LONDON CANCER ALLIANCE West and South

Breast Pathway Group – Gemcitabine & Carboplatin in Advanced Breast Cancer

Indication:	Palliative therapy for triple negative advanced breast cancer			
Regimen details:	Gemcitabine	1000mg/m^2	IV	Day 1 & 8
	Carboplatin*	AUC 5* (EDTA)	IV	Day 1

*Carboplatin dose is calculated using the Calvert formula:
Dose = Target AUC x (25 + GFR)
Gold standard GFR is measured using EDTA wherever possible. If not available, Cockcroft & Gault equation may be used to estimate GFR for the first cycle; if the calculated GFR <60 or >120ml/min measure EDTA clearance or creatinine clearance before prescribing. Monitor trends in serum creatinine between treatments: if >25% from baseline value re-calculate GFR using the Cockcroft & Gault equation.

Due to haematological toxicity, starting doses may be reduced in heavily pre-treated patients:

Gemcitabine	800mg/m^2	IV	Day 1 & 8
Carboplatin	AUC 4	IV	Day 1

Administration:

Gemcitabine in 100-500ml Sodium Chloride 0.9% IV over 30 min
Carboplatin in 250-500ml Glucose 5% IV over 1 hour

Carboplatin infusion-related hypersensitivity reactions may occur, such as flushing, rash with or without pruritus, chest tightness, dyspnoea and fever or chills following the start of the infusion; the infusion should be slowed down or interrupted and the necessary supportive medication should be administered.
Severe reactions such as hypotension and/or bronchospasm or generalised rash/erythema requires immediate discontinuation. Availability of resuscitation equipment must be ensured as a standard precaution.

Frequency: Day 1 & 8, every 21 days, for 6 cycles

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Reason for Update: LCA Protocol Development	Approved by LCA Joint Delivery Subgroup Co-Chairs: Pauline McCalla & Rebecca Johl
Prepared by: Wendy Ng	Approved by LCA Medicines & Chemotherapy Steering Group Chair: Jamie Ferguson
Second check by: Lisa Yuen	Date prepared: November 2014 Review Date: November 2016

Pre-medication: Paracetamol / Chlorphenamine / Hydrocortisone can be given for infusion-related reactions such as chills / fever

Anti- emetics: Day 1: High emetogenicity
Day 8: Mild emetogenicity
Follow local anti-emetic policy

Supportive medication: Mouthcare as per local policy

Extravasation: Gemcitabine – Non-vesicant
Carboplatin – Irritant

Regular investigations:

Prior to Cycle 1:

EDTA	Prior to cycle 1
FBC	Day 1 (within 14 days)
LFTs	Day 1 (within 14 days)
U&Es	Day 1 (within 14 days)

Prior to Day 8 (all cycles):

FBC	Day 8 (within 48 hours)

Prior to Day 1 (all cycles):

FBC	Day 1 (within 72 hours)
LFTs	Day 1 (within 72 hours)
U&Es	Day 1 (within 72 hours)

Toxicities: Myelosuppression (particularly thrombocytopenia), fatigue, alopecia (mild), mucositis, somnolence, proteinuria and haematuria, allergic skin rashes, oedema, asthenia, rarely pneumonitis, elevation of transaminases, neurotoxicity (ototoxicity), nephrotoxicity, infertility/ ovarian failure

DOSE MODIFICATIONS

Haematological Toxicity
Day 1

Neutrophils (x 10^9/L)		Platelets (x 10^9/L)	Dose
≥ 1.5	**&**	≥ 100	100% dose
< 1.5	**or**	< 100	Delay for 1 week. Repeat FBC – if recovered to above these levels, resume treatment with 100% dose. Consider dose reduction for > 1 delay

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Dose reduction and / or delay is more appropriate in the advanced setting.

- If during the preceding cycle, the patient has experienced neutrophils < 0.5 x 10^9/L or has febrile neutropenia diagnosed, GCSF should be considered.
- If platelets persistently < 100 x 10^9/L on Day 1 despite dose delay – seek Consultant advice and consider dose reduction by 25%

Prior day 8 – Gemcitabine

Neutrophils (x 10^9/L)		Platelets (x 10^9/L)	Gemcitabine Dose
≥ 1.0	**&**	≥ 100	100% dose
0.5 – 0.9	**or**	75 - 100	75% dose
< 0.5	**or**	< 75	Omit Re-assess on day 1 of the next cycle

Non-haematological Toxicities

Renal Impairment

Creatinine Clearance	Gemcitabine Dose	Carboplatin Dose
> 30ml/min	100%	Contra-indicated if GFR <20ml/min.
< 30ml/min	Gemcitabine should be used with caution in patients with CrCl <30ml/min; however, no specific dosing recommendations have been made.	

Hepatic Impairment

	Gemcitabine Dose	Carboplatin Dose
Hepatic Impairment	AST elevations do not seem to cause dose limiting toxicities If bilirubin >27μmol/L, initiate treatment with 800mg/m^2	Probably no dose reduction necessary

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Dose modifications for other toxicities as appropriate

In case of grade 3 or 4 **neurotoxicity**, Carboplatin should be discontinued.

Grade	Stomatitis	Diarrhoea	Dose Reductions
1	Painless ulcers, erythema or mild soreness	Increase of 2-3 stools/day or mild increase in loose watery colostomy output	100% doses
2	Painful erythema, edema, or ulcers but can eat	Increase of 4-6 stools, or nocturnal stools or mild increase in loose watery colostomy output	Omit until resolved, then resume at 100% doses
3	Painful erythema, edema, or ulcers and cannot eat	Increase of 7-9 stools/day or incontinence, malabsorption, or severe increase in loose watery colostomy output	Omit until resolved, then resume gemcitabine at 75% dose and carboplatin at 75% dose
4	Mucosal necrosis, requires parenteral support	Increase of 10 or more stools/day or grossly bloody diarrhoea, or grossly bloody colostomy output or loose watery colostomy output requiring parenteral support, dehydration	Omit until resolved, then resume gemcitabine at 50% dose and carboplatin at 75% dose

Location of regimen: delivery

Outpatient setting
Availability of resuscitation equipment must be ensured as a standard precaution.

Comments:

<u>Haemolytic anaemia</u>
Gemcitabine should be discontinued at the first signs of any evidence of micro-angiopathic haemolytic anaemia, such as rapidly falling haemoglobin with concomitant thrombocytopenia, elevation of serum bilirubin, serum creatinine, blood urea nitrogen, or LDH, which may indicate development of haemolytic uraemic syndrome. Renal failure may not be reversible, even with discontinuation of therapy, and dialysis may be required

Drug interactions:

Gemcitabine is radiosensitiser

- Warfarin - increased risk of bleeding (Gemcitabine)
- Phenytoin – Carboplatin decreases efficiency
- Nephrotoxic drugs (with Carboplatin)
- Aminoglycoside antibiotics-increased risk of ototoxicity (with Carboplatin)

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References:

Mount Vernon Gem/carbo protocol
NWLCN Breast Regimen Version 7 01
British Oncology Pharmacy Association (BOPA) Guidelines for Dose Adjustment of Cytotoxics in Hepatic and Renal impairment January 2009 accessed from www.bopawebsite.org
Summary of product characteristics – gemcitabine, carboplatin available at www.medicines.org.uk
LCA Breast Cancer Clinical Guidelines October 2013

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