefits, the paper is almost certainly being over supportive of the current standard treatment. It is likely that CP does provide increased benefits over carboplatin, however, the current evidence fails to prove this conclusively.

3.7 Life Years Gained Benefits

The following clinical benefits have been derived from the survival outcomes of the GOG trial. Lower and upper levels for the 95% Confidence Interval (CI) have been provided.

Table 9: Life Years Gained Comparison

	REGIONAL LEVEL			PER PERSON		
	Lower	Median	Upper	Lower	Median	Upper
Paclitaxel/Cisplatin	499.02	592.59	686.16	2.67	3.17	3.67
Carboplatin	327.48	374.27	467.83	1.75	2.00	2.50
Median LYG Difference	218.32	(31.19-358.67)		1.17	(0.17-1.92)	

The Median LYG Difference compares the two median point estimates. The confidence intervals are provided in the bracketed figures based on the trial data.

This implies a **Number Needed to Treat** to gain an extra 1 LYG of 0.86 (range 0.52 - 6.00).

3.8 Progression Free Years Gained

The following benefits have been derived from the progression free outcomes of the trial. Lower and upper levels for the 95% CI have been provided.

Table 10: Progression Free Years Gained Comparison

	REGIONAL LEVEL			PER PERSON		
	Lower	Median	Upper	Lower	Median	Upper
Paclitaxel/Cisplatin	249.51	280.70	327.48	1.33	1.50	1.75
Carboplatin	171.54	202.73	233.92	0.92	1.08	1.25
Median LYG Difference	77.97	(15.59-155.94)		0.42	(0.08-0.83)	

The Median LYG Difference compares the two median point estimates. The confidence intervals are explored in the bracketed figures based on the trial data.

This implies a **Number Needed to Treat** to gain an extra 1 PFYG of 2.4 (range 1.2 - 12.0).

3.9 Cost-effectiveness

The following table lists the cost-effectiveness of using paclitaxel/cisplatin over the current standard treatment of carboplatin. The calculations are based on the expected increase in median clinical benefit and link this with the expected increase in cost per patient between the treatments.

Table 11: Cost per extra Life Year Gained

(A)	Extra LYG per person	1.17	
(B)	Extra Treatment Cost per person	£8,368	
(B/A)	Cost per Extra LYG	£7,173	*(£4,366 -£50,209)*

The bracketed figures provide the values at around the confidence intervals.

Table 12 : Cost per extra Progression Free Year Gained

(A)	Extra PFYG per person	0.42	
(B)	Extra Treatment Cost per person	£8,368	
(B/A)	Cost per Extra PFYG	£20,084	*(£10,042- £100,418)*

The bracketed figures provide the values at around the confidence intervals.

On the basis of this analysis there is an obvious clinical benefit from using a paclitaxel/cisplatin combination therapy in first line ovarian cancer treatment, although this is still very much based on the results of a single phase III RCT.

The extra cost of such a treatment is significant to Trent as a region at a figure of approximately £2.5 million per annum.

In terms of extra LYG the treatment is expected to give each patient an average of 1.17 years' extra survival. This equates to a cost per extra LYG of approximately £7,200 which compares favourably with other treatments. The figure is below the £20,000 threshold often quoted as the breakpoint for recommended treatments.

The cost per extra PFYG is provided to give an extra dimension to the analysis which focuses the benefit more towards a quality survival.

3.10. Sensitivity Analysis

In order to expand on the analysis and to explore the cost-effectiveness further the results have been considered under a set of different scenarios. Under each scenario the calculated cost per extra LYG is shown.

3.10.1 Scenario Analysis

The scenarios explore the use of national costs, increases in relative adverse effects costs and the calculation of carboplatin's clinical benefits from separate trial sources.

Table 13: Results of Sensitivity Analysis

SCENARIO	COST PER EXTRA LYG
BASECASE set to current cost benefit analysis	£7,173
1. Using standard national pharmaceutical costs instead of Trent costs	£6,663
2. Using carboplatin benefits at 20 months (as in the Wessex DEC report [3])	£5,579
3. Using carboplatin benefits at 28 months (increase benefits of carboplatin from 24 months)	£10,042
4. Increasing hospital IP/OP costs by 100%	£9,333
5. Increasing hospital IP/OP costs by 400%	£13,649
6. Increasing adverse effects costs for paclitaxel by 100%	£7,264
7. Increasing adverse effects costs for paclitaxel by 400%	£7,443
8. Combination of scenarios 1, 2	£5,183
9. Combination of scenarios 1, 3	£9,329
10. Combination of scenarios 3, 5	£19,098
11. Combination of scenarios 3, 5 and 7	£19,476
12. Increase the cost of paclitaxel by 100%	£13,099

Overall, the scenario analysis indicates that the cost-effectiveness measures are reasonably robust to quite dramatic variations in expected benefits and in expected drug and management costs. The use of national costs actually strengthens the arguments for paclitaxel. Even an increase of 100% in the cost of paclitaxel fails to damage the cost-effectiveness argument.

3.10.2 Analysis of Cost per Extra Life Year Gained

The following tables assist in exploring further the underlying assumptions made in deriving the median survival data, in order to provide a better feel for the degree of overall effect that these underlying assumptions have on clinical benefit. The analysis has been performed using the original Trent costings.

Table 14: Analysis of Carboplatin Benefit Assumptions

Question : If the paclitaxel/cisplatin treatment benefit and costs remained constant, what would the carboplatin benefits have to be to imply the costs per extra LYG as listed?

COST PER EXTRA LYG	PACLITAXEL/CISPLATIN MEDIAN SURVIVAL (months)	IMPLIED DIFFERENCE IN MEDIAN SURVIVAL (months)	IMPLIED CARBOPLATIN MEDIAN SURVIVAL (months)
£10,000	38	10	28
£20,000	38	5	33
£30,000	38	3.4	34.6
£40,000	38	2.5	35.5
£50,000	38	2	36

Table 15: Analysis of Paclitaxel/Cisplatin Benefit Assumptions

Question : If the carboplatin treatment benefit and costs remained constant what would the paclitaxel/cisplatin benefits have to be to imply the costs per extra LYG as listed?

COST PER EXTRA LYG	CARBOPLATIN MEDIAN SURVIVAL (months)	IMPLIED DIFFERENCE IN MEDIAN SURVIVAL (months)	IMPLIED PACLITAXEL/CISPLATIN MEDIAN SURVIVAL (months)
£10,000	24	10	34
£20,000	24	5	29
£30,000	24	3.4	27.4
£40,000	24	2.5	26.5
£50,000	24	2	26

Table 16: Analysis of Paclitaxel/Cisplatin Benefit Assumptions Based on a 20 month Carboplatin Benefit

Question : If the carboplatin treatment benefit remained constant at the 20 month level and costs also remained constant, what would the paclitaxel/cisplatin benefits have to be to imply the costs per extra LYG as listed?

COST PER EXTRA LYG	CARBOPLATIN MEDIAN SURVIVAL (months)	IMPLIED DIFFERENCE IN MEDIAN SURVIVAL (months)	IMPLIED PACLITAXEL/CISPLATIN MEDIAN SURVIVAL (months)
£10,000	20	10	30
£20,000	20	5	25
£30,000	20	3.4	23.4
£40,000	20	2.5	22.5
£50,000	20	2	22

Given that the costs used in the analysis remain as expressed in the report, the critical difference in clinical benefit between the two treatments arms is five months. Below this difference the cost per extra LYG exceeds the £20,000 which would typically put the treatment in a high cost recommended category. Considering the current analysis is using a difference of 14 months (TP 38 months / Carboplatin 24 months) this suggests that the cost-benefit results are reasonably robust to any possible changes in the clinical benefit data. The benefits of TP would have to reduce by around 23% before crossing the £20,000 conceptual barrier. Likewise, the CP benefits would have to increase by around 37%.

3.10.3 Sensitivity Summary

In summary, the sensitivity analysis suggests that, given the existing treatment costs and clinical benefits, the overall cost-benefit between the treatments remains consistently below the £20,000 per extra LYG mark. This is encouraging as it provides a level of confidence in the overall effects of the key assumptions made in the analysis around the clinical benefits of carboplatin and the cost of adverse effects.

3.11. Summary of Existing Economic Evidence

Since the publication of the GOG 111 RCT results and the Trent Working Group's initial analysis, there have been two further sets of economic analyses published which consider the cost-benefit case for the use of paclitaxel as a first line treatment. Due to the fact that the GOG 111 trial is the only RCT available, these analyses are based on the same source data, however, each has its own individual approach. The reports are discussed below.

3.11.1 Wessex DEC Report No 56[3] 'Paclitaxel as a First Line Chemotherapy Agent in the Treatment of Ovarian Cancer'

The report compares three possible treatments (paclitaxel/cisplatin, carboplatin and CAP) for ovarian cancer with a baseline assumption of 'No Treatment'.

The benefits of the individual treatments have all been based on median survival times. The clinical benefits of paclitaxel/cisplatin have also been sourced directly from the GOG 111 paper. However, the individual benefits of the CAP and carboplatin treatments have been derived from the combination of a number of smaller published RCT trials. The exact methodology for combining these data is not clear from the report itself. The report also highlights that there are a number of issues with regard to extracting data in this way due to differences between trial design and the treated cohorts.

Table 17: Wessex DEC Median Survival Data [3]

TREATMENT	MEDIAN SURVIVAL
Carboplatin	20 months
CAP	24 months
Paclitaxel/Cisplatin	38 months
No Treatment	6 months

The cost-benefit analysis uses the concept of QALYs as a benefit measure. This methodology uses a measure of quality of life to patients in order to adjust or weight the standard LYG values. This approach has not been followed in our analysis.

In analysing the cost-benefits, when comparing to a baseline of 'No Treatment', the report indicates that paclitaxel/cisplatin provides an extra 200 QALYs per 100 patients at a cost of £868,000.

This equates to a cost of £4,340 per extra QALY as can be seen in the table below.

Table 18: Wessex DEC Cost Benefits - No Treatment Baseline[3]

COSTS AND BENEFITS	Paclitaxel and Cisplatin	Carboplatin
Cost per 100 patients	£868,000	£288,000
Extra QALYs gained per 100 patients above 'No Treatment' baseline	200	90.5
Cost per extra QALY	£4,340	£3,180

Using these figures to calculate the extra cost benefit of paclitaxel/cisplatin when comparing to the baseline of carboplatin treatment, a figure of £5,297 per QALY is generated.

Table 19: Wessex DEC Cost Benefits - Carboplatin Baseline[3]

COSTS AND BENEFITS	Paclitaxel and Cisplatin	Carboplatin
Extra Cost per 100 patients above Carboplatin	£580,000	-
Extra QALYs gained per 100 patients above Carboplatin baseline	109.5	-
Cost per extra QALY	£5,297	-

The Wessex DEC[3] concludes that the clinical evidence for paclitaxel does exist and the cost-benefit analysis rates the treatment as **recommended,** against its own judgement scale, along with the standard treatments of CAP and carboplatin. However, reference is made to the fact that the clinical benefit data used in the analysis come from a range of

independent sources and that the underlying evidence for paclitaxel is also based on a single trial.

In view of this, the recommendation has also proposed a later review in the light of the final publication of RCT evidence from ICON 2[21] and 3[1] and other possible trials.

3.11.2 GOG 111 Cost-effectiveness Paper

This GOG economic analysis is again based on the direct results of the GOG 111 RCT and reflects the overall costs taken in a US setting. The resource implications are derived from the trial itself with supporting clinical opinion in order to put a non-trial 'real world' view to the cost analysis. The costs used in the analysis covered a wide range of direct costs:-

- pharmaceutical costs
- physician costs
- laboratory and diagnostic costs
- adverse reaction management costs
- in-patient/out-patient costs
- follow-up costs.

Costs were limited to the direct treatment costs and did not extend to cover the cost of future treatments. The analysis was performed using the median point survival data and the equivalent mean survival data. This was done as it was felt that, although clinically relevant, the median survival data may tend to over-estimate the cost-efficiency ratios. These data were obtained directly from the GOG statistical office and advice was taken to avoid any conflicts of interest in the analysis.

Interestingly, the analysis considered the mean survival data using figures up to the end of the trial period and on the basis of a present day measure by considering post trial survival rates.
The analysis concluded that, based on GOG 111 mean survival data (to present time), the extra cost per LYG for TP is estimated to be £6,534 ($10,454 @ $1.60=£1) above that of the CP arm.

The analysis concluded that, based on GOG 111 mean survival data (to end of trial), the extra cost per LYG for TP is estimated to be £12,388 ($19,820 @ $1.60=£1) above that of the CP arm.

The analysis concluded that, based on GOG 111 median survival data, the extra cost per LYG for TP is estimated to be £5,827 ($9,323 @ $1.60=£1) above that of the CP arm.

A separate multivariate Monte Carlo analysis was also performed which varied the mean survival time (to end of trial) around the published values using sets of unspecified distributions. This extra analysis provides an expected distribution of the extra cost per LYG of £12,417 ± £680 ($19,868 ± $1087).

The conclusion of the analysis was that the TP treatment fell within the accepted criteria for it to be deemed as being a cost-effective treatment.

However, in critically reviewing this paper from a health economics perspective, there are a number of issues which throw some doubt as to the relative strength of evidence this represents in terms of a UK based treatment.

- Analysis is based on a wide range of clinical assumptions which may not necessarily hold true in the UK setting, particularly those in relation to adverse effects management.

- A number of similarities are assumed between the two treatments with approximately 46% of the costs identical for both treatments.

- The analysis does not bring in the wider range of indirect costs and community costs which may impact on the cost-effectiveness argument.

- The analysis is necessarily made using the CP treatment as the baseline, which is not representative of the standard UK treatment of carboplatin as a single agent.

The conclusion, in terms of the paper's relevance, is that, whilst the results provide further evidence as to paclitaxel's cost-effectiveness, with an extra cost per LYG of £12,388, it is certainly not enough in isolation to imply expected treatment costs within the UK.

However, the paper does add to the evidence gained from both the Wessex[3] analysis and Trent's own work, which have been based within the context of UK costs and standard treatment comparitors.

3.12. Calculation of Survival Benefits Based on Survival Curve Estimates

It is interesting to note that the two economic analyses published have both approached the measurement of the clinical benefit of the treatments using a standard median point measure.

An alternative to this methodology is to focus not on median or mean data points, which are essentially single point estimates, but to look more at the complete experience of the cohort via the area under the survival curve (AUC).

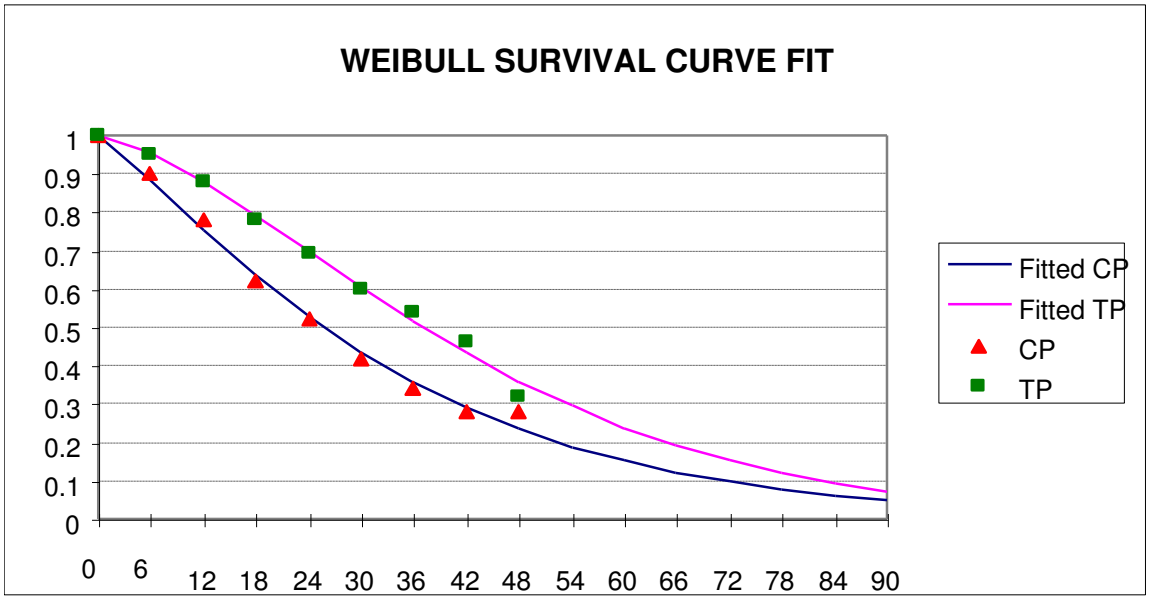
Therefore, to provide an extra added value to the cost-effectiveness analysis a second economic evaluation has been compiled using AUC estimated survival benefits.

The survival data have been derived directly from the GOG 111 paper using the published survival curves.

Using these data a Weibull curve has been fitted to the survival data for both treatments. This was achieved using a method of minimising the sum of the squared differences between the fitted curve and the observed values via a statistical curve fitting routine in Microsoft Excel.

The fitted curves provided area under the curve, AUC, estimates for both treatments

Figure 1: Curve estimates of Survival Data



The curves have been extrapolated beyond the 48 months of trial data to estimate potential future benefits; a limit of 90 months was fixed on this forward projection.

There are obvious problems with uncertainty when projecting a fitted curve forward in time as it is necessary to make the assumption that the form of the curve will remain the same over time, this may or may not be the case. Therefore, the results are expressed for scenarios which include or exclude the forward looking projection.

Table 20: Area Under Curve - Estimates

TREATMENT	AUC to 48 months	AUC to 90 months
TP	2.78 LYG	3.43 LYG
CP	2.25 LYG	2.67 LYG
Difference	0.53 LYG	0.76 LYG

Table 21: Area Under Curve - Costings

TREATMENT	AUC to 48 months	AUC to 90 months
Extra Cost per patient	£8,368	£8,368
Extra LYG per patient	0.53 LYG	0.76 LYG
Cost per extra LYG	£15,788	£11,010

Compared to the initial analysis based on median point survival data, using a fitted Weibull curve estimate of the survival data decreases the overall relative benefits of paclitaxel although they still remain significant.

The cost per marginal LYG increases from £7,173 to a value of £15,788. However, when the AUC is considered over a period beyond the trial period the value does return to a projected level of £11,010 per extra LYG.

These alternative AUC estimated cost per extra LYG values still remain within the recommended category guidelines.

4. OPTIONS FOR PURCHASERS AND PROVIDERS

The current published clinical evidence points strongly towards there being a clear benefit from the use of paclitaxel/cisplatin as a first line treatment for ovarian cancer.

Also, the economic cost-benefit analysis further supports the treatment with a cost per life year gained which is comparable with other existing treatments.

Interestingly, the recent Wessex DEC report[3] similarly compares both paclitaxel/cisplatin and carboplatin to a 'No-Treatment' baseline. This report was also based on the GOG trial, as this is the only phase III RCT available. Using a Quality of Life, rather than LYG, approach to their economic analysis, they too have supported the treatment as a recommended therapy.

There are a number of issues concerning the use of paclitaxel as a first line treatment which are either the focus of general clinical discussion or are being addressed via current RCTs.

Firstly, there are still issues to be answered about possible second line treatment options, as these could impact on paclitaxel costs if paclitaxel were re-administered to patients where first line treatment had failed. The conventional treatment option for patients with relapsed disease is to re-treat them with the agent to which they first responded. Patients with progressive disease, or that responsive to platinum agents, may be given a second line agent. The treatment response to disease progression after failed first line paclitaxel is yet to be determined. It is assumed in this paper that patients with relapsed disease will be offered one of the current platinum or second line agents and not be re-challenged with paclitaxel.

Secondly, four phase III RCTs are currently underway looking further at paclitaxel as a first line treatment for ovarian cancer.

Trial	**Treatment Arms**
1. GOG 132 trial	• cisplatin • paclitaxel • paclitaxel/cisplatin

Trial	**Treatment Arms**
2. GOG 114 trial	• cisplatin/cyclophosphamide • paclitaxel/cisplatin • carboplatin/paclitaxel/cisplatin
3. EORTC/NIC trial	• paclitaxel(3 hour)/cisplatin • cisplatin/cyclophosphamide
4. ICON 3[1](MRC)	• carboplatin • paclitaxel (3 hour)/ carboplatin • CAP

Further issues now being explored around the use of paclitaxel include :-

- length of the infusion;
- optimum dose intensity;
- optimum number of cycles; and
- combination with carboplatin.

A number of centres have begun to use a short three hour duration paclitaxel infusion which allows day case therapy; this is based on the results of a European-Canadian study of paclitaxel in relapsed ovarian cancer.[22] The efficacy of the three hour regime has not yet been verified for primary chemotherapy.

Finally, the possibility of using a paclitaxel/carboplatin combination has been investigated with a phase I evaluation using 3- (175 mg/m2), 24- (135 mg/m2) and 96- (120 mg/m2) hour regimes. The 96 hour regime was abandoned due to excessive myelosuppression. Overall response rate was 75% (n=24) with a median progression free survival time of 15 months.[23] Another phase I study also concluded that paclitaxel (185 mg/m2) given with carboplatin could be administered safely.[24] In patient terms this type of treatment would reduce the need for in-patient care and reduce the side effects related to cisplatin.

Within Trent's analysis a secondary supportive set of economic evaluations has been performed based on a paclitaxel/carboplatin combination therapy. However, based on the current drug costs and assuming the same expected clinical benefits as with the paclitaxel/cisplatin combination, this treatment is still less cost-effective in the long run (Cost

per extra LYG per person = £8,400 compared to £7,200 for TP). Also, it is important to stress that no published phase III evidence exists for the efficacy of carboplatin/paclitaxel.

In the light of such existing evidence purchasers are faced with three possible options:

1. To continue with the standard UK treatments and wait for further supportive evidence of paclitaxel's clinical effectiveness;

2. To continue with current standard treatments but engage in the ICON 3[1] trial, with suitable patients, in order to provide paclitaxel treatment. (The ICON 3[1] trial is recruiting 2,000 patients in total and is rapidly filling its patient cohort).

3. To engage in the ICON 3[1] RCT and also fund paclitaxel treatment for suitable patients outside the trial, in support of existing first line treatments based on carboplatin and CAP.

A further issue which purchasers should consider is the current pricing strategy adopted by Bristol Myers regarding paclitaxel. Currently the US are benefiting from a 30% discount on standard costs compared to the rest of the world. There is potential for a similar discounting to be experienced in the UK, particularly if paclitaxel is adopted as a first line treatment and pharmaceutical contracts are negotiated effectively.

5. DISCUSSION AND CONCLUSION

The key concern about the current evidence is that there is at present only one single published RCT trial, GOG 111. There is also some concern expressed by a group of clinicians around the choice of control treatment used in the GOG 111 trial, as the US standard treatment differs from that of the UK. Within the economic analysis the UK base treatment of carboplatin has been used as the comparitor, as identified in the ICON 3[1] protocol.

The EORTC trial is beginning to demonstrate a clear clinical benefit of using paclitaxel/cisplatin versus CP with a 4.6 month difference in progression-free survival between the two arms in favour of paclitaxel/cisplatin. This effect was reported at the median 20 month follow-up period. These preliminary, and as yet unpublished, results are likely to confirm the benefits of GOG 111.

The forthcoming publication of ICON 2[21] and later the ICON 3[1] trial, will hopefully provide a clearer picture of the benefits of paclitaxel in the UK setting.

The GOG 132 trial has provided a first interim report which is less conclusive showing no benefit for paclitaxel/cisplatin. The trial compares paclitaxel/cisplatin versus two control arms - single agent cisplatin and single agent paclitaxel. Importantly, the allowed crossover between the control arms can be argued strongly to cloud interpretation and as such must be viewed with some care.

In conclusion, the clinicians would argue strongly that the evidence base is sufficiently strong to support the purchase of paclitaxel and cisplatin combined therapy as a first line treatment for ovarian cancer, with opportunity to review after the publication of ICON 3.[1] However, the purchasers on the Working Group do not feel able to endorse fully this view until the findings of GOG 111 have been confirmed, although they do fully support the ongoing ICON 3[1] trial.

6. USE OF PACLITAXEL AND CISPLATIN IN THE TREATMENT OF OVARIAN CANCER : SUMMARY MATRIX

PATIENT GROUP	PATIENT CRITERIA (GUIDELINES NOT PROTOCOLS)	ESTIMATED FUTURE ACTIVITY	OPPORTUNITY FOR COST SAVING	AUDIT POINTS	EFFECTS THAT COULD BE EXPECTED IN RELATION TO STARTING POINT	COST-EFFECTIVENESS
Patients with stage II/III/IV ovarian cancer.	Likely to be used for patients who are <65 years of age and who are functionally suitable for treatment.	Expected annual activity of 299 cases within Trent . (31 cases in a typical district of size 500,000).	None.	Continued review of survival and progression-free survival rates. Recording of adverse effects, especially those which imply cost.	Increased median survival and an increase in progression-free survival compared to the current UK base treatment. A projected extra LYG of 1.17 per patient.	Costs per extra LYG above the current standard treatment of single agent carboplatin. £7,173 per LYG . Cost per extra PFY above the current standard treatment of single agent carboplatin. £20,084 per PFY.

APPENDIX : COSTING INFORMATION

Drug Costs

	Drug	Dosage	Trent Cost	UK COST
A	Cisplatin - iv	135mg	£39.66	-
C	Paclitaxel - iv	240mg	£1173.04	-
E	Chlorpheniramine - iv	10mg	£0.14	-
F	Cimetidine - iv	300mg	£0.61	-
G	Carboplatin - iv	720mg	£271.02	£371.26
H	Cyclophosphamide	900mg	£3.64	£4.80
J	Doxorubicin	90mg	£146.84	
K	Granisetron - iv	3mg	£9.99	£42.30
L	Dexamethasone - oral	40 X 2mg tablets	£1.72	£4.06
M	Dexamethasone - iv	8mg	£0.70	£2.07

Hospital Costs

A	Day Case Treatment	£206
B	Out-Patient Treatment	£59
C	In-Patient Treatment	£229

Management of Adverse Effects - Drug Costs

A	Alopecia	£69
B	Allergic Reaction	£10
C	Fever	£200

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