

BC Cancer Protocol Summary for Adjuvant Therapy for Breast Cancer Using Fluorouracil, Epirubicin and Cyclophosphamide Followed by DOCEtaxel and Trastuzumab (HERCEPTIN)

Protocol Code
Tumour Group
Contact Physician

BRAJFECDT
Breast
Dr. Stephen Chia

ELIGIBILITY:

- Node positive (any T, N1-3) or high risk, node negative early stage breast cancer showing over-expression of HER-2
- HER-2 over-expression defined as either IHC3+, or FISH amplification ratio greater than or equal to 2 per BC Cancer central laboratory
- Less than or equal to 65 years of age or fit patients greater than 65 years deemed appropriate by supervising physician
- ECOG 0-1
- Anticipated survival of greater than 5 years
- Adequate marrow, renal, and hepatic function
- No clinically significant cardiac disease
- LVEF greater than or equal to 50%*
* If the LVEF is between 45-50%, the oncologist may decide to treat based on clinical assessment

EXCLUSIONS:

- ECOG 2-4
- Significant hepatic dysfunction
- Significant cardiovascular disease and/or LVEF less than 50%; if initial reading is less than 50%, physician may consider repeating for validity, or assessing LVEF by the other modality, e.g. echocardiogram instead of MUGA
- Greater than or equal to grade 2 sensory or motor neuropathy
- Pregnancy or lactation
- Unsuitable for aggressive adjuvant chemotherapy

TESTS:

- Baseline: CBC & diff, platelets, creatinine, bilirubin, liver enzymes
- Before each treatment (Day 1): CBC & diff, platelets
- Prior to **Cycle #4**: CBC & diff, platelets, bilirubin, liver enzymes (see Precaution #5 for guidelines regarding hepatic dysfunction and DOCEtaxel)
- MUGA scan or echocardiogram: prior to first treatment with trastuzumab and every 3-4 months until completion of treatment per the discretion of the treating physician. The maximum time between cardiac monitoring should be 4 months (see dose modification #5 for adjustment of trastuzumab based on changes in LVEF)
- If clinically indicated: bilirubin, liver enzymes, creatinine, MUGA scan or echocardiogram

PREMEDICATIONS:

- For the 3 cycles of Epirubicin, Fluorouracil and Cyclophosphamide Antiemetic protocol for highly emetogenic chemotherapy (see protocol [SCNAUSEA](#))
- For the 3 cycles of DOCEtaxel and Trastuzumab:
 - Dexamethasone 8 mg PO bid for 3 days, starting one day prior to each DOCEtaxel administration. Patient must receive minimum of 3 doses pre-treatment.
 - Additional antiemetics not usually required.
 - DOCEtaxel-induced onycholysis and cutaneous toxicity of the hands may be prevented by wearing frozen gloves starting 15 minutes before DOCEtaxel infusion until 15 minutes after end of DOCEtaxel infusion; gloves should be changed after 45 minutes of wearing to ensure they remain cold during the entire DOCEtaxel infusion.

TREATMENT:**Cycles 1-3**

Drug	Dose	BC Cancer Administration Standard
epirubicin	100 mg/m ² on Day 1	IV push
fluorouracil	500 mg/m ² on Day 1	IV push
cyclophosphamide	500 mg/m ² on Day 1	IV in 100 to 250* mL NS over 20 min to 1 hour

*Use 250 mL for dose greater than 1000 mg

- Repeat every 21 days x 3 cycles
- Followed by 3 consecutive cycles of DOCEtaxel and trastuzumab to start **21 days after final cycle of epirubicin, fluorouracil and cyclophosphamide**

Cycle 4

Drug	Dose	BC Cancer Administration Guideline
trastuzumab (HERCEPTIN)	8 mg/kg	IV in 250 mL NS over 1 hour 30 min Observe for 1 hour post-infusion
DOCEtaxel	100 mg/m ²	IV in 250 to 500 mL* NS over 1 hour. (use non-DEHP equipment)

*Use 250 mL for doses 74-185 mg, use 500 mL for doses greater than 185 mg

Cycles 5 and 6

Drug	Dose	BC Cancer Administration Guideline
trastuzumab (HERCEPTIN)	6 mg/kg	<ul style="list-style-type: none"> IV in 250 mL NS over 1 hour on the second dose (Cycle 5). Observe for 30 minutes post infusion IV IN 250 ml NS over 30 min on the third dose (Cycle 6), Observe for 30 min post infusion
DOCEtaxel	100 mg/m ²	IV in 250 to 500 mL* NS over 1 hour (use non-DEHP equipment)

* Use 250 mL for doses 74-185 mg, use 500 mL for doses greater than 185 mg

Repeat every 21 days x 3 cycles.

Followed by 14 consecutive cycles of trastuzumab to start 21 days after the final cycle of DOCEtaxel/trastuzumab for a total of 1 year of trastuzumab treatment. See [BC Cancer Protocol BRAJTR](#)

Radiation:

For patients with indications for radiation, the radiation treatment should be given at the usual time after the completion of the chemotherapy with the trastuzumab continued during the radiation therapy. There has been no increased toxicity reported in the clinical trials at this time, but there is no long term data; therefore, patients should be monitored. There have been no studies of concurrent trastuzumab and internal mammary node radiation, so it is unclear at this time whether there would be an enhanced risk of cardiotoxicity. If there is an anticipated need for internal mammary node radiation, it may be helpful to discuss the overall treatment program and timing with the treating radiation oncologist at the outset of chemotherapy.

DOSE MODIFICATIONS

Doses are adjusted based on Day 1 counts (Tables 1 to 3) and previous cycle febrile neutropenia (Table 4). No dose reduction for nadir counts.

1. Hematological

For Cycles of epirubicin, fluorouracil, and cyclophosphamide

Table 1. Cycle 1, Day 1

ANC (x 10 ⁹ /L)		Platelets (x 10 ⁹ /L)	Dose (all drugs)
greater than or equal to 1.5	and	greater than or equal to 90	100%
1 to 1.49	and	greater than or equal to 90	75%
less than 1	or	less than 90	ineligible for treatment

Table 2. Cycles 2 to 3, Day 1

FIRST OCCURRENCE OF LOW COUNTS

when ANC less than $1.5 \times 10^9/L$ and/or platelets less than $90 \times 10^9/L$

after a one week delay and no febrile neutropenia in a previous cycle

ANC ($\times 10^9/L$)		Platelets ($\times 10^9/L$)	All Chemotherapy Drugs % Dose of Previous Cycle
greater than or equal to 1.5	and	greater than or equal to 90	100%
1 to 1.49	and	greater than or equal to 90	75%
less than 1	or	less than 90	Delay until ANC greater than or equal to 1.5 and platelets greater than or equal to 90 then give 75%

Table 3. Cycles 2 to 3, Day 1

SECOND OCCURRENCE OF LOW COUNTS

when ANC less than $1.5 \times 10^9/L$ and/or platelets less than $90 \times 10^9/L$

after a one week delay and no febrile neutropenia in a previous cycle

ANC ($\times 10^9/L$)		Platelets ($\times 10^9/L$)	All Chemotherapy Drugs % of Previous Cycle Dose	Filgrastim (G-CSF) Option
greater than or equal to 1.5	and	greater than or equal to 90	75 % of previous cycle dose	100% regimen with G-CSF 300 mcg sc daily on Days 5 to 12 (adjust as needed)
less than 1.5	and	greater than or equal to 90	Delay 1 week or until ANC greater than or equal to 1.5 - then give 75% of previous cycle dose	75% regimen with G-CSF 300 mcg sc daily on Days 5 to 12 (adjust as needed)
		less than 90	Delay 1 week or until ANC greater than or equal to 1.5 and platelets greater than or equal to 90 then give 75% of previous cycle dose	

For cycles of DOCEtaxel only:

Table 4.

ANC ($\times 10^9/L$)		Platelets ($\times 10^9/L$)	Dose	Dose after Febrile Neutropenia on DOCEtaxel
greater than or equal to 1.5	and	greater than 90	100%	75%
1 to 1.49	or	70 to 90	75%	Delay till recovery then 75%
less than 1	or	less than 70	delay	Delay till recovery then 75%

Table 5. Febrile Neutropenia

Event	Dose Reduction Option	Filgrastim (G-CSF) Option
1 st episode	75% of previous cycle dose if Day 1 ANC greater than or equal to 1.5 and platelets greater than or equal to 90	100% regimen with G-CSF 300 mcg sc daily on Days 5 to 12 (adjust as needed)
2 nd episode	50% of original cycle dose if Day 1 ANC greater than or equal to 1.5 and platelets greater than or equal to 90	75% regimen with G-CSF 300 mcg sc daily on Days 5 to 12 (adjust as needed)
3 rd episode	No dose reduction option	75% regimen with G-CSF 300 mcg sc daily on Days 5 to 12 (adjust as needed)

- Stomatitis:** For Grade 3 or 4 stomatitis (painful erythema, edema or ulcers and cannot eat, mucosal necrosis and/or requires enteral support; dehydration), delay until recovered then give 75% dose of Day 1 of previous cycle. Maintain dose reduction for all subsequent cycles.
- Hepatic Dysfunction:** Dose modification required for epirubicin if total bilirubin greater than or equal to 25 micromol/L, for fluorouracil if greater than 85 micromol/L (see Cancer Drug Manual) and for DOCEtaxel (Refer Cancer Drug Manual monograph for DOCEtaxel).
- Renal Dysfunction:** Dose modification may be required for cyclophosphamide if creatinine clearance less than 0.3 mL/sec, i.e., less than 18 mL/minute (see Cancer Drug Manual)
- Cardiac Dysfunction**

Asymptomatic Patients – Trastuzumab continuation based on serial LVEFs

Relationship of LVEF to LLN	Absolute Decrease Of less than 10 points from baseline	Absolute Decrease Of 10 -15 points from baseline	Absolute Decrease Of greater than or equal to 16 points from baseline
Within Normal Limits	Continue	Continue	Hold *
1 to 5 points below LLN	Continue	Hold *	Hold *
greater than or equal to 6 points below LLN	Continue *	Hold *	Hold *

- *Repeat LVEF assessment after 3 to 4 weeks, consider cardiac assessment
- If criteria for continuation are met – resume trastuzumab
- If 2 consecutive holds or a total of 3 holds occur, discontinue trastuzumab

Symptomatic Patients

- Symptomatic patients with evidence of cardiac dysfunction should have trastuzumab discontinued

For evidence of cardiac dysfunction likely related to trastuzumab and/or chemotherapy protocols, consider consulting a cardiologist, or review the following reference: Mackey JR, et al. Cardiac management during adjuvant trastuzumab therapy: recommendations of the Canadian Trastuzumab Working Group. *Curr Oncol* 2008;15(1): 24-31.

6. Treatment Interruptions – Trastuzumab

If an interruption in treatment of greater than 6 weeks occurs (ie more than 6 weeks has elapsed since the last treatment was given), consider repeating the loading dose of 8 mg/kg, and then resume usual dosing.

PRECAUTIONS:

1. **Extravasation:** *Epirubicin and DOCEtaxel* cause pain and tissue necrosis if extravasated. Refer to [BC Cancer Extravasation Guidelines](#).
2. **Febrile Neutropenia:** DOCEtaxel containing adjuvant chemotherapy for breast cancer is associated with an extreme risk of febrile neutropenia approaching 40% in real practice settings, as reported in two outcome studies from Ontario. Thus, strong consideration should be given to using prophylactic G-CSF. Febrile neutropenia rates with prophylactic G-CSF are lower (5 to 7%) making this the safer option. Fever or other evidence of infection must be assessed promptly and treated aggressively.
3. **Cardiac Toxicity:** Clinical cardiac assessment is required prior to FEC if cardiac function is equivocal and recommended at any time if clinically indicated with a formal evaluation of LVEF (MUGA scan or ECHO). **Myocardial ischemia and angina occurs rarely in patients receiving fluorouracil or capecitabine.** Development of cardiac symptoms including signs suggestive of ischemia or of cardiac arrhythmia is an indication to discontinue treatment. If there is development of cardiac symptoms patients should have urgent cardiac assessment. Generally re-challenge with either fluorouracil or capecitabine is not recommended as symptoms potentially have a high likelihood of recurrence which can be severe or even fatal. Seeking opinion from cardiologists and oncologists with expert knowledge about fluorouracil or capecitabine toxicity is strongly advised under these circumstances. The toxicity should also be noted in the patient's allergy profile.
4. **Fluid Retention (DOCEtaxel):** Dexamethasone premedication must be given to reduce incidence and severity of fluid retention with DOCEtaxel.
5. **Hepatic Dysfunction (DOCEtaxel):** DOCEtaxel undergoes hepatic metabolism. Hepatic dysfunction (particularly elevated AST) may lead to increased toxicity and usually requires a dose reduction. Baseline liver enzymes are recommended before cycle 1 and then if clinically indicated (e.g., repeat liver enzymes prior to each treatment if liver enzymes are elevated or there is severe toxicity such as neutropenia). Note: this information is intended to provide guidance but physicians must use their clinical judgment when making decisions regarding monitoring and dose adjustments.
6. **Hypersensitivity** reactions to DOCEtaxel are common but it is not necessary to routinely initiate the infusion slowly. If slow initiation of infusion is needed, start infusion at 30 mL/h x 5 minutes, then 60 mL/h x 5 minutes, then 120 mL/h x 5 minutes, then complete infusion at 250 mL/h (for 500 mL bag, continue 250 mL/h for 5 minutes and then complete infusion at 500 mL/h). Refer to [BC Cancer Hypersensitivity Guidelines](#).

7. **Interstitial pneumonitis (DOCEtaxel)** may occur. Risk may be increased with radiation therapy.
8. **Possible drug interactions with fluorouracil and warfarin, phenytoin and fosphenytoin** have been reported and may occur at any time. Close monitoring is recommended (e.g., for warfarin, monitor INR weekly during fluorouracil therapy and for 1 month after stopping fluorouracil).
9. **Trastuzumab infusion-associated symptoms**, usually chills and fever, occur in 40% of patients during the first trastuzumab infusion (infrequent with subsequent infusions). Other signs and symptoms may include nausea, vomiting, pain (sometimes at tumour sites), rigors, headache, dizziness, dyspnea, hypotension, rash and asthenia. Symptoms may be treated with acetaminophen, diphenhydramine and meperidine with or without an infusion rate reduction.

Rarely, serious infusion-related reactions have been reported (3 per 1000 patients) sometimes leading to death (4 per 10,000). Reactions include dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation and respiratory distress, and, uncommonly, allergic-like reactions. Patients experiencing dyspnea at rest due to pulmonary metastases and other pulmonary/cardiac conditions may be at increased risk of a fatal infusion reaction and should be treated with extreme caution, if at all. For serious reactions, discontinue the trastuzumab infusion and provide supportive therapy such as oxygen, beta-agonists and corticosteroids.

10. **CNS Metastases on Adjuvant Trastuzumab:** Patients with HER-2/neu over-expression have been observed to have a higher than usual risk of developing CNS metastases. The CNS is a sanctuary site, unreached by most adjuvant systemic agents. There is little or no data to guide physicians in the circumstance of a patient developing isolated CNS metastasis while on adjuvant therapy with a trastuzumab-containing regimen. Aggressive local therapy (whole brain radiation with or without surgical resection) has resulted in some durable remissions. The Breast Tumour Group supports resection of metastases and CNS radiation if feasible for patients who develop limited and isolated CNS metastases while on an adjuvant trastuzumab regimen. A metastatic survey should be done to determine the best systemic management plan. Completion of the adjuvant course of trastuzumab, or continuing beyond the adjuvant course (changing to BRAVTR regimen) due to concern for occult systemic metastases is at the discretion of the treating oncologist and dependent on the individual circumstances.
11. **A possible interaction between warfarin and trastuzumab** has been reported. An increased INR and bleeding may occur in patients previously stabilized on warfarin. The interaction was noted in two patients after 8-10 doses of trastuzumab. An INR prior to starting the trastuzumab is recommended, then every 2 weeks for the first 3 months and then monthly if stable. Inform patient to watch for any bleeding. Modification of the warfarin dose may be needed.

Contact Dr. Stephen Chia or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

References:

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3. Gelmon K, Arnold A, Verma S, et al. Pharmacokinetics (PK) and safety of trastuzumab (Herceptin[®]) when administered every three weeks to women with metastatic breast cancer. [Abstract 271] Proc Am Soc Clin Oncol 2001;20(1):69a.
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