Accelerated EC – DOCETAXEL

For neo-adjuvant use in HER2+ve early stage node-positive breast cancer and high risk node-negative breast cancer

To be given in combination with neo-adjuvant pertuzumab and trastuzumab, in all patients who meet the criteria
Blueteq registration is required before treatment with pertuzumab may start

Drugs / Dosage / Frequency:	Epirubicin	90mg/m^2	IV	Day 1 }	every **2 weeks** for 3 cycles
	Cyclophosphamide	600mg/m^2	IV	Day 1 }	
	*followed by (**2 weeks** after Cycle 3 of EC):*				
	Docetaxel	75 mg/m^2	IV	Day 1	every 3 weeks for 4 cycles
	with				
	Pertuzumab IV and Trastuzumab IV (see separate protocol) every 3 weeks for 4 cycles				

Other Drugs:

Accelerated EC:
Primary G-CSF prophylaxis s/c once daily for **7** days, starting on Day 3
With the third cycle of EC, remember to prescribe the dexamethasone pre-med for the first cycle of docetaxel

Docetaxel:
Primary G-CSF prophylaxis s/c once daily for 5 days, starting on Day 3.
Dexamethasone 8mg po bd for 3 days, starting the morning of the day prior to docetaxel chemotherapy (to prevent hypersensitivity reactions and fluid retention)
If the patient has not taken the oral pre-med for any reason, intravenous dexamethasone is not recommended and can only be substituted if prescribed by a Consultant.

Administration:

Epirubicin via fast running infusion of 0.9% sodium chloride
Cyclophosphamide may be given as bolus injections
Docetaxel doses ≤ 185mg, in 250ml sodium chloride 0.9% over 1 hour
Docetaxel doses > 185mg, in 500ml sodium chloride 0.9% over 1 hour

Main Toxicities:

EC: myelosuppression; alopecia; mucositis; cardiomyopathy; haemorrhagic cystitis; ovarian failure/infertility

Docetaxel: hypersensitivity reactions (infusion-related and ↑ risk with 1st/2nd treatment); myelosuppression; alopecia; fluid retention; stomatitis; skin reactions & nail changes; peripheral neurotoxicity; diarrhoea; myalgia / arthralgia; ovarian failure / infertility

Anti-emetics: EC: highly emetogenic Docetaxel: moderately emetogenic

Extravasation: epirubicin is a vesicant

Regular Investigations:	FBC	Day 1 of each cycle
	U&Es & LFTs	Day 1 of each cycle
	Echo/MUGA	baseline pre chemotherapy, see Comments plus post-anthracycline LVEF result required before HER2 therapy starts

Comments:

Offer scalp cooling

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. MUGA scan should be

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

Anti-HER2 therapy may commence with the first cycle of docetaxel (loading doses of IV trastuzumab + pertuzumab to be given on the day before Cycle 1 of docetaxel)

For patients with severe hypersensitivity reactions to docetaxel, paclitaxel substitution may be attempted by switching to the Accelerated EC - Accelerated paclitaxel protocol at the appropriate cycle:
- *if replacing 3 or 4 doses of docetaxel, give 4 cycles of paclitaxel*
- *if replacing 2 doses of docetaxel, give 3 doses of paclitaxel*

Dose Modifications

Haematological Toxicity:

In neo-adjuvant treatment, dose reduction and/or delays can compromise outcome.
Primary G-CSF prophylaxis is standard with all cycles.
If any delay due to neutropenia or episode of febrile neutropenia occurs despite the use of G-CSF, consider a longer course of G-CSF. The doses of epirubicin or docetaxel should be reduced by 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	**EC**: Contact the Consultant (preferably) or SpR for his decision on whether to delay treatment as below, or to proceed. **Docetaxel**: Delay for 1 week as below
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:

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

If Bilirubin > 22 µmol/l **or** ALT/AST > 3.5 x ULN **with** ALP > 6 x ULN, docetaxel is not recommended; should only be administered with Consultant approval.

Other Docetaxel-Related Toxicities:

If Grade 2 neuropathy, reduce docetaxel dose by 25%. If symptoms return, stop docetaxel.
If Grade 3 or 4 neuropathy, discontinue treatment.
If Grade 3 or 4 cutaneous reactions, once patient recovered, reduce dose by 25%. If symptoms return, stop docetaxel.

Myalgia and arthralgia often co-exist, 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:

Roche, H et al; JCO (2006); 24 (36) (PACS 01 trial)
Del Maestro, L et al; Lancet 2015; 385: 1863 – 1872