BC Cancer Protocol Summary for Neoadjuvant or Adjuvant Therapy for Breast Cancer Using Trastuzumab, DOCEtaxel and Cyclophosphamide

Protocol Code	*BRAJTDC*
Tumour Group	*Breast*
Contact Physician	*Dr. Caroline Lohrisch*

ELIGIBILITY:

- HER-2 over-expression defined as either IHC 3+, or FISH amplification ratio greater than or equal to 2 per BC Cancer central laboratory
- High risk, node negative or node positive patients, not otherwise considered best treated with a longer standard 6 to 8 cycle anthracycline or anthracycline plus taxane regimen (e.g. BRAJFECDT, BRAJACTT, BRAJDCARBT, etc) as decided by their treating physician
- ECOG 0 to 1
- Adequate renal and hepatic function
- Adequate hematological parameters (ANC greater than 1.5 x 10^9/L and platelets greater than 90 x 10^9/L)
- 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 to 4
- Pregnancy or lactation
- Significant hepatic dysfunction
- Greater than or equal to grade 2 sensory or motor neuropathy
- 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

TESTS:

- Baseline: CBC & diff, platelets, bilirubin, ALT, creatinine (see Precaution #5 for guidelines regarding hepatic dysfunction and DOCEtaxel). If clinically indicated: GGT, LDH, Alk Phos
- MUGA scan or echocardiogram: prior to first treatment with trastuzumab, 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 #3 for adjustment of trastuzumab based on changes in LVEF)
- Before each treatment (Day 1): CBC & diff, platelets
- If clinically indicated: creatinine, bilirubin, albumin, GGT, LDH, ALT, Alk Phos, urea, MUGA scan or echocardiogram

PREMEDICATIONS:

- Antiemetic protocol for High/Moderate emetogenic chemotherapy (see protocol SCNAUSEA)
- For DOCEtaxel:
  - 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.
- 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:

Administer cyclophosphamide prior to DOCEtaxel to reduce hypersensitivity response to DOCEtaxel.

Cycle 1 only

Drug	Dose	BC Cancer Administration Guideline
trastuzumab	8 mg/kg	IV in 250 mL NS over 1 hour 30 min Observe for 1 hour post-infusion
cyclophosphamide	600 mg/m^2	IV in 100 to 250 mL* NS over 20 min to 1 hour
DOCEtaxel	75 mg/m^2	IV in 250 to 500 mL NS over 1 hour (use non-DEHP equipment)

Cycle 2 to **4**

Drug	Dose	BC Cancer Administration Guideline
trastuzumab	6 mg/kg	• Cycle 2: IV in 250 mL NS over 1 hour. Observe for 30 minutes post infusion. • Cycles 3 and 4: IV in 250 mL NS over 30 min. Observe for 30 min post infusion**
cyclophosphamide	600 mg/m^2	IV in 100 to 250 mL* NS over 20 min to 1 hour
DOCEtaxel	75 mg/m^2	IV in 250 to 500 mL NS over 1 hour (use non-DEHP equipment)

* Cyclophosphamide – If less than or equal to 1000 mg, use 100 mL bag; if greater than 1000 mg use 250 mL bag

** Trastuzumab – Observation period not required after 3 consecutive treatments with no reaction

Repeat every 21 days x 4 cycles.

Followed by 13 consecutive cycles of trastuzumab to start 21 days after the final cycle of DOCEtaxel/cyclophosphamide/trastuzumab for a total of 1 year of trastuzumab treatment (maximum of 17 cycles of trastuzumab). 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:

1. Hematological

ANC (x 10^9/L)		Platelets (x10^9/L)	Dose (DOCEtaxel and cyclophosphamide)	Filgrastim (G-CSF) Option
greater than or equal to 1.5	and	greater than or equal to 90	100%	
1.0 to less than 1.5	or	70 to less than 90	75%	100 % regimen with filgrastim 300 mcg SC daily on Days 5 to 12 (adjust as needed)
less than 1.0	or	less than 70	Delay until ANC greater than 1.5 and Plts greater than 90, then give 75% of previous cycle doses	Delay until ANC greater than 1.5 and Plts greater than 90, then give 100 % regimen with filgrastim 300 mcg SC daily on Days 5 to 12 (adjust as needed)

Febrile Neutropenia

Event	Dose Reduction Option (DOCEtaxel and cyclophosphamide)	Filgrastim (G-CSF) Option
1st episode	75% of previous cycle dose if Day 1 ANC greater than or equal to 1.5 and Plts greater than or equal to100	100% regimen with filgrastim 300 mcg SC daily on Days 5 to 12 (adjust as needed)
2nd episode	50% of original cycle dose if Day 1 ANC greater than or equal to 1.5 and Plts greater than or equal to100	75% regimen with filgrastim 300 mcg SC daily on Days 5 to 12 (adjust as needed)
3rd episode	Discontinue protocol or switch to Filgrastim (G-CSF) Option	50% regimen with filgrastim 300 mcg SC daily on Days 5 to 12 (adjust as needed)
4th episode	N/A	Discontinue protocol

2. Hepatic

Alkaline Phosphatase		AST or ALT	DOCEtaxel Dose
less than 2.5 x ULN	and	less than or equal to 1.5 x ULN	100%
2.5 to 5 x ULN	and	1.6 to 5 x ULN	75%
greater than 5 x ULN	or	greater than 5 ULN	discuss with contact physician

ULN = upper limit of normal

3. **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 to 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.

4. **Treatment Interruptions – Trastuzumab**
   If an interruption in treatment of greater than 6 weeks occurs (i.e. 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. **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 filgrastim. Febrile neutropenia rates with prophylactic filgrastim are lower (5% to 7%) making this the safer option. Fever or other evidence of infection must be assessed promptly and treated aggressively.
2. **Extravasation:** DOCEtaxel causes pain and tissue necrosis if extravasated. Refer to BC Cancer Extravasation Guidelines.
3. **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).
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 ASTor ALT) 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. **Interstitial pneumonitis (DOCEtaxel)** may occur. Risk may be increased with radiation therapy.
7. **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.

   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.
8. **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.
9. **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 to 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. Caroline Lohrisch or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

References:

1. Slamon et al.,Adjuvant Trastuzumab in HER2-Positive Breast Cancer. N Engl J Med 2011;365(14):1273-83.
2. Jones et al., Phase III Trial Comparing Doxorubicin plus cyclophosphamide with docetaxel plus cyclophosphamide as adjuvant therapy for operable breast cancer. J Clin Oncol 2006;24(34):5381-7.
3. Jones S, Holmes, F, O'Shaughnessy, J, et al. Extended follow-up and analysis by age of the US Oncology adjuvant trial 9735: docetaxel/cyclophosphamide is associated with an overall survival benefit compared to doxorubicin/cyclophosphamide and is well tolerated in women 65 or older. San Antonio Breast Cancer Symposium 2007, abstract 12.
4. Koch et al. Retrospective Analysis of the incidence of allergic reactions with the use of docetaxel in different combinations (TC vs TAC vs AC-T). ASCO 2009 Breast Cancer Symposium, abstract 309.
5. Vandenberg T, Younus J, and Al-Hkayyat S. Febrile neutropenia rates with adjuvant docetaxel and cyclophophamide chemotherapy in early breast cancer: discrepancy between published reports and community practice – a retrospective analysis. Curr Oncol 2010l;17(2):2-3.
6. Soong D et al. High rate of febrile neutropenia in patients with operable breast cancer receiving docetaxel and cyclophosphamide. J Clin Oncol 2009;27(26):101-2.
7. Chan A et al. Impact of colony-stimulating factors to reduce febrile neutropenic events in breast cancer patients receiving docetaxel plus cyclophosphamide chemotherapy. Supp Care Cancer 2011;19:497-504.
8. Jones S et al. Docetaxel with cyclophosphamide is associated with an overall survival benefit compared with doxorubicin and cyclophosphamide: 7-year follow-up of US Oncology Research Trial 9735. J Clin Oncol 2009;27(8):1177-83.