ACCELERATED EC x 4, *followed by* CARBOPLATIN & PACLITAXEL x 4

For neo-adjuvant use in patients with triple negative, early stage, breast cancer
For younger, fit patients with a large primary +/- axillary lymphadenopathy, where down-staging will have an impact on management
May also be used in the adjuvant setting, in selected high-risk patients with TNBC

Drugs / Dosage/ Frequency:	**Epirubicin**	90mg/m^2	IV	Day 1	every **2 weeks** for up to 4 cycles*
	Cyclophosphamide	600mg/m^2	IV	Day 1	every **2 weeks** for up to 4 cycles*
	*followed by (**2** weeks after last cycle of EC):*				
	Carboplatin	AUC 5	IV	Day 1 every **3 weeks** for 4 cycles	
	Paclitaxel	80mg/m^2	IV	Day 1, 8 & 15 every 3 weeks for 4 cycles	

*according to response, the decision may be taken to proceed to paclitaxel/carboplatin after 3 cycles of EC.

Administration:

Epirubicin via fast running infusion of 0.9% sodium chloride
Cyclophosphamide may be given as bolus injections

Carboplatin in 250 ml 5% glucose over 30 - 60 minutes
Paclitaxel < 160mg in 250ml (≥ 160mg in 500ml) 0.9% sodium chloride over 1 hour
Administer paclitaxel with PVC-free giving set with a 0.2 micron in-line filter
Paclitaxel premedication:

Dexamethasone	8mg**	IV	
Chlorphenamine	10mg	IV	Give 30 minutes prior to administration
Ranitidine	50mg	IV	

**To minimise steroid side effects, the dose of dexamethasone may be reduced, and in some cases stopped, if there has been no evidence of hypersensitivity.

Main Toxicities:

myelosuppression; alopecia; diarrhoea; mucositis;
cardiotoxicity (epirubicin); haemorrhagic cystitis (cyclophosphamide);
hypersensitivity reactions to paclitaxel (infusion-related and ↑ risk with 1st/2nd treatment);
myalgia/arthralgia (paclitaxel); neurotoxicity (paclitaxel); ovarian failure / infertility

Anti-emetics:

EC and Carboplatin: highly emetogenic Paclitaxel: mildly emetogenic

Other Drugs:

Accelerated EC: Primary G-CSF prophylaxis s/c once daily for **7** days, starting on Day 3.

Paclitaxel & carbo: Primary G-CSF prophylaxis s/c once daily for 5 days, starting on Day 3

Extravasation:

epirubicin and paclitaxel are vesicants

Regular Investigations:

FBC	Day 1 of each cycle, and before each paclitaxel dose (Day 8 & Day 15)
U&Es & LFTs	Day 1 of each cycle
Echo/MUGA	baseline pre chemotherapy, see Comments
EDTA	prior to 1st carboplatin dose

Comments:

Maximum cumulative dose of epirubicin = 950mg/m^2
A baseline echo/MUGA should be performed where the patient is considered at risk of having impaired cardiac function e.g. significant cardiac history, hypertension, obese, smoker, elderly, previous exposure to anthracyclines, previous thoracic radiotherapy. Echo/MUGA should be

repeated if there is suspicion of cardiac toxicity at any point during treatment, or if cumulative anthracycline dose approaches maximum.

Carboplatin dose should be calculated using the Calvert Formula:
Dose = Target AUC x (25+GFR)
Cycle 1 may be given using the Cockcroft and Gault (C&G) formula to predict creatinine clearance if the EDTA is not yet available. When using C&G, a "cap" of 125 ml/min should be used for carboplatin dose calculations.
Carboplatin dose should be re-calculated using the EDTA result for subsequent cycles (do not "cap"). EDTA should only be repeated if there is a 30% change in serum creatinine.

Dose Modifications

Haematological Toxicity:

Dose reduction and / or delays can compromise outcome.
Primary G-CSF prophylaxis is standard with all cycles.
If any delay or episode of febrile neutropenia occurs despite the use of G-CSF, or any delay due to low platelets, the doses of epirubicin, or paclitaxel +/- carboplatin may be reduced by 20 - 25%. If in doubt, contact the relevant Consultant.

Neutrophils ≥ 1.5 x 10^9/l and Platelets > 100 x 10^9/l	Proceed with chemotherapy.
Neutrophils 1.1 - 1.4 x 10^9/l and Platelets > 100 x 10^9/l	Contact the Consultant (preferably) or SpR for the decision on whether to delay treatment as below, or to proceed.
Neutrophils ≤ 1.0 x 10^9/l or Platelets ≤ 100 x 10^9/l	Delay for 1 week. Repeat FBC - if within normal parameters, resume treatment, as discussed above.

Renal Impairment:

Carboplatin is contra-indicated if GFR < 20 ml/min

CrCl (ml/min)	Cyclophosphamide Dose
10 – 20	Give 75%
< 10	Give 50%

Hepatic Impairment:

Bilirubin (µmol/l)	Epirubicin Dose
24 – 51	Give 50% dose
52 – 85	Give 25% dose
> 85	Omit

A paclitaxel dose reduction should probably be given initially if impaired hepatic function. Due to lack of data, dose recommendations not available. If in doubt, contact the relevant Consultant.

Other paclitaxel-related toxicities:

If Grade 1-2 peripheral neuropathy develops, seek advice from Consultant regarding a paclitaxel dose reduction.
Myalgia and arthralgia often co-exist while on taxanes, usually Grade 1 or Grade 2. Management consists of reassuring patients that it is self-limiting. Consider use of NSAIDs, although not always effective.

References:

von Minckwitz, G et al; Lancet 2014; 15 (7): 746 – 756
Sikov, W et al; JCO 2015; 33 (1): 13 - 21