Pegylated liposomal doxorubicin hydrochloride (Caelyx®) and Carboplatin (gynae)

Indication
Palliative therapy for relapsed ovarian, fallopian tube or primary peritoneal cancer with late relapse (> 6 months) after previous treatment with a platinum or platinum and taxane.

(NICE TA 389)

ICD-10 codes
Codes prefixed with C48, 56 and 57.

Regimen details

Day	Drug	Dose	Route
1	Caelyx®	30mg/m^2	IV infusion
1	Carboplatin	AUC 5 or 6*	IV infusion

* Carboplatin dose calculated using the Calvert equation: **Carboplatin dose (mg) = AUC (CrCl +25)**
The creatinine clearance (CrCl) is estimated using the Cockcroft and Gault equation, however for patients where the creatinine level may not truly reflect renal function (e.g. in extremes of BSA or debilitated patients) a formal GFR measurement should be performed. If using a measured GFR consider dosing at AUC 5 and if using Cockcroft and Gault consider dosing at AUC 6.
CrCl should be capped at 125mL/min.

Cycle frequency
28 days

Number of cycles
6 cycles

Administration
Caelyx® is administered in 250mL glucose 5%. For the first dose Caelyx® should be given over 60 minutes or at a rate of 1mg/minute (whichever is longer). If well tolerated subsequent infusions can be administered over 60 minutes. Infusions of Caelyx® **must not** be filtered.

Carboplatin is administered in 250-500mL glucose 5% over 30-60 minutes.

Patients should be observed closely for hypersensitivity reactions, particularly during the first and second infusions. Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of Caelyx® or carboplatin. Facilities for the treatment of hypotension and bronchospasm **must** be available.

If hypersensitivity reactions occur, minor symptoms such as flushing or localised cutaneous reactions do not require discontinuation of therapy. The infusion may be temporarily interrupted and when symptoms improve restarted at a slower infusion rate. Chlorphenamine 10mg IV may be administered. Severe reactions, such as hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of the infusion and appropriate therapy initiated.

Pre-medication
Chlorphenamine 10mg IV and hydrocortisone 100mg IV may be given if there has been more than a 6 month gap between courses of treatment due to a possible reaction to carboplatin antibodies.

Emetogenicity

This regimen has a moderate - high emetogenic potential

Additional supportive medication

Mouthwashes as per local policy.
Emollients as per local policy.
Loperamide if required.

Extravasation

Carboplatin is an irritant (Group 3)
Caelyx® is an irritant (Group 3)

Investigations – pre first cycle

Investigation	**Validity period** (or as per local policy)
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days
Magnesium	14 days
CA125	28 days

Baseline measured GFR if suspected or significant renal dysfunction.
ECHO if history of cardiac dysfunction.

Investigations – pre subsequent cycles

Investigation	**Validity period** (or as per local policy)
FBC	96 hours
U+E (including creatinine)	7 days
LFTs	7 days
Magnesium	7 days

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant.

Investigation	**Limit**
Neutrophils	> 1.0 x 10^9/L
Platelets	> 100 x 10^9/L
Creatinine Clearance (CrCl)	> 30mL/min (and <10% change in CrCl from previous cycle)
Bilirubin	< ULN

Dose modifications

- **Haematological toxicity**

If neutrophils < 1.0 x 10^9/L and/or platelets < 100 x 10^9/L delay treatment for 1 week or until count recovery.

In the case of febrile neutropenia (neutrophils < 0.5 × 10^9/L and fever > 38.5°C requiring IV antibiotics) or if nadir neutrophils <0.5 x 10^9/L or platelets < 25 x 10^9/L reduce Caelyx® to 75% and carboplatin by 1 x AUC for all future cycles.

- **Renal impairment**

CrCl (mL/min)	**Carboplatin dose**
> 30	100%
20-30	Measured GFR then 100% dose or discuss with consultant
< 20	Discuss with consultant

If the calculated CrCl falls by more than 10% from the previous cycle consider dose adjustment.

No dose modifications are required for Caelyx® for renal impairment.

- **Hepatic impairment**

Bilirubin (x ULN)	**Caelyx® dose**
≤ 1.0	30mg/m2
1.0-2.5	25mg/m2
2.5-4.0	15mg/m2
> 4.0	Avoid

*If the first dose is tolerated without an increase in bilirubin or LFTs the second dose can be increased to the next dose increment and then titrated back to full dose on subsequent cycles if tolerated.

Transient increases in liver enzymes have been seen in patients being treated with carboplatin although no dose reduction is usually required. In severe hepatic dysfunction consider a dose reduction (discuss with consultant).

- **Other toxicities**

Cutaneous toxicity (stomatitis or palmar plantar erythema – PPE) – treat symptomatically until toxicity resolved then Caelyx dose as per table below:

Toxicity grade	**Toxicity resolved day 28 (day next cycle due)**	**Toxicity resolved day 35 (1 week delay)**	**Toxicity not resolved by day 42 (2 weeks delay)**
Grade 1	Continue 100% dose	Continue 75% dose	Discontinue
Grade 2	Continue 75% dose	Continue 75% dose	Discontinue
Grade 3 or 4	Discontinue	Discontinue	Discontinue

To minimise the risk of PPE for the first week after Caelyx® infusion:

- Keep hands and feet as cool as possible.
- Avoid tight-fitting gloves, sock, footwear and high-heeled shoes.
- Avoid exposing the skin to very hot water.
- Avoid vigorous rubbing of skin-pat skin dry after washing.
- Avoid use of topical anaesthetics as these can worsen skin reactions.

For all other grade 3 toxicities (except alopecia) delay treatment until resolved to ≤ grade 1 and resume with Caelyx® 75% and/or carboplatin at 1 x AUC dose reduction. If further toxicity occurs or grade 4 toxicity withhold treatment or consider an additional dose reduction (discuss with consultant).

If delays of ≥ 4weeks weeks or > 2 dose reductions, discontinue treatment.

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Peripheral neuropathy
Thromboembolism
Optic neuritis
Convulsions
Pulmonary fibrosis (rare)
Nephrotoxicity

- **Frequently occurring side effects**

Myelosuppression
Nausea and vomiting
Alopecia
Constipation, diarrhoea
Stomatitis and mucositis
Fatigue
Allergic reactions
Palmar Plantar Erythema (PPE)

- **Other side effects**

Discoloured urine

Significant drug interactions – for full details consult product literature/ reference texts

Warfarin/coumarin anticoagulants: Avoid use due to elevations in INR. Switch to low molecular weight heparin or DOAC during treatment.

Carboplatin only:
Aminoglycoside antibiotics: increased risk of nephrotoxicity and ototoxicity
Clozapine: increased risk of agranulocytosis, avoid concomitant use
Diuretics: increased risk of nephrotoxicity and ototoxicity
Nephrotoxic drugs: increased nephrotoxicity; not recommended
Phenytoin: carboplatin reduces absorption and efficacy of phenytoin

Additional comments Consider previous anthracyclines exposure. Doxorubicin has a lifetime maximum cumulative dose of 450mg/m^2.

References

- National Institute for Clinical Excellence. Technology Appraisal Guidance 389. Accessed 12 August 2021 via www.nice.org.uk
- Summary of Product Characteristics Carboplatin (Hospira) accessed 14 12 August 2021 via www.medicines.org.uk
- Summary of Product Characteristics Caelyx (Janssen-Cilag) accessed 12 August 2021 via www.medicines.org.uk
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- Pujade-Lauraine E, Wagner U, Aavall-Lundqvist E *et al*. Pegylated liposomal Doxorubicin and Carboplatin compared with Paclitaxel and Carboplatin for patients with platinum-sensitive ovarian cancer in late relapse. *J Clin Oncol.* 2010 28(20):3323-3329

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