PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Carboplatin and Paclitaxel Carcinoma of Unknown Primary (CUP)

PROTOCOL REF: MPHACUPMIS
Version No: 1.0

Approved for use in:

Metastatic adenocarcinoma of unknown primary or squamous cell carcinoma of unknown primary (including adults with predominantly nodal/pleural metastases or in women with peritoneal carcinomatosis).

Dosage:

Drug	Dosage	Route	Frequency
Paclitaxel	60mg/m²	IV infusion	Days 1,8 and 15
Carboplatin	AUC 2	IV infusion	

Repeated every 21 days for 6 cycles.

Calvert formula for Carboplatin dosage

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

Meditech calculates creatinine clearance using the Wright formula, the Carboplatin Dose Calculator application for calculating creatinine is available on the Remote Citrix Web Portal. 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 formulae as it is less accurate.

Emetogenic risk:

Moderately emetogenic.

Supportive treatments:

Domperidone tablets 10mg to be taken orally three times a day as required.

Famotidine tablets 40mg to be taken orally at least 1 hour before each chemotherapy treatment.

Extravasation risk:

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

Carboplatin- IRRITANT

Paclitaxel- VESICANT

Dosing in renal and hepatic impairment:

<table>
<tr><td rowspan="2">Renal</td><td>Paclitaxel</td><td>All grades including patients on HDx - no dose adjustment required.</td></tr>
<tr><td>Carboplatin</td><td>Patients with creatinine clearance values of less than 60 mL/min are at greater risk to develop myelosuppression.

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.

Carboplatin is contraindicated if GFR or CrCl ≤ 20 ml/min. Do not give carboplatin and discuss with Oncologist.</td></tr>
<tr><td rowspan="2">Hepatic</td><td>Paclitaxel</td><td><table><tr><th>LFTs</th><th>Dose</th></tr><tr><td>Bilirubin less than 1.25 times ULN and AST < 10 x ULN</td><td>Give 100% dose</td></tr><tr><td>Bilirubin greater than 1.25 times ULN</td><td>Consider dose reduction</td></tr><tr><td>ALP more than 3 times ULN</td><td>Consider dose reduction</td></tr><tr><td>ALT and/or AST ≥10 x ULN or bilirubin > 5 x ULN:</td><td>Contra-.indicated</td></tr></table></td></tr>
<tr><td>Carboplatin</td><td>No need for dose adjustment is required.</td></tr>
</table>

Interactions:

Carboplatin
Concomitant use contraindicated Yellow fever vaccine: risk of generalized disease mortality. Concomitant use not recommended • Live attenuated vaccines (except yellow fever): Risk of systemic, possible fatal disease. This is increased in subjects who are already immunosuppressed by their underlying disease. Use inactivated vaccine where this exist (poliomyelitis). • Phenytoin, fosphenytoin: Risk of exacerbation of convulsions (resulting from the decrease of phenytoin digestive absorption by the cytotoxic drug), risk of toxicity enhancement or loss of efficacy of the cytotoxic drug (due to increased hepatic metabolism by phenytoin). Concomitant use to take into consideration • Ciclosporin (and by extrapolation tacrolimus and sirolimus): Excessive immunosuppression with risk of lymphoproliferation. • Concurrent therapy with nephrotoxic drugs or ototoxic drugs such as amino glycosides, vancomycin, capreomycin and diuretics, may increase or exacerbate toxicity, particularly in renal failure patients, due to Carboplatin induced changes in renal clearance. • Loop diuretics (e.g. furosemide, indapamide): The concomitant use of carboplatin with loop diuretic should be approached with caution due to the cumulative nephrotoxicity and ototoxicity.

Paclitaxel
Caution should be exercised when administering paclitaxel concomitantly with medicines known to inhibit either CYP2C8 or CYP3A4 (e.g. ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, clopidogrel, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) because toxicity of paclitaxel may be increased due to higher paclitaxel exposure. Administering paclitaxel concomitantly with medicines known to induce either CYP2C8 or CYP3A4 (e.g. rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine) is not recommended because efficacy may be compromised because of lower paclitaxel exposures. Studies in KS patients, who were taking multiple concomitant medicinal product, suggest that the systemic clearance of paclitaxel was significantly lower in the presence of nelfinavir and ritonavir, but not with indinavir. Insufficient information is available on interactions with other protease inhibitors. Consequently, paclitaxel should be administered with caution in patients receiving protease inhibitors as concomitant therapy.

For more detailed interactions please refer to the SmPC for each agent.

Treatment schedule:

Day	Drug	Dose	Route	Diluent and rate
1,8 and 15	Chlorphenamine	10mg	IV Infusion	30 minutes prior to paclitaxel
	Dexamethasone	8mg	IV Infusion	30 minutes prior to paclitaxel
	Famotidine	40mg	Orally	60 minutes prior to paclitaxel
	Ondansetron	8mg	Orally	30 minutes prior to paclitaxel
	Paclitaxel	**60mg/m²**	**IV Infusion**	**250 to 500mL Sodium Chloride 0.9% over 60 minutes via a non-PVC giving set with a 0.22 micron filter.**
	Carboplatin	**AUC 2**	**IV Infusion**	**500mL Glucose 5% over 30 to 60 minutes**

Cycle is repeated every 21 days for 6 cycles.

Main toxicities:

Cardiac and Vascular disorders	Risk of bradycardia and hypotension is common with paclitaxel
Gastrointestinal	Nausea, vomiting, diarrhoea, constipation, mucositis
General disorders and administration site conditions	Malaise, fever, chills, urticaria, flu-like syndrome, rash, pruritus. **Carboplatin:** Decreases in serum electrolytes (sodium, magnesium, potassium and calcium) Hyperuricaemia: Serum levels of uric acid can be decreased by allopurinol. **Paclitaxel:** Injection site reactions (including localized oedema, pain, erythema, induration, on occasion extravasation can result in cellulitis, skin fibrosis and skin necrosis) Severe elevation in aspartate aminotransferase (AST) and alkaline phosphatase.
Haematological	Neutropenia, anaemia, thrombocytopenia
Infections/Infestations	Paclitaxel: Infection (mainly urinary tract and upper respiratory tract infections) are very common, with reported cases of fatal outcome
Musculoskeletal	Arthralgia, myalgia common with paclitaxel
Nervous system	Carboplatin: Paraesthesia and decreased deep tendon reflexes. Paclitaxel: peripheral neuropathy is very common
Ototoxicity	Hearing loss
Skin and subcutaneous tissue disorders	Alopecia Allergic skin rash frequently associated with pruritus
Urological	Carboplatin: Renal function impairment

Investigations and treatment plan:

	Pre	Cycle 1			Cycle 2			Ongoing
		D1	D8	15	D1	D8	D15	
Clinical Assessment	X				X			Every 2-3 cycles thereafter*
SACT assessment (including toxicities and PS)		X	X	X	X	X	X	Every cycle
FBC	X	X	X	X	X	X	X	Every cycle
U&E (including magnesium) & LFT	X	X	X	X	X	X	X	Every cycle
Calculate GFR or CrCl (refer to 'Dosage' section for full information) and check carboplatin dose using the carboplatin calculator		X	X	X	X	X	X	Every cycle
Tumour markers dependent on tumour biology	X				X			**It is the responsibility of the clinical team to specify which tumour marker is to be requested** (AFP, hCG, PSA or CA125) as part of routine blood tests for day 1 of each cycle and **the ongoing monitoring of the results.**
Informed Consent	X							
Weight recorded	X	X	X	X	X	X	X	Every treatment
Height	X							

***Clinical review can be requested earlier if:**

- Treatment is differed by 2 weeks
- Hospital admission following last cycle of chemotherapy
- Deterioration in performance status (PS) to PS 3
- Poorly controlled symptoms
- Patient experiencing any Grade 2 or more SACT-induced toxicity.

Dose Modifications and Toxicity Management:

Haematological toxicity:

Proceed with day 1, 8 and 15 if:

Platelets ≥ 75 x 10^9/L	ANC ≥ 1.0 x 10^9/L

Omit treatment on day 1, 18 and 15 if:

Platelets ≤ 74 x 10^9/L	ANC ≤ 0.99 x 10^9/L

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:

Paraesthesia	Description	Dose adjustment
Grade 0-1	Asymptomatic	No dose change
Grade 2	Moderate symptoms. Limiting instrumental ADL	Delay treatment until dose resolution to grade 0-1, up to 2 weeks. If resolved in 2 weeks then dose reduce. if not resolved to grade 0-1 by 2 weeks then discontinue
Grade 3	Severe symptoms. Limiting self-care ADL	Delay treatment until dose resolution to grade 0-1, up to 2 weeks. If resolved in 2 weeks then dose reduce. if not resolved to grade 0-1 by 2 weeks then discontinue

References:

Briasoulis E, Kalofonos H, Bafaloukos D, et al. Carboplatin plus paclitaxel in unknown primary carcinoma: a phase II Hellenic Cooperative Oncology Group Study. *J Clin Oncol* 2000;18(17):3101-7.

Carboplatin 10 mg/ml concentrate for solution for infusion.
Summary of Product Characteristics. Accord Healthcare Ltd, Middlesex. Last updated 31/08/2018. Available from www.medicines.org.uk/emc/medicine.

K. Fizazi1 et al. (2015) Cancers of unknown primary site: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology* 26 (Supplement 5): v133–v138.

Paclitaxel 6 mg/ml concentrate for solution for infusion.
Summary of Product Characteristics. Hospira UK Ltd, Warwickshire
Available from www.medicines.org.uk/emc/medicine last updated 27/04/2020.

Supplement to: 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.

Circulation/Dissemination

Date added into Q-Pulse	23rd November 2021
Date document posted on the Intranet	23rd November 2021

Version History

Date	Version	Author name and designation	Summary of main changes
October 2021	1.0	Hala Ghoz - Protocols Pharmacist	New Regimen Protocol