SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Pegylated Liposomal Doxorubicin

Gynaecological cancer

PROTOCOL REF: MPHAGYNCAE
(Version No. 1.2)

Approved for use in:

- Second/third line treatment of platinum resistant or platinum refractory advanced ovarian cancer

Dosage:

Drug	Dose	Route	Frequency
Pegylated Liposomal doxorubicin	**40mg/m^2 ***	IV infusion	Every 28 days

Until disease progression or unacceptable toxicity.

*Clatterbridge Cancer Centre approved dose lower than dose recommended in NICE and SPC due to anecdotal evidence of 50mg/m^2 being too toxic.

Administration:

- Pegylated liposomal doxorubicin is not suitable for anyone with a peanut or soya allergy
- To avoid cardiomyopathy, **it is recommended that the cumulative total lifetime dose of anthracycline should not exceed 450mg/m² body surface area (BSA)**. Any doses that exceed the recommended cumulative dose require evaluation of Left Ventricular Ejection Fraction (LVEF) via ECHO or MUGA prior to each dose.
- Pregnancy and Breast-feeding

- Doxorubicin hydrochloride is suspected to cause serious birth defects when administered during pregnancy. Women of child-bearing potential must be advised to avoid pregnancy while they or their male partner are receiving liposomal doxorubicin and in the six months following discontinuation of treatment.
- Breastfeeding is contraindicated in those receiving liposomal doxorubicin.

Emetogenic risk:

Mild emetogenic.

Supportive treatments:

Metoclopramide 10mg tablets, to be taken orally three times a day for a maximum of five consecutive days.

Extravasation risk:

Pegylated liposomal doxorubicin: IRRITANT

Refer to the CCC policy for the 'Prevention and Management of Extravasation Injuries'

Interactions:

No formal medicinal product interaction studies have been performed with pegylated liposomal doxorubicin but care is required in the concomitant use of medicinal products known to interact with standard doxorubicin:-

- Doxorubicin undergoes metabolism via CYP450 so concomitant use of inhibitors may increase toxicity and inducers may reduce efficacy.
- Ciclosporin and cimetidine increase the AUC of doxorubicin; dose adjustments may be required.

- Barbiturates may lead to an accelerated plasma clearance of doxorubicin, while the concomitant administration of phenytoin may result in lower plasma phenytoin levels.
- Doxorubicin is a potent, radio-sensitizing agent.

Treatment schedule:

Day	Drug	Dose	Route	Diluent and rate
1	Dexamethasone	8mg	PO	30 minutes before chemotherapy
	Pegylated Liposomal doxorubicin	40mg/m^2	PO	250 to 500mL glucose 5%*. Initial infusion over 90 min. Subsequent infusions over 60 minutes* **Do not use in-line filters**

Every 28 days until disease progression or unacceptable toxicity

*For doses < 90 mg: liposomal doxorubicin is diluted in 250 ml 5% glucose solution for infusion.

For doses ≥ 90 mg: liposomal doxorubicin is diluted in 500 ml 5% glucose solution for infusion.

liposomal doxorubicin is incompatible with 0.9% sodium chloride.

For patients who experience an infusion reaction, the step up method of infusion should be followed:

1. 5% of the total dose should be infused slowly over the first 15 minutes.
2. If tolerated without reaction, the infusion rate may then be doubled for the next 15 minutes.
3. If tolerated, the infusion may then be completed over the next hour for a total infusion time of 90 minutes.

Please refer to the **CCC Hypersensitivity; Management Prevention Policy**

Diabetic patients: please note that each vial of liposomal doxorubicin contains sucrose and the dose is administered in 5% (50 mg/ml) glucose solution for infusion

Main toxicities:

Cardiac Disorders	Cardiomyopathy, ventricular arrhythmias
Eye Disorders	Lacrimation, blurred vision
Gastrointestinal and Nutritional Disorders	Constipation, diarrhoea, nausea, vomiting, stomatitis
General disorders and administration site conditions	Asthenia, fatigue, mucositis, weakness, fever, Paresthesia, somnolence, headache, dizziness, neuropathy, hypertonia. Back pain, myalgia
Haematological	Neutropenia, anaemia, thrombocytopenia
Hypersensitivity reactions	Flushing, urticarial rash, chest pain, fever, hypertension, tachycardia, pruritus, sweating, shortness of breath, facial oedema, chills, back pain, tightness in the chest and throat and/or hypotension
Skin and subcutaneous tissue disorders	Palmar-plantar erythrodysesthesia (Hand-foot syndrome), alopecia, rash. Dry skin, skin discolouration, pigmentation abnormal, erythema

	To minimise PPE for the first 4 to 7 days after liposomal doxorubicin 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.

Please refer to SmPC for further information

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Ongoing
Informed Consent	X							
Clinical Assessment	X						X**	As clinically indicated or at the end of treatment
SACT Assessment (to include PS and toxicities)	X	X	X	X	X	X	X	Every cycle
On treatment review/Go ahead	X	X	X	X	X	X	X	Every cycle
FBC	X	X	X	X	X	X	X	Every cycle
U&E & LFTs & Magnesium	X	X	X	X	X	X	X	Every Cycle
CrCl (Cockcroft and Gault)	X	X	X	X	X	X	X	Every cycle
CA125*	X	X	X	X	X	X	X	Every cycle *For ovarian patients only
CT scan	X				X			After cycles 3 and 6
ECHO/MUGA/ECG								When clinically indicated based on cardiac risk factors and/or co-morbidities
Full Observations *(Temp,HR,BP,RR, O_2 Sats)*	X	X	X	X	X	X	X	Every cycle
Weight recorded	X	X	X	X	X	X	X	Every cycle
Blood glucose	X							Repeat if clinically indicated
Height	X							

Dose Modifications and Toxicity Management:

Dosing in renal and hepatic impairment:

Renal impairment	
CrCl (ml/min)	**Dose**
≥ 30	100%
< 30	Not studied. No dose adjustments expected.

Hepatic impairment	
Bilirubin (micromole/L)	**Dose adjustment**
20 to 50	75% of original dose for the first cycle. If tolerated without an increase in bilirubin or ALT then dose can be increased to 100% for cycle 2
>51	50% of original dose for the first cycle. If tolerated without an increase in bilirubin or ALT then dose can be increased to 75% for cycle 2 and 100% for cycle 3.

Haematological toxicity:

ANC (x 10^9/L)	**Platelets (x 10^9/L)**	**Action**
≥ 1.0	≥ 50	Proceed with treatment
0.5 to 0.9	25 to 49	Wait until ANC ≥ 1.0 x 10^9/L and/or platelets ≥ 50 x 10^9/L and then restart at previous dose

<0.5	<25	Wait until ANC ≥ 1.0 x 10^9/L and/or platelets ≥ 50 x 10^9/L and then decrease dose by 25% or continue previous dose with GCSF support

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

Non-Haematological toxicity:

Grading and management of toxicity:

Toxicity should be grading according to the CTCAE 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		

References:

Caelyx pegylated liposomal 2 mg/ml concentrate for solution for infusion, summary of Product Characteristics, Baxter Healthcare Limited available via https://www.medicines.org.uk/emc (last updated 14th March 2023).

Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. *Lancet Oncol* 2019; 20: e201–08.

NICE TA389: Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for treating recurrent ovarian cancer. Published 27th April 2016. Accessed 23/01/2023.

Rose PG. Pegylated liposomal doxorubicin in recurrent ovarian cancer, *Cancer Treat Rev* 2002 28(2):121-125

Circulation/Dissemination

Date added into Q-Pulse	31st August 2023
Date document posted on the Intranet	31st August 2023

Version History

Date	Version	Author name and designation	Summary of main changes
May 2023	1.0	**Anna Burke** **Advanced Pharmacist**	V1.2 Routine Protocol Update