PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Carboplatin and Gemcitabine Breast Cancer

PROTOCOL REF: MPHACGBC
(Version No. 1.0)

Approved for use in:

- Second or subsequent line treatment in metastatic breast cancer.
- First line treatment of triple negative breast cancer (TNBC) which has relapsed early (within 6 months) following completion of neo-adjuvant or adjuvant SACT containing anthracycline and taxane.
- Advanced or metastatic PD-L1 negative (TPS < 1%) TNBC
- Advanced or metastatic BRCA 1/2 mutated TNBC not previously treated with platinum agent.

PS 0-2

Dosage:

Drug	Dose	Route	Frequency
Carboplatin	AUC 2.5	IV infusion	Days 1 and 8 of a 21 day cycle
Gemcitabine	1000mg/m^2	IV infusion	

OR ALTERNATE DOSING PLAN

Drug	Dose	Route	Frequency
Carboplatin	AUC 5	IV infusion	Day 1 of a 21 day cycle
Gemcitabine	1000mg/m^2	IV infusion	Days 1 and 8 of a 21 day cycle

To be continued until progression or unacceptable toxicity (at the discretion of the treating consultant)

NOTE: gemcitabine has radiosensitising activity. Significant toxicity may occur including; mucositis, oesophagitis, colitis and pneumonitis. When administered non-concurrently i.e.

gemcitabine is administered more than 7 days before or after radiotherapy (RT) data does not indicate any enhanced toxicity. However radiation recall reaction (inflammatory reaction confined to previously irradiated areas as result of SACT administration) can still occur. Data suggest that gemcitabine can be started after the acute effects of radiation have resolved or at least one week after radiotherapy.

Meditech calculates creatinine clearance using the Wright formula and therefore **creatinine clearance will need to be entered manually to use Cockroft and Gault formula** (applications for calculating creatinine using both formulas are available on the Remote Citrix Web Portal). If estimated GFR is used the Wright formula must be used for creatinine clearance. GFR via either the Wright or Cockroft and Gault formula should be capped at 125ml/min.

Note that either calculation is an estimate and the dose should be reviewed with the patients clinical condition taken into account

Calvert formula for Carboplatin dosage-:

Carboplatin dose in mg = AUC x (GFR or CrCl + 25)

Emetogenic risk:

Moderately emetogenic.

Supportive treatments:

Dexamethasone tablets 4mg orally twice daily for three days on day 1 and day 8 of split dose regimen (only required on day 1 of carbo AUC5 day 1 dosing)

Metoclopramide 10mg orally three times a day when required for nausea and vomiting. Maximum 5 consecutive days.

Extravasation risk:

Carboplatin- Irritant

Gemcitabine- Neutral

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

Dosing in renal and hepatic impairment:

Renal	Carboplatin	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 clinical team.
	Gemcitabine	GFR ≥ 30ml/min: no dose adjustment is needed GFR < 30 ml/min: no need for dose adjustment is expected Haemodialysis (HDx): no need for dose adjustment is expected. Start HDx 6-12 h after administration.

Hepatic	Gemcitabine	Total bilirubin < 27 µmol/L: no dose adjustment is needed. Total bilirubin ≥ 27 µmol/L: discuss with clinical team. Options are: Start at 80% of the original dose and increase the dose if tolerated. OR Start with full dose with active monitoring and/or followup.
	Carboplatin	No need for dose adjustment is required.

Interactions:

Please refer to the SmPC for full list of interactions.

Carboplatin	Concomitant use contraindicated- **Yellow fever vaccine** Use not recommended- Live attenuated vaccines, phenytoin and fosphenytoin Use with caution in combination with immunosuppressants (tacrolimus, sirolimus and ciclosporin), nephrotoxic drugs (**amino glycosides, vancomycin, capreomycin and diuretics**. Concomitant use with loop diuretics (furosemide,indapamide,bumetanide): increased the risk of nephrotoxicity and ototoxicity.
Gemcitabine	Yellow fever and other live attenuated vaccines are not recommended due to the risk of systemic, possibly fatal, disease, particularly in immunosuppressed patients.

Treatment schedule:

Day	Drug	Dose	Route	Diluent and rate
1	Sodium Chloride 0.9%	250ml	IV Infusion	Flush
	Dexamethasone	8mg	Oral	30 minutes before chemotherapy
	Ondansetron	16mg	Oral	30 minutes before chemotherapy
	Gemcitabine	**1000mg/m²**	**IV Infusion**	**250mL sodium chloride 0.9% over 30 minutes**
	Carboplatin	**AUC 2.5**	**IV Infusion**	**500mL glucose over 30-60 minutes**
8	Sodium Chloride 0.9%	250ml	IV Infusion	Flush
	Dexamethasone	8mg	Oral	30 minutes before chemotherapy
	Ondansetron	16mg	Oral	30 minutes before chemotherapy
	Gemcitabine	**1000mg/m²**	**IV Infusion**	**250mL sodium chloride 0.9% over 30 minutes**
	Carboplatin	**AUC 2.5**	**IV Infusion**	**500mL glucose over 30-60 minutes**

OR

Day	Drug	Dose	Route	Diluent and rate
1	Sodium Chloride 0.9%	250ml	IV Infusion	Flush
	Dexamethasone	8mg	Oral	30 minutes before chemotherapy
	Ondansetron	16mg	Oral	30 minutes before chemotherapy
	Gemcitabine	**1000mg/m²**	**IV Infusion**	**250mL sodium chloride 0.9% over 30 minutes**
	Carboplatin	**AUC 5**	**IV Infusion**	**500mL glucose over 30-60 minutes**
8	Sodium Chloride 0.9%	250ml	IV Infusion	Flush
	Dexamethasone	8mg	Oral	30 minutes before chemotherapy
	Gemcitabine	**1000mg/m²**	**IV Infusion**	**250mL sodium chloride 0.9% over 30 minutes**

Repeated every 21 days until progression or unacceptable toxicity (at the discretion of the treating consultant).

A heat pack can be applied throughout the **gemcitabine** infusion to relieve vein discomfort. **Gemcitabine is a radiation sensitizer:** be aware if patients are also receiving radiotherapy (refer to NOTE in 'Dosage' section for further details).

As with all platinum-based chemotherapy, patients may experience hypersensitivity reactions during **carboplatin** administration. Risk of hypersensitivity and anaphylaxis may increase with previous exposure to platinum therapy. Please refer to the CCC Hypersensitivity; Management Prevention Policy.

For severe reactions, discuss with Consultant before continuing with treatment. It should be strongly noted that patients who have severe reactions should not be re-challenged.

Main toxicities:

Gastrointestinal	Nausea, vomiting, diarrhoea, constipation, mucositis

General disorders	Decreases in serum electrolytes (sodium, magnesium, potassium and calcium) Renal function impairment Hyperuricaemia: Serum levels of uric acid can be decreased by allopurinol. Malaise, urticaria. flu-like syndrome, rash, pruritus, alopecia
Haematological	Neutropenia, anaemia, thrombocytopenia Myelosuppression may be more severe and prolonged in patients with impaired renal function, extensive prior treatment, poor performance status and age above 65.
Hepatobiliary	Gemcitabine- raised liver transaminases (AST/ALT) raised alkaline phosphatase and increased bilirubin.
Renal and Urological	Carboplatin- nephrotoxicity. Gemcitabine- haematuria and mild proteinuria.
Skin	Skin rash, urticaria, erythematous rash, and fever with no apparent cause or pruritus
Hypersensitivity reactions	Risk of hypersensitivity and anaphylaxis may increase with previous exposure to platinum therapy
Nervous system	Carboplatin causes paraesthesia and decreased deep tendon reflexes.
Ototoxicity	Carboplatin- tinnitus and hearing loss

Investigations and treatment plan:

	Pre	Cycle 1		Cycle 2		Cycle 33		Ongoing
		D1	D8	D1	D8	D1	D8	
Informed Consent	x							
Clinical Assessment	x			x				Prior to cycle 2 then as clinically indicated.
SACT Assessment (to include PS and toxicities)	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
Calculate GFR or CrCl and check carboplatin dose using the carboplatin calculator*	x	x	x	x	x	x	x	Every cycle
CT scan	x							As clinically indicated

ECG								If clinically indicated
Full observations		x	x	x	x	x	x	Every cycle
Weight recorded	x							Every cycle
Height	x							

*

Please refer to:

- 'Dosage' section for full details on carboplatin dosing.
- 'Carboplatin Dosing Calculator' SOP outlining process for checking carboplatin dose ahead of each cycle of treatment.

Dose Modifications and Toxicity Management:

Haematological toxicity:

Proceed on day 1 if-

Plt ≥ 100 x 10^9/L	ANC ≥ 1.0

Delay 1 week on day 1 if-

Plt ≤ 99 x 10^9/L	ANC ≤ 0.9

Proceed on day 8 if-

Plt ≥ 75 x 10^9/L	ANC ≥ 1.0

Omit on day 8 if-

Plt ≤ 74 x 10^9/L	ANC ≤ 0.9

On day 8 of the cycle **if blood results do not meet the above proceed rules then the day 8 dose will be OMITTED** and patient will proceed to the next cycle.

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 CTCAEV5 criteria. Following assessment treatment should be withheld for any toxicity until resolved to grade 0/1.

References:

1. SmPC for Carboplatin 10 mg/ml Intravenous Infusion, Hospira – accessed via electronic medicines compendium at https://www.medicines.org.uk/emc (Last updated June 2020)

2. SmPC for Gemcitabine 38 mg/ml Concentrate for Solution for Infusion, Hospira- accessed via electronic medicines compendium at https://www.medicines.org.uk/emc (Last updated 11th February 2021).
3. Loesch D, Asmar L, McIntyre K, et al. Phase II trial of gemcitabine/carboplatin (plus trastuzumab in HER2-positive disease) in patients with metastatic breast cancer. Clin Breast Cancer 2008;8:178-86.
4. Yardley DA, Burris HA III, Simons L, et al. A phase II trial of
5. gemcitabine/carboplatin with or without trastuzumab in the first-line treatment of patients with metastatic breast cancer. Clin Breast Cancer 2008;8:425-31. 3.
6. Chew HK, Doroshow JH, Frankel P, et al. Phase II studies of gemcitabine and cisplatin in heavily and minimally pretreated metastatic breast cancer. J Clin Oncol 2009;27:2163-9.
7. Maisano, R., M. Zavettieri, D. Azzarello, et al. Carboplatin and gemcitabine combination in metastatic triple-negative anthracycline- and taxane-pretreated breast cancer patients: a phase II study J Chemother 2011;23(1):40-43. 5.
8. Laessig, D., H. J. Stemmler, U. Vehling-Kaiser, et al. 2007. "Gemcitabine and carboplatin in intensively pretreated patients with metastatic breast cancer." Oncology 73(5-6):407-414.
9. 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.

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Version History

		Author name and designation	Summary of main changes
		Hala Ghoz **Lead Pharmacist for Protocols**	New Protocol Regimen V1.0