Pharmacotherapeutic value and cost-effectiveness of gemcitabine, pegylated liposomal doxorubicin and paclitaxel for the treatment of metastatic ovarian cancer

Review on paclitaxel, pegylated liposomal doxorubicin and gemcitabine in metastatic ovarian cancer for ZonMw

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SUMMARY [Dutch]

Introductie
Ongeveer 90% van de ovariumkankers (OC) behoort tot de epitheliale OC. OC wordt in de regel gediagnosticeerd in de gemetastaseerde fase en heeft meestal een slechte prognose. OC wordt ingedeeld volgens het FIGO systeem, waarbij stadium I gedefinieerd is als OC waarbij één van de ovaria is aangedaan. Bij stadium IV zijn metastasen op afstand aangetoond. In Nederland is OC de vijfde doodsoorzaak bij vrouwen en 5% van de kankers bij vrouwen is OC. In 2008 werden in Nederland 1200 nieuwe gevallen van OC gevonden. In dit review wordt de literatuur over de werkzaamheid, effectiviteit, veiligheid, kwaliteit van leven en kosten-effectiviteit van chemotherapie bij eerste en tweedelijnsbehandeling van gemetastaseerd ovariumkanker (MOC) samengevat. Hierbij wordt de behandeling ook belicht vanuit het perspectief van de patiënt, de medisch oncoloog en de apotheker.

Methode
In de databases MEDLINE, EMBASE en Cochrane is met trefwoorden gezocht naar reviews van gerandomiseerde klinische trials (RCT) en economische evaluaties van de behandeling van MOC met paclitaxel (PAC), gepegyleerd liposomaal doxorubicine (PLD) en gemcitabine (GEM). Met trefwoorden is gezocht of na het verschijnen van het meest recente review nog gegevens van nieuwe RCT´s zijn gepubliceerd.
Een vertegenwoordiger van de patiëntenvereniging en drie medisch oncologen zijn geïnterviewd. Hierbij zijn vragen gesteld over de behandeling van MOC, de toxiciteit van de deze behandeling en de voorlichting bij het maken van keuzes omtrent de behandeling.

Resultaten
Vier RCT´s naar de werkzaamheid, effectiviteit en veiligheid van PAC als eerstelijnsbehandeling van MOC, toegepast in combinatie met cisplatine of carboplatine (CISPAC, CARPAC), zijn beschreven in twee reviews. In later fase III onderzoek is CARPAC vergeleken met carboplatine/docetaxel (CARDOC). In twee van de onderzoeken leidde behandeling met CISPAC in vergelijking met de combinatie cisplatine/cyclofosfamide tot een langere overlevingsduur. In twee andere onderzoeken was PAC in combinatie met carboplatine of cisplatine even effectief als alleen carboplatine of cisplatine of de combinatie cyclofosfamide, doxorubicine, cisplatine (CAP). CARPAC was even effectief als CARDOC. Het responspercentage bij de behandeling met PAC in combinatie met een platinaverbinding varieerde over de onderzoeken van 59% tot 73%. Voor behandeling met cisplatine in combinatie met cyclofosfamide van 45% tot 60% en voor behandeling met alleen platina was dit 67%. De mediane overleving varieerde voor de behandeling met PAC in combinatie met

een platinaverbinding, behandeling met cisplatine/cyclofosfamide en hoge dosering van alleen een platinumverbinding, respectievelijk, van 26.6 tot 38.0 maanden, van 24.0 tot 26.8 maanden en van 30.2 tot 36.1 maanden. Er zijn verschillende verklaringen voor de verschillen in de uitkomsten van de onderzoeken in de literatuur beschreven. Het zou mogelijk kunnen zijn dat cross-over tussen de groepen tot een verdunning van het effect heeft geleid. Ook wordt als verklaring gegeven dat hoge dosering van een platinaverbinding mogelijk effectiever is dan cisplatine met cyclofosfamide en dat cyclofosfamide misschien zelf een negatief effect heeft op de uitkomst.

CISPAC veroorzaakte vooral neutropenie. Alleen cisplatine in hoge dosering leidde in het bijzonder tot neurotoxiciteit en gastrointestinale bijwerkingen. Dosisescalatie van PAC (als CISPAC) leidde tot een toename van de neurotoxiciteit. CISPAC veroorzaakte meer neuropathie en minder neutropenie dan CISDOC.

Er zijn weinig gegevens over de kwaliteit van leven. In onderzoeken van de kosten-effectiviteit bleek CISPAC kosten-effectief in vergelijking met cisplatine/cyclofosfamide. Er is geen vergelijking gemaakt met cisplatine of carboplatine alleen of CAP.

Er zijn ook onderzoeken verricht naar de werkzaamheid en veiligheid van de combinatie CARPAC waarbij de intraveuze en intraperitoneale toediening is vergeleken. Door intraperitoneaale toediening van CARPAC werd de overlevingsduur verlengd. Dit effect ging echter gepaard met meer bijwerkingen. Onderzoek van de kosten-effectiviteit wees uit dat intraperitoneale behandeling tot meer QALY’s leidde, maar ook tot meer kosten.

In een drietal reviews zijn verschillende onderzoeken naar de werkzaamheid, effectiviteit, veiligheid en kwaliteit van leven van PAC, PLD en GEM als tweedelijnsbehandeling van MOC beschreven. Tot 2004 is in de tweede lijn bij de behandeling van platina-gevoelige MOC de werkzaamheid van PAC en PLD alleen aangetoond in onderzoek waarbij deze middelen als monotherapie zijn toegepast bij patiënten die doorgaans nog niet met een taxaan waren behandeld. In een kleine RCT en in een recent gepubliceerd groot onderzoek is de effectiviteit van CARPAC vergeleken met carboplatine in combinatie met PLD (CARPLD). In het eerste onderzoek was de effectiviteit van de twee behandelingen vergelijkbaar. In het grote onderzoek werd een verschil van twee maanden in de overlevingsduur in het voordeel van CARPLD gevonden. Een systematisch review van onderzoeken van de combinaties carboplatine met GEM (CARGEM) en CARPLD liet een beter effect van de CARPLD op de respons en de overleving zien. CARPAC leidde tot meer ernstige tot zeer ernstige neutropenie, allergische reacties en haaruitval. CARPLD was

vooral geassocieerd met trombocytopenie, mucositis en hand-voetsyndroom. De hematologische toxiciteit van CARGEM was vergelijkbaar met die van CARPLD. Anemie en neutropenie kwamen wel vaker voor bij CARGEM.
Er is weinig onderzoek naar de effectiviteit van PAC, PLD en GEM bij de behandeling van teruggekeerde platina-resistente MOC verricht. GEM is overigens voor deze indicatie niet geregistreerd. De middelen zijn beperkt werkzaam met responspercentages en progressievrije overlevingsduren variërend van respectievelijk 8% tot 43% en 9 tot 24 weken.

Er zijn één nationale en verschillende internationale richtlijnen voor de behandeling van OC. Deze richtlijnen verschillen met betrekking tot de adviezen voor de keuze van chemotherapie in de eerste lijn. De NICE richtlijn adviseert alleen carboplatine of CARPAC toe te passen. In andere richtlijnen wordt alleen de toepassing van CARPAC geadviseerd. Deze verschillen zijn gelegen in het feit dat de NCCN richtlijn wel de vergelijkende onderzoeken van CISPAC met hoge dosering van alleen een platinaverbinding in de beoordeling betrekt, terwijl de andere richtlijnen deze onderzoeken niet (lijken) te betrekken. De NCCN richtlijn noemt ook nog de mogelijkheid om CARDOC toe te passen, wanneer verwacht wordt dat neuropathische bijwerkingen van CARPAC niet acceptabel zijn. Voor wat betreft de adviezen ten aanzien van tweedelijnsbehandeling wordt in het algemeen gesteld dat de behandeling met CARPAC kan worden herhaald bij platina-sensitieve MOC. Wanneer dit niet mogelijk is vanwege toxiciteit of omdat het een platina-resistente vorm betreft, wordt monotherapie met middelen, zoals PLD, GEM en topotecan geadviseerd. Hierbij worden geen adviezen over de toe te passen dosering en duur van de behandeling gegeven.

De geïnterviewde medisch oncologen gaven unaniem aan de behandeling van MOC te starten met CARPAC. Voor de tweedelijnsbehandeling wordt, op basis van de toxiciteit, ofwel CARPAC herhaald ofwel CARPLD of CARGEM. Over de behandeling wordt met de patiënten uitgebreid gesproken, waarbij in de regel ook schriftelijk voorlichtingsmateriaal wordt gebruikt. Vaak is meer dan één sessie nodig om tot een beslissing te komen. Dit wordt door de vertegenwoordiger van de patiëntenvereniging bevestigd. Zowel de behandelaren als de vertegenwoordiger van de patiëntenvereniging brengen geen knelpunten naar voren.

Conclusie
De resultaten van de RCT’s naar de werkzaamheid en effectiviteit van PAC in combinatie met platina in de eerstelijnsbehandeling van MOC zijn niet éénduidig. Gesteld kan worden dat zowel cisplatine of carboplatine monotherapie als deze platinaverbindingen in combinatie met PAC hiervoor kunnen worden toegepast.

In de onderzoeken van de kosten-effectiviteit zijn alleen de twee onderzoeken meegenomen waarin CISPAC een groter effect had op de progressie-vrije overleving dan cisplatine met cyclofosfamide. Het kan daarom zinvol zijn farmaco-economisch onderzoek te verrichten op basis van de vijf trials van de werkzaamheid en veiligheid van PAC met een platinaverbinding. Om meer inzicht te krijgen in de waarde van de behandeling voor patiënten is het nodig onderzoek naar de kwaliteit van leven te doen.
Op grond van de resultaten van verschillende onderzoeken lijken de werkzaamheid en effectiviteit van tweedelijnsbehandelingen van platina-gevoelige MOC met combinaties van carboplatine met PAC, PLD of GEM vergelijkbaar te zijn. Echter, de toxiciteitprofielen van de verschillende combinaties verschillen. Op basis van de te verwachten toxiciteit kan de keuze voor één van de combinaties worden gemaakt.
De economische evaluaties zijn gebaseerd op de oudere (vóór 2006) onderzoeken en lieten zien dat de kosten-effectiviteit van CARPAC beter was dan die van andere middelen. Daarentegen werd uit een ander onderzoek geconcludeerd dat de kosten-effectiviteit van PLD beter is dan die van PAC monotherapie en topotecan. Er zijn geen onderzoeken waarbij gegevens van meer recente onderzoeken zijn gebruikt. Het kan zinvol zijn om farmaco-economisch onderzoek te gaan verrichten, omdat de tegenwoordig gangbare tweedelijnsbehandelingen, CARPAC of CARPLD met carboplatin op deze nieuwere onderzoeken zijn gebaseerd.

INTRODUCTION

Type of disease

Ovarian carcinoma (OC) may arise from different types of cells of the ovary. There are three principal types of OC. Around 90% are classified as epithelial and result from malignant transformation of the epithelium of the ovarian surface. Other types of ovarian tumours are stromal and germ cell tumours, accounting for around 1% of cases. The aetiology of OC remains unclear. Factors suspected to be associated with an increased risk of developing OC include an advancing age, early age at menarche, a late menopause, infertility and the use of fertility drugs (1;2). About 5 to 10% of OC cases can be subscribed to a family history, including linkage with mutations in the genes BRCA1 and BRCA2 or families affected by the hereditary non-polyposis colorectal cancer gene (HNPCC) (2;3). Most patients with OC are diagnosed at advanced stage, largely because earlier stages usually do not cause obvious symptoms. Therefore, the prognosis of OC is generally poor. As the tumour grows and seeds in the peritoneal cavity, the most common symptoms include abdominal pain and distension, urinary symptoms, abdominal mass and postmenopausal or abnormal bleeding (4). According to the International Federation of Gynaecologists and Obstetricians (FIGO) system, stage I of bladder cancer refers to malignant growth that is still confined to one or both ovaries. Stage IV refers to disease where distant metastasis beyond the peritoneal cavity can be detected. The 5-year survival rate in the Netherlands ranges from 14% in patients with metastatic ovarian cancer (MOC), FIGO IV, to 90% in patients with an earlier stage of disease, FIGO I (5). .

Epidemiology

OC is the fifth leading cause of cancer-related death in Dutch women and accounts for 5% of all female cancer deaths (5). Worldwide there were more than 225,000 new cases of OC in 2008 (6). In the Netherlands, approximately 1,200 new cases of OC were diagnosed in 2008, giving an age standardised incidence rate (ESR) of 11.5 per 100,000 women. Comparing cancer networks within the Netherlands, the incidence rates were lowest in the Northern cancer networks, 10.7–11.3 per 100,000 population, and highest in the Southern cancer networks, 11.3–12.6 (5). In comparison with other European countries, the Netherlands is among those with the lowest incidence rates of OC (6). Data show the trends in the age standardised incidence and mortality rates of OC in the Netherlands from 1989 to 2008. The rates have been steadily decreasing over the past 20 years, from respectively 15.1 and 11.6 per 100,000 in 1989 to 11.5 and 8.7 in 2008. The majority of OC patients are older, post-menopausal women with, in the Netherlands, over 85% of cases being diagnosed in women over 50 years (1,032 out of 1,203 cases). The number of deaths is highest in the 65-84 years

age group (553 out of 1,021), but the highest mortality rate is in the 80-94 years age group, 68.3 per 100,000 population.

Standard chemotherapy for MOC

Primary treatment for MOC consists of optimal surgical staging and cytoreduction, followed by systemic chemotherapy. Chemotherapy is used to minimize residual disease after surgery but may also be used to down-size the tumour lesions before surgery. The current standard of care chemotherapy for MOC includes a platinum compound and a taxane. Until the mid-1990s the standard first-line treatment included platinum monotherapy or cisplatin (CIS) plus cyclophosphamide. In 1996 platinum (CIS or carboplatin (CAR)) plus taxane (paclitaxel (PAC)) combination regimens were introduced. These regimens have replaced the previous standard care (7;8). As the majority of patients relapse and require treatment with second-line therapy, pegylated liposomal doxorubicin (PLD), topotecan, PAC and gemcitabine (GEM) may be considered for second-line therapy in MOC.

The present review concerns the use of PAC, PLD and GEM which are registered on the 'Beleidsregel dure geneesmiddelen in ziekenhuizen' as expensive medicine.

PAC has been licensed in the Netherlands since 1993 for the first- and second-line treatment of MOC. PAC is also indicated for other malignancies, including breast cancer, non-small cell lung cancer, and HIV-related Kaposi's sarcoma. PAC is a cytostatic agent that prevents cell division by promoting disassembly of microtubules. PAC stabilizes microtubules and as a result, interferes with the normal breakdown of microtubules required for cell division. In the presence of this drug, cancer cells become clogged with microtubules resulting in a mitotic arrest. The recommended dose for first-line treatment MOC includes 175 mg/m2 body surface area of PAC, administered over a period of 24 hours on day 1, followed by either 75 mg/m2 of CIS, administered on day 2 in a 3-hour infusion or CAR dosage employing an area under the curve (AUC) of 6, with an interval of 3 weeks between cycles. The recommended dose for PAC as second-line treatment for MOC includes 175 mg/m2, administered over a period of 3 hours, with an interval of 3 weeks between cycles.

PLD has been registered in the Netherlands since 1996 for the treatment of MOC in women in whom a first-line platinum-based chemotherapy regimen has failed. PLD is also indicated for other malignancies, including breast cancer, multiple myeloma, and HIV-related Kaposi's sarcoma. PLD infusion contains the active ingredient doxorubicin hydrochloride. In PLD doxorubicin molecules are encapsulated in a bilayer sphere of pegylated lipids called liposomes. The effect of doxorubicin is based on the inhibition of DNA, RNA and protein synthesis. The recommended dose for PLD as second-line treatment for MOC is 40-50

mg/m2, administered intravenously once every 4 weeks for as long as the disease does not progress and the patient continues to tolerate treatment.
GEM has been licensed in the Netherlands since 1995, in combination with CAR for the treatment of MOC that has returned at least 6 months after the patient had finished platinum-based therapy (platinum-sensitive recurrent MOC). GEM is also indicated for other malignancies, including non-small cell lung cancer, bladder cancer, pancreatic cancer, and breast cancer. GEM is a pyrimidine nucleoside antimetabolite exhibiting cell phase specificity, primarily killing cells undergoing DNA synthesis. The recommended dose for GEM as second-line treatment of MOC is 1000 mg/m2, administered on days 1 and 8, in combination with CAR dosage employing an area under the curve (AUC) of 4 on day 1, every 3 weeks for up to six cycles.

Objective
A systematic review of the recent literature on treatment with an ‘expensive’ medicine in metastatic ovarian cancer (MOC) was performed. The objectives for the review were to evaluate the pharmacotherapeutic value and cost-effectiveness of paclitaxel (PAC), pegylated liposomal doxorubicin (PLD) and gemcitabine (GEM) for the treatment of MOC and to evaluate the impact on quality of life.

METHODS

Search strategy

A search was performed by an experienced librarian using the MEDLINE, EMBASE and Cochrane databases. The search strategies, based on terms on MOC, the three expensive medicines under review for the treatment of MOC and either randomised clinical trial (RCT) or economic evaluations, are presented in Appendix A. The search included both Medical Subject Headings (MeSH) terms, e.g. “Ovarian Neoplasms”, as well as text words. The search strategy was adapted accordingly for the EMBASE and Cochrane databases.

Selection criteria

Selection criteria that were used to include studies:

- Systematic reviews (and RCTs and economic evaluations if published after inclusion date for studies in the review)
- Patients with MOC
- Treatment with PAC, PLD or GEM

Criteria for considering studies for inclusion

Systematic reviews that investigated the pharmacotherapeutic value and cost-effectiveness of at least one of the three expensive medicine for the treatment of MOC under review, were included. Additional phase III RCTs and economic evaluations published after the publication date of the most recently performed reviews were also included. Inclusion criteria for economic evaluations were cost-effectiveness analysis, cost-utility analysis and cost-minimisation analysis.

Type of studies included

Patients

Studies that included women with MOC were included.

Type of intervention

Treatment with GEM, PLD or PAC used alone or in combination with other chemotherapeutic therapy as part of the following stages of treatment were eligible for inclusion. First-line treatment (defined as the first chemotherapy regimen administered) of MOC or second-line treatment (defined as the second chemotherapy regimen administered either as a result of relapse after first-line platinum-based treatment, or immediately following on first-line platinum-based therapy in patients with progressive or stable disease).

Data collection and analysis

Two reviewers (JH and CB) independently evaluated all titles and abstracts. To streamline the data collection process, all references were exported and managed using Reference Manager, Version 11 (Thomson ISI ResearchSoft, Berkeley, CA, USA). Full paper manuscripts of potentially relevant titles/abstracts were obtained and assessed for inclusion. Studies that did not fulfil all criteria were excluded. Disagreements were resolved by discussion until consensus was reached.

Outcomes

Data on the following outcome measures were eligible for inclusion in this review:

- Efficacy, effectiveness, toxicity, and quality of life is based on a systematic search of the literature on RCTs.
- Ongoing clinical trials on MOC were searched on the Clinical Trials Registry of the U.S. National Library of Medicine (www.clinicaltrials.org, accessed February 2011) and the Dutch Trial Registry (www.trialregister.nl, accessed February 2011).
- Clinical guidelines are reviewed including VIKC-Landelijke richtlijn (Dutch), National Institute for Health and Clinical Excellence (NICE) guidelines (UK), European Society for Medical Oncology (ESMO) guidelines (Europe), and National Comprehensive Cancer Network (NCCN) guidelines (US).
- Daily clinical practice includes a summary of interviews with three oncologists, dispension data of a hospital pharmacy of an academic medical centre in the Netherlands, and input of the patients association.
- Data on generic products are retrieved from the Dutch Medicines Evaluation Board (CBG).
- Data on costs are retrieved from the Dutch Foundation for Pharmaceutical Statistics (SFK).
- Economic evaluation is based on a systematic search of the literature including cost-effectiveness analysis and cost-utility analysis.

RESULTS

REVIEW OF PHARMACOTHERAPEUTIC VALUE

In total 836 publications were identified. Of these 836 publications, two reviews of first-line treatment for MOC were identified (9;10) that included all RCTs until 2001. In addition, two systematic reviews on the effectiveness of intraperitoneal versus intravenous chemotherapy (11;12) were identified. Of the 836 publications, three reviews and one systematic review of the clinical effectiveness and safety of second-line treatment with PAC, PLD and GEM were included (2;13-15).

First-line treatment

First-line chemotherapy of MOC has been reviewed by Sandercock et al. (10) and Covens et al. (9). In their reviews the results of four RCTs on the effectiveness and safety of PAC are discussed. One additional phase III trial that was not included in these reviews has been included in the present review (16).

These five trials are described below.

In the **GOG-111** trial the efficacy of PAC (135 mg/m2)/CIS (75 mg/m2) (CISPAC) and CIS (75 mg/m2)/cyclophosphamide (750 mg/m2) in 410 women with MOC and sub-optimal tumour reduction following surgery (7). No significant difference in overall response rate (complete and partial response) (ORR) was found (relative risk (RR) = 1.19 [95%CI: 0.95-1.5]). However, median progression free survival (PFS) was significantly longer for patients receiving CISPAC (18 months vs. 13 months, RR = 0.7 [95%CI: 0.5-0.8] $p < 0.001$). Median overall survival (OS) was also significantly longer in these patients (38 months vs. 24 months, RR = 0.6 [95%CI: 0.5-0.8] $p < 0.001$). Estimates from updated longer-term study results suggest that the death rate is 30% less among those treated with CISPAC (relative hazard: 0.7 [95%CI: 0.57-0.87]).

In the **OV10** trial CISPAC (75 mg/m2 and 175 mg/m2, respectively) has also been compared with CIS (75 mg/m2)/cyclophosphamide (750 mg/m2) in 680 women with optimal or sub-optimal tumour reduction following surgery, of whom 93% had stage III or IV disease (8). A significant difference in ORR in favour of the PAC combination was detected (RR = 1.92 [95%CI: 1.52-2.42]). Like GOG111, the study also measured a significantly longer median PFS for the PAC combination (15.3 months vs. 11.5 months, HR = 0.74 [95%CI: 0.63-0.88] p

= 0.0005). OS was also significantly higher in this group (35.6 months vs. 25.8 months, HR = 0.73 [95%CI: 0.60-0.89] p = 0.0016).

In the **GOG132** trial combination CISPAC (75 mg/m2 and 135 mg/m2, respectively) has been compared with CIS monotherapy (100 mg/m2) (17). All 424 women had stage III or IV disease and suboptimal tumour reduction following surgery. No significant difference in ORR was found between the group receiving CIS monotherapy and those receiving the CISPAC (RR = 0.97 [95%CI: 0.86-1.09]). However, unlike **GOG111** and **OV10**, no significant differences were found in PFS (14.1 months vs. 16.4 months, HR = 1.06 [95%CI: 0.86-1.30]), and OS (26.6 months vs. 30.2 months, HR = 0.99 [95%CI: 0.80-1.23]). The difference between the results of this trial and those reported for the GOG111 and OV10 studies may be explained by the extent of patient cross-over between treatments before the disease progressed. However, it is unlikely that this is sufficient to explain such markedly different results. Another explanation is that high dose platinum is more effective than the combination CIS/cyclophosphamide. It has been suggested that cyclophosphamide even may have a worsening effect on the patient outcome (Sandercroft 2002).

In the **ICON3** trial combination of PAC (175 mg/m2)/CAR (5 AUC) (CARPAC) with either CAR monotherapy (5 AUC) or a combination of cyclophosphamide (750 mg/m2)/doxorubicin (75 mg/m2)/CIS (75 mg/m2) (CAP) (18). This trial differs from the others, since patients had a wider range of residual tumour following surgery (54% had optimally reduced tumours), and a smaller proportion (80%) had stage III and IV disease. Of the total 2,074 women recruited, 1421 were randomised to receive CARPAC or CAR alone. The results of the ICON3 trial after more than 3 years' follow-up also differ from those of the GOG111 and OV10 studies. No significant difference was found between the groups receiving CARPAC or CAR alone, in terms of PFS (17.1 months vs. 16.1 months, HR = 0.94 [95%CI: 0.84-1.05] p = 0.24) or OS (37.6 months vs. 36.1 months, HR = 0.96 [95%CI: 0.84-1.09] p = 0.53). There were no significant differences in the anxiety and depression score results. Recruitment of more patients with less extensive disease might have diluted the effect of PAC treatment. However, sub-group analyses by FIGO stage and extent of residual tumour did not support this tenet. The trial design allowed choice of the control arm before randomisation.This could also have diluted any treatment effect. On the other hand, it may be that this may better reflect clinical practice in some aspects.

In an RCT by Vasey et al. (2004) 1077 patients were randomised to receive docetaxel at 75 mg/m2 and CAR (CARDOC) or CARPAC (PAC 175 mg/m2), every 3 weeks for six cycles (16). In responding patients, an additional three cycles of single-agent CAR was permitted.

Both groups had similar PFS (15 months for CARDOC and 14.8 months for CARPAC (HR docetaxel/paclitaxel = 0.97 [95%CI: 0.83-1.13] p = 0.707), OS rates at 2 years (64.2% and 68.9%, respectively; HR = 1.13 [95%CI: 0.92-1.39] p = 0.238), and ORR (58.7% and 59.5%, respectively; difference = -0.8% [95%CI: -8.6% - 7.1%] p = 0.868) and CA-125 (75.8% and 76.8%, respectively; difference = -1.0% [95%CI: -7.2% - 5.1%; p = 0.794). CARDOC appears to be similar to CARPAC in terms of PFS and ORR, although longer follow-up is required for a definitive statement on survival. Thus, CARDOC represents an alternative first-line chemotherapy regimen for patients with newly diagnosed MOC.

Table 1 : Studies on first-line treatment in MOC,

Study	N	Regimen	ORR (%)	PFS (months)	OS (months)
GOG111 trial McGuire et al. 1996	410	paclitaxel + cisplatin	73	18.0	38.0
		cisplatin + cyclophosphamide	60	13.0	24.0
OV10 trial Piccart et al. 2000	680	paclitaxel + cisplatin	59	15.3	35.6
		cisplatin + cyclophosphamide	45	11.5	25.8
GOG132 trial Muggia et al. 2000	424	paclitaxel + cisplatin	66	14.1	26.6
		cisplatin	67	16.4	30.2
ICON3 ICON group 2002	2074	paclitaxel + carboplatin	NA	17.1	37.6
		carboplatin or CAP	NA	16.1	36.1
Vasey et al. 2004	1077	paclitaxel + carboplatin	58.7	15.0	OS at 2 years 64.2%
		docetaxel + carboplatin	59.5	14.8	68.9%

Abbreviations: CAP= cyclophosphamide/doxorubicin/cisplatin; ORR=overall response rate; PFS=progression-free survival; OS=overall survival; NA=not available.

Intraperitoneal vs. intravenous treatment

Because of improved local activity, the use of intraperitoneal chemotherapy may increase the survival rate. The effectiveness of intraperitoneal versus intravenous chemotherapy was reviewed in two systematic reviews (11;12). The pooled data from up to eight trials suggested that chemotherapy given directly into the peritoneal cavity as part of adjuvant treatment, may significantly reduce the risk of death (HR = 0.80 [95%CI: 0.71-0.90] p = 0.0003) and disease recurrence (HR = 0.79 [95%CI: 0.69-0.90] p = 0.0004). An effect was also seen after five years of follow-up (RR of death = 0.88 [95%CI: 0.81-0.95] p=0.002; RR of disease progression = 0.91 [95%CI: 0.85-0.98] p = 0.02). However, incidences of pain, fever, fatigue, hearing loss, infection and gastrointestinal and metabolic effects occurred up to eight times more frequently in women receiving intra-peritoneal chemotherapy. Health-related quality of life was measured in one trial and found to be significantly worse for women receiving intra-peritoneal chemotherapy in the early days of treatment and shortly (3 to 6 weeks) after all study treatment, but a difference between study arms was not apparent after

one year of follow-up. Intraperitoneal treatment is more effective, but is accompanied with more toxicity.

Second-line treatment

Platinum-sensitive recurrent MOC

Three reviews and one systematic review on the clinical effectiveness and safety of second-line treatment with PAC, PLD and GEM were included (2;13-15).

The aim of the review of Main et al. (2) was to examine the clinical effectiveness and cost-effectiveness of intravenous formulations of topotecan, PLD and PAC used alone or in combination with a platinum-based compound for the second-line or subsequent treatment of MOC. Main et al. included nine RCTs in their review. In five trials, both comparators were used within their licensed indications. Of these five trials, three included patients with both platinum-resistant and platinum-sensitive MOC, and a further two only included patients with platinum-sensitive disease.

The comparators that were assessed in the three trials that included both subtypes of patients were PLD vs. topotecan, topotecan vs. PAC and PLD vs. PAC. In the further two trials that included patients with the subtype of platinum-sensitive disease, the comparators were single-agent PAC vs. CAP and PAC plus platinum-based chemotherapy vs. conventional platinum-based therapy alone. The results of the four remaining trials are not addressed in the present review, because one of the comparators in the trials was outside its licenced indication. The five RCTs included in the present review are described below. The results obtained in patients with platinum-sensitive disease are summarized in Table 2 and the results obtained in patients with platinum-resistant disease are summarized in Table 4.

Gordon et al. compared PLD monotherapy (50 mg/m^2) with topotecan monotherapy (1.5 mg/m^2) and included 474 patients (19;20). Most patients (73%) had been previously treated with platinum and taxanes. Median OS was 63 weeks for patients treated with PLD and 60 weeks for patients treated with topotecan (HR = 1.22 [95%CI: 1.00-1.48]). The 3-year survival rate in the PLD group was 20.2% (95%CI: 14.9-25.5), compared with 13.2% (95%CI: 8.8-17.7) for topotecan-treated patients. There were no statistically significant differences in median PFS (16 weeks for PLD vs. 17 weeks for topotecan (HR = 1.12 [95%CI: 0.93-1.35]) or in response rates (total response rates: 19.7% for PLD [95%CI: 14.6-24.7] vs. 17% for topotecan [95%CI: 12.2-21.8]). The survival benefit associated with PLD was most pronounced in platinum-sensitive patients, among whom the median survival time was significantly higher in the PLD arm compared with the topotecan arm (108 weeks for PLD vs. 70 weeks for topotecan; HR = 1.43 [95%CI: 1.07-1.92]). No significant treatment-related

differences in median OS were shown for the group defined as platinum-refractory (54% of the trial population), which included women with platinum-resistant and platinum-refractory disease (38 weeks vs. 42 weeks for PLD and topotecan, respectively; HR = 1.07 [95%CI: 0.82-1.39]). There were no significant differences between treatment groups for PFS and response rates when the results were analysed according to baseline platinum sensitivity.

The RCT that compared topotecan monotherapy (1.5 mg/m^2) with PAC monotherapy (175 mg/m^2) included 235 patients all of whom were taxane naïve (21;22). At long-term follow-up (4 years after randomisation), no significant differences between treatment groups were reported, other than in median time to response, which favoured PAC (6 weeks vs. 9 weeks, p = 0.041 [95%CIs not given]). Median survival times were 63 weeks (95%CI: 47-72) and 53 weeks (95%CI: 42-69) for the topotecan and PAC arms, respectively. Median time to progression was 19 weeks (95%CI: 12-24) for topotecan and 15 weeks (95%CI: 12-18) for single-agent PAC. There were no significant differences between treatment groups when the results were analysed according to baseline platinum sensitivity. Median survival times in the topotecan and PAC groups, respectively, were 28 weeks and 40 weeks in participants with platinum-refractory disease, 72 weeks and 35 weeks in those with platinum-resistant disease and 63 weeks and 85 weeks in those with platinum-sensitive disease. Participants whose best response was stable disease after six courses of treatment could be removed from the study or switched to the alternative therapy (61 participants crossed over to topotecan and 49 to single-agent PAC). There were no significant differences in efficacy from the initiation of crossover therapy (median survival was 40 weeks and 48 weeks for participants treated third-line with topotecan and single-agent PAC, respectively).

The RCT that compared PLD monotherapy (50 mg/m^2) with PAC monotherapy (175 mg/m^2) (23) aimed to include 438 (taxane-naive) patients. However, only 216 patients were randomised and the study was terminated prematurely. Data were reported for survival and adverse events only. No significant differences in median survival between treatment groups were reported (47 weeks in the PLD group vs. 56 weeks in the single-agent PAC group; HR = 0.931 [95%CI: 0.70-1.23]).

In a RCT including 97 (taxane-naïve) whose disease had progressed or recurred more than 12 months after the end of the previous treatment, PAC monotherapy (175 mg/m^2) was also compared with CAP (cyclophosphamide 500 mg/m^2, doxorubicin 50 mg/m^2, CIS 50 mg/m^2) (24). At a median follow-up of 49 months, by which time 57% of the CAP group and 72% of the PAC group had died, median survival times were higher in the CAP treatment group than in the PAC group (34.7 months vs. 25.8 months; HR, adjusted for differences in residual

tumour, length of treatment-free interval and age = 0.58 [95%CI: 0.34-0.98). The mean PFS was also higher in the CAP treatment group (15.7 months vs. 9 months; adjusted HR = 0.60 [95%CI: 0.37-0.97]). There were no significant differences in ORR. Patients who did not respond to their randomised treatment were crossed over to the alternative treatment arm. Of the 23 participants who crossed over to PAC, five (22%) achieved an ORR, compared with 14 of the 30 participants (46%) who switched to CAP.

PAC platinum combination (175 mg/m^2) plus CIS or (185 mg/m^2) plus CAR has been compared with platinum monotherapy (25) in the **ICON4/AGO-OVAR-2.2** trial which included 802 patients with platinum-sensitive MOC, 75% of whom had a treatment-free interval greater than 12 months and 43% of whom had received taxanes as part of their first-line treatment. The platinum agent used in the majority of cases was CAR. At a median follow-up of 42 months, 66% of participants had died. There was a significant difference in median survival (29 months vs. 24 months) for patients receiving PAC and platinum combination therapy and platinum monotherapy, respectively (HR = 0.82 [95%CI: 0.69-0.97]). A significant difference in median PFS favouring the PAC and platinum combination therapy arm was also detected (12 months vs. 9 months; HR = 0.76 [95%CI: 0.66-0.89). There were

Table 2 : Summary of the ORR, PFS, and median survival reviewed by Main et al. (2006) for patients with platinum-sensitive MOC

Study	N	Agent	Taxane at first-line	Treatment free interval	ORR (%)	Median PFS (weeks)	Median survival (weeks)
Trial 30-49 Gordon et al. 2001; 2004	109	PLD	74% received taxane first-line	54% relapsed within 6 months	29.4 (95%CI: 28.8-37.9)	27.3	107.9
	110	Topotecan	72% received taxane first-line	53% relapsed within 6 months	28.2 (95%CI: 19.8-36.6)	22.7	70.1
Trial 039 Ten Bokkel-Huinink et al. 2000 ; Gore et al. 2001	52	Topotecan	Taxane naïve	54% relapsed within 6 months	13.3	NA	NA
	55	Paclitaxel	Taxane naive	53% relapsed within 6 months	6.7	NA	NA
Trial 30-57 Johnson & Johnson Pharmac. Res. and Developm. 2004	44	PLD	Taxane naïve	NA	NA	NA	65.4
	41	Paclitaxel	Taxane naive	NA	NA	NA	75.7
Cantu et al. 2002	47	Paclitaxel	Taxane naive	136 weeks	45	40	116
	47	CAP	Taxane naive	175 weeks	55	70	156
ICON and AGO Collab, Parmar et al. 2003	392	Paclitaxel + Platinum	41% received taxane first-line	25% ≤12 months 75% >12 months	66	54	130
	410	Platinum	39% received taxane first-line	25% ≤12 months 75% >12 months	54	40	108

Abbreviations: PLD=pegylated liposomal doxorubicin; CI=confidence interval; ORR=overall response rate; PFS=progression-free survival; NA=not available.

no significant differences in response rate between the two arms. Subgroup analyses based on previous exposure to taxanes, coordinating country, age and time since last chemotherapy cycle showed no significant differences in outcomes between treatment groups.

Across the five trials there was a considerable difference in the median OS which ranged from 65.4 to 156 weeks. Moreover, due to the heterogeneity of the prior chemotherapy regimens that participants had received and also the differences in the treatment-free intervals between the trials it is difficult to compare the results of the trials. Therefore, data are inconclusive.

In the review of Pignata et al. studies on the effectiveness and safety of PLD in platinum-sensitive recurrent MOC were described (14). Three non-randomised trials and four randomised trials of the effectiveness and safety of CAR with PLD (CARPLD) in platinum-sensitive MOC were included. The randomised trials are described below and summarized in Table 3.

In a randomized phase III trial CARPLD has been compared with CAR alone (26), though terminated prematurely and therefore not definitive, demonstrated efficacy of the combination. The Southwest Oncology Group (SWOG) S0200 trial compared CARPLD (PLD 30 mg/m2) with CAR alone. Of a planned 900 patients, only 61 were enrolled, and the study was discontinued due to slow accrual. Eligible patients had an progression-free interval of 6–24 months (non-platinum therapy was allowed during this interval). Median progression-free interval was 14.1 months in the CARPLD arm and 12.5 months in the CAR alone arm. Efficacy results for the CARPLD arm vs. the CAR alone arm, respectively, were: ORR, 52% vs. 29% (p = 0.1); median PFS, 12 months vs. 8 months (adjusted HR = 0.59 [95%CI: 0.34-1.02] p = 0.06); and median OS (primary endpoint), 26 months vs. 18 months (adjusted HR = 0.42 [95%CI: 0.20-0.89] p = 0.02).

Two RCT´s compared CARPLD with CARPAC. The Hellenic Cooperative Oncology Group conducted a randomized phase II trial comparing CARPLD with CARPAC in 204 patients with recurrent OC (PFI≥6 months, median 16.5 months) (27). CAR was dosed to AUC 5 in both arms with either PLD 45 mg/m2 every 4 weeks or PAC 175 mg/m2 every 3 weeks. One hundred eighty-nine eligible patients received a median of 6 cycles. No significant differences were observed between CARPLD and CARPAC in ORR (51% vs. 58%), TTP (11.7 months vs. 10.8 months), or OS (24.4 months vs. 30.4 months).

The RCT trial (**CALYPSO**) by the Gynecologic Cancer Intergroup (GCIG) included 976 patients with recurrent MOC relapsing >6 months after first- or second-line platinum based therapy and has been recently presented in abstract form (28). CALYPSO compared CARPLD with CARPAC but with a 30 mg/m2 dose of PLD every 4 weeks. Median PFS, the primary endpoint, was significantly superior in the CARPLD arm compared with the CARPAC arm (11.3 months vs. 9.4 months, p = 0.005). OS was too early to report, with 308 deaths.

Table 3 : Summary of data on efficacy of randomised trials reviewed by Pignata et al. (2010) in recurrent platinum-sensitive MOC

Study	N	Drug	ORR (%)	PFS (months)	OS (months)
Bafaloukos et al. 2010	204	PLD + carboplatin	51	NA	24.4
		Paclitaxel + carboplatin	58	NA	30.4
SWOG 0200 Alberts et al. 2008	61	PLD + carboplatin	52	12	26
		Carboplatin	29	8	8
CALYPSO Pujade-Lauraine et al. 2009	976	PLD + carboplatin	57	11.3	NA
		Paclitaxel + carboplatin	59	9.4	NA

Abbreviations: PLD=pegylated liposomal doxorubicin; ORR=overall response rate; PFS=progression-free survival; OS=overall survival; NA=not available.

Holloway and co-workers performed a systematic review of ten studies on the efficacy and toxicity of CARPLD versus CAR plus GEM (CARGEM) in platinum-sensitive MOC (14). Two of the studies included were also included in the review of Pignata et al. (15). In the systematic review five studies on CARPLD, 278 patients and 5 studies on CARGEM, 330 patients. Among patients receiving CARPLD, 60.2% achieved a response (complete, 27.0%; partial, 33.2%) versus 51.4% of patients treated with the CARGEM regimen (complete, 19.2%; partial, 32.2%). The proportion of patients with stable disease was greater in the CARGEM group than in the CARPLD group (30.0% vs. 23.6%). The median PFS intervals were 10.6 months and 8.9 months in the CARPLD and the CARGEM populations, respectively. The median OS time was longer for patients treated with CARPLD (27.1 months) than for those treated with the CARGEM (19.7 months).

In second-line treatment of platinum-sensitive MOC, CARPLD seems more effective than CAR alone. The combination is similarly effective as CARPAC. Patients treated with CARPLD had a better response rate than those treated with the CARGEM regimen (60.2% vs. 51.4%), despite the slightly lower proportion of patients with a PFS of12 months observed in the CARPLD group (54% vs. 61%). Whereas the PFS times were comparable in the two

groups (10.6 months and 8.9 months in CARPLD and CARGEM populations, respectively), the OS time was 7 months longer in CARPLD group.
The phase III study of Pfisterer et al. (29) included in the meta-analysis of Holloway is described in more detail. Three hundred fifty-six patients with platinum-sensitive recurrent OC were randomly assigned to receive either CARGEM or CAR alone, every 21 days. With a median follow-up of 17 months, median PFS was 8.6 months (95%CI: 7.9-9.7) for CARGEM and 5.8 months (95%CI: 5.2-7.1) for CAR. The HR for PFS was 0.72 (95%CI: 0.58-0.90; p = 0.0031). ORR was 47.2% (95%CI: 39.9-54.5) for CARGEM and 30.9% (95%CI: 24.1-37.7) for CAR (p = 0.0016). The HR for OS was 0.96 (95%CI: 0.75-1.23; p = 0.7349).

Platinum-resistant recurrent OC
Results of studies on the efficacy of PAC, PLD and GEM in recurrent platinum-resistant MOC are described below. It should be noted that PAC and PLD, but not GEM, are licensed for platinum-resistant recurrent MOC.
Three trials described in the review of Main et al. (2) included patients with platinum-resistant disease. The median survival, median PFS and ORR data for the platinum-resistant subgroups of participants from these three trials are summarised in Table 4.

The summary data of the three trials that included taxane naïve patients with platinum-resistant disease, showed that there was a low probability of response to treatment with PLD, topotecan or PAC, ranging from 6.7 to 13.3%. There were no substantial differences in the median OS across the three trials, with values ranging from 36.7 to 54.3 weeks. The most favourable median OS was observed for the PAC treatment arm within the trial of PLD versus PAC, at 54.3.

Table 4: Summary of the ORR, PFS, and median survival reviewed by Main et al. (2006) for patients with platinum-resistant MOC

Study	N	Agent	Taxane at first-line	Treatment free interval	ORR (%)	Median PFS (weeks)	Median survival (weeks)
Trial 30-49 Gordon et al. 2001; 2004	130	PLD	74% received taxane first-line	54% relapsed within 6 months	11.5 (95%CI: 6.0-17.0)	9.1	38.3
	125	Topotecan	72% received taxane first-line	53% relapsed within 6 months	7.2 (95%CI: 2.7-11.7)	13.6	42.1
Trial 039 Ten Bokkel-Huinink et al. 2000 ; Gore et al. 2001	60	Topotecan	Taxane naïve	54% relapsed within 6 months	13.3	NA	NA
	59	Paclitaxel	Taxane naive	53% relapsed within 6 months	6.7	NA	NA
Trial 30-57 Johnson & Johnson Pharmac. Res. and Developm. 2004	64	PLD	Taxane naïve	NA	NA	NA	36.7
	67	Paclitaxel	Taxane naive	NA	NA	NA	54.3

Abbreviations: PLD=pegylated liposomal doxorubicin; CI=confidence interval; ORR=overall response rate; PFS=progression-free survival; NA=not available.

In the review of Rocconi et al. (15) the results of phase II and III studies on the effectiveness and costs of second-line treatment of platinum-resistant MOC were described. The ORR for PLD ranged from 8% to 27%, with a mean ORR of 16%. Based on eight studies evaluating 575 patients with platinum-resistant MOC, the median PFS was 4.1 months. Two studies on CISGEM were included. In 35 patients an ORR of nearly 43%, with a PFS of 6 months was seen. Similar results were also reported in a Gynecologic Oncology Group (GOG) study, showing a 15.8% ORR and a PFS of 6 months.

TOXICITY

First-line treatment

PAC with platinum in first-line treatment

In the reviews of Sandercock et al. (10) and Covens et al. (9) the toxicity of CISPAC and CARPAC in first-line treatment were described. Toxicity of CIS versus CAR was compared on the basis of pooled data of ten randomised controlled trials. While hematological adverse effects were more frequent with CAR than with CIS (pooled RR = 0.19 [95%CI: 0.14-0.25] for grade 3 or 4 thrombocytopenia), non-hematological adverse effects were more frequent with CIS (pooled RR for grade 3 or 4 nausea and vomiting = 1.63 [95%CI: 1.28-2.07]; RR for neurotoxicity = 2.40 [95%CI: 1.67-3.45]). Data on renal toxicity were reported for seven trials (30-36). Grade 3 or 4 renal toxicity was reported in only 2 of 631 women treated with CIS and in none of those who received CAR.

In the Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) study (37) the long-term effects of first-line chemotherapy has been evaluated and has reported that 41% of patients had some degree of neuropathy 12 months after completing treatment with CISPAC, in contrast with 18% of those treated with CARPAC. After 24 months of follow-up, neuropathy was present in 13% of the CISPAC group but in none of the CARPAC group. Ten deaths possibly related to treatment were reported among 386 participants in the **GOG 111** trial (6 in the CIS/cyclophosphamide group and 4 in the CISPAC group) (7). In the **GOG 132** trial (17), there was significantly more neutropenia with CISPAC than with CIS alone and significantly more gastrointestinal and neurologic toxicity with CIS monotherapy at a dose of 100 mg/m2 versus CIS at a dose of 75 mg/m2 combined with PAC. Granulocyte colony-stimulating factors do not appear to have been used as primary prophylaxis for neutropenia in any of the three trials. No significant differences in grade 3 or 4 adverse effects were detected between CISPAC and CIS/cyclophosphamide. The high rate of neurotoxicity observed in the CISPAC arm of the Intergroup trial may be related to the dose of PAC used (71% of patients had the

dose escalated to 200 mg/m2) or the fact that CIS was used in combination with a 3-h PAC infusion (a regimen previously noted to be associated with more neurotoxicity than CIS plus a 24-h PAC infusion) (8;9;38).
CARPAC was associated with substantially more overall and grade ≥2 neurotoxicity than CARDOC (grade ≥2 neurosensory toxicity in 30% vs. 11%; grade ≥2 neuromotor toxicity in 7% vs. 3%) (16). Treatment with CARPAC was associated with less grade 3-4 neutropenia (84% vs. 94%).

Second-line treatment

PAC
The toxicity data of the four studies included in the review of Main et al. (2) are described below. In the RCT that has compared topotecan with single-agent PAC in 235 taxane naïve patients (21;22) grade 3 and 4 hematological toxicities (leucopenia, neutropenia, thrombocytopenia and anaemia) occurred more often in the topotecan arm compared with PAC monotherapy. This was significant in all categories other than grade 4 anaemia. The only exception was grade 3 neutropenia, which was significantly higher in the single-agent PAC group. Non-hematological grade 3 and grade 4 adverse events that were reported more commonly in the topotecan group were nausea (9.8% vs. 1.8%), vomiting (9.9% vs. 2.7%), constipation (5.4% vs. 0%), abdominal pain (5.4% vs. 3.5%), asthenia (5.4% vs. 3.5%), fatigue (8.0% vs. 6.1%), fever/infection (0.9% vs. 0%), diarrhoea (6.3% vs. 0.9%) and dyspnoea (6.3% vs. 5.3%), whilst those reported more commonly for single-agent PAC were arthralgia (2.6% vs. 0.9%), myalgia (2.6% vs. 0%), skeletal pain (5.3% vs. 0%) and alopecia (all grades – 93.0% vs. 75.9%). The toxicity profiles for the treatment groups were similar to those recorded in the randomised study.

In the RCT that has compared PLD with single-agent PAC in 216 taxane naïve patients, grade 3 toxicities that occurred significantly less frequently in the single-agent PAC group relative to the PLD group were PPE (RR = 0.03 [95%CI: 0.003-0.30]), stomatitis (RR = 0.091 95%CI: 0.02-0.53]) and dyspnoea (RR = 0.17 [95%CI: 0.03-1.03]) (23). Alopecia was the only grade 3 toxicity that occurred significantly more frequently in the single-agent PAC group (RR = 6.67 [95%CI: 2.20-20.66]). The incidence of grade 4 adverse events was relatively low in both treatment groups.

The RCT that has compared single-agent PAC with CAP in 97 taxane-naive patients whose disease had progressed or recurred more than 12 months after the end of the previous treatment (24), single-agent PAC was associated with significantly less grade 3 and grade 4

leucopenia (RR = 0.13 [95%CI: 0.03-0.45]), neutropenia (RR = 0.35 [95%CI: 0.15-0.78]) and thrombocytopenia (RR = 0.08 [95%CI: 0.01-0.81]), and with significantly less grade 2 and grade 3 nausea and/or vomiting (RR = 0.33 [95%CI: 0.17-0.64]). Patients in the single-agent PAC arm did however experience significantly more alopecia (RR = 1.46 [95%CI: 1.15-1.95]), myalgia (RR = 4.50 [95%CI: 1.18-17.91]) and allergic reactions (RR = 7.00 [95%CI: 1.19-42.86]).

The phase III RCT that compared PAC and platinum combination therapy with platinum monotherapy included 802 participants with platinum-sensitive disease (25), 75% of whom had a treatment-free interval greater than 12 months and 43% of whom had received taxanes as part of their first-line treatment. Nausea and/or vomiting were significantly worse in the platinum monotherapy group, but this difference lasted for the first 15 weeks of treatment only. The relative risk of experiencing a grade 2 to 4 neurological event was significantly higher among participants receiving PAC and platinum combination therapy (RR = 19.1 [95%CI: 7.4-49.9]), as was the relative risk of experiencing alopecia (RR = 3.5 [95%CI: 2.9-4.2]). By contrast, fewer women in the platinum combination therapy arm experienced hematological adverse events (RR = 0.6 [95%CI: 0.52-0.75]). The incidence of nausea and/or vomiting was also slightly less in this group (RR = 0.9 [95%CI: 0.7-1.0]).

PLD in combination with CAR

The safety data of the three randomised trials included in the review of Pignata et al. (14) are presented below. In the phase III trial of CARPLD of the Southwest Oncology Group (SWOG) **S0200** trial comparing CARPLD (PLD 30 mg/m2) with CAR (26), grade 3/4 hematological toxicities in CARPLD vs. the CAR arm, respectively, were neutropenia (48% vs. 3%), thrombocytopenia (39% vs. 10%), anemia (16% vs. 0%), and febrile neutropenia (10% vs. 0%). The rate of grade 3/4 PPE in CARPLD was low (3%), no patients in the CARPLD arm experienced grade 3/4 allergic reactions vs. 16% in the CAR alone arm.
In the randomized phase II trial the Hellenic Cooperative Oncology Group, CARPLD has been compared with CARPAC in 204 patients with recurrent MOC (27). Discontinuation due to toxicity was higher with CARPAC. Severe thrombocytopenia was more frequent in the CARPLD group whereas severe neurotoxicity and alopecia were more frequent in the CARPAC group.

The randomized phase III trial by the Gynecologic Cancer Intergroup (GCIG) (**CALYPSO)** including 976 patients with recurrent MOC relapsing >6 months after first- or second-line platinum-based therapy compared CARPLD with CARPAC (28). Premature discontinuation of therapy due to toxicity was more frequent in the CARPAC arm (15% vs. 7%). Non-

hematological grade 3/4 toxicities were also greater in the CARPAC (37% vs. 28%). The CARPLD treatment was associated with more grade 3/4 thrombocytopenia and more grade ≥2 mucositis and PPE. In contrast, CARPAC was associated with more grade 3/4 neutropenia, grade ≥2 allergic reactions, alopecia, and neuropathy.

CARPLD vs. CARGEM

In the systematic review of Holloway et al. the toxicity of CARPLD has been compared with CARGEM (13). The hematological safety profiles (anemia, thrombocytopenia, and neutropenia) were comparable in the two groups, although grade 3 or 4 anemia (CARPLD, 13.6%; CARGEM, 24.5%) and neutropenia (CARPLD, 45.5%; CARGEM, 62.9%) were more common in patients receiving CARGEM. The mean proportion of patients with grade 3 or 4 hand–foot syndrome was 3.1% in CARPLD studies. The incidences of other grade 3 or 4 non-hematological toxicities were comparable between the two treatment regimens.

QUALITY OF LIFE

First-line treatment

Four randomised trials of the effectiveness and safety of PAC in first-line treatment which have been reviewed by Sandercock et al. (10) and Covens et al. (9). One additional randomised trial was included in the present review (16). These studies did not investigate the quality of life. In the study of Vasey et al. the effects of CARPAC was compared with CARDOC (16). They found that the global quality of life was similar in both arms, but substantive differences in many symptom scores favoured CARDOC.

Second-line treatment

Two of the five studies included in the review of Main et al. (2) and included in the present review investigated the effect on quality of life.

The RCT that compared PLD with topotecan included 474 participants (19;20). For quality of life, assessed at 12 weeks using the EORTC QLQ-C30, the only significant difference was that more participants receiving topotecan had a stable or improved pain score (RR = 1.26 [95%CI: 1.08-1.50]). A quality-adjusted survival analysis with Q-TwiST was also undertaken to compare the periods of time during which participants experienced no symptoms and no toxicity. This showed a significant difference favouring PLD (difference = 1.14 months [95%CI: 0.46-1.82]).

The phase III RCT of the ICON and AGO collaborators that compared PAC and platinum combination therapy with platinum monotherapy in 802 participants with platinum-sensitive disease (25), found no statistically significant difference in eight of nine symptom scales in the first 6 months for quality of life, assessed using the EORTC QLQ-C30 questionnaire.

The review of Pignata et al. did not address the quality of life of the different regimens applied in the studies (14). Holloway et al., comparing the results of studies on combinations CARPLD with CARGEM, were not able to address the quality of life because of lack of data (13). Pfisterer et al. found no difference in quality of life of patients with recurrent MOC treated with CARGEM with CAR alone (29).

ONGOING PHASE III TRIALS

The following phase III trials on first-line treatment (Table 5) and second-line treatment (Table 6) of MOC are currently conducted.

Table 5 : Ongoing phase III randomised clinical trials on first-line treatment of MOC

Trial nr.	Study start	Participants	Intervention	Outcome
NCT01081262	2010 Recruiting	n=332	PAC + carboplatin +/- bevacizumab vs. oxaliplatin + capecitabine +/- bevacizumab	1 OS 2 PFS 2 RR 2 Tox 2 QoL
NCT01015118	2009 Recruiting	n=1300	PAC + carboplatin + BIBF 1120 vs. PAC + carboplatin + placebo	1 PFS 2 OS 2 TP 2 RR 2 Tox 2 Safety
NCT00951496 GOG-0252	2009 Recruiting	n=1250	PAC (IV) + carboplatin (IV) + bevacizumab (IV) vs. PAC (IV+IP) + carboplatin/cisplatin (IP) + bevacizumab (IV)	1 PFS 2 OS 2 Tox 2 QoL

Abbreviations: PAC=paclitaxel; IV=intravenous; IP=intraperitoneal; OR=overall response; OS=overall survival; PFS=progression-free survival; QoL=quality of life; RR=response rate; Tox=toxicity; TP=time to progression.

Table 6 : Ongoing phase III randomised clinical trials on second-line treatment of recurrent MOC

Trial nr.	Study start	Participants	Intervention	Outcome
NCT00657878 MITO-8	2008 Recruiting	n=250 platinum-resistant	PLD vs. PAC + carboplatin	1 OS 2 PFS 2 QoL 2 RR 2 Tox
NCT01170650 PROCEED	2010 Not yet recruiting	n=500 platinum-resistant	PLD + EC145 vs. PLD + placebo	1 PFS 2 OS 2 Tox
NCT00976911 AURELIA	2009 Recruiting	n=300 platinum-resistant	PAC or PLD or topotecan vs. PAC or PLD or topotecan + bevacizumab	1 PFS 2 RR 2 QoL

				2 Safety/ Tolerability
NCT01196741 SaPPrOC	2010 Not yet recruiting	n=102 platinum-resistant	PAC + saracatinib vs. PAC + placebo	1 PFS 2 OS 2 RR 2 DR 2 QoL 2 Economics 2 Tox 2 TP
NCT00954174 GOG-0261	2009 Recruiting	n=424	PAC + carboplatin vs. PAC + ifosfamide	1 OS 2 PFS 2 Tox 2 QoL
NCT01204749 TRINOVA-1	2010 Recruiting	n=900 platinum-sensitive or resistant	PAC + AMG 386 vs. PAC + placebo	1 PFS 2 anti-AMG 386 formation 2 QoL 2 OS 2 RR 2 DR 2 Tox 2 PK
NCT00483782 MREC-ICON7	2006 Recruiting	n=1520	PAC + carboplatin + bevacizumab vs. PAC + carboplatin	1 PFS 2 OS 2 RR 2 DR 2 PFI 2 Safety 2 QoL 2 Economics
NCT00544973 ICON6	2007 Recruiting	n=2000	PAC + carboplatin + cediranib vs. PAC + carboplatin	1 Safety 1 PFS 1 OS
NCT01167712 GOG-0262	2010 Recruiting	n=625	PAC + carboplatin + bevacizumab vs. PAC + carboplatin	1 PFS 2 OS 2 RR 2 Tox 2 Translat. Res. 2 QoL
NCT01281254 TRINOVA-2	2011 Not yet recruiting	n=380 platinum-sensitive or resistant	PLD + AMG 386 vs. PLD + placebo	1 PFS 2 OS
NCT00565851 GOG-0213	2007 Recruiting	n=660	PAC + carboplatin + bevacizumab vs. PAC + carboplatin	1 OS 2 PFS 2 Tox

Abbreviations: PAC=paclitaxel; PLD=pegylated liposomal doxorubicin; DR=duration of response; OR=overall response; OS=overall survival; PFI=progression free interval; PFS=progression-free survival; PK=pharmacokinetics; QoL=quality of life; RR=response rate; TP=time to progression; Tox=toxicity.

REVIEW OF GUIDELINES

In the Netherlands, one guideline has been published that is relevant for the treatment of PAC, PLD and GEM in MOC:

- VIKC-Landelijke richtlijn, Epitheliaal Ovariumcarcinoom, versie 1.0, 2009 (39)

Other international guidelines include:

- NICE guideline, The recognition and initial management of ovarian cancer, 2010 (40)
- NICE guideline, Paclitaxel, pegylated liposomal doxorubicin hydrochloride for second-line or subsequent treatment of advanced ovarian cancer, 2008 (41)

- ESMO guideline, Newly diagnosed and relapsed ovarian cancer: Clinical Practice Guideline for the diagnosis, treatment and follow-up, 2010 (42)
- NCCN guideline, Ovarian cancer, including fallopian tube cancer and primary peritoneal cancer, version 2.2011 (43)

The most important aspects of these guidelines in relation to PAC, PLD and GEM are summarised below.

First-line treatment

Recommendations regarding chemotherapy in early stage are not consistent. NICE guidelines and ESMO guidelines recommend chemotherapy also in optimally staged patients. The Dutch guidelines and NCCN guidelines recommend only surgery.
The Dutch VIKC guidelines, ESMO guidelines and NCCN guidelines in MOC is six cycles of CARPAC as first-line treatment. The NICE guidelines, also including the results of the **ICON3** trial, showing similar effectiveness of CARPAC and CAR alone, in the appraisal, recommends CARPAC or CAR alone.
Intraperitoneal chemotherapy is discussed as a possibility to increase the response. This is accompanied with increased toxicity. The NCCN guideline also discusses dose-dense chemotherapy as an option to increase the response. However, this treatment option also increases toxicity.

Second-line treatment

In patients with platinum-sensitive recurrent MOC and patients with relapses between 6 and 12 months CARPAC can be repeated. In addition, the NCCN guidelines mentions CAR with DOC, GEM or PLD as second-line treatment options.
For platinum resistant MOC the guidelines do not offer detailed recommendations. The Dutch VIKC guidelines recommends monotherapy with topotecan, GEM, etoposide or platinum combination therapy as options. De NICE guidelines recommends the use of PLD. The ESMO guidelines recommends the use of topotecan, docetaxel, PLD, GEM, ifosfamide and hexemethylmelamine. Recommendations of the NCCN guidelines include single agent other than platinum, supportive care or observation.

DAILY CLINICAL PRACTICE

Structured interview

Three medical oncologists, representing 2 academic and 1 peripheral medical centre in the north-west of the Netherlands, were invited to participate in a structured interview. The items discussed were the general characteristics of the hospital, number of patients with MOC, treatment regimens used for MOC, treatment and prevention of toxicity, participation in studies, means of informing and counselling patients. The total number of new patients in these hospitals ranges between 10 and 50.

Standard treatment includes surgery and chemotherapy. All patients receive 6 cycles of CARPAC as first-line chemotherapy treatment in MOC. This is similar for all three oncology departments included in the interview and corresponds with the Dutch guidelines (VIKC). For patients relapsing after first-line treatment and requiring second-line treatment, the oncologists concur that there is no standard treatment. All oncologists tend to treat patients, who responded to CARPAC in the beginning of first-line chemotherapy, again with CARPAC but on a dose-dense (regimen) basis, or with CARPLD or PLD alone. One oncologist mentioned that PLD was the first choice of second-line treatment of their department largely on the basis of the more favourable toxicity profile of PLD. Moreover , the recovery (?) (would be)longer and treatment with taxanes remains optional. Although rarely and depending on the toxicity, CARGEM is considered as third- fourth- or fifth-line chemotherapy. The choice of second-line treatment is directed by the personal preference of the oncologist, new trials and the wish of the patient. Furthermore, age, co-morbidity, and quality of life of the patient is taken into account. Quality of life is becoming more relevant in the choice of treatment. Currently this is discussed with the patient in consult but will be implemented as a standardised measurement for oncology treatment. According to the oncologists, patients are well involved in the choice and management of their treatment process. Patients receive written information about the chemotherapy regimen. The oncologists have no contact with the patients' association.

Hospital admission because of toxicity is rare according to all oncologists. Most important toxicities for the patient are alopecia and myelotoxicity. Prevention of toxicity is not possible because toxicities associated with PAC, PLD or GEM are generally not foreseen prior to treatment start. Adaptations are made during treatment. One oncologist mentioned to consider the possible solution to start treatment on a lower dose, i.e. PLD 45mg/m2. One other oncologist mentioned to provide information to the patient on how to manage toxicities like fever.

Participation, inclusion and treatment in trials is preferred by all oncologists but highly dependent on the capacity of the department of the hospital and the number of patients treated. There are several phase II and III studies on different combinations of compound, or the second- or third-line addition of biologicals (i.e. bevacizumab, etc.).

Input of patients' association

The OC patients' association is consulted in the development of guidelines and care management. According to the representative of the OC patients association, there is a growing attention for good patient information. After diagnosis, patients are referred to dedicated hospitals because of the higher survival rates compared to non-dedicated hospitals. In particular, it is important that surgery is performed by experienced surgeons. Patients involvement in the process of decision-making has always been a great issue because of the status and knowledge of the oncologist. However, according to the interviews with the oncologists, patients are well informed and the wishes and the quality of life of the patient is taken into account. The patients' association mention a possible need for patient information regarding the prevention of MOC. This could be done by creating more awareness about this "silent killer" by providing information and symptoms on the detection of MOC.

Generally the patients' association believes that patients are not interested in the costs of the treatment offered. If patients know about new opportunistic treatments, there is no doubt about trying it. It was once a hot item when PAC was first used and because of the high costs only a limited number of patients were treated with PAC.

Illustration of pharmacy dispension data

An illustration based on dispension data of the hospital pharmacy of one academic medical centre is provided (Table 7). In 2010, a total of 40 patients with MOC were treated at the department of medical oncology. The preferred treatment strategy in this medical centre for first-line treatment of MOC is PAC 175 mg/m2, administered over a period of 24 hours on day 1, followed CAR AUC 6, with an interval of 3 weeks between cycles.
Of the 40 patients, 33 patients (83%) were actually treated with chemotherapy of whom 23 (58%) with PAC (175 mg/m2) in combination with CAR (AUC 4-6). Five patients were treated with CAR monotherapy (AUC 4), two patients with GEM (1000 mg/m2) in combination with CAR (AUC 4), one patient with CAR (AUC 5) in combination with DOC (75 mg/m2), and one patient with CIS (60 mg/m2) in combination with epirubicine (50 mg/m2). Six patients were not treated with chemotherapy and one patient was treated with 5-

fluorouracil/epirubicine/cyclofosfamide (FEC) (who is diagnosed probably also with mamma carcinoma). When treated with CARPAC, dose reductions were necessary in 8 out of 23 patients. Three out of these 23 patients changed treatment to PLD varying from 40 to 50 mg/m2.

Table 7 : Illustration of pharmacy dispension data

Patients	Treatment	n
MOC	Paclitaxel 175 mg/m2 + carboplatin AUC 4-6	23
	Carboplatin AUC 6	5
	gemcitabine 1000 mg/m2 + carboplatin AUC 4	2
	carboplatin AUC 5 + docetaxel 75 mg/m2	1
	cisplatin 60 mg/m2 + epirubicine 50 mg/m2	1
	FEC	1
	No chemotherapy	6
Total		40

GENERIC PRODUCTS

PAC was discovered in 1967 in a U.S. National Cancer Institute program at the Research Triangle Institute in North Carolina. It was isolated from the bark of the Pacific yew tree, Taxus brevifolia. It was named taxol. When it was developed commercially by Bristol-Myers Squibb (BMS) the generic name was changed to PAC and the BMS compound was sold under the trademark Taxol® (44). It has been licensed in the Netherlands in 1993 (45) and since then several generic versions were developed (Table 8).

Table 8 : Generic products of PAC

Name	Authorisation date	Marketing Authorisation Holder
Taxol	20-9-1993	Bristol-Myers Squibb B.V.
Paxene	19-7-1999	Norton Healthcare Ltd.
Paclitaxin	5-11-2004	Pharmachemie B.V.
Paclitaxel	26-1-2005	Pharmachemie B.V.
Paclitaxel Hospira	13-9-2005	Hospira Benelux BVBA (B)
Paclitaxel CF	9-10-2006	Centrafarm B.V.
Paclitaxel Sandoz	19-6-2007	Sandoz B.V.
Paclitaxel Mylan	12-7-2007	Mylan B.V.
Paclitaxel Stragen	3-9-2007	Stragen Nordic A/S (D)
Paclitaxel Actavis	20-6-2008	Actavis Group PTC ehf (IS)
Paclitaxel Allgen	29-4-2009	ALL-GEN Pharmaceuticals & Generics BV
Paclitaxel Fresenius Kabi	6-8-2009	Fresenius Kabi Nederland B.V. (B)
Paclitaxel Dr. Schlichtiger	3-12-2009	Dr. Schlichtiger GmbH (G)
Paclitaxel Accord	31-8-2010	Accord Healthcare B.V.

Doxorubicin was originally isolated in the 1950's by an Italian research company, Farmitalia Research Laboratories, from bacteria found in soil samples taken from the area surrounding a 13th century castle in Italy. Researchers discovered that changes in biological activity could be made by minor alterations in the structure of the compound. A strain of Streptomyces was mutated and produced a different, red-colored antibiotic (46). Doxil® (outside the United States known as Caelyx) is a pegylated liposome-encapsulated form of doxorubicin made by Ben Venue Laboratories for Johnson & Johnson in the United States. Caelyx® is marketed by Schering-Plough only and has been licensed in the Netherlands in 1996 (45).

GEM is marketed as Gemzar® by Eli Lilly and Company and has been licensed in the Netherlands in 1995 (45). Patent protection in some major territories has expired in early 2009 and since then, generic versions of GEM have become available (Table 9).

Table 9 : Generic products of GEM

Name	Authorisation date	Marketing Authorisation Holder
Gemzar	27-3-1995	Eli Lilly Nederland BV
Gemcitabine Sandoz	10-12-2007	Sandoz B.V.
Gemcitabine Hospira	21-12-2007	Hospira Benelux BVBA (B)
Gemcitabine SUN 200	15-10-2008	Sun Pharmaceutical Industries Europe B.V.
Gemcitabine "Ebewe"	6-11-2008	Ebewe Pharma Ges.m.b.H. Nfg. KG (A)
Gemcitabine Actavis	22-1-2009	Actavis Group PTC ehf (IS)
Gemcitabine	11-2-2009	Pharmachemie B.V.
Jemta	24-2-2009	Sandoz SpA (I)
Gemcitabine Fresenius Kabi	19-3-2009	Fresenius Kabi Nederland B.V.
Gemcitabine Mylan	3-4-2009	Mylan B.V.
Gemcitabine Accord	12-6-2009	Accord Healthcare Ltd (UK)
Gemcitabine CF	6-7-2009	Centrafarm B.V.
Gemcitabine medac	7-9-2009	Medac Gesellschaft für klinische Spezialpräparate mbH (G)
Gemcitabine Hikma	15-3-2010	Hikma Farmaceutica (P)
Gemcitabine Vianex	20-7-2010	Vianex S.A. (G)
Gemcitabine Sigillata	29-11-2010	Sigillata Ltd. (UK)
Gemalata	22-12-2010	Sigillata Ltd. (UK)

COSTS

Since 1990, the Dutch Foundation for Pharmaceutical Statistics (SFK) has been collecting and analyzing exhaustive data about the use of pharmaceuticals in the Netherlands. The expenditure increase can primarily be traced back to the increasing use of 'expensive' medicines. Along with the increasing use of expensive medicines, the expenditures grew because of a substantial nationwide growth in the number of prescriptions (47). In 2008 in

the Netherlands, the total costs of expensive medicines for the treatment of cancer were € 94.3 million, slightly higher than in 2007 when the total costs were € 90.4 million. PAC was the first expensive drug for which a special financial arrangement was made. Since 2002, PAC is registered as 'expensive' medicine. Several generic preparations are available. Until 2007, a vial containing 300mg of PAC infusionconcentrate was approximately € 1800 which declined to € 960 in 2010 (48). Total cost of PAC decreased from € 13.9 million in 2004 to € 5.3 million in 2008. It is very likely that the patent process is a major cause of these lower costs. PLD is registered as 'expensive' medicine since 2004. The total costs of PLD increased from € 2.1 million in 2004 to € 6.5 million in 2008 (47). In 2010 the costs were € 431 per 10mg vial and € 1080 per 50mg vial (48). GEM is registered as 'expensive' medicine since 2002. The total costs of GEM steadily increased, from € 11.3 million in 2004 to € 15.1 million in 2008. Generic versions of GEM are available since 2009. The costs of GEM as an infusion concentrate decreased from € 47 per 200mg vial in 2008 to € 37.5 in 2010 (48).

These numbers represent the overall costs of expensive cytostatics including all indications. No data are available to estimate what part of the total costs per drug is contributed to the treatment of MOC.

REVIEW OF ECONOMIC EVALUATIONS

In total 219 publications were identified. Of these 219 publications, one review was identified (49) that included all studies until 2005 on the cost-effectiveness of PAC for the first-line treatment of MOC. Two additional economic evaluations of first-line PAC treatment were selected for inclusion (50;51). Of the 219 publications, two reports were identified (2;41) including all studies until 2008 on the cost-effectiveness of second-line treatment PAC and PLD. One review was identified (52) including all studies until 2007 on the cost-effectiveness of second-line treatment GEM. Two additional economic evaluations were identified for the second-line treatment of PAC (53;54), one for the second-line treatment of PLD (15), and three additional studies on second-line treatment of GEM (15;54;55). In addition, one economic evaluation was identified on PAC as first-line chemotherapy followed by PLD as second-line chemotherapy. All figures were recalculated to Euros and corrected for 4% inflation per year from the year of publication till 2011. The results of the economic evaluations are summarized in Table 10 for the first-line treatment of MOC and Table 11 for the second-line treatment of MOC.

First-line treatment

PAC

CISPAC vs. CIS plus cyclophosphamide

One review examined the cost-effectiveness of PAC for the first-line treatment of MOC (49). An electronic search of the Medline database from 1966 to 2005 was performed. The authors identified nine studies of which most were based on data from randomized clinical trials and concluded that CISPAC cost-effective compared with cyclophosphamide/CIS. PAC demonstrated survival and utility gains in combination with CIS as first-line treatment in patients with Stage II-IV OC. The authors concluded that incremental costs of € 6048 - € 20,159 per life-year saved (LYS) are within an accepted range for new treatments (49). In European countries, the incremental costs per LYS were lower compared to USA and Canada. In the Netherlands, the incremental costs per LYS were approximately € 9400, similar to other European countries (56). The total costs for treatment with CISPAC and CIS/cyclophosphamide in the Netherlands were € 19,952 and € 7883, respectively, incremental costs € 12,069. Specific life expectancy from the disease-specific mortality rate and the mortality rate of the standard population were calculated. For patients who received a treatment with CISPAC, the survival rate in the Netherlands was 3.85 years compared to 2.57 years for patients who received a treatment with CIS/cyclophosphamide (56).

CISPAC vs. CARPAC

One decision model has compared the cost-effectiveness of intravenous CARPAC (IV-CARPAC), intravenous CISPAC (IV-CISPAC), or intravenous PAC followed by intraperitoneal CISPAC (IP-CISPAC) at 7, 11.5, and 35-year follow-up (51). Survival data were from women participating in representative Gynecologic Oncology Group (GOG) protocols. Medicare reimbursement rates and the Agency for Healthcare Research and Quality Database were used to estimate costs for treatment regimens and grade 3 to 4 adverse effects, respectively.

Results showed that median predicted survival was 66, 57, 51, and 48 months for IP-CISPAC, IV-CARPAC, IV-CISPAC (**GOG 172**), or IV-CISPAC (**GOG 158**), respectively. IV-CISPAC was more costly and had lower life expectancy than IV-CARPAC. The base case analysis showed that IP-CISPAC had an incremental cost-effectiveness ratio (ICER) of € 146,643 per quality-adjusted life year (QALY) saved at 7 years follow-up, € 58,516 per QALY at 11.5 years follow-up, and € 26,110 per QALY at 35 years follow-up compared with IV-CARPAC. Sensitivity analyses showed that extending the survival advantage of IP-CISPAC over 11.5 and 35 years resulted in ICERs of € 21,382 and € 19,528 per QALY, respectively.

Assuming IP-CISPAC and IV-CISPAC were equally effective when administered on an outpatient basis, the ICER of IP-CISPAC compared with IV-CARPAC was € 21,432 per QALY.
The authors concluded that IV-CISPAC was dominated by IV-CARPAC.

IP-CISPAC vs. IV-CISPAC
Bristow et al (2007) (50) evaluated the cost-effectiveness of IP-CISPAC for patients with stage III epithelial MOC following optimal primary cytoreductive surgery. Based on Gynecologic Oncology Group (GOG) protocols, a decision analysis model was created to compare two treatment strategies: (1) inpatient intravenous PAC (24 h) and intraperitoneal CIS plus outpatient intraperitoneal PAC chemotherapy (IP/IV), and (2) outpatient intravenous PAC (3 h) and CAR chemotherapy (IV/IV). The societal perspective was used.
Results showed that the strategy of IP/IV chemotherapy had an overall cost per patient of € 33,769 and effectiveness of 5.16 QALYs compared to € 15,945 and 4.59 QALYs for IV/IV chemotherapy. The ICER for IP/IV chemotherapy compared with IV/IV therapy was € 31,730 per QALY. Sensitivity analysis confirmed the robustness of the model.
The authors concluded that IP/IV chemotherapy was associated with a modest extension in quality-adjusted survival time but was also more costly than IV/IV chemotherapy.

In summary, results showed that:

- CISPAC treatment is cost-effective as compared with CIS/cyclophosphamide (€ 9400 per LYS)
- IV-CISPAC is dominated by IV-CARPAC
- intraperitoneal CIS plus outpatient intraperitoneal PAC chemotherapy is associated with higher costs but increased QALY as compared with outpatient intravenous CARPAC chemotherapy (€ 31,730 per QALY)

Second-line treatment

PAC

PAC vs. PLD vs. topotecan
The National Institute for Health and Clinical Excellence (NICE) has published guidelines for treatment of recurrent OC based on a systematic review and economic evaluation (2006) (2;41). An economic model was developed in order to evaluate the cost-effectiveness of 1) platinum-sensitive disease only and 2) both platinum-sensitive and platinum

refractory/resistant disease. Costs included were study drugs, pre-medication, monitoring, drug administration and managing adverse events. Three manufacturers each submitted an economic analysis.
The submissions by GlaxoSmithKline (GSK) and Schering-Plough Ltd did not include studies that directly compared the chemotherapies under review. The submission by Bristol-Myers Squibb (BMS) estimated the costs per life year saved (LYS) for four different treatment options. Estimates of LYS were 1.27 for PAC monotherapy, 1.34 for topotecan, 1.42 for PLD, and 1.78 for PAC/platinum combination therapy. Costs of treatment were estimated at € 27,265 for PAC monotherapy, € 36,292 for PAC/platinum combination therapy, € 38,732 for PLD, and € 43,483 for topotecan. The results suggested that PAC/platinum combination therapy was both more effective and less expensive than either PLD or topotecan. The ICER per LYS for combination treatment with PAC/platinum was € 17,393 compared to PAC monotherapy.

For the treatment of platinum-sensitive disease only, four trials were included that compared six different strategies. The numbers of QALYs found were 0.79 for PAC monotherapy, 0.80 for topotecan, 1.13 for PLD, 1.28 for platinum-monotherapy, 1.34 for CAP and 1.56 for PAC/platinum combination therapy. Cost of treatment were estimated at € 4133 for platinum-monotherapy, € 5725 for CAP, € 8997 for PAC monotherapy, € 10,993 for PLD, € 12,686 for PAC/platinum combination therapy, and € 16,188 for topotecan. Of the three alternatives with the highest QALYs, it was platinum-monotherapy that was the least effective and PAC/platinum combination therapy that was the most effective. The ICER per QALY saved for PAC/platinum combination therapy compared with CAP was € 30,065.
For the second analysis two trials were included that compared three different strategies for the treatment of platinum-sensitive or platinum refractory/resistant disease. The numbers of QALYs found were 0.59 for PAC monotherapy, 0.66 for topotecan and 0.79 for PLD for the overall patient population. Costs of treatment were estimated at € 9113 for PAC monotherapy, € 11,064 for PLD and € 16,345 for topotecan. PAC monotherapy turned out to be associated with the lowest costs but also the smallest effects. The ICER per QALY saved in the overall patient population for treatment with PLD was € 10,093 compared with PAC monotherapy. Incorporating data from an additional trial, the ICER of PLD compared with PAC monotherapy increased up to € 29,591 per QALY saved.
The authors concluded that, for platinum-sensitive patients only, the combination of PAC and platinum therapy appeared to be cost-effective compared with five other licensed chemotherapies. Based on both platinum-sensitive and platinum refractory/resistant disease, it appeared that PLD was the most cost-effective compared with topotecan and PAC monotherapy, also when additional trial data were incorporated. However, this economic

model that was used by NICE (2008) has several limitations, which makes it impossible to select the most appropriate treatment for women with MOC.

CAR vs. CARPAC vs. BSC

Investigators from the University of Alabama at Birmingham (53) used a decision analysis model to assess the effectiveness and medical costs of several chemotherapeutic strategies. They analyzed a hypothetical cohort of 10,000 patients with recurrent platinum-sensitive MOC. The following chemotherapeutic strategies were compared: best supportive care (BSC), second-line CAR monotherapy, second-line CARPAC, third-line PLD therapy after disease progression on second-line mono- or combination therapy, fourth-line GEM therapy after disease progression on second- and third-line chemotherapy.

The authors concluded that both CAR monotherapy and CARPAC are cost-effective for patients with platinum-sensitive recurrent MOC. Compared to BSC, CAR monotherapy gained an additional 8 months of OS with an ICER of € 20,525 per LYS. CARPAC compared to CAR monotherapy gained an additional 3 months of OS and demonstrated an ICER of € 39,027 per LYS. Third- and fourth-line chemotherapy showed minimal improvements in OS, and are therefore not cost-effective strategies.

CAR vs. CARPAC vs. CARGEM

Havrilesky et al (2007) (54) developed a Markov decision tree to compare the PFS and costs associated with three chemotherapy regimens: CAR monotherapy, CARPAC, and CARGEM. PFS and adverse event rates were estimated from published RCTs. Medicare reimbursement rates were used to estimate costs of treatment and adverse events.

Mean and median PFS were estimated at 8 and 6 months for CAR alone, 10.1 and 7.8 months for CARPAC, 10.5 and 8.4 months for CARGEM, respectively. Costs of CAR alone were estimated at $501 per progression-free month and were the least expensive strategy. CARPAC compared to CAR alone showed an ICER of € 1099 per additional progression-free month (€ 13,185 per additional progression-free year). CARGEM compared to CARPAC showed an ICER of € 19,653 per additional progression-free month (€ 235,842 per additional progression-free year). Variation in the rates and costs of toxicities over clinically reasonable ranges did not change rankings of strategies. When the PFS of CARGEM was assumed to be equivalent to that of CARPAC, CARGEM was more expensive.

The authors concluded that CARPAC appears to be relatively cost-effective compared to CAR alone for the treatment of recurrent platinum-sensitive MOC.

PLD

PLD vs. PAC vs. topotecan

The first analysis of Main and colleagues (2;41) based on platinum-sensitive disease only found that PLD was less effective (1.13 QALY vs. 1.28 and 1.34, respectively) and more expensive (€ 10,993 vs. € 4133 and € 5725, respectively) than platinum-monotherapy and CAP. PLD was more effective and less expensive than topotecan (0.80 QALY; € 16,187). In addition, PLD was more effective and more expensive compared to PAC monotherapy (0.79 QALY; € 8997).

The second analysis based on both platinum-sensitive and platinum refractory/resistant disease found that PLD was more effective than PAC monotherapy and topotecan (0.79 QALY vs. 0.59 and 0.66, respectively) and less costly than topotecan (€ 11,064 vs. € 16,345). The ICER per QALY in the overall patient population for treatment with PLD was € 10,093 compared with PAC monotherapy. The ICER was lower for patients with platinum-sensitive disease and higher for patients with platinum refractory/resistant disease. Incorporating additional trial data, the ICER per QALY of PLD compared with PAC monotherapy increased up to € 29,591.

In addition, the Assessment Group of NICE identified three published economic evaluations that compared PLD and topotecan. Costs included were only the costs associated with treatment. PLD and topotecan were compared from a UK health service perspective and based on the short-term results of the RCT. The study found that PLD was significantly less costly than topotecan with a difference of € 2325 (95%CI: € 617 to € 2741). The mean costs for topotecan and for PLD were € 13,533 and € 11,208, respectively. Two other published papers reported the results of cost-minimization analyses from Spanish and Italian health service perspectives. Both analyses found that PLD was less costly than topotecan.

Based on both platinum-sensitive and platinum refractory/resistant disease, Main and colleagues concluded that PLD was cost-effective compared with topotecan and PAC monotherapy. Although with an ICER less favourable, PLD compared to PAC monotherapy remained cost-effective when additional data were incorporated.

PLD vs. CISGEM vs. BSC

Rocconi et al (2006) (15) used a decision analysis model to assess the effectiveness and medical costs of several chemotherapeutic strategies. They analyzed a hypothetical cohort of 4000 patients with recurrent platinum-resistant MOC. Several chemotherapy strategies were analyzed: BSC, second-line PLD, second-line CISGEM combination therapy and third-line

topotecan-monotherapy after disease progression on second-line monotherapy and after disease progression on second-line combination therapy.
Cost-effectiveness ratios ranged from € 3582 to € 11,390 per month of OS for BSC and third-line topotecan combination therapy, respectively. BSC was the only treatment for platinum-resistant recurrent OC patients that was considered definitively cost-effective, and PLD therapy was considered a reasonable cost-effective strategy with an ICER of € 56,479 per LYS. Compared with BSC, second-line PLD gained an additional 3 months of OS, with a cost-effectiveness of € 4144 per month of OS. Second-line CISGEM and third-line therapies showed unfavourable ICERs.

GEM

The review of Toschi et al (2007) (52) investigated whether GEM is a cost-effective treatment for several cancer indications. The authors concluded that, concerning the treatment of OC, more accurate and extensive pharmacoeconomic assessments should be performed to determine the cost-effectiveness of GEM.

GEM vs. topotecan
Investigators of the Memorial Sloan Kettering Study (55) compared the costs of topotecan vs. GEM as second-line therapy or greater for patients with platinum- and PAC resistant MOC. The mean total direct cost per cycle per patient of GEM was € 2603, with a median total direct cost per cycle of € 1318. The mean total direct cost per cycle per patient was significantly more expensive for topotecan (€ 2603 vs. € 7463; p = 0.001).

CISGEM vs. PLD vs. BSC
The evaluation of Roconni et al (2006) (15) demonstrated an additional 2 months of OS for CISGEM for the treatment of recurrent platinum-resistant epithelial OS compared with second-line monotherapy. However, the ICER of € 266358 per LYS showed that the combination therapy is not cost-effective.

CARGEM vs. CAR vs. CARPAC
Havrilesky et al (2007) (54) estimated the average costs of CARGEM at € 14,933. CARGEM compared to CARPAC showed an ICER of € 19654 per additional progression-free month (€ 235,842 per additional progression-free year). The authors concluded that CARGEM appears to be less cost-effective compared to CARPAC, with an ICER ten times higher.

In summary, results showed that as second-line treatment:

- CARPAC combination therapy is cost-effective as compared with PAC monotherapy, platinum-monotherapy, topotecan, PLD, CAP, and CARGEM combination therapy for platinum-sensitive patients.
- PLD is cost-effective as compared with PAC monotherapy and topotecan.
- Based on both platinum-sensitive and platinum refractory/resistant disease, it appeared that PLD was more cost-effective as compared with topotecan, PAC monotherapy, and CARGEM.

Combination therapy of first- and second-line treatment

Hartmann et al (2007) (57) developed a Markov model to evaluate the cost-effectiveness of platinum compounds and PAC as first-line chemotherapy followed by topotecan and PLD as second-line chemotherapy for MOC. Patients were treated either in the early (FIGO stage I–IIa) or advanced stage (FIGO stage IIb–IV).
Results showed that CAR followed by topotecan costs € 17,048, CAR followed by PLD € 18,923, CARPAC followed by liposomal topotecan € 25,263 and CARPAC followed by PLD € 26,737 from the time of diagnosis until death or survival within 5 years. Live years saved were 2.55, 2.70, 2.60 and 2.65, respectively and costs amounted to € 6685, € 7006, and € 9704 per life year saved.
The authors concluded that based on a threshold value of social willingness to pay of € 38,547 per year of life saved, platinum compounds with or without PAC as first-line chemotherapy followed by topotecan or PLD as second-line chemotherapy seem to be cost effective.

Table 10 : Results of economic evaluations on first-line treatment in MOC

Study	Type of economic evaluation	Perspective used	Time frame	Unit cost data	Source of effectiveness data	Source of resource use data	Intervention	Effectiveness (Mean survival)	Total costs	Cost-effectiveness (ICER per LYS)
Dedes et al. 2005	Cost-effectiveness review	US healthcare system Canada - Ministry of Health France, Germany, Italy, Spain, U.K, the Netherlands – nation. health service payers	?	Direct medical costs	GOG 111 Intergroup Trials	Local sources	CIS + PAC CYC + CIS	36.8 months 24.9 months	NA NA (for all countries together)	€ 6048 to € 20,159
Berger et al. 1998	Cost-effectiveness analysis	France, Germany, Italy, Spain, U.K, the Netherlands – nation. health service payers	?	Direct medical costs	GOG 111	Local sources	CIS + PAC CYC + CIS	3.2 years * 2 years *	€ 19,952 * € 7883 *	€ 9400 *
Havrilesky et al. 2008	Decision-analysis model	Societal perspective	7.5, 11.5 and 35 years follow-up	Direct medical costs	GOG-172 GOG-158	Medicare reim-bursement rates, AHRQ database	IV-CARBO + PAC IP-CIS + PAC	57 months 66 months	€ 4300 € 47,432	€ 146,643 (at 7-yrs) € 58,516 (at 11,5 yrs) € 26,110 (at 35 yrs)

Abbreviations: CIS=cisplatin; PAC=paclitaxel; CYC=cyclophosphamide; CARBO=carboplatin; ICER=incremental cost-effectiveness ratio; AHRQ=Agency for Healthcare Research and Quality Database; NA=not available.
** Results from the Netherlands.*

Table 11 : Results of economic evaluations on second-line treatment in MOC

Study	Type of economic evaluation	Perspective used	Time frame	Unit cost data	Source of effectiveness data	Source of resource use data	Intervention	Effectiveness	Total costs	Cost-effectiveness (ICER)
Main et al. 2006	Cost-effectiveness review	UK National Health Service	?	Direct medical costs Platinum-sensitive patients only	Trial 30-49 Gordon et al. 2001; 2004 Trial 30-57 Muggia et al. 2000	Local sources	PAC PLD Topotecan Platinum CAP Platinum +PAC	0.79 (QALY saved) 1.13 0.80 1.28 1.34 1.56	€ 8997 € 10,993 € 16,188 € 4133 € 5725 € 12,686	€ 30,065 [a] / QALY

				Platinum-sensitive and platinum-resistant patients			PAC PLD Topotecan	0.59 (QALY saved) 0.79 0.66	€ 9113 € 11,064 € 16,345	€ 10,093 [b] / QALY
Case et al. 2007	Cost-effectiveness model	US third party payer	?	Direct medical costs Platinum-sensitive patients only	Three RCTs CARBO Five RCTs CARBOPAC	Local sources	BSC CARBO CARBO + PAC	6 months (OS) 14 months 17 months	€ 20,610 € 34,209 € 44,007	€ 39,027 [c] / LYS
Havrilesky et al. 2007	Markov-decision model	Payer	42 months	Direct medical costs Platinum-sensitive patients only	RCTs of Parmar et al. 2003 Pfisterer et al. 2006	Medicare reim-bursement rates	CARBO CARBO + PAC CARBO + GEM	8 months (PFS) 10.1 months 10.5 months	? ? ?	€ 19,653 [d] / additional PFM
Roconni et al. 2006	Decision-analysis model	US third party payer	?	Direct medical costs Platinum-resistant patients only	Review of several RCTs	Cost-to-charge ratio of 60%	BSC PLD CIS + GEM	3 months (OS) 6 months 8 months	€ 10,761 € 24,816 € 68,959	€ 56,479 [e] / LYS € 266,358 [f] / LYS

Abbreviations: PAC=paclitaxel; PLD=pegylated liposomal doxorubicine; CAP= ;CARBO=carboplatin; ICER=incremental cost-effectiveness ratio; QALY=quality-adjusted life year; LYS=life year saved; OS=overall survival; PFS=progression-free survival; PFM=progression-free month.

[a] Comparing platinum + PAC with CAP.
[b] Comparing PLD with PAC monotherapy.
[c] Comparing CARBO + PAC with CARBO.
[d] Comparing CARBO + GEM with CARBO + PAC.
[e] Comparing BSC with PLD.
[f] Comparing CISGEM with PLD.

DISCUSSION AND CONCLUSION

First-line treatment

Five randomised studies on the efficacy and safety of PAC in combination with CIS or CAR in MOC have been found. In two of these studies CISPAC resulted in an improved OS as compared to CIS with cyclophosphamide. In two other trials CISPAC or CARPAC were similarly effective as high dose CAR and CIS alone or CAP. The difference between the results of these trial and those reported for the studies comparing CISPAC with CIS/cyclophophamide may be explained by the extent of patient cross-over between treatments before the disease progressed. However, it is unlikely that this is sufficient to explain such markedly different results. Another expanation is that high dose platinum is more effective than the combination CIS/cyclophosphamide. It has also been suggested that cyclophosphamide even may have a worsening effect on the patient outcome.
CISPAC has generally resulted in more neutropenia than high dose CIS, while high dose CIS was associated with more neurotoxicity and gastrointestinal effects. In the Intergroup trial the incidence of neurotoxicity was higher with CISPAC. It has been suggested that this was caused by the escalated dose of PAC used in a large part of the patients or the short duration of time of the infusion. Data on the quality of life of these regimens were not available.
It can be concluded that CISPAC or CARPAC or CIS or CAR alone can be used for the first-line treatment of MOC. However, toxicity with combined PAC with CIS or CAR may be more severe than with CIS or CAR alone.
The results of the economic evaluation have shown that CISPAC treatment is cost-effective as compared with CIS/cyclophosphamide. It has also been shown that CISPAC is dominated by CARPAC. When compared with intravenous CARPAC, intraperitoneal CISPAC is associated with increased QALY, but at the expense of increased costs. It is important to note that the available studies were generally performed from the perspective of health service providers. The few studies which were carried out from a societal perspective did not take indirect costs into consideration. It is known that indirect costs, i.e. costs of production losses due to work absenteeism or presenteeism, may account for 68% of the total costs of MOC. Future cost-effectiveness studies should be conducted from a societal perspective and include costs of production losses.

Second-line treatment

Several studies on the efficacy, safety and quality of life of PAC, PLD and GEM have been described in a number of reviews. In studies performed in the years until 2004, PAC and PLD

have been investigated as monotherapy in mostly taxane naïve patients. Although at present most patients have been treated with CARPAC given as first-line treatment, these studies have demonstrated effectiveness of PAC and PLD in second-line treatment of platinum-sensitive recurrent MOC. In more recent studies PAC, PLD and GEM have been combined with CAR. One small and one large randomised trial, compared the efficacy, safety and quality of life of combination therapy with CARPLD with CAR. With respect to PFS the small study showed no difference, but the large study showed an advance of about 2 months in favour of the PLD combination.
The results of a systematic review comparing combination of CAR with either PLD or GEM showed a better outcome of the CARPLD, with respect to OS and ORR, but not to PFS.
In recurrent platinum-resistant MOC PAC, PLD and GEM as monotherapy or in combination with a platinum compound showed only limited efficacy. ORR varied from 8% to 43% with PFS varying from 9 to 24 weeks. Comparative trials are not available.
CARPAC is associated with more grade 3/4 neutropenia, allergic reactions, alopecia and neuropathy. CARPLD is associated with more grade 3/4 thrombocytopenia, mucositis and PPE. CARGEM has a different toxicity profile. The haematological adverse effects are similar to those of the CARPLD, although anemia and neutropenia occurred more frequently with CARGEM. Only limited data on the quality of life of these regimes were found in the literature. In second-line treatment CARPAC, PLD or GEM seem similarly effective. The combination can be selected on the basis of the toxicity profile of the combination.
The results of the economic evaluation have shown that PAC combined with platinum is cost-effective as compared with PAC monotherapy, platinum-monotherapy, topotecan, PLD, CAP, and CARGEM for platinum-sensitive patients. In addition, PLD is cost-effective as compared with PAC monotherapy and topotecan. Based on both platinum-sensitive and platinum refractory/resistant disease, it appeared that PLD was more cost-effective compared with topotecan, PAC monotherapy, and CARGEM. A limitation of these studies was that toxicity and quality of life was not included in the analysis. Third- and fourth-line chemotherapy, including PAC, PLD or GEM have been shown to be not cost-effective strategies. Because of the limited effectiveness of second-line treatment of patients with platinum-resistant MOC, it is important to investigate the effectiveness of new non-platinum based therapies.

Guidelines

One Dutch and several international guidelines on the treatment of OC are available. The recommendations described in the guidelines are not consistent. With respect to first-line line treatment one of the NICE guideline recommends CARPAC or CAR monotherapy, while in all other guidelines CARPAC is recommended. The NICE guideline also includes the RTC comparing CISPAC with CIS monotherapy, showing similar efficacy both treatments, while

the recommendations of the other guidelines are based on the trials, in which CISPAC is compared with CIS/cyclophosphamide, showing an better efficacy of CISPAC. For second-line treatment of platinum sensitive it is generally recommended to repeat treatment with CARPAC. When the repeat of this combination is not possible because of toxicity, as well as for the treatment of platinum resistant MOC, the guidelines often suggest a number of drugs without detailed information about the dose and duration of treatment.

Daily clinical practice

All oncologist reported to treat their patients according to the Dutch guidelines for OC. They all consider CARPAC as first-line treatment for MOC. For the treatment of recurrent MOC, CARPAC, CARPLD or CARGEM are options. According to the oncologists, the regimen is generally chosen on the basis of the toxicity profile. All oncologists counsel their patients with oral and written information. It often takes more than one session for decision making.

Overall conclusion

The results of the RCTs on the effectiveness and safety of PAC with CIS or CAR in first-line treatment of MOC, show that the combination is more effective than CIS/cyclophosphamide. In addition, the combination is similarly effective as high dose CIS or CAR monotherapy. Therefore, it can be concluded that PAC in combination with platinum or a high dose platinum compound alone can be used to treat MOC. In studies on the cost-effectiveness of PAC with platinum the two studies showing an improved PFS for CISPAC as compared with CIS/cyclophosphamide were included. Since both treatment options have shown similar effectiveness, it would be worthwhile to study the pharmaco-economics of PAC and platinum versus platinum treatment alone.

Second-line treatment combinations of PAC, PLD or GEM with CAR seem similar effective in patients with recurrent platinum-sensitive MOC. However, toxicity profile of the three combinations is different. Choice for one of the regimens depends on the expected toxicity. The economic evaluations are based on the studies published before 2004. It was suggested that the cost-effectiveness of CARPAC was better than of other treatments. In addition, the cost-effectiveness of PLD monotherapy was better than PAC monotherapy and topotecan. However, cost-effectiveness studies using the data from more recently performed studies are not available. It would be interesting to perform these studies because currently applied chemotherapy in the second-line treatment is based on these more recent studies.

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For the last 15 years Cordula has been involved in a substantial number of projects focussing on a) the state-of-the-art of the implementation of quality systems among healthcare institutions and professionals, b) the evaluation of quality activities such as guidelines and break through projects, c) the relation between quality systems, care process and clinical outcomes, and d) risk management and patient safety. The research takes place

in various health care fields, e.g. hospital, nursing homes, home health care organisations and mental health care. At the moment Cordula is also participating in a number of European projects focussing on quality and patient safety. (no conflict of interest)

Jacqueline Hugtenburg (PhD, pharmacist, clinical pharmacologist, pharmacologist, epidemiologist) works as an assistant professor at the Department of Clinical Pharmacology and Pharmacy. She is responsible for the pharmacoepidemiological studies of the department. For the last 10 years Jacqueline has been involved in a substantial number of projects focussing a) Pharmacoepidemiology of diabetes mellitus, anxiety and depression and cancer, b) Pharmaceutical care for elderly patients, patients with diabetes and patients with cancer, and c) Studies on drug utilization, drug use in daily practice, and drug safety. (no conflict of interest)

APPENDIX 1

Search strategy.

PUBMED Search History (22-11-2010)

Search	Most Recent Queries	Time	Result
#22	Search #19 AND #11	09:04:54	90
#21	Search #20 Limits: Publication Date from 2008	09:04:19	507
#20	Search #19 AND #8	09:02:49	2762
#19	Search #5 AND #18	09:02:13	3300
#18	Search paclitaxel[tw] OR taxol[tw]	09:01:58	20442
#17	Search #14 AND #11	09:00:38	26
#16	Search #8 AND #14 Limits: Publication Date from 2008	08:59:55	182
#15	Search #8 AND #14	08:59:42	1941
#14	Search #5 AND #13	08:58:03	2386
#13	Search doxorubicin*[tw] OR adriamycin*[tw] OR doxil[tw] OR rubex[tw]	08:56:35	44142
#12	Search #7 AND #11	08:53:09	14
#11	Search "Costs and Cost Analysis"[Mesh] OR economic*[tw] OR Cost[tiab] OR Costa*[tiab] OR Costb*[tiab] OR Costc*[tiab] OR Costd*[tiab] OR Coste*[tiab] OR Costf*[tiab] OR Costg*[tiab] OR Costh*[tiab] OR Costi*[tiab] OR Costj*[tiab] OR Costk*[tiab] OR Costl*[tiab] OR Costm*[tiab] OR Costn*[tiab] OR Costo*[tiab] OR Costp*[tiab] OR Costq*[tiab] OR Costr*[tiab] OR Costs*[tiab] OR Costt*[tiab] OR Costu*[tiab] OR Costv*[tiab] OR Costw*[tiab] OR Costx*[tiab] OR Costy*[tiab] OR Costz*[tiab]	08:52:22	594304
#10	Search #7 AND #8 Limits: Publication Date from 2008	08:49:46	90
#9	Search #7 AND #8	08:46:53	428
#8	Search randomized controlled trial [pt] OR controlled clinical trial [pt] OR clinical trial [pt] OR comparative study [pt] OR evaluation studies [pt] OR "randomized controlled trials as topic"[MeSH Terms] OR "random allocation"[MeSH Terms] OR "double-blind method"[MeSH Terms] OR "single-blind method"[MeSH Terms] OR "clinical trials as topic"[MeSH Terms] OR "placebos"[MeSH Terms] OR "research design"[MeSH Terms:noexp] OR "follow-up studies"[MeSH Terms] OR "prospective studies"[MeSH Terms] OR "cross-over studies"[MeSH Terms] OR "drug therapy"[Subheading] OR "clinical trial" [tw] OR "latin square" [tw] OR placebo* [tw] OR random* [tw] OR control[tw] OR controll*[tw] OR prospectiv* [tw] OR volunteer* [tw] OR trial[tiab] OR groups[tiab] OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw]))	08:46:41	6207977
#7	Search #5 AND #6	08:27:55	484
#6	Search gemcitabin*[tw] OR gemzar[tw]	08:27:44	7206
#5	Search #1 OR #4	08:27:26	74457
#4	Search #2 AND #3	08:27:14	59214
#3	Search (ovary[tiab] OR ovarian[tiab])	08:27:08	139543
#2	Search (cancer*[tiab] OR carcinoma*[tiab] OR neoplas*[tiab] OR tumour*[tiab] OR Tumor[tiab] OR tumora*[tiab] OR tumorb*[tiab] OR tumorc*[tiab] OR tumord*[tiab] OR tumore*[tiab] OR tumorf*[tiab] OR tumorg*[tiab] OR tumorh*[tiab] OR tumori*[tiab] OR tumorj*[tiab] OR tumork*[tiab] OR tumorl*[tiab] OR tumorm*[tiab] OR tumorn*[tiab] OR tumoro*[tiab] OR tumorp*[tiab] OR tumorq*[tiab] OR tumorr*[tiab] OR tumors*[tiab] OR tumort*[tiab] OR tumoru*[tiab] OR tumorv*[tiab] OR tumorw*[tiab] OR tumorx*[tiab] OR tumory*[tiab] OR tumorz*[tiab])	08:26:43	1701621
#1	Search "Ovarian Neoplasms"[Mesh]	08:26:22	53469

EMBASE Search History (22-11-2010)

No.	Query	Results	Date
#19	#13 AND #17	117	22 Nov 2010
#18	#17 AND ([cochrane review]/lim OR [controlled clinical trial]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim OR [systematic review]/lim) AND [2008-2011]/py	152	22 Nov 2010
#17	#3 AND #16	7699	22 Nov 2010
#16	'paclitaxel'/exp OR paclitaxel:mn,tn,ab,ti OR taxol:mn,tn,ab,ti	45926	22 Nov 2010
#15	#11 AND #13	77	22 Nov 2010
#14	#5 AND #13	41	22 Nov 2010
#13	'cost benefit analysis'/exp OR 'cost effectiveness analysis'/exp OR 'cost utility analysis'/exp	119234	22 Nov 2010
#12	#11 AND ([cochrane review]/lim OR [controlled clinical trial]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim OR [systematic review]/lim) AND [2008-2011]/py	113	22 Nov 2010
#11	#3 AND #10	7047	22 Nov 2010
#10	'doxorubicin'/exp OR doxorubicin*:mn,tn,ab,ti OR adriamycin*:mn,tn,ab,ti OR doxil:mn,tn,ab,ti OR rubex:mn,tn,ab,ti	111498	22 Nov 2010
#6	#5 AND ([cochrane review]/lim OR [controlled clinical trial]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim OR [systematic review]/lim) AND [2008-2011]/py	66	22 Nov 2010
#5	#3 AND #4	2061	22 Nov 2010
#4	'gemcitabine'/exp OR 'gemcitabine triphosphate'/exp OR gemcitabin*:mn,tn,ab,ti OR gemzar:mn,tn,ab,ti	20236	22 Nov 2010
#3	#1 OR #2	92078	22 Nov 2010
#2	ovary:ab,ti OR ovarian:ab,ti AND (cancer*:ab,ti OR tumor*:ab,ti OR tumour*:ab,ti OR carcinoma*:ab,ti OR neoplas*:ab,ti)	67934	22 Nov 2010
#1	'ovary tumor'/exp	74307	22 Nov 2010

Cochrane Search History (23-11-2010)

ID	Search	Hits	Edit	Delete
#1	(ovary OR ovarian):ti,ab,kw and (cancer* OR tumor* OR tumour* OR carcinoma* OR neoplas*):ti,ab,kw	2722	edit	delete
#2	(paclitaxel OR taxol):ti,ab,kw	2106	edit	delete
#3	(#1 AND #2)	468	edit	delete
#1	(ovary OR ovarian):ti,ab,kw and (cancer* OR tumor* OR tumour* OR carcinoma* OR neoplas*):ti,ab,kw	2722	edit	delete
#2	(doxorubicin* OR adriamycin* OR doxil OR rubex):ti,ab,kw	4662	edit	delete
#3	(#1 AND #2)	376	edit	delete
#1	(ovary OR ovarian):ti,ab,kw and (cancer* OR tumor* OR tumour* OR carcinoma* OR neoplas*):ti,ab,kw	2722	edit	delete
#2	(gemcitabin* OR gemzar):ti,ab,kw	1010	edit	delete
#3	(#1 AND #2)	56	edit	Delete