

**PROPOSAL FOR THE INCLUSION OF CARBOPLATIN (AS A
REPRESENTATIVE OF THE ANTINEOPLASTIC – CYTOTOXIC DRUG CLASS)
IN THE WHO MODEL LIST OF ESSENTIAL MEDICINES**

FINAL REPORT

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1. Summary statement of the proposal

Carboplatin is proposed for the inclusion in the World Health Organisation (WHO) Model List of Essential Medicines for the treatment of advanced ovarian carcinoma (FDA approved indication). Non-FDA approved uses of intravenous carboplatin include: brain tumours, endometrial cancer, germ cell tumours, head and neck cancer, bladder cancer, breast cancer, cervical cancer, Ewing's sarcoma, acute lymphocytic leukaemia, non-small cell lung cancer, small cell lung cancer, non-Hodgkin's lymphoma, melanoma, neuroblastoma, osteosarcoma, rhabdomyosarcoma, retinoblastoma, testicular cancer, and Wilm's tumour.¹

2. Name of focal point in WHO submitting or supporting the application

3. Name of the organisation(s) consulted and/or supporting the application

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4. International Nonpropriety Name (INN, generic name) of the medicine

INN: Carboplatin.

Chemical name: cis-Diammine (cyclobutane-1, 1-dicarboxylato) platinum.

5. Formulation proposed for inclusion

Injection: 50 mg / 5 ml, 150 mg / 15 ml, 450 mg / 45 ml, 600 mg / 60 ml

6. International availability – sources, if possible manufactures (Appendix A)

Carboplatin is marketed under various trade names worldwide. A detailed list of manufacturers and distributors is presented in Appendix A.

7. Whether listing is requested as an individual medicine or as an example of a therapeutic group

Listing is requested on the Model List of Essential Medicines as an individual medicine.

8. Information supporting the public health relevance (epidemiological information on disease burden, assessment of current use, target population)

8.1 Global burden of disease - Cancer

The global burden of cancer continues to increase with the number of new cases expected to grow by 50% over the next 20 years to reach 15 million by 2020 (World Cancer Report 2003).² Data available from the International Agency for Research on Cancer (IARC: Globocan 2002)³ indicates that in 2002 cancer claimed 6.7 million lives worldwide. In 2002 there were 10.9 million new cases of cancer diagnosed worldwide and between 1998-2002 there were 24.6 million people living with cancer. Cancer is the second leading cause of death in developed countries and is among the three leading causes of death in developing countries. A summary of global cancer deaths by region is presented in Table 1.1.

Table 1.1: Summary of worldwide cancer deaths by region

Region	Deaths 2002	Predicted deaths 2020
North America	631,900	951,400
Central America, South America, and Caribbean	479,900	833,800
Northern Europe	241,100	297,600
Central and Eastern Europe	637,000	742,800
Western Europe	475,100	617,100
Southern Europe	348,400	427,300
Eastern Asia	2,016,300	3,223,700
South-Central Asia	845,200	1,389,800
South-Eastern Asia	363,400	709,300
Northern Africa and Western Asia	224,000	389,200
Sub-Saharan Africa	412,100	626,400
Oceania	49,500	77,300
Total	6,723,900	10,285,700

Source: IARC, Globocan 2002³

More recent data indicates that in 2005 cancer killed 7.6 million people which accounts for around 13% of all deaths worldwide.⁴ Of all these cancer deaths 70% occurred in low and middle income countries. The WHO predicts that deaths from cancer in the world will continue to rise with an estimated 9 million people dying from cancer in 2015 and by 2030 the number of deaths from cancer is anticipated to be 11.4 million of whom 8.9 million will be from low-middle income countries compared to 2.5 million will be from high income countries.⁴ A summary of the types of cancer leading to overall cancer mortality in 2002 is presented in Table 1.2 and Figure 1.1.

Table 1.2: Summary of the types of cancer leading to overall cancer mortality in 2002

Type of cancer	Number of cases
Mouth and oropharynx cancers	317,894
Oesophagus cancer	446,166
Stomach cancer	850,401
Colon and rectum cancers	622,256
Liver cancer	618,124
Pancreas cancer	230,957
Trachea, bronchus, lung cancers	1,243,199
Melanoma and other skin cancers	66,034
Breast cancer	477,196
Cervix uteri cancer	238,814
Corpus uteri cancer	71,387
Ovarian cancer	134,623
Prostate cancer	269,292
Bladder cancer	178,850
Lymphomas, multiple myeloma	334,421
Leukemia	264,229
Other malignant neoplasms	756,924
Other neoplasms	148,910

Source: Global Action Against Cancer - Updated Edition 2005⁵

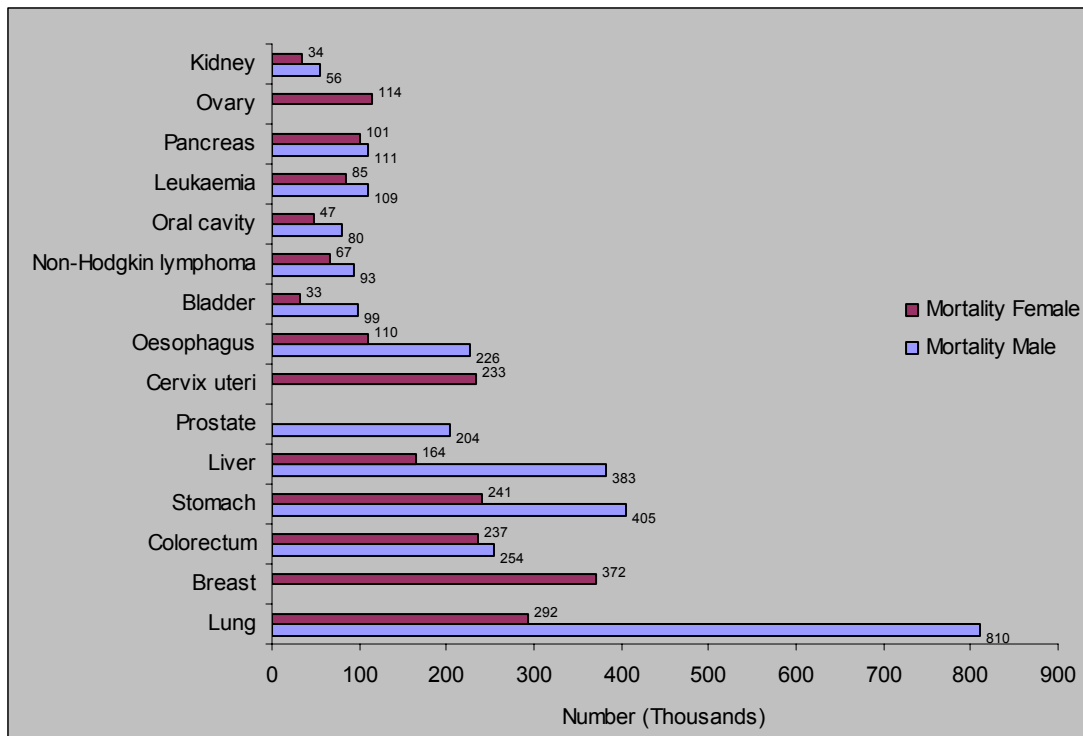


Fig. 1.1 Mortality of the most common cancers worldwide by sex. Source: World Cancer Report 2003.²

In terms of incidence, the most common cancers worldwide (excluding non-melanoma skin cancers) are lung (12.3% of all cancers), breast (10.4%) and colorectal (9.4%) (Fig.1.2). As stated in the World Cancer Report (2003),² “For any disease the relationship of incidence to mortality is an indication of prognosis, similar incidence and mortality rates being indicative of an essentially fatal condition. Thus, lung cancer is the largest single cause of deaths from cancer in the world (1.1 million annually), since it is almost invariably associated with poor prognosis.”

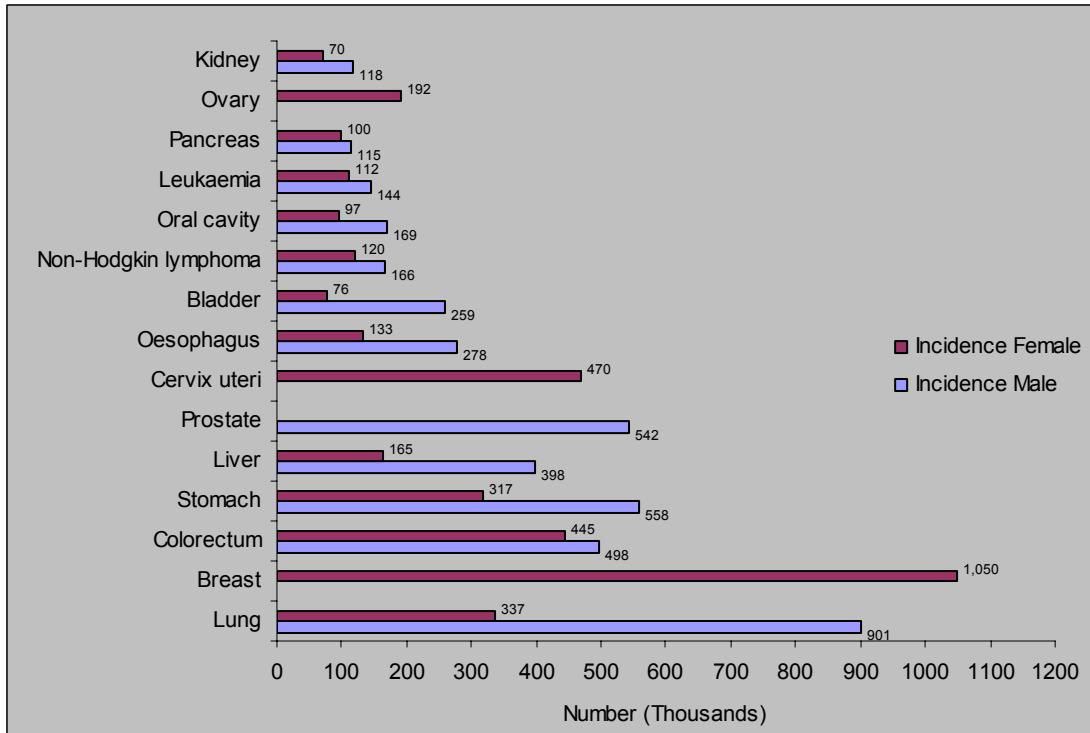


Fig. 1.2 Incidence of the most common cancers worldwide by sex. Source: World Cancer Report 2003.²

The burden of cancer is not distributed evenly between the developing and developed world, with specific cancer types displaying different patterns of distribution (Fig.1.3 and Fig.1.4). As discussed in the World Cancer Report (2003),² many differences in the distribution of cancer between regions are explicable with reference to etiological factors. In developing countries for example, populations are vulnerable to cancers in which infectious agents (and associated non-malignant diseases) play a major role. These include cancers of the stomach, uterine cervix, liver and possibly oesophagus. Whereas other cancers such as colorectal and prostate cancers, the burden of disease falls disproportionately on the developed world.²

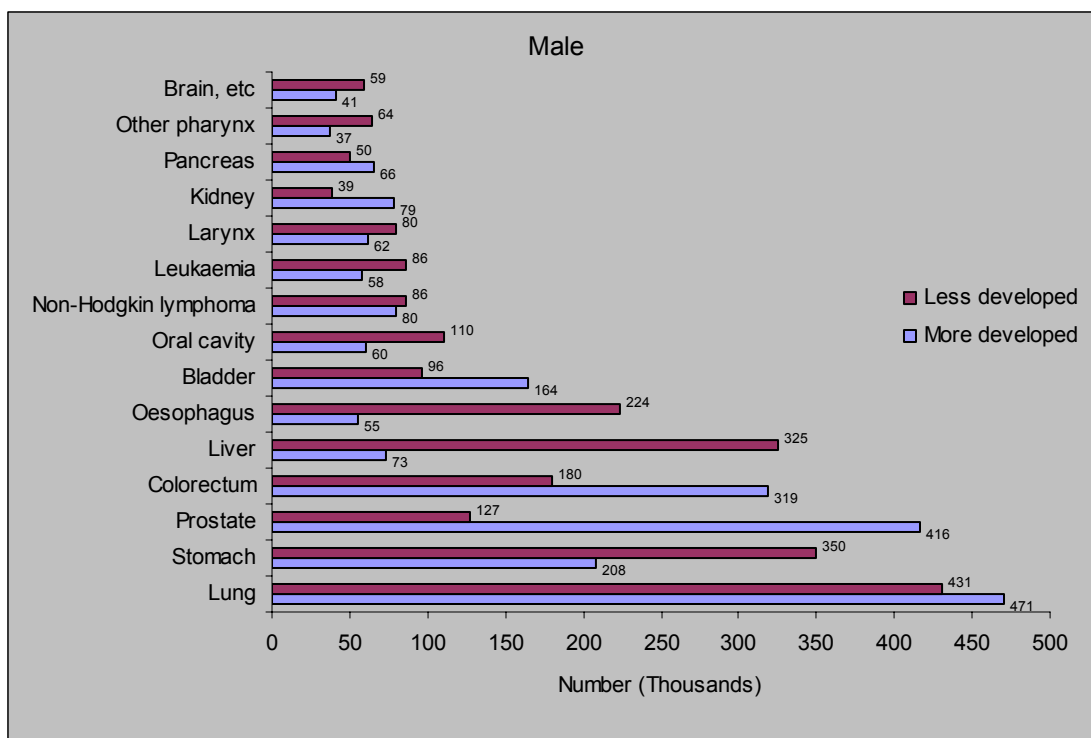


Fig. 1.3 Comparison of the most common cancers in males in more and less developed countries in 2000. NHL = Non Hodgkin lymphoma. Source: World Cancer Report, 2003.²

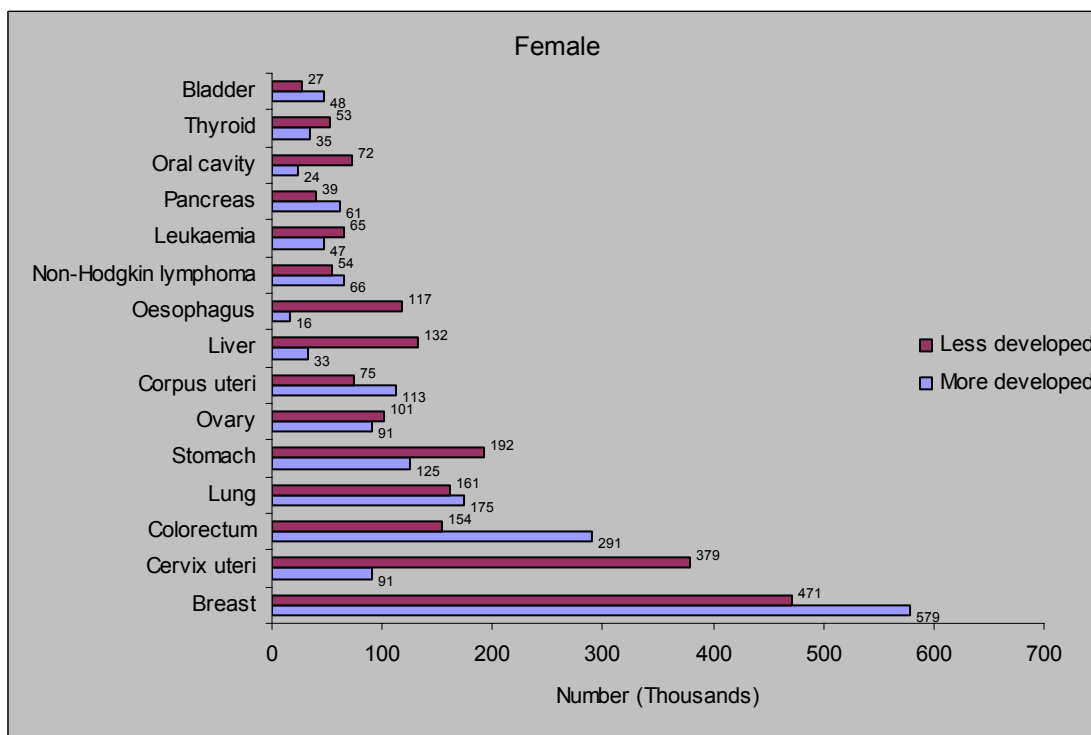


Fig. 1.4 Comparison of the most common cancers in females in more and less developed countries in 2000. NHL = Non Hodgkin lymphoma. Source: World Cancer Report, 2003.²

8.1.1 Global burden of disease - Ovarian cancer

Global Cancer Statistics 2002⁶ indicated ovarian cancer is the sixth most common cancer (204,000 cases) and the seventh cause of death (125,000 deaths) from cancer in women (4.0% of cases and 4.2% of deaths). Incidence rates are highest in developed countries (Fig.1.5), with rates in these areas exceeding 9 per 100,000 except for Japan (6.4 per 100,000). The incidence of ovarian cancer in South Africa is relatively high with a rate of 7.7 per 100,000. The incidence rates for ovarian cancer have been slowly increasing in many Western countries and Japan, with the risk of ovarian cancer reduced by the use of oral contraceptives.⁶

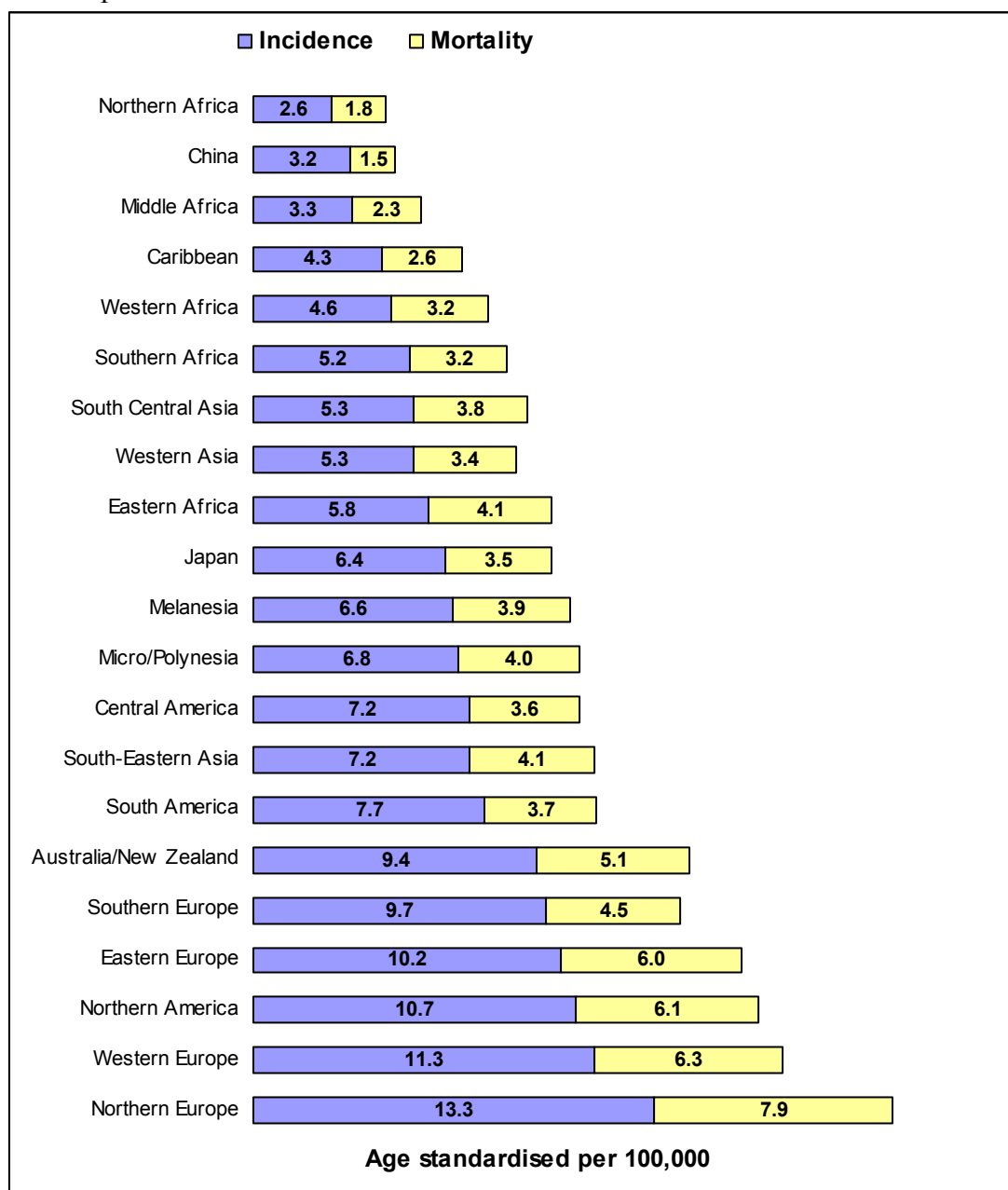


Fig.1.5. Age-standardised incidence and mortality rates for ovarian cancer. Source: Parkin *et al.* 2005⁶

As stated in the 2007 NCCN (National Comprehensive Cancer Network) Ovarian Cancer Guidelines,⁷ epithelial ovarian cancer is the leading cause of death from gynaecologic cancer in the United States and the country's fifth most common cause of cancer mortality in

women. In 2006, it was estimated that there would be 20,180 new diagnoses and an estimated 15,310 deaths from this neoplasm in the United States. The incidence of ovarian cancer increases with age and is most prevalent in the eighth decade of life, with an incidence rate of 57 per 100,000 women. In the United States the median age at the time of diagnosis is 63 years, and 70% of patients present with advanced disease. These guidelines also state that less than 40% of women with ovarian cancer are cured. A 30% to 60% decreased risk of ovarian cancer is associated with younger age at pregnancy and first birth (25 years or younger), the use of oral contraceptives, and/or breast feeding. Conversely, nulliparity or older age at first birth (older than 35 years) confers an increased risk of ovarian cancer.⁷

As stated in the NICE (National Institute for Clinical Excellence) Technology Appraisal 91,⁸ ovarian cancer is the fourth most common cause of cancer mortality in the United Kingdom (UK) with over 4000 reported deaths in England and Wales in 2002. The age-standardised incidence per 100,000 women in 2000 was 17.9 in England and 20.6 in Wales. The total number of new cases in England and Wales registered in 2000 was almost 6000. In the UK the 5-year survival rate for ovarian cancer is around 30% compared to around 40% in some European countries.⁹ In the UK 80% of ovarian cancers occur in women over the age of 50 years, with between 5% and 10% of cases occurring in women with mutations in the genes BRCA1 and BRCA2 or who carry the hereditary non-polyposis colorectal cancer (HNPCC) gene.⁸

The NICE Technology Appraisal No.91⁸ states that ovarian cancer is often asymptomatic in the early stages and over 75% of cases are diagnosed with advanced disease (i.e. Stage III or IV). Of those women diagnosed in the late stages of ovarian cancer 70% to 80% will ultimately die despite significant advances in the management of this disease. Although, more than 90% of patients can be cured with conventional surgery and chemotherapy when ovarian cancer is diagnosed in stage 1, only 25% of ovarian cancers are detected in this early stage.¹⁰

8.2 Chemotherapy – Carboplatin

Carboplatin was first introduced clinically in 1981 and gained FDA approval for the treatment of ovarian cancer in March 1989. Carboplatin (Paraplatin[®]) became a generic drug in October 2004.¹¹

The BC Cancer Agency Cancer Drug Manual[©] states:

Carboplatin is an inorganic heavy metal complex containing a central atom of platinum. Carboplatin is an analog of cisplatin and contains a platinum atom surrounded in a plane by two ammonia groups and two other ligands in the cis position. The other two ligands in carboplatin are present in a ring structure rather than as two chloride atoms in cisplatin. This difference makes carboplatin more stable and has less nephrotoxicity, neurotoxicity, ototoxicity and emetogenesis. The exact mechanism of action of carboplatin is not known. Carboplatin undergoes intracellular activation to form reactive platinum complexes which are believed to inhibit DNA synthesis by forming interstrand and intrastrand cross-linking of DNA molecules. Carboplatin is a radiation-sensitizing agent and is cell cycle-phase nonspecific.¹²

Carboplatin pharmacokinetics

MIMS Full Prescribing Information (<http://mims.com.au>) for carboplatin injection states:

After intravenous infusion of a single dose over one hour, plasma concentrations of total platinum and free platinum decline biphasically following first order kinetics. For free platinum, reported value for the initial phase of the half-life ($t_{1/2\alpha}$) is about 90 minutes and in the later phase the half-life ($t_{1/2\beta}$) is about six hours. Total platinum elimination has a similar initial half-life, while in the later phase the half-life of total platinum may be > 24 hours. Carboplatin is mainly excreted by the kidneys. Most excretion occurs within the first six hours of administration with 50 to 70% excreted within 24 hours. Thirty-two percent of the dose is

excreted as unchanged drug. A reduction in dosage is recommended for patients with poor renal function. Protein binding is less than with cisplatin. Initially protein binding is low, with up to 29% of carboplatin bound during the first four hours. After 24 hours 85 to 89% is protein bound.¹³

9.0 Treatment details (dosage regimen, duration; reference to existing WHO and other clinical guidelines; need for special diagnostic or treatment facilities and skills)

9.1 Indications for use

Although carboplatin is used in the treatment of a wide range of cancers, it has only gained regulatory approval for the treatment of advanced ovarian carcinoma of epithelial origin, alone or in combination regimens (United States FDA approved,¹ Australia TGA approved,¹⁴ Health Canada Therapeutic Products Programme approved¹²).

As stated in the Product Information (Bristol-Myers Squibb, January, 2004),¹⁵ Paraplatin[®] (carboplatin aqueous solution - injection) is indicated for the initial treatment of advanced ovarian carcinoma in established combination with other approved chemotherapeutic agents; and, secondary treatment of advanced ovarian carcinoma for the palliative treatment of patients with ovarian carcinoma recurrent after prior chemotherapy, including patients who have been previously treated with cisplatin.

9.2 Dosage regimens

Based on trial data the Product Information (Bristol-Myers Squibb, January, 2004),¹⁵ for Paraplatin[®] recommends that in patients with recurrent ovarian carcinoma, Paraplatin[®] as single-agent therapy (carboplatin aqueous solution - injection) should be given at a dosage of 360 mg/m² IV over 15-60 minutes on day 1 every 4 weeks. Single intermittent courses of Paraplatin[®] (carboplatin aqueous solution - injection) should not be repeated until the neutrophil count is at least 2,000 and the platelet count is at least 100,000. In combination therapy with cyclophosphamide for previously untreated patients the PI (Product Information) indicates that Paraplatin[®] should be administered intravenously as 300 mg/m² over 15-60 minutes on day 1 every four weeks for six cycles plus intravenous cyclophosphamide 600 mg/m² on day 1 every four weeks for six cycles. Intermittent courses of Paraplatin[®] in combination with cyclophosphamide should not be repeated until the neutrophil count is at least 2,000 and the platelet count is at least 100,000. The recommended dose adjustments for Paraplatin[®] (carboplatin) are summarised in Table 1.3.

Table 1.3: Dose adjustments recommended for Paraplatin[®] single agent or combination therapy

Platelets	Neutrophils	Adjusted dose (from prior course)
> 100,000	> 2000	125%
50-100,000	500-2000	No adjustment
< 50,000	<500	75%

Source: Paraplatin[®] - Product Information¹⁵

Patients with creatinine clearance values below 60 mL/min are at increased risk of severe bone marrow suppression including severe leukopenia, neutropenia, or thrombocytopenia. A summary of the recommended dose adjustments in patients with impaired kidney function are presented in Table 1.4.

Table 1.4: Recommended dose adjustments in patients with impaired kidney function

Baseline creatinine clearance	Recommended dose on Day 1
41-59 ml/min	250 mg/m ²
16-40 ml/min	200 mg/m ²

Source: Paraplatin[®] - Product Information¹⁵

Given that renal excretion is the major route of elimination for carboplatin another approach for determining the initial dose of Paraplatin[®] is the use of the mathematical formulae proposed by Calvert (Calvert formula), which are based on a patient's pre-existing renal function or renal function and desired platelet nadir. The use of the dosing formulae, as compared to empirical dose calculation based on body surface area, allows compensation for patient variations in pre-treatment renal function that might otherwise result in either underdosing (in patients with above average renal function) or overdosing (in patients with impaired renal function). The formula for calculating dosage is based upon a patient's glomerular filtration rate (GFR in mL/min) and Paraplatin[®] (carboplatin) target area under the concentration versus time curve (AUC in mg/mL/min) (refer to Table 1.5). Trial data indicates the target AUC of 4-6 mg/mL/min using single-agent carboplatin appears to provide the most appropriate dose range in previously treated patients.¹⁵

Table 1.5: Calvert formula

Calvert formula for carboplatin dosing
Total dose (mg) = (target AUC) × (GFR + 25)

Source: Paraplatin[®] - Product Information¹⁵

MIMS Full Prescribing Information (<http://mims.com.au>) for carboplatin injection states that the recommended dosage for previously untreated adults (with normal renal function) is 400 mg/m² as a single intravenous infusion over 15 to 60 minutes diluted in 5% glucose intravenous infusion to concentrations as low as 0.1 mg/mL. The carboplatin infusion should be completed within 24 hours of preparation and any residue discarded. Therapy should not be repeated again until four weeks have elapsed. In patients with risk factors, such as previous myelosuppressive therapy or in the aged, the initial dosage may need to be reduced by 20 to 25%. Determination of the haematological nadir by weekly blood counts is recommended for adjusting future doses and scheduling of carboplatin therapy.¹³

In patients with renal impairment it is recommended that the optimum the dosage of carboplatin should be determined by frequent monitoring of the haematological nadir and renal function as carboplatin is excreted by the kidney and is nephrotoxic.¹³ The suggested dosage schedule for patients with impaired renal function based on creatinine clearance (ClCr) is as follows:

- For ClCr > 40 mL/minute, carboplatin dose is 400 mg/m²
- For ClCr 20 to 39 mL/minute, carboplatin dose is 250 mg/m²
- For ClCr 0 to 19 mL/minute, carboplatin dose is 150 mg/m²

MIMS Full Prescribing Information (<http://mims.com.au>) for carboplatin injection recommends that when carboplatin is used in combination with other antineoplastic agents dosage adjustments should be made according to the treatment regimen adopted and the results obtained from haematological monitoring.¹³

The 2007 (Version 1) NCCN (National Comprehensive Cancer Network) Ovarian Cancer Guidelines,⁷ states that recommendations for the number of cycles of treatment vary with the stage of disease. For patients with advanced-stage disease (Stages II-IV), 6 cycles of

chemotherapy are recommended, whereas 3 to 6 cycles are recommended for earlier stage disease (Stage I). The recommended regimens accepted by a consensus of the NCCN Ovarian Cancer Panel Members include: carboplatin, dosed at an area under the curve (AUC) of 5-7.5, plus paclitaxel, 175 mg/m² 3-hour intravenous infusion given every 3 weeks (21-day cycle) for 6 weeks.

In May 2000, the National Institute for Clinical Excellence (NICE)⁹ issued the following guidance for the treatment of ovarian cancer:

- Paclitaxel (175 mg/m² intravenous infusion over 3-hours at 3-weekly intervals) in combination with a platinum-based therapy (cisplatin or carboplatin) should be the standard initial therapy for patients with ovarian cancer following surgery.
- The use of paclitaxel/platinum combination therapy in the treatment of recurrent (or resistant) ovarian cancer is recommended if the patient has not previously received this drug combination. If the patient has already received both drugs, the combination of paclitaxel and platinum-based therapy in recurrent (or resistant) ovarian cancer is not recommended, outside the context of clinical trials.

In January 2003, after taking into account new trial evidence, the NICE Appraisal Committee updated its guidance for paclitaxel for the treatment of ovarian cancer.⁹ As stated in the NICE Technology Appraisal No.55, “the Committee took into account a range of trial evidence as well as other factors that would differentiate between the two regimens including the side-effect profiles of the treatments, and the broad range of cost-effectiveness estimates presented.” On the basis of this information the Committee considered that, “paclitaxel/platinum combination treatment should no longer be recommended exclusively as standard therapy for women receiving first-line chemotherapy for ovarian cancer.” As a consequence the Committee considered that both platinum therapy alone and a combination of paclitaxel and a platinum compound were appropriate first-line treatments for women with ovarian cancer. These guidelines were further updated in May 2005 (Technology Appraisal No.91).⁸

The BC Cancer Agency (BCCA – Provincial Health Services Authority, Canada) provides open access to a number chemotherapy protocols for ovarian cancer.¹⁶ Reference to these protocols indicates that there are numerous dosing schedules modified to patient response and concomitant therapy. As stated in the BC Cancer Agency Cancer Drug Manual^{©12} guidelines for carboplatin dosing include consideration of absolute neutrophil count (ANC) with dosage reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities. The BC Cancer Agency protocol (Protocol code: GOOVCARB) for first or second-line therapy for invasive epithelial ovarian cancer using single-agent carboplatin is as follows:

Table 1.6: BC Cancer Agency (BCCA) – carboplatin dosing schedule

Drug	Dose	BCCA administration guideline
Carboplatin	Dose (mg) = AUC* × (GFR + 25)	IV in 250 ml D5W over 30 minutes
* AUC = 6 - repeat every 28 days x 6 to 9 cycles.		
N.B. If extensive prior radiation therapy, significant cytopenia with prior therapy, or age >80 years use AUC = 5.		

AUC = area under the curve, GFR = glomerular filtration rate, D5W = 5% dextrose

Source: BC Cancer Agency Protocol Summary¹⁶

The BC Cancer Agency protocol (Protocol code: GOOVCARB) states that measured GFR (e.g. nuclear renogram) is preferred whenever feasible, particularly in circumstances of comorbidity that could affect renal function (i.e. third-space fluid accumulations, hypoproteinaemia, potentially inadequate fluid intake, etc.). Laboratory reported GFR

(MDRD formula) may be used as an alternative to the Cockcroft-Gault estimate of GFR. However, it is recommended that the same method of estimation should be used throughout the treatment course (i.e. if lab reported GFR was used initially, this should be used for dosing in all subsequent cycles and not the Cockcroft-Gault estimate).¹⁶

Carboplatin dose modifications (BCCA Protocol GOOVCARB)

GFR should be used to determine the initial dose, with subsequent doses adjusted according to the following:

On treatment day:

ANC (x 10 ⁹ /L)	Platelets (x 10 ⁹ /L)		Dose
> 1.0	AND	> 100	100%
< 1.0	OR	< 100	delay 1 week or until recovery

At nadir:

ANC (x 10 ⁹ /L)	Platelets (x 10 ⁹ /L)		Carboplatin
> 1.5	AND	> 100	120%*
0.5-1.4	AND	> 75	100%
< 0.5	AND	< 75	80%
< 0.5	AND	> 75	100%
> 0.5	AND	< 75	80%
Febrile neutropenia at any time			80%

* Do not escalate above 120% of Cycle 1 dose.
Source: BC Cancer Agency Protocol Summary¹⁶

In the case of renal dysfunction the use of nuclear renogram or predictive formula to calculate cycle 1 dose is recommended (as above). Re-calculation of dose is recommended if the serum creatinine changes 20% from baseline. In the case of neutropenic fever the subsequent carboplatin doses should be reduced to 80% (as above).

9.3 Need for special diagnostic or treatment facilities and skills

As a potent cytotoxic agent, carboplatin administration requires specialist oncology facilities capable of delivering this drug in a safe and effective manner by suitably qualified staff. Only specialist oncologists should supervise the provision of chemotherapy in ovarian cancer.

10. Summary of comparative effectiveness in a variety of clinical settings

10.1 Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data)

To identify systematic reviews and randomised clinical trials of carboplatin the following databases were searched: Medline (1950 to July, 2007), EMBASE (1980 to July, 2007), CancerLit (to July, 2007), the Cochrane Database of Systematic Reviews (Issue 2, 2007), and the Cochrane Central Register of Controlled Trials (CENTRAL). To maximise the sensitivity for the retrieval of all potentially relevant studies, the electronic searches of these databases were searched initially using an unrestricted search strategy, employing exploded MeSH terms (exp Carboplatin/) and specific text-word terms for carboplatin. Text-word terms included: 'cis-Diammine cyclobutane-1', '1-dicarboxylato platinum', or 'paraplatin' or 'biocarb' or 'biocarbo' or 'biplatinex' or 'blastocarb' or 'boplatex' or 'B-Platin' or 'carbo-cell' or 'carbokebir' or 'carbomedac' or 'carboplat' or 'carbosin' or 'carbosal' or 'carbotec' or 'carboxtie' or 'cycloplatin' or 'cyctocarb' or 'displata' or 'emorzim' or 'ercar' or 'evocarb' or 'ifacap' or 'kemocarb' or 'megaplatin' or 'nealorin' or 'neocarb' or 'novoplat' or 'novoplatinum' or 'omilipis' or 'oncocarb' or 'paraplatine' or 'platamine' or 'platicarb' or

‘platinwas’ or ‘ribocarbo’ or ‘tecnocarb’ or ‘CBDCA’. To restrict and improve the specificity of these searches, two search filters were used. First, a filter to identify randomised controlled trials,¹⁷ and secondly a filter to identify systematic reviews and meta-analyses (Medline and EMBASE search strategies are provided in Appendix B). The internet was widely searched using Google™ and Google™ Scholar. The reference lists of identified trials, reviews, reports and guidelines were searched for potentially relevant studies.

Studies were included for review if they were either systematic reviews, randomised controlled parallel group trials, or randomised head-to-head comparative trials, and evaluated the effectiveness of intravenous carboplatin in treating ovarian cancer. Studies that evaluated the use of carboplatin outside its FDA approved indication for the treatment of ovarian cancer were not included for review.

As the literature search identified three relevant systematic reviews¹⁸⁻²⁰ published between 1991 and 1998, the search for randomised clinical trials of carboplatin were limited to the years 1998-2007 (inclusive).

10.2 Summary of available data (appraisal of quality, outcome measures, summary of results)

Systematic reviews

The Advanced Ovarian Cancer Trialists’ Group (AOCTG) have published three systematic reviews of chemotherapy in advanced ovarian cancer, with the first of these reviews being published in 1991¹⁸ and the two subsequent updated meta-analyses both being published in 1998.^{19,20}

The systematic review by AOCTG published in 1991¹⁸ included a meta-analysis of individual patient data from published and unpublished randomised trials of single-agent and combination chemotherapy in the treatment of advanced ovarian cancer. This systematic review included a total of 8139 patients (6408 deaths) in 45 different trials originating from 11 different countries. Chemotherapy regimens studied included: (1) single non-platinum agent versus non-platinum combination; (2) single non-platinum agent versus platinum combination; (3) addition of platinum to a regimen; (4) single-agent platinum versus platinum combination; (5) cisplatin versus carboplatin. A summary of the numbers of patients and deaths for each comparison is presented in Table 1.7.

Table 1.7: Summary of the numbers of patients and deaths for each comparison

Comparison	Number of available trials	Number of unavailable trials	Number of deaths	Number of patients
1	16	6	2817	3146
2	11	2	1136	1329
3	8	0	1134	1408
4	6	0	712	925
5	11	0	1771	2061
Total	45	8	6408	8139

Source: Table I, Advanced Ovarian Cancer Trialists’ Group(AOCTG)¹⁸

The overall results of the meta-analysis showed that in terms of survival immediate platinum based treatment was no better than non-platinum regimens (overall relative risk [RR] 0.93, 95% confidence interval [CI] 0.83 to 1.05); platinum combination was no better than single agent platinum when used in the same dose (overall RR 0.85, 95% CI 0.72 to 1.00); and cisplatin and carboplatin were equally effective (overall RR 1.05, 95% CI 0.94 to 1.18). The forest plot for the cisplatin versus carboplatin comparison is presented in Figure 1.6.

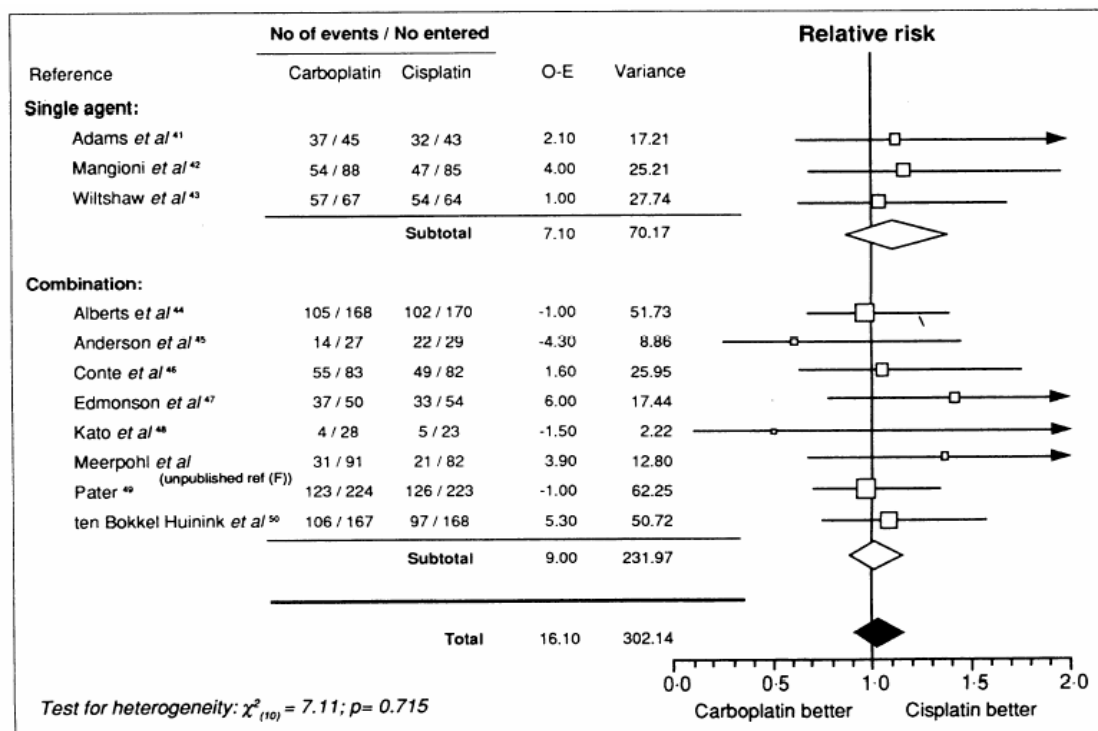


Figure 1.6: Relative risks for comparison 5 – Carboplatin versus Cisplatin
 Source: Figure 10, Advanced Ovarian Cancer Trialists' Group(AOCTG)¹⁸

Interestingly, the authors of this review¹⁸ stated that, “despite over 50 randomised clinical trials having examined the relative efficacy of different chemotherapeutic regimens in advanced disease (FIGO: International Federation of Gynaecology and Obstetrics; stages III and IV), individually these trials have been too small to show clear benefit of one type of chemotherapy over another.” Further to this it was stated that, “currently it is unclear what constitutes optimal chemotherapy for advanced disease and treatment strategies vary both nationally and internationally. What is clear is that to date no individual clinical trial has been large enough to detect survival differences of the magnitude that could reasonably be expected with available treatment. Consequently the inconclusive results of over 50 such trials reported could be consistent with moderate treatment benefits.”¹⁸

In 1998 the Advanced Ovarian Cancer Trialists' Group (AOCTG) published the results of four meta-analyses of individual patient data (IPD) from 37 randomised trials.¹⁹ This updated systematic review and meta-analysis provided a quantitative summary of the relative benefits of various types of chemotherapy regimens including; (1) single-agent non-platinum versus platinum based combination chemotherapy, (2) non-platinum drug regimen with the same regimen plus cisplatin, (3) single-agent platinum versus platinum combination, and (4) carboplatin versus cisplatin. Meta-analyses were based on updated individual patient data from all available randomised controlled trials (published and unpublished), including a total of 5667 patients (4664 deaths) from 37 trials. For the single-agent non-platinum versus platinum based combination comparison, data were available from a total of 11 trials including 1329 patients and 1169 deaths. The results of the meta-analysis indicated that the overall results were inconclusive ($P = 0.23$) with the hazard ratio for the risk of death being 0.93 (95% CI 0.83 to 1.05). For the non-platinum drug regimen with the same regimen plus cisplatin comparison, data were available from nine trials including a total of 1704 patients and 1428 deaths. The meta-analysis showed that for overall survival the HR of 0.88 favoured

the addition of platinum ($P = 0.02$). This result was translated as a 12% reduction in the risk of death and a 5% (95% CI 1% to 8% benefit) improvement in survival at both 2 years (45-50%) and 5 years (25-30%). In the case of the single-agent platinum versus platinum combination comparison, the overall results for the risk of death were inconclusive with a HR of 0.91 ($P = 0.21$). For the carboplatin versus cisplatin comparison, data were available from 12 trials including a total of 2219 patients and 1745 deaths. The results of the meta-analysis indicated that for overall survival there was no statistically significant difference between cisplatin and carboplatin (HR 1.01, 95% CI 0.81 to 1.26; $P = 0.92$)(Refer to Fig.1.7 and Fig.1.8). The authors of this study concluded that, “there is no good evidence that cisplatin is more or less effective than carboplatin in any particular subgroup of patients.”¹⁹

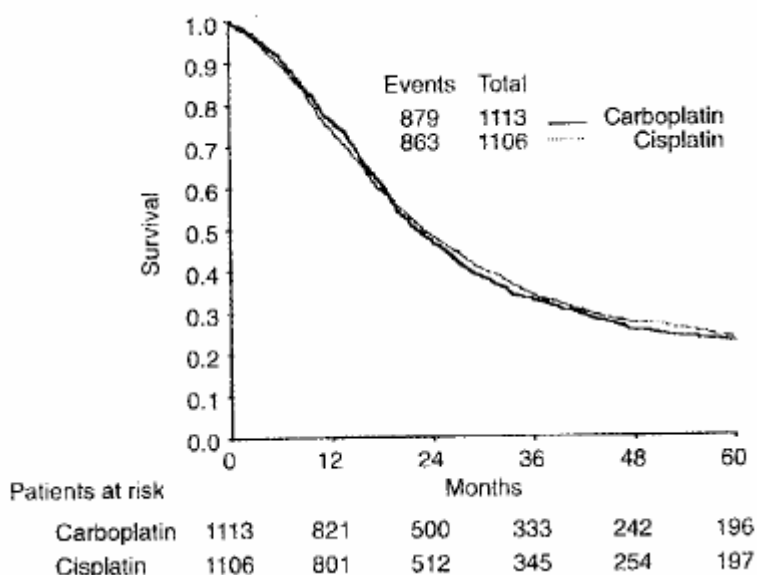
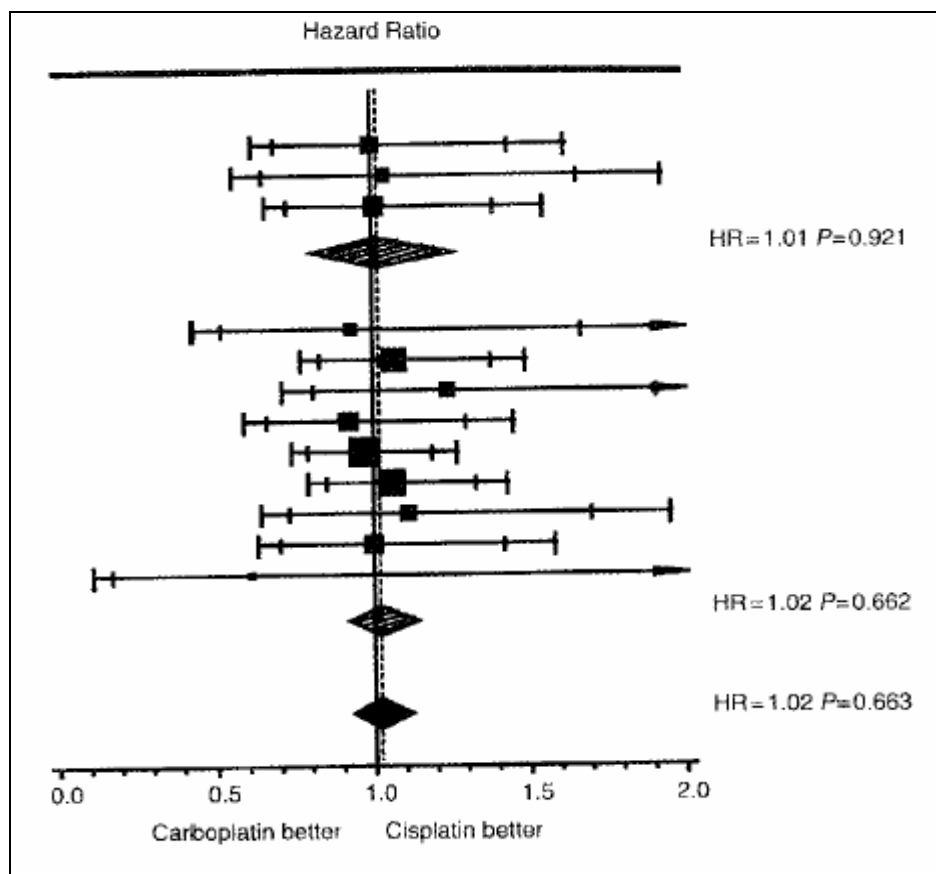


Figure 1.7: Survival curves for carboplatin and cisplatin
 Source: Figure 3B AOCTG 1998¹⁹



Single agent:

HR = 1.01 (95% CI 0.81–1.26), $\chi^2_{(1)} = 0.01$, $P = 0.92$; Het $\chi^2_{(2)} = 0.02$, $P = 0.99$

Combination:

HR = 1.02 (95% CI 0.92–1.13), $\chi^2_{(1)} = 0.19$, $P = 0.66$; Het $\chi^2_{(8)} = 2.54$, $P = 0.96$

Overall:

HR = 1.02 (95% CI 0.93–1.12), $\chi^2_{(1)} = 0.19$, $P = 0.66$; Het $\chi^2_{(11)} = 2.57$, $P = 0.99$

Interaction $\chi^2_{(11)} = 0.01$, $P = 0.92$

Figure 1.8: Forest plot for cisplatin versus carboplatin

Source: Source: Figure 3A AOCTG 1998¹⁹

In 1998 the Advanced Ovarian Cancer Trialists' Group (AOCTG) converted its previous systematic review and meta-analysis of IPD¹⁹ into a Cochrane review.²⁰ This systematic review included a total of 8763 patients from 49 randomised trials (published or unpublished). Trials were eligible for inclusion if they examined first-line treatment for advanced ovarian cancer and studied one or more of the following treatment regimens: (1) single non-platinum agent versus non-platinum combination; (2) single non-platinum agent versus platinum combination; (3) non-platinum regimen versus the same regimen plus cisplatin; (4) single-agent platinum versus platinum combination chemotherapy; (5) cisplatin versus carboplatin. In summary, the results of the meta-analysis showed that for single non-platinum versus platinum combination chemotherapy the overall hazard ratio (HR) for survival was 0.93 (95% CI 0.83 to 1.05)(unchanged from previous meta-analysis). For non-platinum regimens compared with the same regimen plus cisplatin the survival HR was 0.88 (95% CI 0.79 to 0.98) in favour of adding platinum to drug regimens. Single platinum compared with platinum combination gave a HR of 0.91 (95% CI 0.79 to 1.05)(Refer to Fig.1.9).

Review: Chemotherapy for advanced ovarian cancer

Comparison: 04 single platinum vs platinum combination

Outcome: 01 survival

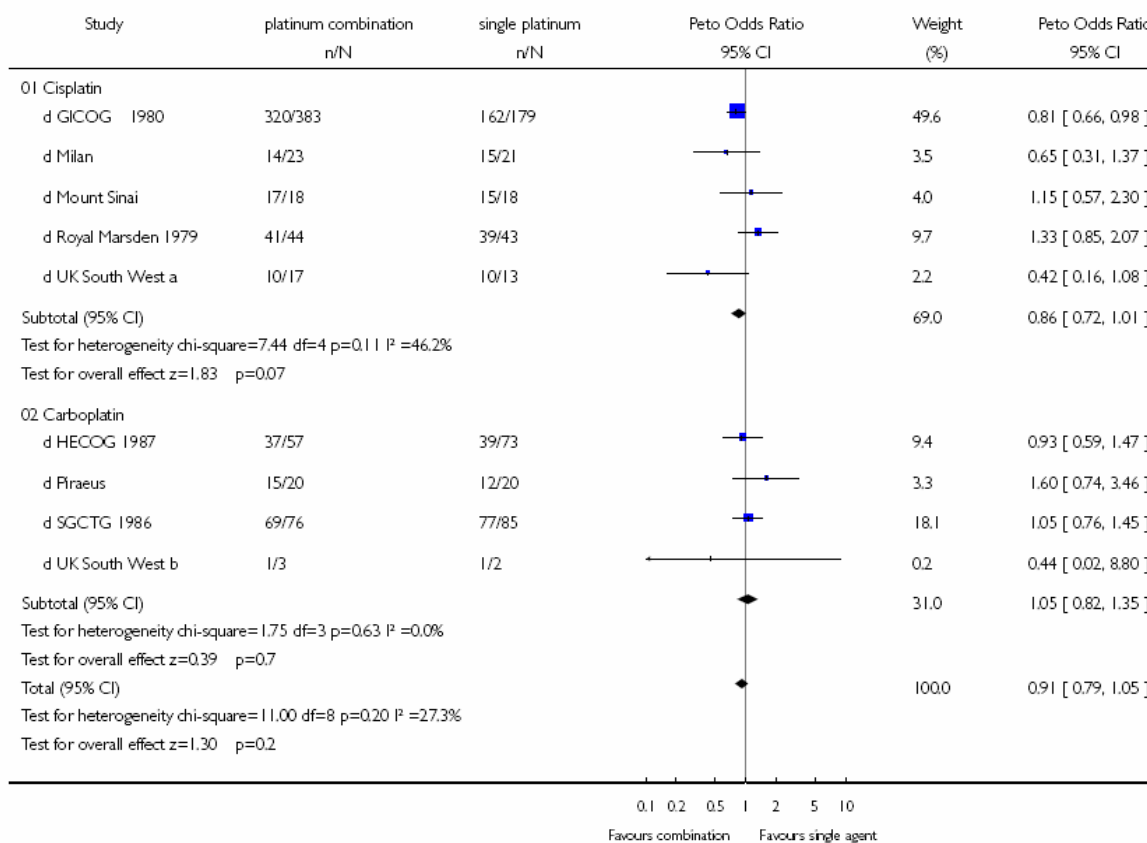


Figure 1.9: Single platinum versus platinum combination
Source: Advance Ovarian Cancer Trialists Group (AOCTG)²⁰

There were 12 eligible trials that compared cisplatin and carboplatin either as single agents or each in combination with the same drugs in multi-drug regimens. In total this includes 2219 patients and 1745 deaths. There was no statistically significant difference between cisplatin and carboplatin when given either as a single agent (HR 1.01, 95% CI 0.81 to 1.26) or in combination (HR 1.02, 95% CI 0.92 to 1.14). There was no evidence of statistically significant heterogeneity ($P > 0.95$, $I^2 = 0.0\%$) (Refer to Fig. 1.10).

As stated in the review, “the overall HR of 1.02 (95% CI 0.93 to 1.12) suggests a 2% benefit of cisplatin, but the confidence intervals are such that it could be consistent with modest benefits of either drug. In terms of absolute survival at both two and five years, the 95% confidence interval is consistent with improvements in overall survival of 3% benefit for cisplatin and 4% benefit for carboplatin. Different patient subgroups were analysed using data provided for 11 of the trials included in the carboplatin/cisplatin comparison. There is no good evidence that any group of women specified by age (interaction chi-square = 0.18, $P = 0.67$), stage (trend chi-square = 0.64, $P = 0.42$), performance status (interaction chi-square = 0.68, $P = 0.41$), residual tumour bulk (interaction chi-square = 0.68, $P = 0.41$), extent of operation (trend chi-square= 0.04, $p = 0.84$), histology (interaction chi-square = 11.56, $P = 0.07$) or grade (interaction chi-square = 2.30, $P = 0.13$) do any better or worse when treated with either cisplatin or carboplatin. There is perhaps some suggestion that stage II tumours may benefit more from cisplatin. However, very few stage II tumours were included, the confidence intervals are wide and it is difficult to draw any conclusions from the result.”²⁰

WHO EML – Final Report – CARBOPLATIN – February 2008

Review: Chemotherapy for advanced ovarian cancer

Comparison: 05 carboplatin versus cisplatin

Outcome: 01 survival

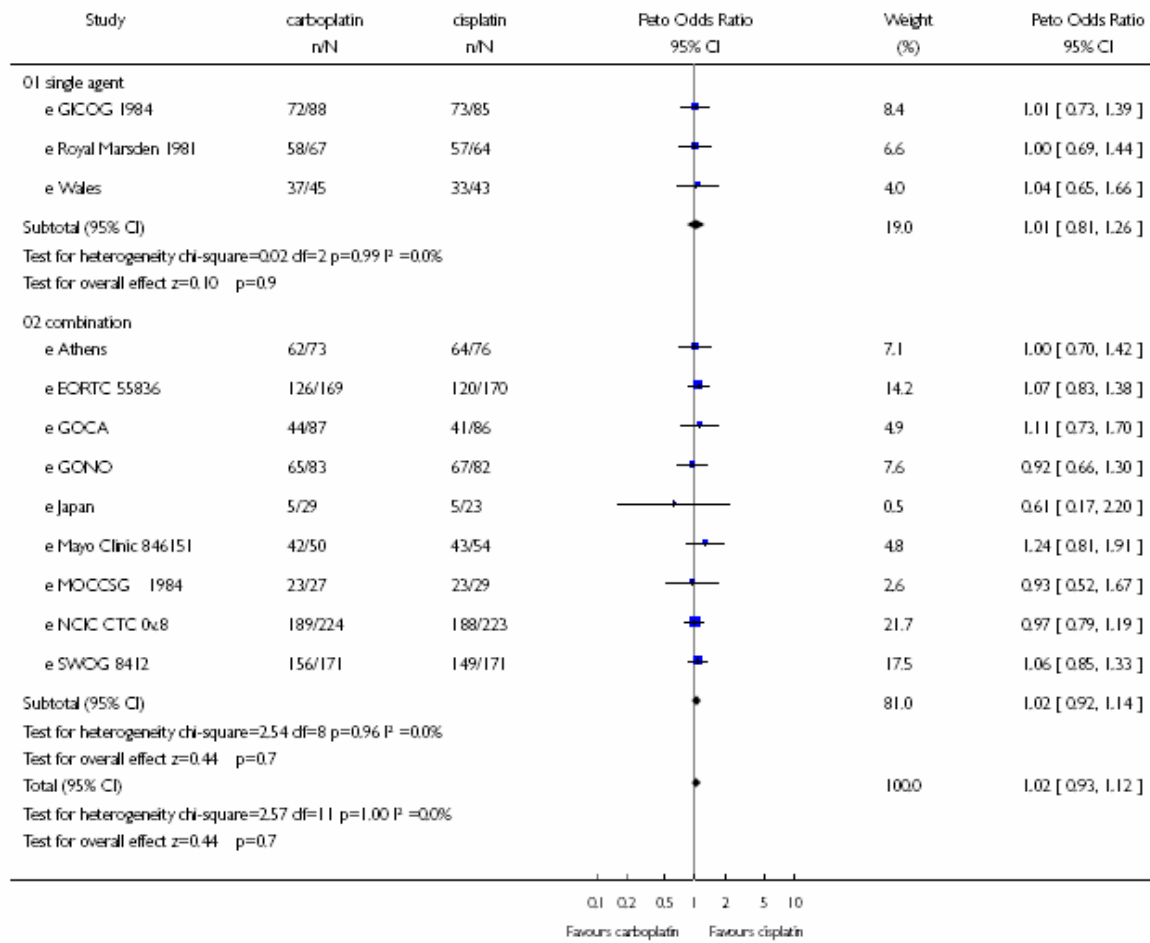


Figure 1.10: Single platinum versus platinum combination
Source: Advance Ovarian Cancer Trialists Group (AOCTG)²⁰

*Randomised controlled trials**Carboplatin versus control (no carboplatin)*

In a prospective randomized multi-centre trial by Trope *et al.* (2000)²¹ 162 patients were randomly allocated to receive carboplatin adjuvant chemotherapy or observation without carboplatin chemotherapy. Patients received either adjuvant carboplatin AUC 7 every 28 days for six courses (n = 81) or no adjuvant treatment (n = 81). Eligibility included surgically staged and treated patients with FIGO (International Federation of Gynecology and Obstetrics) stage I disease, grade 1 aneuploid or grade 2 or 3 non-clear cell carcinomas or clear cell carcinomas. The primary study end-points were disease-free survival (DFS) and disease-specific survival (DSS). The results of this trial showed that the median follow-up time was 46 months and progression was observed in 20 patients in the treatment group and 19 in the control group. Estimated five-year DFS and DSS were 70% and 86% in the treatment group and 71% and 85% in the control group. The hazard ratio for DFS was 0.98 (95% CI 0.52 to 1.83) and 0.94 (95% CI 0.37 to 2.36) for DSS. No statistically significant differences in DFS or DSS could be seen when the log-rank test was stratified for prognostic variables. Data from both groups were then pooled for the analysis of prognostic factors: DNA-ploidy ($P = 0.003$), extracapsular growth ($P = 0.005$), tumor rupture ($P = 0.04$), and WHO histologic grade ($P = 0.04$) were significant independent prognostic factors for DFS with $P < 0.0001$ for the model in the multi-variate Cox analysis. FIGO substage ($P = 0.01$), DNA ploidy ($P < 0.05$), and histologic grade ($P = 0.05$) were prognostic for DSS with a P value for the model < 0.0001 . The authors of this trial concluded that due to the small number of patients in the study and given the survival curves were superimposable with wide confidence intervals, the results were inconclusive regarding the efficacy of carboplatin adjuvant chemotherapy. However, DNA-ploidy added objective independent prognostic information regarding both DFS and DSS in early ovarian cancer.

*Randomised head-to-head comparison trials – carboplatin combination chemotherapy**Carboplatin/paclitaxel combination versus cisplatin/paclitaxel combination*

In a randomised, head-to-head comparison trial by Neijt *et al.* (2000)²² 208 patients were randomly allocated to receive paclitaxel 175 mg/m² intravenously as a 3-hour infusion followed by either cisplatin 75 mg/m² (n = 108) or carboplatin (area under the plasma concentration time curve of 5) (n = 100), both on day 1. The schedule was repeated every 3 weeks for at least six cycles. This trial was designed to determine the side effects and feasibility of cisplatin and carboplatin each in combination with paclitaxel as front-line therapy in advanced epithelial ovarian cancer. Women allocated to paclitaxel-cisplatin were admitted to hospital, whereas the carboplatin regimen was administered in an outpatient setting. Eligible patients were required to have histologically verified epithelial ovarian carcinoma (based on the 1973 World Health Organization histologic classification), International Federation of Gynecology and Obstetrics (FIGO) stages IIB to IV. The mean age of patients in both treatment arms was 56 years. The results of this trial showed that paclitaxel-carboplatin produced significantly less nausea and vomiting ($P < 0.01$) and less peripheral neurotoxicity ($P = 0.04$) but more granulocytopenia and thrombocytopenia ($P < 0.01$). It should be noted that more cycles were administered in the patients treated with the carboplatin-based schedule (701 versus 666; $P = 0.003$) and there was slightly more delay between cycles observed in the carboplatin-treated patients. The actual mean doses of drug delivered as percentage of the dose planned were, for the paclitaxel-cisplatin and paclitaxel-carboplatin regimens, respectively, 99% for paclitaxel, 96% for cisplatin, 98% for paclitaxel, and 103% for carboplatin. Median overall survival times were 30 and 32 months for patients allocated to paclitaxel-cisplatin and paclitaxel-carboplatin, respectively. The hazard ratios for carboplatin compared with cisplatin were as follows: 1.07 for progression-free survival (95%

CI 0.78 to 1.48), 0.85 for overall survival (95% CI 0.59 to 1.24), and 1.27 for CA 125 progression-free survival (95% CI 0.90 to 1.80). In the multivariate model, the tumor diameter before chemotherapy ($P = 0.01$) and stage ($P = 0.05$) were the only factors with a significant impact on progression-free survival. The treatment effect remained unchanged when a multivariate model with treatment and residual tumor as a prognostic factor was considered. After adjustment for tumor diameter and stage, the hazard ratio for carboplatin compared with cisplatin on progression-free survival was similar: 1.03 (95% CI, 0.75 to 1.42). Based on the results of this trial the authors concluded that paclitaxel-carboplatin is a feasible regimen for outpatients with ovarian cancer and has a better toxicity profile than paclitaxel-cisplatin.

In a randomised, head-to-head, phase III non-inferiority trial by Ozols *et al.* (2003)²³ 792 patients with advanced ovarian cancer and no residual mass greater than 1.0 cm after surgery were randomly allocated to receive either cisplatin 75 mg/m² intravenously at 1 mg/min plus a 24-hour infusion of paclitaxel 135 mg/m² (n = 400) every 3 weeks for a total of six courses, or carboplatin area under the curve (AUC) 7.5 mg/mL/min intravenously plus paclitaxel 175 mg/m² over 3 hours (n = 392). The carboplatin dose in milligrams was based on the Calvert formula. Premedication consisted of dexamethasone 20 mg orally 12 and 6 hours before the infusion or 20 mg intravenously 30 minutes before the paclitaxel infusion. Both diphenhydramine 50 mg and cimetidine 300 mg were administered intravenously 30 minutes before the paclitaxel infusion. Women with pathologically verified stage III epithelial ovarian cancer (borderline tumors were excluded) underwent a staging laparotomy with cytoreduction. Those who were left with no residual disease greater than 1.0 cm in diameter were eligible for the study.

The results of this trial showed that 285 (73%) patients treated with carboplatin and paclitaxel experienced a recurrence of disease compared with 303 (76%) treated with cisplatin and paclitaxel. The median progression-free survival (PFS) in the carboplatin group was 20.7 months compared with 19.4 months for the cisplatin group ($P > 0.05$) (Fig.1.11). When carboplatin plus paclitaxel was compared with cisplatin plus paclitaxel the relative risk (RR) of treatment failure was 0.88 (95% CI 0.75 to 1.03). The RR of treatment failure for carboplatin plus paclitaxel to cisplatin plus paclitaxel was 0.89 and 0.85 in patients with gross residual disease and those with microscopic or no residual disease, respectively. Two hundred seven patients (53%) treated with carboplatin plus paclitaxel died compared with 230 patients (58%) treated with cisplatin plus paclitaxel. The median survival was 57.4 months for carboplatin plus paclitaxel versus 48.7 months for cisplatin plus paclitaxel (RR 0.84, 95% CI 0.70 to 1.02) (Fig.1.12).

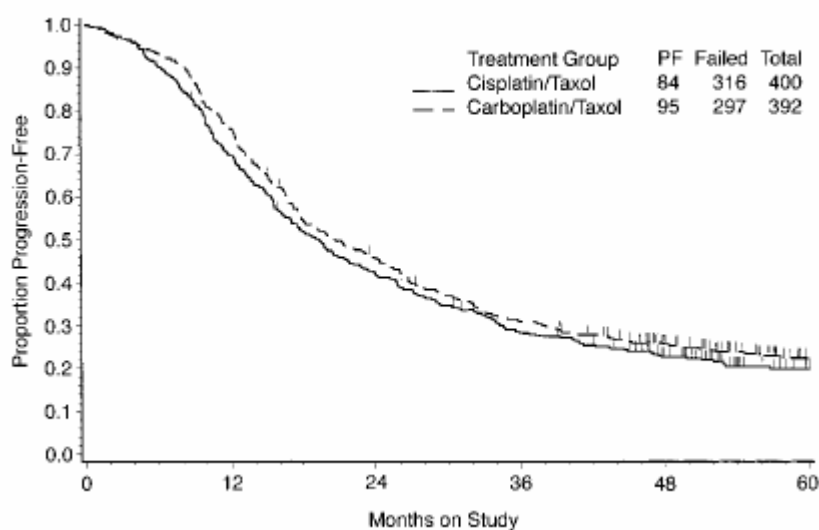


Figure 1.11: Progression-free survival by treatment group
Source: Ozols et al.(2003)²³

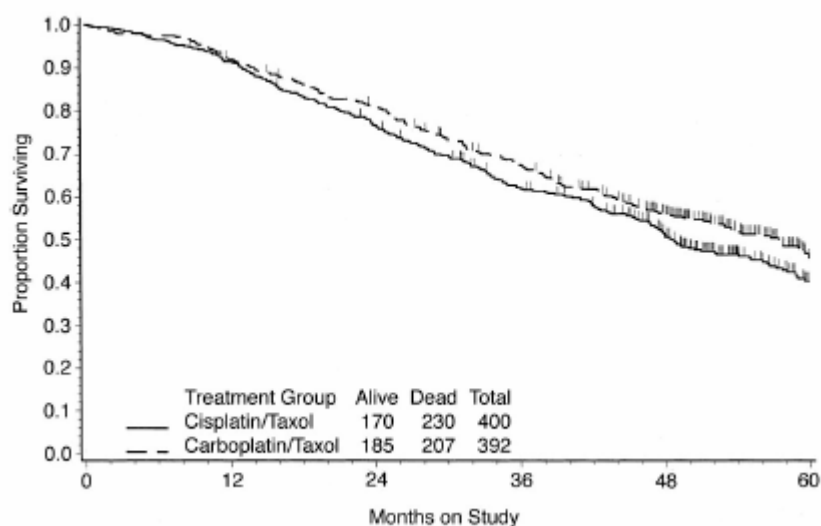


Figure 1.12: Observed survival by treatment group
Source: Source: Ozols et al.(2003)²³

Patients treated with the cisplatin regimen experienced statistically significantly more leukopenia, gastrointestinal, renal (genitourinary), and metabolic (hypomagnesemia or abnormal electrolytes) toxicities than did those treated with carboplatin. Patients treated with the carboplatin regimen experienced statistically significantly more grade 2 to 4 thrombocytopenia and grade 1 to 2 pain. Grade 3 or 4 neutropenia occurred in the majority of women in this trial, with few patients having documented infection or requiring hospitalization. In regards to thrombocytopenia, there were no reports of clinically significant bleeding or the need for platelet transfusion. Grade 2 to 4 neurologic toxicity (primarily peripheral neuropathy) occurred with similar frequency; 31% in the cisplatin arm and 28% in the carboplatin arm (Fig.1.13).

Adverse Effect	Cisplatin + Paclitaxel (n = 400)				Carboplatin + Paclitaxel (n = 392)			
	Grade 3		Grade 4		Grade 3		Grade 4	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Leukopenia*	205	51	49	12	207	53	23	6
Thrombocytopenia*	11	3	9	2	74	19	80	20
Granulocytopenia	60	15	312	78	67	17	284	72
Gastrointestinal*	55	14	35	9	20	5	19	5
Neurologic	30	8	1	0	26	7	1	0
Alopecia	0	0	0	0	0	0	0	0
Metabolic*	24	6	7	2	6	2	3	1
Genitourinary*	11	3	1	0	3	1	0	0
Pain*†	2	1	1	0	2	1	1	0

*Statistically significant difference at the .05 level.

†Grade 1 to 2 pain: carboplatin + paclitaxel = 101 (26%); cisplatin + paclitaxel = 60 (15%).

Figure 1.13: Grade 3 to 4 adverse effects

Source: Source: Ozols et al.(2003)²³

In the discussion the authors stated that, “this study was designed as a non-inferiority trial and the results essentially exclude the possibility that the carboplatin regimen is inferior to the cisplatin regimen. This trial was not designed to determine whether the carboplatin regimen was superior to the cisplatin regimen. Nonetheless, the 16% reduced risk of death is of interest because it is suggestive that carboplatin may provide a slight increase in efficacy over cisplatin.”

In a randomised, head-to-head, unblinded phase III non-inferiority trial by du Bois *et al.*(2003)²⁴ 798 patients with FIGO stage IIB-IV advanced ovarian cancer were randomly assigned to receive paclitaxel plus carboplatin (TC arm: n = 397) or paclitaxel plus cisplatin (PT arm: n = 386). Patients in the TC arm received paclitaxel (185 mg/m²) administered intravenously over 3 hours, followed by carboplatin (AUC 6) administered intravenously over 30–60 minutes. The carboplatin dose was calculated using the Calvert formula. Patients in the PT arm received paclitaxel at the same dose and schedule as patients in the TC arm, followed by cisplatin (75 mg/m²) administered intravenously over 30 minutes. Regardless of calculated doses, the maximal absolute dose that was given to each patient was limited to 400 mg for paclitaxel, 880 mg for carboplatin, and 165 mg for cisplatin. Dose reductions were allowed depending on predefined levels of hematologic or non-hematologic toxicity, with dose reduction levels as follows: carboplatin AUC 5 (level 1) or AUC 4 (level 2), cisplatin at 60 mg/m² (level 1) or 50 mg/m² (level 2), and paclitaxel at 160 mg/m² (level 1) or 135 mg/m² (level 2). Any subsequent treatment cycle was delayed when the patient’s ANC was less than 1.5×10^9 cells/L or platelet count was less than 100×10^9 cells/L. Primary prophylaxis using granulocyte colony-stimulating factor (G-CSF) was not allowed. However, supportive G-CSF treatment was initiated at the discretion of the investigator if the patient’s ANC recovery took more than 36 days. All patients received premedication consisting of a single dose of dexamethasone (20 mg), clemastine (2 mg), and cimetidine (300 mg) administered 30 minutes before the start of the paclitaxel infusion. Anti-emetic prophylaxis consisted of serotonin type 3 receptor antagonists and corticoids. In addition, patients in the PT arm received pre- and post-chemotherapy hydration to avoid cisplatin-induced nephrotoxicity. Chemotherapy cycles were repeated every 3 weeks. Patients with disease progression during therapy went off protocol treatment. Patients who achieved partial remission and who exhibited residual tumor after six treatment cycles could receive additional treatment cycles if recommended by their physician. The same treatment rules applied to all cycles.

The results of this trial showed that the PT regimen (Paclitaxel/cisplatin arm) was associated with statistically significantly more clinically complete and partial responses than the TC regimen (81.4% versus 67.7%, respectively) with the difference in proportions = 13.7% (95% CI 0.9% to 26.4%). However, no statistically significant difference in complete or partial pathologic response was observed between the two treatment regimens at second-look surgery (76.6% in the PT regimen versus 78.4% in the TC regimen; difference in proportions = -1.7%; 95% CI -15.9% to 12.5%). Approximately half of the patients undergoing second-look surgery exhibited non-evaluable disease or a clinically complete response (36.5% in the TC arm versus 43.3% in the PT arm). The higher response rates following treatment with the PT regimen did not result in superior progression-free or overall survival.

Median progression-free survival time in the TC arm (17.2 months, 95% CI 15.2 to 19.3 months) was not statistically significantly different from that in the PT arm (19.1 months, 95% CI 16.7 to 21.5 months), corresponding to an HR of 1.05 (95% CI 0.893 to 1.234). Similarly, median overall survival time was not statistically significantly different between the treatment arms (43.3 months, 95% CI 37.2 to 47.8 months in the TC arm versus 44.1 months, 95% CI 40.2 to 49.4 months in the PT arm), corresponding to an HR of 1.045 (95% CI 0.869 to 1.257). With respect to the primary endpoint, the difference in the proportion of patients without disease progression at 2 years was not statistically significant between the treatment arms (40.0% for the PT arm versus 37.5% for the TC arm, difference in proportions = 2.5%, two-sided 95% CI -4.4% to 9.4%, one-sided 95% CI $-\infty$ to 8.2%).

In regards to treatment toxicity (graded according to the National Cancer Institute Common Toxicity Criteria) and quality of life measures (evaluated using global health status/quality-of-life score from the European Organization for Research and Treatment of Cancer quality-of-life questionnaire (QLQ)-C30, version 2.0), the TC regimen was associated with a higher frequency of hematologic toxicity, but a lower frequency of gastrointestinal and neurologic toxicity, than the PT regimen. Mean global quality-of-life scores at the end of treatment were statistically significantly better in the TC arm than in the PT arm (65.25 versus 51.97, respectively; difference = -13.28, 95% CI -18.88 to -7.68).

Based on the results of this trial the authors stated that, the paclitaxel/carboplatin regimen achieved comparable efficacy to the paclitaxel/cisplatin regimen but was associated with better tolerability and quality of life, and should, therefore, be considered as an important alternative for standard first-line chemotherapy in patients with advanced ovarian cancer.²⁴

The International Collaborative Ovarian Neoplasm Study (ICON2)²⁵ compared single-agent carboplatin to the three drug combination of CAP (cyclophosphamide, doxorubicin, and cisplatin) in women with ovarian cancer. The ICON2 study was an international, multi-centre, randomised trial involving 1526 patients from 132 centres in nine countries. Patients were eligible for inclusion if they had histologically confirmed invasive ovarian cancer of epithelial origin; there was no contraindication to chemotherapy (including adequate renal function); there was no evidence of previous malignant disease (except non-melanoma skin cancer); and no previous radiotherapy or chemotherapy. No restrictions were placed on the extent of surgery, although total hysterectomy, bilateral salpingo-oophorectomy, and thorough staging were recommended as minimal surgical procedures. Patients were randomised to receive either intravenous single-agent carboplatin (n = 760) or CAP (n = 766) over six cycles of treatment with 3-week intervals (21-day cycle). Treatment commenced as soon as possible after surgery. Patients randomised to the carboplatin arm of the trial received carboplatin (AUC 5: using the Calvert formula). Patients randomised to the CAP regimen

received cyclophosphamide 500 mg/m², doxorubicin 50 mg/m², and cisplatin 50 mg/m². Pre-treatment data were collected at the time of randomisation. Treatment and initial follow-up data were collected 6 months later and further follow-up data were collected 12 months after randomisation and annually thereafter. All data were collected either at the Istituto Mario Negri (Italian centres) or the MRC Cancer Trials Office (UK, Swiss, and other centres). Patient randomisation was performed by telephone or fax using computer number generation in all three randomisation centres.

The results of this trial²⁵ showed that in both groups, about 80% of patients received six cycles of chemotherapy (79.6% CAP, versus 81.5% carboplatin). Only a small proportion of patients (n = 34 CAP, n = 14 carboplatin) received no chemotherapy at all. The hazard ratio (HR) for progression-free survival was 0.92 in favour of CAP (95% CI 0.81 to 1.04; *P* = 0.20). This finding translates into an estimated absolute improvement in 1-year progression-free survival of 3% in favour of CAP from 60% to 63% (95% CI 21% to 6%). These results also translate into median progression-free survivals of 15.5 and 17.0 months for carboplatin and CAP, respectively. A small number of women (CAP, n = 40; carboplatin, n = 46) received some additional anticancer treatment before disease progression. A further analysis censoring these women at time of start of treatment produced similar results with a hazard ratio of 0.94 (*P* = 0.33; 95% CI 0.81 to 1.06). The hazard ratio for overall survival was 1.00 (95% CI 0.86 to 1.16; *P* = 0.98) suggesting equivalent risks of death in the two groups. The results translate into an absolute difference in 2-year survival of 0% (95% CI 4% in favour of carboplatin to 6% in favour of CAP) with about 60% survival in both groups. The median survival in both groups was estimated as 33 months. Analyses of progression-free survival and overall survival with Cox's proportional-hazards model to allow for all pre-treatment characteristics produced similar results. There was no evidence that CAP was more or less effective than carboplatin in any subgroup.²⁵

In conclusion, the authors of this trial stated that they, “found no evidence of a difference in progression-free or overall survival between CAP and carboplatin. The absolute difference in 2-year survival was 0%; the 95% CI was sufficiently narrow to allow us to exclude reliably absolute differences in 2-year survival of 4% in favour of carboplatin, and of 6% in favour of CAP. CAP was more toxic than carboplatin. In particular, it caused more alopecia, leucopenia, nausea, and vomiting. More thrombocytopenia occurred with carboplatin.”²⁵

11. Summary of comparative evidence on safety

The American Society of Health-System Pharmacists - AHFS Drug Information (Electronic version: 2007)²⁶ states that, although carboplatin and cisplatin are both platinum compounds and have similar mechanisms of action, their toxicity profiles are different, with carboplatin being better tolerated overall than cisplatin. AHFS Drug Information (Electronic version: 2007)²⁶ states that the major dose-limiting adverse effects associated with cisplatin therapy include non-haematologic toxicities such as nephrotoxicity, ototoxicity, neurotoxicity, and emesis whereas the major dose-limiting adverse effects associated with carboplatin include haematologic toxicities such as thrombocytopenia and leukopenia. The PI for Paraplatin^{®15} presents comparative toxicity data from two prospective randomised trials; (1) National Cancer Institute of Canada, Clinical Trials Group (NCIC), and (2) Southwest Oncology Group (SWOG). These trials included a total of 789 chemotherapy naive patients with advanced ovarian cancer whom were treated with carboplatin or cisplatin, both in combination with cyclophosphamide every 28 days for six courses before surgical reevaluation. A summary of patient characteristics is presented in Table 1.8.

Table 1.8: Summary of patient characteristics for the NCIC and SWOG trials

	NCIC	SWOG
Number of patients randomized	447	342
Median age (years)	60	62
Dose of cisplatin	75 mg/m ²	100 mg/m ²
Dose of carboplatin	300 mg/m ²	300 mg/m ²
Dose of cyclophosphamide	600 mg/m ²	600 mg/m ²
Residual tumor < 2 cm (no. patients)	39% (174/447)	14% (49/342)

Source: Product Information - Paraplatin®¹⁵

As stated in the PI for Paraplatin®:

The pattern of toxicity exerted by the carboplatin containing regimen was significantly different from that of the cisplatin-containing combinations. Differences between the two studies may be explained by different cisplatin dosages and by different supportive care. The carboplatin-containing regimen induced significantly more thrombocytopenia and, in one study, significantly more leukopenia and more need for transfusional support. The cisplatin containing regimen produced significantly more anemia in one study. However, no significant differences occurred in incidences of infections and hemorrhagic episodes. Non-hematologic toxicities (emesis, neurotoxicity, ototoxicity, renal toxicity, hypomagnesemia, and alopecia) were significantly more frequent in the cisplatin-containing arms.¹⁵

A summary of these results are presented in Tables 1.9 and 1.10.

Table 1.9: Adverse Experiences In Patients With Ovarian Cancer - NCIC Study

	Carboplatin Arm	Cisplatin Arm	P-values
	%*	%*	
Bone Marrow			
Thrombocytopenia < 100,000/mm ³	70	29	< 0.001
< 50,000/mm ³	41	6	< 0.001
Neutropenia < 2000 cells/mm ³	97	96	n.s.
< 1000 cells/mm ³	81	79	n.s.
Leukopenia < 4000 cells/mm ³	98	97	n.s.
< 2000 cells/mm ³	68	52	0.001
Anemia < 11 g/dL	91	91	n.s.
< 8 g/dL	18	12	n.s.
Infections	14	12	n.s.
Bleeding	10	4	n.s.
Transfusions	42	31	0.018
Gastrointestinal			
Nausea and vomiting	93	98	0.010
Vomiting	84	97	< 0.001
Other GI side effects	50	62	0.013
Neurologic			
Peripheral neuropathies	16	42	< 0.001
Ototoxicity	13	33	< 0.001
Other sensory side effects	6	10	n.s.
Central neurotoxicity	28	40	0.009
Renal			
Serum creatinine elevations	5	13	0.006
Blood urea elevations	17	31	< 0.001
Hepatic			
Bilirubin elevations	5	3	n.s.
SGOT elevations	17	13	n.s.
Alkaline phosphatase elevations	-	-	-
Electrolytes loss			
Sodium	10	20	0.005
Potassium	16	22	n.s.
Calcium	16	19	n.s.

	Carboplatin Arm %*	Cisplatin Arm %*	P-values
Magnesium	63	88	< 0.001
Other side effects			
Pain	36	37	n.s.
Asthenia	40	33	n.s.
Cardiovascular	15	19	n.s.
Respiratory	8	9	n.s.
Allergic	12	9	n.s.
Genitourinary	10	10	n.s.
Alopecia [†]	50	62	0.017
Mucositis	10	9	n.s.

NS = not statistically significant, $P > 0.05$

* Percentage of evaluable patients

[†] May have been affected by cyclophosphamide dosage delivered.

Source: Product Information - Paraplatin^{®15}

Table 1.10: Adverse Experiences In Patients With Ovarian Cancer - SWOG Study

	Carboplatin Arm %*	Cisplatin Arm %*	P-values
Bone Marrow			
Thrombocytopenia < 100,000/mm ³	59	35	< 0.001
< 50,000/mm ³	22	11	0.006
Neutropenia < 2000 cells/mm ³	95	97	n.s.
< 1000 cells/mm ³	84	78	n.s.
Leukopenia < 4000 cells/mm ³	97	97	n.s.
< 2000 cells/mm ³	76	67	n.s.
Anemia < 11 g/dL	88	87	n.s.
< 8 g/dL	8	24	< 0.001
Infections	18	21	n.s.
Bleeding	6	4	n.s.
Transfusions	25	33	n.s.
Gastrointestinal			
Nausea and vomiting	94	96	n.s.
Vomiting	82	91	0.007
Other GI side effects	40	48	n.s.
Neurologic			
Peripheral neuropathies	13	28	0.001
Ototoxicity	12	30	< 0.001
Other sensory side effects	4	6	n.s.
Central neurotoxicity	23	29	n.s.
Renal			
Serum creatinine elevations	7	38	< 0.001
Blood urea elevations	-	-	-
Hepatic			
Bilirubin elevations	5	3	n.s.
SGOT elevations	23	16	n.s.
Alkaline phosphatase elevations	29	20	n.s.
Electrolytes loss			
Sodium	-	-	-
Potassium	-	-	-
Calcium	-	-	-
Magnesium	58	77	< 0.001
Other side effects			
Pain	54	52	n.s.
Asthenia	43	46	n.s.
Cardiovascular	23	30	n.s.
Respiratory	12	11	n.s.

	Carboplatin Arm %*	Cisplatin Arm %*	P-values
Allergic	10	11	n.s.
Genitourinary	11	13	n.s.
Alopecia†	43	57	0.009
Mucositis	6	11	n.s.

NS = not statistically significant, $P > 0.05$

* Percentage of evaluable patients

† May have been affected by cyclophosphamide dosage delivered.

Source: Product Information - Paraplatin®¹⁵

12. Summary of available data on comparative cost and cost effectiveness within the pharmacological class or therapeutic group

12.1 Global costs of carboplatin

British National Formulary (2007)

Carboplatin (Non-proprietary)

Injection, carboplatin 10 mg/mL, net price 5-mL vial = £22.04, 15-mL vial = £56.29, 45-mL vial = £168.85, 60-mL vial = £260.00.

Paraplatin® (Bristol-Myers Squibb)

Concentrate for intravenous infusion, carboplatin 10 mg/mL, net price 5-mL vial = £21.26, 15-mL vial = £61.22, 45-mL vial = £183.66, 60-mL vial = £244.88.

Australian Pharmaceutical Benefits Scheme (PBS) pricing details (<http://mims.com.au>) – (Australian dollars)

Pack: 50 mg /5 mL x 2 - PBS = \$68.58

Pack: 50 mg /5 mL x 2 - Section 100 CT (Chemotherapy Scheme) PBS = \$53.38

Pack: 150 mg /15 mL x 6 - PBS = \$439.30

Pack: 150 mg /15 mL x 6 - Section 100 CT (Chemotherapy Scheme) PBS = \$386.76

Pack: 450 mg /45 mL x 2 - PBS = \$284.62

Pack: 450 mg /45 mL x 2 - Section 100 - CT (Chemotherapy Scheme) PBS = \$242.92

12.2 Comparative cost effectiveness

Khan *et al.* (1999)²⁷ conducted a prospective, multicentre, cost-minimisation evaluation on the use of carboplatin versus cisplatin in patients with non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), or ovarian cancer. Direct medical resource utilisation and costs associated with carboplatin and cisplatin administration over 3 to 6 courses of treatment were measured and compared. Costs included: medication costs, the cost of emergency room visits, physician/clinic/laboratory visits, home healthcare visits, transfusions, special procedures, consultations, hospitalisations, and other miscellaneous costs. This evaluation was taken from the perspective of the payer. A convenience sample of 16 sites representing a mix of cancer centres, outpatient clinics, managed-care sites and medical centres/private hospitals were selected. Patients were included in the study if they were newly diagnosed with NSCLC, SCLC, or ovarian cancer, had not received prior chemotherapy, received either carboplatin or cisplatin treatment (additional chemotherapy was allowed), and received at least 3 courses of therapy up to a maximum of 6 courses. Discounting was not applied to the data as the collection period did not exceed 12 months. The cost of carboplatin and cisplatin was determined by cost per patient (CPP) and cost per course (CPC) analyses.²⁷

In the case of ovarian cancer only 44 patients met the inclusion criteria (carboplatin n = 32; cisplatin n = 12). The results of this study showed that the overall total CPP associated with

the use of carboplatin was approximately \$US1200 less than that for cisplatin treated patients (\$US12,466.46 versus \$US13,662.55, respectively). The overall total CPC associated with the use of carboplatin was approximately \$30 less than that for cisplatin (\$US2659.49 versus \$US2687.72, respectively). These results are summarised in Table 1.11.

Table 1.11: Overall mean total costs per patient (CPP) and costs per course (CPC)

Resource variable	Mean total PFR and AWP costs (\$US; 1996 values)			
	Carboplatin		Cisplatin	
	CPP	CPC	CPP	CPC
Treatment resource variables	11 955.19	2550.43	11 471.38	2256.67
Toxicity management resource variables	511.27	109.06	2191.17	431.05
Total	12 466.46	2659.49	13 662.55	2687.72

AWP = average wholesale price; PFR = physicians' fee reference

Source: Khan *et al.*(1999)²⁷

As outlined by the authors (Khan *et al.*²⁷), the limitations of this study included: lack of generalisability of the results to settings that differ substantially from the study sites, study sites were not selected at random, sample sizes were small and therefore the power to detect significant differences was low, some patient information may not have been captured due to logistical problems, and the total cost estimates reported did not reflect all costs with the treatment and therefore the estimates are conservative.

Khan *et al.*²⁷ identified three previously published economic evaluations of carboplatin. These were studies conducted by Alberts *et al.* (1994),²⁸ Calvert and Urie (1991),²⁹ and George *et al.* (1989).³⁰ These studies focused on the use and costs of carboplatin versus cisplatin in ovarian cancer. Khan *et al.*²⁷ stated that the study conducted by Alberts *et al.*²⁸ was the only study to have examined the toxicity-related costs in ovarian cancer over several courses of therapy. In this study, retrospective data from a clinical trial were collected and results showed that over time, the total toxicity-related costs for 6 cycles of chemotherapy with carboplatin was \$US1808 less than with cisplatin (combination therapy with cyclophosphamide plus cisplatin or carboplatin). Even after accounting for initial drug costs, the total savings of \$US554 favored carboplatin. Average wholesale price (AWP) was determined from the 1992 Redbook and hospitalisation charge data were based upon analysis of the Medicare Medical Claims Database (MEDPAR). Alberts *et al.*,²⁸ and Calvert and Urie²⁹ claimed that the overall costs were lower for carboplatin while George *et al.*³⁰ suggested that the overall costs were similar. However, Calvert and Urie²⁹ estimated the costs of carboplatin and cisplatin in the treatment of only 4 patients. In addition, patients were treated per study protocol in all three studies. As stated by Khan *et al.*,²⁷ “in a real world everyday treatment setting, research protocols are typically not followed in detail.”

Case *et al.*(2007)³¹ conducted a cost-effectiveness analysis of chemotherapy in patients with recurrent platinum-sensitive advanced epithelial ovarian cancer (EOC) using a decision analysis model in a hypothetical cohort of 10,000 EOC patients (based on 2005 EOC incidence). All patients were initially treated with primary cytoreduction surgery and combination platinum/taxane-based chemotherapy. Chemotherapeutic strategies included: (a) best supportive care (BSC); (b) second-line chemotherapy with a single drug (carboplatin monotherapy); (c) second-line chemotherapy with two drugs (carboplatin/paclitaxel combination therapy); (d) third-line chemotherapy after disease progression on second-line monotherapy or combination therapy; (e) fourth-line chemotherapy after disease progression on second- and third-line chemotherapy. Clinical and survival estimates for each strategy

were calculated from a review of Phase II and III chemotherapy trials. All costs were evaluated from the perspective of a third party payer in 2004 US dollars (USD). Direct costs were estimated by adjusting local charges using a cost-to-charge ratio of 60%. The costs of chemotherapy-related toxicity and complications were not included in the estimates.³¹

BSC consisted of a multi-disciplinary approach with a team of physicians, nurses, healthcare aides, and social workers to address palliative care symptoms. All aspects of outpatient office visits, emergency department visits, hospitalisations, and home health care was included in the costs of BSC. In the second-line monotherapy strategy patients received carboplatin (Paraplatin[®]) at an AUC dose of 5 every 3 weeks for 6 cycles. In combination chemotherapy strategy patients received carboplatin (AUC = 5) and paclitaxel (Taxol[®]) at a dose of 175 mg/m² every 3 weeks for six cycles. In the third-line strategy patients received liposomal doxorubicin (Doxil[®]) monthly at a dose of 40 mg/m² for six cycles. In the fourth-line strategy patients received gemcitabine (Gemzar[®]) at a dose of 1000 mg/m² on day 1 and day 8 for four cycles. The costs of each strategy included chemotherapy costs, infusion costs, laboratory tests, intravenous fluids, and support medications such as antiemetics and steroids. Costs for each individual chemotherapeutic agent were based on the recommended dosage for a patient with a BSA of 1.75.³¹

The cost of BSC was estimated at \$135.50/day resulting in a cost of \$24,390 per patient for 6 months of BSC. The cost of carboplatin in the second-line monotherapy strategy included six cycles of chemotherapy (\$5916), chemotherapy associated costs (\$24,282) and costs of hospice after progression. The total cost of second-line monotherapy was \$40,544 per patient. In the second-line combination chemotherapy strategy six cycles of both drugs and its associated costs totalled \$52,062 per patient. The cost of third-line chemotherapy utilizing liposomal doxorubicin for six cycles was \$5022 per cycle. The total cost of third-line therapy after second-line previous monotherapy was \$62,548 compared to \$74,066 after second-line combination therapy. Both fourth-line strategies utilized gemcitabine with a cost of \$5588 per cycle. Four treatment cycles after second-line monotherapy and third-line chemotherapy yielded a total cost of \$103,187 per patient. Utilizing previous second-line combination therapy plus third-line chemotherapy increased the cost to \$114,705 per patient.³¹ These cost estimates are summarised in Table 1.12.

Table 1.12: Summary of cost estimates

Treatment	Costs (USD\$)
Best supportive care costs	
1 month	4065
Chemotherapy associated costs (per cycle)	
Intravenous infusion	222
Associated infusion fees	378
Laboratory evaluation	151
Intravenous hydration	75
Support medications	1722
Nonmedical associated costs	513
Chemotherapy costs (per cycle)	
Carboplatin	986
Paclitaxel	1920
Liposomal doxorubicin	1961
Gemcitabine	2527

Source: Case *et al.* (2007)³¹

In the study by Case *et al.*³¹ effectiveness was defined as months of overall survival (OS) and costs were calculated as total costs per strategy. The cost-effectiveness (C/E) ratio was

defined as cost per month of survival. The incremental cost–effectiveness ratio (ICER) was calculated as the costs per life year saved (LYS). The incremental costs, incremental survival, and ICER for a given strategy were compared to the next most favorable strategy.

The results of this study showed that, compared to BSC, second-line monotherapy gained an additional 8 months of OS. This strategy demonstrated an ICER of \$24,228 per life year saved (LYS). This strategy was also noted to have the lowest cost-effectiveness ratio at \$2896. Second-line combination chemotherapy compared to monotherapy gained an additional 3 months of OS and demonstrated an ICER of \$46,068 per LYS. The third- and fourth-line strategies were associated with substantial costs with marginal improvements in survival.³¹ These results are summarised in Tables 1.13 and 1.14.

Table 1.13: Results of cost-effectiveness analysis

Strategy	Total cost (USD\$) ^a	OS (months)	C/E ratio (per month OS, \$)
Best supportive care	244 M	6	4065
Second-line monotherapy	405 M	14	2896
Second-line combination	521 M	17	3062
Third-line previous monotherapy	625 M	18	3475
Third-line previous combination	741 M	21	3527
Fourth-line previous monotherapy	1032 M	21	4914
Fourth-line previous combination	1147 M	24	4779

USD = US dollars, OS = overall survival, C/E ratio = cost–effectiveness ratio, M = million.

^a Per 10,000 patients

Source: Source: Case *et al.*(2007)³¹

Table 1.14: Incremental costs and effectiveness^a

Strategy ^b	Incremental cost (USD\$) ^c	Incremental OS (months)	ICER (cost/LYS, \$)
Best supportive care	n/a	n/a	n/a
Second-line monotherapy	161 M	8	24,228
Second-line combination	116 M	3	46,068
Third-line previous combination	220 M	4	66,012
Fourth-line previous combination	406 M	3	162,552

USD = US dollars, OS = overall survival, ICER = incremental cost–effectiveness ratio, M = million.

^a For each strategy the incremental results (cost, OS, and ICER) are compared to the previous strategy or next best strategy. For example, second-line combination is compared to second-line monotherapy.

^b Third- and fourth-line previous monotherapy strategies were dominated by the other strategies.

^c Per 10,000 patients

Source: Source: Case *et al.*(2007)³¹

The NICE Technology Appraisal Guidance – No. 55⁹ identified 11 cost-effectiveness analyses and three cost-utility analyses on the first-line use of paclitaxel. As stated in this document all analyses were based on trials favouring paclitaxel (i.e. GOG111 or OV10), and therefore found the paclitaxel/platinum combination to be more costly and more effective than control treatments. Appraisal of these economic analyses by NICE are as follows:

- Two published UK cost-effectiveness analyses found that the incremental cost per life-year gained for paclitaxel/platinum ranged between £7173 and £12,417, depending on the effectiveness trial results and drug doses applied. One of the studies reported the incremental cost per progression-free life-year gained to be between £20,084 and £22,021, again depending on the trial results applied.
- One published UK cost-utility analysis was available, but its methods were not well reported, and its results need to be interpreted with caution. An incremental cost-utility estimate based

on this analysis, for paclitaxel/platinum compared with carboplatin alone, showed the incremental cost per quality-adjusted life year to be £5273.

- A cost-effectiveness analysis undertaken by the manufacturer of paclitaxel was also available. The analysis was based on resource use and outcomes from GOG111, though carboplatin was substituted as the control treatment, as this better reflects UK practice. Consequently the analysis assumed equivalent efficacy between carboplatin and cisplatin in combination with paclitaxel. UK unit costs were incorporated from routine sources, and included: chemotherapy drugs, pre-medication, drug administration, management of febrile neutropenia, and other inpatient and outpatient care. For the paclitaxel/carboplatin combination vs carboplatin alone, the analysis reported an incremental cost of £7074 per life-year gained and £10,808 per progression-free life-year gained.
- Given that this analysis was based on the survival in the most favourable survival findings available (that is, a hazard ratio of 0.61 in favour of paclitaxel/platinum combination for overall survival), sensitivity analyses were undertaken by NICE to indicate the likely magnitude of effect on the cost-effectiveness ratio of changing the survival gains attributed to paclitaxel/platinum. Simply adjusting the manufacturer's analysis to the survival difference reported by ICON3 (hazard ratio of 0.96) suggests an incremental cost per life-year gained in the region of £45,000. However, other NICE analyses undertaken by NICE suggest that the cost per life-year gained could be much higher.

13. Summary of regulatory status of the medicine (in country of origin, and preferably in other countries as well)

As stated previously, carboplatin is used in the treatment of a wide range of cancers, however it has only gained regulatory approval for the treatment of advanced ovarian carcinoma of epithelial origin, alone or in combination regimens (United States FDA approved,¹ Australia TGA approved,¹⁴ Health Canada Therapeutic Products Programme approved¹²).

14. Availability of pharmacopoeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia)

British Pharmacopoeia: Yes (2007, *British National Formulary*, 53 ed.)

International Pharmacopoeia: Yes (2007, Martindale: The Complete Drug Reference)

United States Pharmacopoeia: Yes

15. Proposed (new/adapted) text for the WHO Model Formulary

Information sourced from MIMS Australia Pty Ltd 2003 (<http://www.mims.com.au>)

Indications

Treatment of advanced ovarian carcinoma of epithelial origin.

Contraindications

Contraindications include, pre-existing severe renal impairment, severe myelosuppression, hypersensitivity to carboplatin or platinum containing compounds, and during pregnancy or lactation.

Precautions

Carboplatin should be administered only under constant supervision by doctors experienced in therapy with cytotoxic agents and only when potential benefits of carboplatin therapy outweigh the possible risks. Appropriate facilities should be available for adequate management of complications should they arise.

Myelosuppression: Myelosuppression associated with carboplatin is closely related to the renal clearance of the drug, therefore, patients with impaired renal function are more susceptible. Myelosuppression, particularly thrombocytopenia (reduction in platelet count), will also be more severe in patients receiving concomitant therapy with other nephrotoxic drugs such as aminoglycoside antibiotics. Toxicity is more likely to be prolonged and more severe in patients who have undergone previous chemotherapy, are more advanced in age or who are debilitated. Dosage reductions may be necessary in these cases.

The nadir for platelets (peak detrimental effect) is usually between days 14 to 21 following initial treatment and days 14 to 28 for white blood cells. Minimum counts should be 50,000/mm³ for platelets and 2,000/mm³ for white blood cells. If counts fall below this level, therapy should be suspended until recovery is complete, usually five to six weeks. Supportive transfusional therapy may be necessary in severe cases. It is important, therefore, that the assessment of renal function and peripheral blood counts (including white blood cells, platelets and haemoglobin) be made prior to, during and following treatment with carboplatin. In order to ensure that the peak detrimental effect on blood cells has occurred, repeat courses of treatment with carboplatin should not be given more frequently than monthly under normal circumstances.

Nephrotoxicity: Renal toxicity is not usually dose limiting. Unlike cisplatin therapy, pretreatment and post-treatment hydration is not necessary, although some patients may show a decrease in creatinine clearance. Renal impairment is more likely to be seen in patients who have previously experienced nephrotoxicity as a result of chemotherapy.

Neurotoxicity: Neurological evaluations and auditory monitoring should be performed regularly during and after carboplatin therapy.

Ototoxicity: Ototoxicity is cumulative and frequency and severity of hearing disorder increases with high dose regimens and repeated doses, or prior treatment with cisplatin (also ototoxic). Auditory function should be monitored during treatment.

Carcinogenesis, mutagenesis, impairment of fertility: Animal studies demonstrate that carboplatin is mutagenic and teratogenic. The carcinogenic potential of carboplatin has not been studied, however, compounds with a similar mechanism of action have been reported to be carcinogenic.

Use in pregnancy

Carboplatin has been shown to be embryotoxic and mutagenic, and its use in pregnant women is not recommended. Women of childbearing potential should use adequate contraception, and carboplatin should only be used in women of childbearing potential if the expected benefits outweigh the risks of such therapy. If the patient becomes pregnant while receiving the drug she should be advised of the potential hazard to the fetus.

Use in lactation

It is not known whether or not carboplatin is excreted in breast milk so breastfeeding should be discontinued during carboplatin therapy in lactating women.

Adverse reactions

Myelosuppression: Haematological toxicity is the most common dose limiting toxicity, with leucopenia in 55% of patients, thrombocytopenia in 62% of patients and anaemia in up to

59% of patients. When used as single agent therapy, toxicity is not usually cumulative and is reversible, although transfusional therapy may be necessary in severe cases.

Nephrotoxicity: Manifests as reduced creatinine clearance, elevated serum creatinine, blood urea nitrogen and uric acid levels.

Gastrointestinal effects: Nausea and vomiting. Onset may be delayed for 6 to 12 hours after administration of carboplatin and usually disappears within 24 hours. Antiemetic medication can be used to adequately control these effects. Diarrhoea and constipation have been reported with carboplatin therapy.

Hepatotoxicity: Abnormalities of liver function tests have been reported in up to 30% of patients. These changes are normally only transient in nature and disappear spontaneously.

Ototoxicity: Manifests as tinnitus and hearing loss in the higher frequency range. Hearing impairment may persist or worsen with carboplatin therapy.

Allergic reactions: Erythematous rash, fever and pruritus may occur (< 2% of patients).

Neurotoxicity: In the majority of patients, neurotoxicity manifests mainly as paraesthesiae and decreased deep tendon reflexes. Pre-existing paraesthesiae (especially those related to previous cisplatin treatment) may worsen during carboplatin therapy.

Electrolyte disturbances: Decreases in magnesium, potassium and calcium levels have occurred but are usually not severe enough to produce clinical symptoms.

Others: Alopecia (2%), flu-like symptoms (1%) and reactions at injection site (< 1%).

Interactions

The combination of carboplatin therapy and other myelosuppressive agents may warrant dosage adjustments in order to avoid cumulative toxic effects. Due to the possibility of impairment in renal function, it is recommended that carboplatin therapy be avoided in patients receiving aminoglycoside antibiotics or other nephrotoxic drugs.

Carboplatin interacts with the aluminium containing components of needles, syringes, catheters and intravenous administration sets to form a black precipitate so these items should not be used for the administration of carboplatin injections.

Dosage and administration

The recommended dosage for previously untreated adults (with normal renal function) is 400 mg/m² as a single intravenous infusion over 15 to 60 minutes. Dilutions may be made in glucose 5% intravenous infusion to concentrations as low as 0.1 mg/mL. The product and admixture contain no antimicrobial agent. In order to reduce microbiological hazards it is recommended that further dilution should be effected immediately prior to use and infusion commenced as soon as practicable after preparation of the admixture. Infusion should be completed within 24 hours of preparation and any residue discarded. Therapy should not be repeated again until four weeks have elapsed. In patients with risk factors, such as previous myelosuppressive therapy or in the aged, the initial dosage may need to be reduced by 20 to 25%. Determination of the haematological nadir by weekly blood counts is recommended for adjusting future doses and scheduling of carboplatin therapy.

Renal impairment: As carboplatin is excreted by the kidney and is nephrotoxic, the optimum dosage should be determined by frequent monitoring of the haematological nadir and renal function. The suggested dosage schedule for patients with impaired renal function based on creatinine clearance is as follows. For creatinine clearance (ClCr) > 40 mL/minute, carboplatin dose is 400 mg/m². For ClCr 20 to 39 mL/minute dose is 250 mg/m². For ClCr 0 to 19 mL/minute dose is 150 mg/m².

Paediatric: Insufficient information is available to make specific recommendations.

Combination therapy: Carboplatin has been used in combination with other antineoplastic agents and the dosage varies according to the protocol used. Dosage adjustments should be made according to the treatment regimen adopted and the results obtained from haematological monitoring.

Handling precautions: As with all antineoplastic agents, trained personnel should prepare Carboplatin Injection. This should be performed in a designated area (preferably a cytotoxic laminar flow cabinet). Protective gown, mask, gloves and appropriate eye protection should be worn when handling carboplatin. Where solution accidentally contacts skin or mucosa, the affected area should be immediately washed thoroughly with soap and water. It is recommended that pregnant personnel not handle cytotoxic agents such as carboplatin. Luer-Lok fitting syringes are recommended. Large bore needles are recommended to minimise pressure and possible formation of aerosols. Aerosols may also be reduced by using a venting needle during preparation. Items used to prepare carboplatin or articles associated with body waste should be disposed of by placing in a double sealed polythene bag and incinerating at 1,100 deg. C.

Spills and disposal: If spills occur, restrict access to the affected area. Wear two pairs of gloves (latex rubber), a respirator mask, a protective gown and safety glasses. Limit the spread of the spill by covering with a suitable material such as absorbent towel or adsorbent granules. Spills may also be treated with 3 M sulfuric acid with 0.3 M potassium permanganate (2:1) or sodium hypochlorite 5%. Collect up absorbent/ adsorbent material and other debris from spill and place in a leak proof plastic container and label accordingly. Cytotoxic waste should be regarded as hazardous or toxic and clearly labelled 'Cytotoxic waste for incineration at 1,100 deg. C'. Waste material should be incinerated at 1,100 deg. C for at least one second. Cleanse the remaining spill area with copious amounts of water.

Overdosage

The patient may need to be sustained through complications relating to myelosuppression, renal and hepatic impairment. Diarrhoea and alopecia may develop.

Reference List

- 1 CARBOPLATIN - DRUGDEX[®] Evaluations. *Thomson MICROMEDEX 1974-2006*. 2006.
- 2 Stewart BW, Kleihues P. (Eds). *World Cancer Report*. IARC Press. Lyon. 2003.
- 3 Globocan 2002. *International Agency for Research on Cancer*. 2002.
- 4 Cancer - Fact Sheet No.297. World Health Organisation. February. 2006.
- 5 Global Action Against Cancer - Updated Edition. World Health Organisation. 2005.
- 6 Parkin DM, Bray F, Ferlay J, Pisani P. *et al*. Global cancer statistics, 2002. *CA Cancer J Clin*. 2005; 55(2): 74-108.
- 7 Morgan RJJ, Alvarez RD, Armstrong DK, Chen LM, Copeland L, Fowler J, *et al*. Ovarian cancer: Clinical Practice Guidelines in Oncology[™]. *Journal of the National Comprehensive Cancer Network*. 2007; V.1(9): 912-939.
- 8 National Institute for Clinical Excellence (NICE). Paclitaxel, pegylated liposomal doxorubicin hydrochloride and topotecan for second-line or subsequent treatment of advanced ovarian cancer. Technology Appraisal 91. 2005.
- 9 National Institute for Clinical Excellence (NICE). Guidance on the use of paclitaxel in the treatment of ovarian cancer. Technology Appraisal Guidance - No. 55. 2003.
- 10 Bast RC, Jr. Status of tumor markers in ovarian cancer screening. [Review] [44 refs]. *J Clin Oncol*. 2003; 21(10 Suppl): 200s-205s.
- 11 Alberts DS, Dorr RT. New perspectives on an old friend: Optimizing carboplatin for the treatment of solid tumors. *Oncologist*. 1998; 3(1): 15-34.
- 12 Carboplatin - Paraplatin[®] (Limited revision: May 2007). <http://www.bccancer.bc.ca/HPI/DrugDatabase/DrugIndexPro/carboplatin.htm>.
- 13 MIMS Online. Carboplatin Injection. 2007. <http://mims.com.au>.
- 14 Rossi S (Ed.). Carboplatin - Australian Medicines Handbook (Electronic edition - 2007).
- 15 Bristol-Myers Squibb. Product Information - Paraplatin[®] (carboplatin) Injection. *Product Information - Paraplatin[®] (carboplatin) Injection*. Revised January, 2004.
- 16 B.C.Cancer Agency. Gynecology Chemotherapy Protocols. 2007. <http://www.bccancer.bc.ca/HPI/ChemotherapyProtocols/Gynecology/default.htm>.

- 17 Dickersin K, Larson K. Establishing and maintaining an international register of RCTs. In: The Cochrane Library. Oxford: Update Software, 1996. Appendix 5c. Optimal Search Strategy for RCTS. Cochrane Collaboration.
- 18 Chemotherapy in advanced ovarian cancer: an overview of randomised clinical trials. Advanced Ovarian Cancer Trialists Group.[see comment]. *BMJ*. 1991; 303(6807): 884-893.
- 19 Aabo K, Adams M, Adnitt P, Alberts DS, Athanazziou A, Barley V et al. Chemotherapy in advanced ovarian cancer: four systematic meta-analyses of individual patient data from 37 randomized trials. Advanced Ovarian Cancer Trialists' Group. *Br J Cancer*. 1998; 78(11): 1479-1487.
- 20 Advanced Ovarian Cancer Trialists Group. Chemotherapy for advanced ovarian cancer. *Cochrane Database of Systematic Reviews: Reviews 1999 Issue 1 John Wiley & Sons, Ltd Chichester, UK DOI: 101002/14651858CD001418*.
- 21 Trope C, Kaern J, Hogberg T, Abeler V, Hagen B, Kristensen G, et al. Randomized study on adjuvant chemotherapy in stage I high-risk ovarian cancer with evaluation of DNA-ploidy as prognostic instrument. *Ann Oncol*. 2000; 11: 281-288.
- 22 Neijt JP, Engelholm SA, Tuxen MK, et al. Exploratory phase III study of paclitaxel and cisplatin versus paclitaxel and carboplatin in advanced ovarian cancer. *J Clin Oncol*. 2000; 18(17): 3084-3092.
- 23 Ozols RF, Bundy BN, Greer BE, Fowler JM, et al. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: A Gynecologic Oncology Group Study. *J Clin Oncol*. 2003; 21(17): 3194-3200.
- 24 du Bois A, Luck HJ, Meier W, Adams H-P, et al. A randomized clinical trial of cisplatin/paclitaxel versus carboplatin/paclitaxel as first-line treatment of ovarian cancer. *J Natl Cancer Inst*. 2003; 95(17): 1320-1330.
- 25 ICON Collaborators. ICON2: randomised trial of single-agent carboplatin against three-drug combination of CAP (cyclophosphamide, doxorubicin, and cisplatin) in women with ovarian cancer. International Collaborative Ovarian Neoplasm Study.[see comment]. *Lancet*. 1998; 352(9140): 1571-1576.
- 26 American Society of Health-System Pharmacists. Carboplatin - AHFS Drug Information, Bethesda, MD 20814. 2007.
<http://www.medicinescomplete.com/mc/ahfs/2007/a395034.htm>.
- 27 Khan ZM, Rascati KL, Koeller JM. Economic analysis of carboplatin versus cisplatin in lung and ovarian cancer. *Pharmacoeconomics*. 1999; 16(1): 43-57.

- 28 Alberts DH, Hannigan E, Canetta R, *et al.* Cisplatin versus carboplatin in advanced ovarian cancer: An economic analysis. *P and T*. 1994; 19(7): 692-706.
- 29 Calvert AH, Urie J. The costs of carboplatin treatment. *Semin Oncol*. 1991;(1 SUPPL. 2): 28-31.
- 30 George MJ, Lenfant-Pejovic MH, Lhomme C. Comparative costs of two chemotherapy regimens: cyclophosphamide (C) and cisplatin (P) vs C and carboplatin (JM8) in advanced ovarian cancer (OC) [abstract 598. *Proceedings of the American Society of Clinical Oncology*. 1989; 8: 154.
- 31 Case AS, Rocconi RP, Partridge EE, Straughn JM, Jr. A cost-effectiveness analysis of chemotherapy for patients with recurrent platinum-sensitive epithelial ovarian cancer. *Gynecol Oncol*. 2007; 105(1): 223-227.

Appendix A

DRUGDEX[®] Tradename List	
Tradename list for: CARBOPLATIN	
Name, Form & Strength	Contact
Biocarbo	Biosintetica, Braz.
Biplatinex	Biogalenic, Venez.
Blastocarb (FM)	Laboratorios Chile, Chile
Blastocarb	Lemery, Mex.
Blastocarb	Lemery, Thai.
Boplatex	Pisa, Mex.
B-Platin	Blausiegel, Braz.
Carbo-cell	Cell Pharm, Ger.
Carbomedac	Medac, Ger.
Carboplat	Asofarma, Mex.
Carboplat	BMS, Ger.
Carboplatin - 10 MG/ML - Intravenous Solution	Abraxis Pharmaceutical Products
Carboplatin - 10 MG/ML - solution for injection	Mayne Pharma
Carboplatin - 10 MG/ML - Intravenous Solution	Hospira
Carboplatin - 10 MG/ML - Intravenous Solution	Hospira
Carboplatin - 10 MG/ML - Intravenous Solution	OTN Generics
Carboplatin - 10 MG/ML - Intravenous Solution	Sicor Pharmaceuticals
Carboplatin - 10 MG/ML - Intravenous Solution	OTN Generics
Carboplatin - 10 MG/ML - Intravenous Solution	Watson Laboratories
CARBOplatin - 50 MG - Intravenous Powder for Solution	Teva Pharmaceuticals
CARBOplatin - 150 MG - Intravenous Powder for Solution	Teva Pharmaceuticals
CARBOplatin - 450 MG - Intravenous Powder for Solution	Teva Pharmaceuticals
Carboplatin for Injection USP 29	
Carboplatin Injection - 10 MG/ML - solution for injection	Novopharm
Carboplatin Injection BP 2005	
Carbosin (FM)	Asta Medica, NZ
Carbosin (FM)	Nettopharma, Denm.
Carbosin (FM)	Nycomed, Fin.
Carbosin	Chemipharma, Gr.
Carbosin	Er-Kim, Turk.

DRUGDEX[®] Tradename List	
Tradename list for: CARBOPLATIN	
Name, Form & Strength	Contact
Carbosin	Nycomed, Norw.
Carbosin	Pharmachemie, Neth.
Carbosin	Pharmachemie, S.Afr.
Carbosin	Pharmachemie, Thai.
Carbosin	Teva, Belg.
Carbosol	Sanova, Austria
Carbotec	Columbia, Mex.
Cycloplatin	Lachema, Cz.
Cycloplatin	Pliva, Hung.
Displata (FM)	Serono, Mex.
Displata	Itaca, Braz.
Emorzim	Pfizer, Gr.
Ercar (FM)	Almirall, Spain
Evocarb	Sinterapico, Braz.
Ifacap (FM)	Andromaco, Mex.
Kemocarb	Dabur, Thai.
Megaplatin	Genepfarm, Gr.
Nealorin (FM)	Probios, Port.
Nealorin	Prasfarma, Spain
Neocarbo	Neocorp, Ger.
Novoplat	Pfizer, Mex.
Novoplatinum	Faulding, Port.
Oncocarb	Asta Oncologia, Braz.
Paraplatin - 50 MG/5 ML - Intravenous Solution	Bristol-Myers Squibb
Paraplatin - 150 MG/15 ML - Intravenous Solution	Bristol-Myers Squibb
Paraplatin - 150 MG/20 ML - Injection lyophilized powder	Bristol-Myers Squibb
Paraplatin - 450 MG/45 ML - Intravenous Solution	Bristol-Myers Squibb
Paraplatin Aq - 10 MG/ML - solution for injection	Bristol-Myers Squibb
Paraplatine	BMS, Fr.
Paraplatin (FM)	BMS, Austral.
Paraplatin (FM)	BMS, Neth.
Paraplatin	BMS, Austria
Paraplatin	BMS, Belg.
Paraplatin	BMS, Braz.
Paraplatin	BMS, Chile
Paraplatin	BMS, Cz.

DRUGDEX® Tradename List	
Tradename list for: CARBOPLATIN	
Name, Form & Strength	Contact
Paraplatin	BMS, Denm.
Paraplatin	BMS, Fin.
Paraplatin	BMS, Gr.
Paraplatin	BMS, Hong Kong
Paraplatin	BMS, Hung.
Paraplatin	BMS, Irl.
Paraplatin	BMS, Ital.
Paraplatin	BMS, Malaysia
Paraplatin	BMS, Mex.
Paraplatin	BMS, Norw.
Paraplatin	BMS, NZ
Paraplatin	BMS Oncology, USA
Paraplatin	BMS, Port.
Paraplatin	BMS, S.Afr.
Paraplatin	BMS, Singapore
Paraplatin	BMS, Spain
Paraplatin	BMS, Swed.
Paraplatin	BMS, Chile
Paraplatin	BMS, Switz.
Paraplatin	BMS, Thai.
Paraplatin	BMS, Turk.
Paraplatin	BMS, UK
Paraplatin	Bristol, Canad.
Paraplatin Vha Plus - 50 MG - powder for injection	Bristol-Myers Oncology
Paraplatin Vha Plus - 150 MG - powder for injection	Bristol-Myers Oncology
Paraplatin Vha Plus - 450 MG - powder for injection	Bristol-Myers Oncology
Platamine (DI)	Pharmacia, Braz.
Platicarb	Eurofarma, Braz.
Platinwas	Chiesi, Spain
Platinwas	Farma-Tek, Turk.
Ribocarbo	Ribosepharm, Ger.
Tecnocarb	Zodiac, Braz.
Martindale Products	
Tradename List for: CARBOPLATIN	
Name, Form & Strength	Contact
B-Platin (Blausiegel, Braz.)	Blausiegel, Braz. Blausiegel Industria e Comercio Ltda
Biocarb (Biochem, India)	Biochem, India Biochem Pharmaceutical Industries

Martindale Products	
Tradename List for: CARBOPLATIN	
Name, Form & Strength	Contact
Biocarbo (Biosintetica, Braz.)	Biosintetica, Braz. Laboratorios Biosintetica Ltda
Biplatinex (Biogalenic, Venez.)	Biogalenic, Venez. Laboratorios Biogalenic C.A.
Blastocarb (Laboratorios Chile, Chile)(FM)	Laboratorios Chile, Chile Laboratorios Chile SA
Blastocarb (Lemery, Mex.)	Lemery, Mex. Lemery S.A. de C.V.
Blastocarb (Lemery, Rus.)	Lemery, Rus.
Blastocarb (Lemery, Thai.)	Lemery, Thai.
Boplatex (Pisa, Mex.)	Pisa, Mex. Laboratorios Pisa S.A. de C.V.
Carbo-cell (Cell Pharm, Ger.)	Cell Pharm, Ger. cell pharm Gesellschaft fur pharmazeutische und diagnostische Präparate mbH
Carbokebir (Aspen, Arg.)	Aspen, Arg. Lab. Aspen S.A.
Carbomedac (Medac, Ger.)	Medac, Ger. medac Gesellschaft fur klinische Spezialpräparate mbH
Carboplat (Asofarma, Mex.)	Asofarma, Mex. Asofarma de Mexico S.A. de C.V.
Carboplat (BMS, Ger.)	BMS, Ger. Bristol-Myers Squibb GmbH
Carboplat (Pfizer, Arg.)	Pfizer, Arg. Pfizer S.R.L.
Carboplatin Injection BP 2005	
Carboplatin for Injection USP 29	
Carbosin (Asta Medica, NZ ; NZ Medical & Scientific, NZ)(FM)	Asta Medica, NZ
Carbosin (Nettopharma, Denm.)(FM)	Nettopharma, Denm.
Carbosin (Nycomed, Fin.)(FM)	Nycomed, Fin.
Carbosin (Chemipharma, Gr.)	Chemipharma, Gr. Iasis Chemipharma A.E.
Carbosin (Er-Kim, Turk.)	Er-Kim, Turk. Er-Kim Ilac San. ve Tic. Ltd. Sti.
Carbosin (Nycomed, Norw.)	Nycomed, Norw. Nycomed Pharma AS
Carbosin (Pharmachemie, Neth.)	Pharmachemie, Neth. Pharmachemie BV
Carbosin (Pharmachemie, S.Afr.)	Pharmachemie, S.Afr. Pharmachemie (Pty) Ltd
Carbosin (Pharmachemie, Thai.; Teva, Thai.)	Pharmachemie, Thai.
Carbosin (Teva, Belg.)	Teva, Belg. Teva Belgium
Carbosol (Sanova, Austria)	Sanova, Austria Sanova Pharma GmbH
Carbotec (Columbia, Mex.)	Columbia, Mex. Laboratorios Columbia, S.A. de C.V.
Carboxtie (Bioprofarma, Arg.)	Bioprofarma, Arg. Bioprofarma SA
Cycloplatin (Lachema, Cz.)	Lachema, Cz.
Cycloplatin (Pliva, Hung.)	Pliva, Hung. Pliva d d Magyarországi Kereskedelmi Képviselete
Cycloplatin (Pliva, Rus.)	Pliva, Rus. Pliva AO
Cytocarb (Cipla, India)	Cipla, India Cipla Ltd
Displata (Serono, Mex.)(FM)	Serono, Mex. Serono de Mexico S.A. de C.V.
Displata (Itaca, Braz.)	Itaca, Braz. Itaca Laboratorios Ltda

Martindale Products	
Tradename List for: CARBOPLATIN	
Name, Form & Strength	Contact
Emorzim (Pfizer, Gr.)	Pfizer, Gr. Pfizer
Ercar (Almirall, Spain)(FM)	Almirall, Spain Almirall Prodesfarma S.A.
Evocarb (Sinterapico, Braz.)	Sinterapico, Braz. Laboratorio Sinterapico Industrial e Farmaceutico Ltda
Ifacap (Andromaco, Mex.)(FM)	Andromaco, Mex. Industria Farmaceutica Andromaco, S.A. de C.V.
Kemocarb (Dabur, India)	Dabur, India Dabur Pharmaceuticals Ltd
Kemocarb (Dabur, Thai.)	Dabur, Thai.
Megaplatin (Genepharma, Gr.)	Genepharma, Gr. Genepharma Group A.E.
Nealorin (Probios, Port.)(FM)	Probios, Port. Probios, Lda
Nealorin (Prasfarma, Spain)	Prasfarma, Spain
Neocarbo (Neocorp, Ger.)	Neocorp, Ger. Neocorp AG
Novoplat (Pfizer, Mex.)	Pfizer, Mex. Pfizer S.A. de C.V.
Novoplatinum (Faulding, Port.)	Faulding, Port. Faulding Farmaceutica, Lda
Omilipis (Richmond, Arg.)	Richmond, Arg. Lab. Richmond
Oncocarb (Asta Oncologia, Braz.)	Asta Oncologia, Braz. Asta Medica Oncologia Ltda
Paraplatin (BMS, Austral.)(FM)	BMS, Austral. Bristol-Myers Squibb, Division of Bristol-Myers Australia P/L
Paraplatin (BMS, Israel)(FM)	BMS, Israel Bristol-Myers Squibb Ltd
Paraplatin (BMS, Neth.)(FM)	BMS, Neth. Bristol-Myers Squibb
Paraplatin (BMS Oncology, USA)	BMS Oncology, USA
Paraplatin (BMS, Arg.)	BMS, Arg. Bristol-Myers Squibb Argentina S.A.
Paraplatin (BMS, Austria)	BMS, Austria Bristol-Myers Squibb GmbH
Paraplatin (BMS, Belg.)	BMS, Belg. Bristol-Myers Squibb Belgium SA
Paraplatin (BMS, Braz.)	BMS, Braz. Bristol-Myers Squibb Farmaceutica Ltda
Paraplatin (BMS, Chile)	BMS, Chile Bristol-Myers Squibb
Paraplatin (BMS, Cz.)	BMS, Cz. Bristol-Myers Squibb sro
Paraplatin (BMS, Denm.)	BMS, Denm. Bristol-Myers Squibb
Paraplatin (BMS, Fin.)	BMS, Fin. Oy Bristol-Myers Squibb (Finland) AB
Paraplatin (BMS, Gr.)	BMS, Gr. Bristol-Myers Squibb
Paraplatin (BMS, Hong Kong)	BMS, Hong Kong Bristol-Myers Squibb (Hong Kong) Ltd
Paraplatin (BMS, Austral.)(FM)	BMS, Austral. Bristol-Myers Squibb, Division of Bristol-Myers Australia P/L
Paraplatin (BMS, Israel)(FM)	BMS, Israel Bristol-Myers Squibb Ltd
Paraplatin (BMS, Neth.)(FM)	BMS, Neth. Bristol-Myers Squibb
Paraplatin (BMS, Hung.)	BMS, Hung. Bristol-Myers Squibb Gyogyszerkereskedelmi Kft
Paraplatin (BMS, Irl.)	BMS, Irl. Bristol-Myers Squibb Pharmaceuticals
Paraplatin (BMS, Ital.)	BMS, Ital. Bristol-Myers Squibb S.r.l.
Paraplatin (BMS, Malaysia)	BMS, Malaysia Bristol-Myers Squibb (Malaysia)

Martindale Products	
Tradename List for: CARBOPLATIN	
Name, Form & Strength	Contact
	Sdn Bhd
Paraplatin (BMS, Mex.)	BMS, Mex. Bristol-Myers Squibb de Mexico S. de R.L. de C.V.
Paraplatin (BMS, NZ)	BMS, NZ Bristol-Myers Squibb
Paraplatin (BMS, Norw.)	BMS, Norw. Bristol-Myers Squibb Norway Ltd
Paraplatin (BMS, Port.)	BMS, Port. Bristol-Myers Squibb Farmaceutica Portuguesa, Lda
Paraplatin (BMS, Rus.)	BMS, Rus. Bristol-Myers Squibb
Paraplatin (BMS, S.Afr.)	BMS, S.Afr. Bristol-Myers Squibb (Pty) Ltd
Paraplatin (BMS, Singapore)	BMS, Singapore Bristol-Myers Squibb (S) Pte Ltd
Paraplatin (BMS, Spain)	BMS, Spain Bristol Myers Squibb Espana
Paraplatin (BMS, Swed.)	BMS, Swed. Bristol-Myers Squibb AB
Paraplatin (BMS, Switz.)	BMS, Switz. Bristol-Myers Squibb AG
Paraplatin (BMS, Ital.)	BMS, Ital. Bristol-Myers Squibb S.r.l.
Paraplatin (BMS, Thai.)	BMS, Thai. Bristol-Myers Squibb (Thailand) Ltd
Paraplatin (BMS, Turk.)	BMS, Turk. Bristol-Myers Squibb Ilaclari Ltd. Sti.
Paraplatin (BMS, UK)	BMS, UK Bristol-Myers Squibb Pharmaceuticals Ltd
Paraplatin (Bristol, Canad.)	Bristol, Canad.
Paraplatine (BMS, Fr.)	BMS, Fr. Bristol-Myers Squibb
Platamine (Pharmacia, Braz.)(DI)	Pharmacia, Braz. Pharmacia Brasil Ltda
Platicarb (Eurofarma, Braz.)	Eurofarma, Braz. Eurofarma Laboratorios Ltda
Platinwas (Chiesi, Spain)	Chiesi, Spain Chiesi Espana
Platinwas (Farma-Tek, Turk.)	Farma-Tek, Turk. Farma-Tek Ilac Ltd. Sti.
Ribocarbo (Ribosepharm, Ger.)	Ribosepharm, Ger. ribosepharm GmbH
Tecnocarb (Zodiac, Braz.)	Zodiac, Braz. Zodiac Prods. Farms. S.A.

Appendix B

Database: Ovid MEDLINE(R) 1950 to Present with Daily Update

Search Strategy:

```
-----  
1      exp Carboplatin/ (5900)  
2      carboplatin.mp. (7772)  
3      cis-Diammine cyclobutane-1, 1-dicarboxylato platinum.mp. (1)  
4      (paraplatin or biocarb or biocarbo or bioplatinex or blastocarb or  
boplatex or B-Platin or carbo-cell or carbokebir or carbomedac or carboplat  
or carbosin or carbosol or carbotec or carboxtie or cycloplatin or  
cytocab or displata or emorzim or ercar or evocab or ifacap or kemocab  
or megaplatin or nealorin or neocab or novoplat or novoplatinum or  
omilipis or onocab or paraplatine or platamine or platicarb or platinwas  
or ribocarbo or tecnocab or CBDCA).mp. (693)  
5      or/1-4 (7853)
```

Database: Ovid MEDLINE(R) 1950 to Present with Daily Update

Search Strategy:

```
-----  
1      exp Carboplatin/ (5900)  
2      carboplatin.mp. (7772)  
3      cis-Diammine cyclobutane-1, 1-dicarboxylato platinum.mp. (1)  
4      (paraplatin or biocarb or biocarbo or bioplatinex or blastocarb or  
boplatex or B-Platin or carbo-cell or carbokebir or carbomedac or carboplat  
or carbosin or carbosol or carbotec or carboxtie or cycloplatin or  
cytocab or displata or emorzim or ercar or evocab or ifacap or kemocab  
or megaplatin or nealorin or neocab or novoplat or novoplatinum or  
omilipis or onocab or paraplatine or platamine or platicarb or platinwas  
or ribocarbo or tecnocab or CBDCA).mp. (693)  
5      or/1-4 (7853)  
6      exp Meta-Analysis/ (7675)  
7      meta-analys$.mp. (28638)  
8      systematic review$.mp. (11806)  
9      critical review$.mp. (6752)  
10     cochrane review$.mp. (539)  
11     literature review$.mp. (19784)  
12     overview$.mp. (46076)  
13     or/6-12 (106455)  
14     5 and 13 (167)
```

WHO EML – Final Report – CARBOPLATIN – February 2008

Database: Ovid MEDLINE(R) 1950 to Present with Daily Update
Search Strategy:

```
-----  
1      exp Carboplatin/ (5900)  
2      carboplatin.mp. (7772)  
3      cis-Diammine cyclobutane-1, 1-dicarboxylato platinum.mp. (1)  
4      (paraplatin or biocarb or biocarbo or bioplatinex or blastocarb or  
boplatex or B-Platin or carbo-cell or carbokebir or carbomedac or carboplat  
or carbosin or carbosol or carbotec or carboxtie or cycloplatin or  
cytocarb or displata or emorzim or ercar or evocarb or ifacap or kemocarb  
or megaplatin or nealorin or neocarb or novoplat or novoplatinum or  
omilipis or oncocarb or paraplatine or platamine or platicarb or platinwas  
or ribocarbo or tecnocarb or CBDCA).mp. (693)  
5      or/1-4 (7853)  
6      randomized controlled trial.pt. (240898)  
7      controlled clinical trial.pt. (75789)  
8      randomized controlled trials.sh. (50566)  
9      random allocation.sh. (58813)  
10     double blind method.sh. (92923)  
11     single blind method.sh. (11257)  
12     or/6-11 (408274)  
13     (animal not human).sh. (0)  
14     12 not 13 (408274)  
15     clinical trial.pt. (439940)  
16     exp Clinical trials/ (195560)  
17     (clin$ adj25 trial$).ti,ab. (134625)  
18     ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or  
mask$)).ti,ab. (92348)  
19     placebos.sh. (26458)  
20     placebo$.ti,ab. (104522)  
21     random$.ti,ab. (382943)  
22     research design.sh. (48951)  
23     or/15-22 (866499)  
24     23 not 13 (866499)  
25     24 not 14 (490950)  
26     comparative study.sh. (0)  
27     exp Evaluation studies/ (611785)  
28     follow up studies.sh. (344736)  
29     prospective studies.sh. (227061)  
30     (control$ or prospectiv$ or volunteer$).ti,ab. (1829339)  
31     or/26-30 (2636301)  
32     31 not 13 (2636301)  
33     31 not (14 or 25) (2101177)  
34     14 or 25 or 33 (3000401)  
35     5 and 34 (4595)  
36     limit 35 to human (4364)
```

WHO EML – Final Report – CARBOPLATIN – February 2008

Database: EMBASE <1980 to 2007 Week 33>

Search Strategy:

```
-----  
1      exp Carboplatin/ (19896)  
2      carboplatin.mp. (20191)  
3      cis-Diammine cyclobutane-1, 1-dicarboxylato platinum.mp. (1)  
4      (paraplatin or biocarb or biocarbo or bioplatinex or blastocarb or  
boplatex or B-Platin or carbo-cell or carbokebir or carbomedac or carboplat  
or carbosin or carbosol or carbotec or carboxtie or cycloplatin or  
cyctocarb or displata or emorzim or ercar or evocarb or ifacap or kemocarb  
or megaplatin or nealorin or neocarb or novoplat or novoplatinum or  
omilipis or oncocarb or paraplatine or platamine or platicarb or platinwas  
or ribocarbo or tecnocarb or CBDCA).mp. (1141)  
5      or/1-4 (20279)
```

Database: EMBASE <1980 to 2007 Week 33>

Search Strategy:

```
-----  
1      exp Carboplatin/ (19896)  
2      carboplatin.mp. (20191)  
3      cis-Diammine cyclobutane-1, 1-dicarboxylato platinum.mp. (1)  
4      (paraplatin or biocarb or biocarbo or bioplatinex or blastocarb or  
boplatex or B-Platin or carbo-cell or carbokebir or carbomedac or carboplat  
or carbosin or carbosol or carbotec or carboxtie or cycloplatin or  
cyctocarb or displata or emorzim or ercar or evocarb or ifacap or kemocarb  
or megaplatin or nealorin or neocarb or novoplat or novoplatinum or  
omilipis or oncocarb or paraplatine or platamine or platicarb or platinwas  
or ribocarbo or tecnocarb or CBDCA).mp. (1141)  
5      or/1-4 (20279)  
6      Meta Analysis/ (31652)  
7      exp "Systematic Review"/ (19368)  
8      meta-analys$.mp. (38180)  
9      systematic review$.mp. (25702)  
10     critical review$.mp. (5221)  
11     Cochrane review$.mp. (453)  
12     literature review$.mp. (16764)  
13     overview$.mp. (41701)  
14     or/6-13 (111721)  
15     5 and 14 (1231)  
16     limit 15 to human (1217)
```

WHO EML – Final Report – CARBOPLATIN – February 2008

Database: EMBASE <1980 to 2007 Week 33>
Search Strategy: Alternative SR/MA filter

1 exp Carboplatin/ (19896)
2 carboplatin.mp. (20191)
3 cis-Diammine cyclobutane-1, 1-dicarboxylato platinum.mp. (1)
4 (paraplatin or biocarb or biocarbo or bioplatinex or blastocarb or
boplatex or B-Platin or carbo-cell or carbokebir or carbomedac or carboplat
or carbosin or carbosol or carbotec or carboxtie or cycloplatin or
cytlocarb or displata or emorzim or ercar or evocarb or ifacap or kemocarb
or megaplatin or nealorin or neocarb or novoplat or novoplatinum or
omilipis or oncocarb or paraplatine or platamine or platicarb or platinwas
or ribocarbo or tecnocarb or CBDCA).mp. (1141)
5 or/1-4 (20279)
6 Meta Analysis/ (31652)
7 exp "Systematic Review"/ (19368)
8 meta-analys\$.mp. (38180)
9 systematic review\$.mp. (25702)
10 critical review\$.mp. (5221)
11 Cochrane review\$.mp. (453)
12 or/6-11 (56131)
13 5 and 12 (927)
14 limit 15 to human (921)

WHO EML – Final Report – CARBOPLATIN – February 2008

Database: EMBASE <1980 to 2007 Week 33>

Search Strategy:

```
-----  
1     exp Carboplatin/ (19896)  
2     carboplatin.mp. (20191)  
3     cis-Diammine cyclobutane-1, 1-dicarboxylato platinum.mp. (1)  
4     (paraplatin or biocarb or biocarbo or bioplatinex or blastocarb or  
boplatex or B-Platin or carbo-cell or carbokebir or carbomedac or carboplat  
or carbosin or carbosol or carbotec or carboxtie or cycloplatin or  
cytocab or displata or emorzim or ercar or evocarb or ifacap or kemocarb  
or megaplatin or nealorin or neocarb or novoplat or novoplatinum or  
omilipis or oncocarb or paraplatine or platamine or platicarb or platinwas  
or ribocarbo or tecnocarb or CBDCA).mp. (1141)  
5     or/1-4 (20279)  
6     exp clinical trial/ (477583)  
7     controlled study/ (2506386)  
8     randomized controlled trial$.tw. (18987)  
9     comparative stud$.ti,ab. (35182)  
10    random allocation.tw. (582)  
11    crossover trial.ti,ab. (2834)  
12    double blind procedure.sh. (65529)  
13    (cli$ adj25 trial$).ti,ab. (127619)  
14    ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or  
mask$)).ti,ab. (88427)  
15    placebo$.sh. (102620)  
16    placebo$.ti,ab. or placebo$.tw. (100165)  
17    random$.ti,ab. or random$.tw. (345527)  
18    or/6-17 (2941221)  
19    animal/ not (human/ and animal/) (14438)  
20    18 not 19 (2939236)  
21    "COMPARATIVE STUDY".mp. (120355)  
22    "EVALUATION STUDIES".mp. (696)  
23    "FOLLOW UP STUDIES".mp. (5194)  
24    "CROSSOVER TRIAL$".mp. (2993)  
25    exp prospective study/ (67844)  
26    exp longitudinal study/ (16027)  
27    (control$ or prospectiv$ or volunteer$).ti,ab. (1574230)  
28    or/21-27 (1685555)  
29    28 not 19 (1683413)  
30    20 or 29 (3680756)  
31    5 and 30 (12444)  
32    limit 31 to human (11879)
```
