Systemic Anti Cancer Treatment Protocol

Carboplatin / Liposomal Doxorubicin CARBO/CAELYX Gynaecological Cancer

PROCTOCOL REF: MPHAGYNCCX
(Version No: 1.1)

Approved for use in:

- Advanced ovarian cancer in women who have progressed within 6 to 12 months after first-line platinum-based chemotherapy regimen

Dosage

Drug	Dosage	Route	Frequency
Carboplatin	AUC 5 or 6 x (GFR +25)	IV infusion	28 day cycle max 6 cycles
Liposomal Doxorubicin (Caelyx)	30mg/m²	IV infusion	

Calvert formula for Carboplatin dosage-

Carboplatin dose in mg = AUC x (creatinine clearance + 25)

If estimated GFR is used the **Wright formula** must be used for creatinine clearance.

Creatinine clearance should be capped at 125mL/min for carboplatin

Avoid the use of Cockcroft and Gault formula as it is less accurate.

Supportive Treatments:

Dexamethasone tablets 4mg orally twice daily for three days

Domperidone 10mg tablets, to be taken three times a day when required

Interactions

Aminoglycosides e.g. gentamicin, vancomycin and diuretics - increased risk of nephrotoxicity and ototoxicity with carboplatin. Renal function should be well monitored and audiometric tests carried out.

Antiepileptics - barbiturates may lead to an accelerated plasma clearance of doxorubicin whilst plasma levels of phenytoin, carbamezapine and valproate may be reduced with concomitant administration with doxorubicin.

Phenytoin - carboplatin can cause a decrease in phenytoin serum levels. This may lead to reappearance of seizures and may require an increase of phenytoin dosages.

Contraindications

Caelyx is contraindicated in patients with peanut or soya allergies

Extravasation risk

Carboplatin- irritant

Liposomal Doxorubicin- vesicant

Administration

Day	Drug	Dose	Route	Diluent and rate
1	Ondansetron	16mg	Oral	30 minutes before chemotherapy
	Dexamethasone	8mg	Oral	30 minutes before chemotherapy
	Liposomal Doxorubicin (Caelyx)	**30mg/m²**	**IV Infusion**	***250 to 500mL glucose 5%. Initial infusion over 90 min. Subsequent infusions over 60 mins**
	Carboplatin	**AUC 5**	**IV Infusion**	**500mL glucose 5% over 30 to 60 minutes**

* For doses < 90 mg: Caelyx is diluted in 250 ml 5% glucose solution for infusion.
For doses ≥ 90 mg: Caelyx is diluted in 500 ml 5% glucose solution for infusion

Liposomal Doxorubicin (Caelyx)

- Caelyx is incompatible with 0.9% sodium chloride
- In patients who experience an infusion reaction, the method of infusion should be modified as follows:

  5% of the total dose should be infused slowly over the first 15 minutes. If tolerated without reaction, the infusion rate may then be doubled for the next 15 minutes. If tolerated, the infusion may then be completed over the next hour for a total infusion time of 90 minutes.
- Diabetic patients: please note that each vial of Caelyx contains sucrose and the dose is administered in 5% (50 mg/ml) glucose solution for infusion.

Carboplatin

- Carboplatin risk of hypersensitivity and anaphylaxis may increase with previous exposure to platinum therapy.
- Facilities to treat anaphylaxis must be present when administering carboplatin. If a patient experiences an **infusion-related reaction**, give future does with pre-medication cover of IV chlorphenamine 10mg and IV hydrocortisone 100mg.

Main Toxicities

Cardiac Disorders	Caelyx - Cardiomyopathy, ventricular arrhythmias
Eye Disorders	Caelyx - lacrimation, blurred vision
Gastrointestinal	Nausea, vomiting ,diarrhoea, constipation, mucositis Abdominal pain, dyspepsia, mouth ulceration Anorexia and dehydration
General disorders and administration site conditions	Carboplatin: Decreases in serum electrolytes (sodium, magnesium, potassium and calcium). Renal function impairment, dysuria Hearing loss Caelyx: Malaise, urticaria. flu-like syndrome, rash, pruritus Asthenia, fatigue, back pain, myalgia Weakness, fever, pain, dyspnoea, increased cough
Haematological	Neutropenia, anaemia, thrombocytopenia

Hepatobiliary	Abnormalities of liver function tests (usually mild to moderate). Alkaline phosphatase level is increased more frequently than SGOT, SGPT or total bilirubin. The majority of these abnormalities regress spontaneously during the course of treatment.
Hypersensitivity reactions	Skin rash, urticaria, erythematous rash, and fever hypertension, tachycardia, facial oedema, chills, back pain, tightness in the chest and throat and/or hypotension, pruritus. Risk of hypersensitivity and anaphylaxis may increase with previous exposure to platinum therapy
Nervous system	Paraesthesia and decreased deep tendon reflexes. Headache, dizziness, neuropathy, hypertonia
Skin and subcutaneous tissue disorders	Alopecia,dry skin, skin discolouration, rash Caelyx - palmar-plantar erythrodysesthesia (Hand-foot syndrome). To minimize PPE for the first 4 to 7 days after caelyx infusion, keep hands and feet as cool as possible, avoid hot water, pat skin dry after washing, do not wear tight fitting gloves or socks.

Investigations

	Pre	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Ongoing
Medical Assessment	X				X			After cycles 3 and 6 then as per management plan
SACT Assessment	X	X	X	X	X	X	X	Every cycle
FBC	X	X	X	X	X	X	X	Every cycle
U&E & LFT	X	X	X	X	X	X	X	Every cycle
CrCl	X	X	X	X	X	X	X	Every cycle
CA125	X	X	X	X	X	X	X	Every cycle
CT scan	X				X			After cycles 3 and 6
Echo/MUGA/ECG								If clinically indicated based on cardiac fitness
Informed Consent	X							
PS recorded	X	X	X	X	X	X	X	Every cycle
Toxicities documented	X	X	X	X	X	X	X	Every cycle
Weight recorded	X	X	X	X	X	X	X	Every cycle

Dose Modifications and Toxicity Management

Haematological Toxicity

Proceed on day 1 if-

Plt ≥ 100 x 10^9/L	ANC ≥ 1.0 x 10^9/L

Delay 1 week on day 1 if-

Plt ≤ 99 x 10^9/L	ANC ≤ 0.9 x 10^9/L

Non-haematological Toxicities

Grading and Management of Toxicity

Toxicity should be grading according to the CTCAE v4.0 criteria. Following assessment treatment should be withheld for any toxicity until resolved to grade 0/1. For dose modification, follow the general guidance below and discuss with treating clinician.

	Grade 2	Grade 3	Grade 4
1st appearance	Interrupt treatment until resolved to grade 0/1, then continue at 100% of original dose with prophylaxis where possible	Interrupt treatment until resolved to grade 0/1, then continue at 75-80% of original dose with prophylaxis where possible	Discontinue treatment
2nd appearance	Interrupt treatment until resolved to grade 0/1, then continue at 75-80% of original dose	Interrupt treatment until resolved to grade0/1, then continue at 50% of original dose	
3rd appearance	Interrupt treatment until resolved to grade 0/1, then continue at 50% of original dose	Discontinue treatment	
4th appearance	Discontinue treatment		

Hepatic Impairment

Carboplatin – no dose adjustment required

Liposomal Doxorubicin

Bilirubin (µmol/L)	Dose
20 to 50	75%
> 51	50%

Renal Impairment

Carboplatin

Patients with creatinine clearance values of less than 60 ml/min are at greater risk to develop myelosuppression. Carboplatin is contraindicated if glomerular filtration rate is ≤ 20 ml/min.

The optimal use of Carboplatin in patients presenting with impaired renal function requires adequate dosage adjustments and frequent monitoring of both haematological nadirs and renal function.

In patients with impaired renal function, dosage of carboplatin should be reduced (refer to Calvert formula).

Liposomal Doxorubicin

No dose reductions required. Clinical decision in severe impairment.

References:

Dosage Adjustment for Cytotoxics in Hepatic Impairment. January 2009 UCLH – Dosage Adjustment for Cytotoxics in Hepatic Impairment (Version 3 - updated January 2009)

Dosage Adjustment for Cytotoxics in Renal Impairment. January 2009 UCLH - Dosage Adjustment for Cytotoxics in Renal Impairment (Version 3 - updated January 2009)

Stockley's drug interactions. Ninth edition. Edited K. Baxter. Pharmaceutical press. London. 2010

Pegylated liposomal doxorubicin and carboplatin compared with paclitaxel and carboplatin for patients with platinum sensitive ovarian cancer in late relapse
Journal of Clinical Oncology 2010 28(20):3323-3329