Neo-adjuvant FEC-TPH (Fluorouracil, Epirubicin and Cyclophosphamide then Docetaxel, Pertuzumab and Trastuzumab)

Indication

Neo-adjuvant treatment for HER2 positive, locally advanced, inflammatory or early stage breast cancer at high risk of recurrence.

(NICE TA424)

Adjuvant treatment for HER2 positive, early stage breast cancer with lymph node positive disease.

(NICE TA569)

ICD-10 codes

Codes with a prefix C50

Regimen details

Cycles 1-3*

Day	Drug	Dose	Route
1	Epirubicin	100mg/m^2	IV bolus
1	Fluorouracil	500mg/m^2	IV bolus
1	Cyclophosphamide	500mg/m^2	IV bolus

*Other anthracycline based schedules may be used for the first 3 -4 cycles according to local practice eg epirubicin/doxorubicin and cyclophosphamide.

Cycle 4

Day	Drug	Dose	Route
1	Pertuzumab	840mg	IV infusion
1	Trastuzumab	8mg/kg	IV infusion
1	Docetaxel	75mg/m^2	IV infusion

Due to the potential for hypersensitivity reactions, for this cycle pertuzumab may be administered on day 1 and trastuzumab and docetaxel on day 2.

Cycles 5-7:

Day	Drug	Dose	Route
1	Pertuzumab	420mg	IV infusion
1	Trastuzumab	6mg/kg	IV infusion
1	Docetaxel	*75mg/m^2	IV infusion

*Docetaxel may be escalated to 100mg/m^2 for subsequent cycles if the initial dose is tolerated, at the consultants' discretion.

If the dosing interval is > 4 weeks for trastuzumab or ≥ 6 weeks for pertuzumab, a loading dose will be required.

Following surgery, depending on nodal status adjuvant trastuzumab +/- pertuzumab should be continued to complete 1 year of treatment.

For node negative disease:
Trastuzumab may be given as a flat 600mg subcutaneous dose or continue iv dosing at 6mg/kg as above.

Cycles 8-21

Day	Drug	Dose	Route
1	Trastuzumab (Herceptin®)	600mg	SC

For node positive disease:
Pertuzumab and trastuzumab should be continued to complete 1 year of treatment.

Cycles 8-21

Day	Drug	Dose	Route
1	Pertuzumab	420mg	IV infusion
1	Trastuzumab	6mg/kg	IV infusion

Cycle frequency
21 days

Number of cycles
Maximum of 7 cycles (3 x FEC100 followed by 3-4 x TPH).
Adjuvant trastuzumab +/- pertuzumab should be continued to complete 1 year of treatment (maximum 18 cycles in total).

Administration
Cycles 1-3:
Epirubicin, fluorouracil and cyclophosphamide are administered by slow IV bolus into the arm of a fast running drip of sodium chloride 0.9%. Cyclophosphamide may also be given as an IV infusion in 250-500mL sodium chloride 0.9% over 30 minutes.

Cycles 4-7:
Pertuzumab and trastuzumab may be administered in either order but the docetaxel should be administered last.

Pertuzumab is administered in 250mL sodium chloride 0.9% over 60 minutes (cycle 4) followed by a 60 minute observation period (before next drug administration). For cycle 5 onwards (providing pertuzumab is well tolerated) pertuzumab may be administered over 30 minutes followed by a 60 minute observation period.

Trastuzumab is administered in 250mL sodium chloride 0.9% over 90 minutes (cycle 4). The patient should be observed for 6 hours after the start of the infusion for symptoms of infusion related reactions (e.g. fever, chills). For cycle 5 onwards, (providing trastuzumab well tolerated) trastuzumab may be given over 30 minutes. Patients should be observed for 2 hours after the start of the infusion for symptoms of infusion related reactions.

It may not be necessary to stop treatment for minor hypersensitivity reactions e.g. flushing, localised rash but infusions must be stopped for major reactions, e.g. hypotension, dyspnoea, angioedema or generalised urticaria.

Docetaxel is administered as an IV infusion in 250mL or 500mL (concentration dependent) PVC free sodium chloride 0.9% over 60 minutes.

Patients should be observed closely for hypersensitivity reactions, particularly during the first and second infusions. Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of docetaxel and therefore facilities for the treatment of hypotension and bronchospasm must be available.

If hypersensitivity reactions occur, minor symptoms such as flushing or localised cutaneous reactions do not require discontinuation of therapy. The infusion may be temporarily interrupted and when symptoms improve re-started at a slower infusion rate. Severe reactions, such as hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of docetaxel and appropriate therapy.

Patients who have developed severe hypersensitivity reactions should not be re-challenged with docetaxel, unless following a risk assessed desensitisation protocol.

Following surgery:
Node negative: cycles 8-21:
Trastuzumab may be administered by IV infusion as above or as a flat dose of 600mg in a volume of 5mL by subcutaneous injection over 2-5 minutes. The injection site should be alternated between left and right thigh, with new injections at least 2.5cm from the old site. Avoid administration into sites that are bruised, inflamed, tender or hard. Other medicinal products for subcutaneous administration should preferably be injected at different sites. Patients should be observed for administration related reactions for 6 hours after the first dose and 2 hours after subsequent doses (or as per local policy for trastuzumab administration).

Node positive cycles 8-21:
Pertuzumab and trastuzumab are administered by IV infusion as above.

Pre-medication

FEC cycles: none usually required

TPH cycles: Dexamethasone 8 mg BD (morning and lunchtime) for 3 days starting 24 hours prior to chemotherapy. (Note: Patients must receive 3 doses of dexamethasone prior to treatment).
In the case where 3 doses have not been taken, dexamethasone 16-20mg IV should be administered 30-60 minutes prior to chemotherapy and the remaining 3 oral doses should be taken as normal.

Emetogenicity

FEC cycles: moderate - high emetic potential
TPH cycles: moderate-low emetic potential

Additional supportive medication

Primary GCSF prophylaxis as per local policy
Mouthwashes as per local policy
H_2 antagonist or proton-pump inhibitor if required
Loperamide if required. Prior to starting pertuzumab loperamide should be prescribed to be taken if needed for management of diarrhoea
Scalp cooling may be offered.

Extravasation

Epirubicin is a vesicant (Group 5)
Fluorouracil is an inflammatant (Group 2)
Cyclophosphamide, pertuzumab and trastuzumab are neutral (Group 1)
Docetaxel is an exfoliant (Group 4)

Investigations – pre first cycle

Investigation	**Validity period** (or as per local policy)
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days
Echocardiogram	Baseline (or according to local practice)

Investigations – pre subsequent cycles

Investigation	**Validity period** (or as per local policy)
FBC	96 hours
U+E (including creatinine)	7 days
LFTs	7 days
Echocardiogram	Pre cycle 4 and cycle 6. Then every 3 months or according to local practice

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	**Limit**
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥ 100 x 10^9/L
Creatinine Clearance (CrCl)	> 20 mL/min
Bilirubin	≤ 1.0 ULN*
AST/ALT	≤ 1.5 x ULN*
Alkaline Phosphatase	≤ 2.5 x ULN
Echocardiogram (cycle 4 onwards) – LVEF	≥ Lower Limit of Normal for the institution (LNN)

*See table below for standard limits to go ahead for FEC cycles

Dose modifications

- **Haematological toxicity**

If neutrophils <1.0 x 10^9/L and/or platelets <100 x 10^9/L delay 1 week or until recovery.

If febrile neutropenia or neutrophils < 0.5 x 10^9/L for more than 1 week consider reducing doses of all drugs to 80% (except trastuzumab and pertuzumab) for future cycles.

Trastuzumab and pertuzumab may continue during periods of chemotherapy induced myelosuppression.

- **Renal impairment**

CrCl (mL/min)	**Cyclophosphamide dose**
> 20	100%
10-20	75%
<10	50%

There is no data available on the use of epirubicin or fluorouracil in severe renal impairment. Consider dose reduction if CrCl <10mL/min (consultant decision).

Docetaxel: consider dose reduction if CrCl <10mL/min (consultant decision).

No dose modification for renal function is required for trastuzumab.

Pertuzumab has not been studied in renal impairment; no dose recommendations can be made.

- **Hepatic impairment**

FEC cycles:

Bilirubin (x ULN)		**AST/ALT** (x ULN)		**Alkaline phosphatase** (xULN)	**Epirubicin dose**	**Fluorouracil dose**	**Cyclophosphamide dose**
< 1.5	and	≤ 2.0	and	≤ 2.5	100%	100%	100%
1.5 - < 3	or	> 2.0 -3.5	or	> 2.5 - <5	50%	100%	100%*
≥3 - 5	or	> 3.5	and	5-10	25%	Consider dose reduction (discuss with consultant)	Consider dose reduction (discuss with consultant)
> 5			or	> 10	Omit	Omit	Contraindicated

*Cyclophosphamide is not recommended if bilirubin > 1.5 x ULN or AST/ALT > 3 x ULN (consultant decision).

TPH cycles:

AST/ALT (x ULN)		**Alkaline phosphatase*** (x ULN)	**Docetaxel dose**
≤ 1.5	and	< 2.5	100%
> 1.5 – 3.5	or	≥ 2.5- 6	75%
> 3.5	or	≥ 6	60% or discontinue - discuss with consultant

If AST/ALT is 1.5-2.5 x ULN and alkaline phosphatase is <2.5 x ULN the maximum recommended dose of docetaxel is 75 mg/m^2
*unless due to bone metastases only.

If bilirubin > 1.0 x ULN withhold dose (or consultant decision to treat)

No dose modification is required for trastuzumab.

Pertuzumab has not been studied in hepatic impairment; no dose recommendations can be made.

- **Other toxicities**

FEC cycles:
For grade 3 or 4 mucositis/stomatitis – delay until resolved to ≤ grade 1 and reduce dose of fluorouracil and epirubicin to 80% dose.

Any other grade 3 or 4 toxicity- discuss with consultant.

TPH cycles:

Toxicity	**Definition**	**Docetaxel dose**
Peripheral neuropathy	Grade 2	75%
	Grade 3 or 4	Discuss with consultant
Diarrhoea*	Grade 3 or 4	1st occurrence – 75%
		2nd occurrence – 60%
Stomatitis	Grade 3 or 4	1st occurrence – 75%
		2nd occurrence – 60%

*Pertuzumab may cause severe diarrhoea. If severe diarrhoea an anti-diarrhoeal treatment should be instituted and interruption of the treatment with pertuzumab should be considered if no improvement of the condition is achieved. When the diarrhoea is under control the treatment with pertuzumab may be reinstated.

Left ventricular dysfunction

LVEF must be above LLN for treatment to go ahead. The summary of product characteristics (SPC) for pertuzumab states that cardiac monitoring is required every 2 cycles in the neoadjuvant setting. After completion of neo-adjuvant treatment cardiac monitoring should be every 3 – 4 months whilst on trastuzumab with additional monitoring after completion according to local practice or SPC.

LVEF	Trastuzumab/Pertuzumab
> LLN	Continue
40-LLN and decrease < 10% from baseline **and** asymptomatic	Continue. If BP and renal function adequate start an ACE inhibitor (eg ramipril 2.5mg) and consider a beta blocker (eg bisoprolol 2.5mg). Repeat LVEF within 3 weeks
40-LNN and decrease ≥ 10% from baseline **and** asymptomatic	Withhold. If BP and renal function adequate start an ACE inhibitor (eg ramipril 2.5mg) and consider a beta blocker (eg bisoprolol 2.5mg). Repeat LVEF within 3 weeks and if not within 10% from baseline withhold treatment. Discuss with consultant and refer to cardiology
< 40%	Withhold. If BP and renal function adequate start an ACE inhibitor (eg ramipril 2.5mg) and consider a beta blocker (eg bisoprolol 2.5mg). Repeat LVEF within 3 weeks and if < 40% withhold treatment and discuss with consultant. Refer to cardiology
Symptomatic congestive heart failure	Discontinue

Any other grade 3 or 4 toxicity- discuss with consultant.

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Secondary malignancy
Myelosuppression
Infusion related reactions
Anaphylaxis
Teratogenicity
Infertility/Early menopause
Cardiotoxicity
Peripheral neuropathy
Interstitial lung disease

- **Frequently occurring side effects**

Diarrhoea
Constipation
Fatigue
Nausea and vomiting
Myelosuppression
Stomatitis and mucositis
Arthralgia and myalgia
Alopecia

- **Other side effects**

Fluid retention

Red urine (for 24 hours post epirubicin)
Deranged liver function
Phlebitis
Skin toxicity
Nail changes
Taste disturbances
Bladder irritation

Significant drug interactions – for full details consult product literature/ reference texts

Warfarin/coumarin anticoagulants: increased or fluctuating anticoagulant effects. Avoid if possible, consider switching patient to a low molecular weight heparin during treatment or if the patient continues taking an oral anticoagulant monitor the INR at least once a week and adjust dose accordingly.

Phenytoin: requires close monitoring if using concurrently.

Co-trimoxazole/trimethoprim: enhances antifolate effect. Avoid if possible, if essential, monitor FBC regularly.

Cyclophosphamide:
Amiodarone: increased risk of pulmonary fibrosis – avoid if possible
Clozapine: increased risk of agranulocytosis – avoid concomitant use
Digoxin tablets: reduced absorption – give as liquid form
Indapamide: prolonged leucopenia is possible - avoid
Itraconazole: may increase adverse effects of cyclophosphamide
Grapefruit juice: decreased or delayed activation of cyclophosphamide. Patients should be advised to avoid grapefruit juice for 48 hours before and on day of cyclophosphamide dose.

Docetaxel:
CYP3A4 Enzyme inducers/inhibitors: in vitro studies suggest that CYP3A inhibitors (such as ketoconazole, ritonavir, clarithromycin and erythromycin) may raise docetaxel levels, whereas CYP3A inducers (such as rifampicin and barbiturates) may reduce docetaxel levels.

There is no data regarding drug interactions with trastuzumab or pertuzumab.

Additional comments

Dihydropyrimidine dehydrogenase (DPD) deficiency can result in severe toxicity secondary to reduced fluorouracil metabolism – avoid use in patients with known DPD deficiency.

Epirubicin has a life time maximum cumulative dose of 900mg/m^2

Women of childbearing potential should use effective contraception while receiving pertuzumab and for 6 months following treatment.

References

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