

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:

Patient must have:

- 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 [disease](#), not otherwise considered best treated with a longer standard 6 to 8 cycle anthracycline or anthracycline plus taxane regimen (e.g. BRAJFECT, BRAJACTT, BRAJDCARBT, etc.) as decided by their treating physician

Patient should have:

- ECOG 0 to 1
- Adequate hematologic, 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 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 [45%](#)

TESTS:

- Baseline: CBC & Diff, total bilirubin, ALT, creatinine (see Precaution #5 for guidelines regarding hepatic dysfunction and DOCEtaxel).
- Baseline, if clinically indicated: GGT, LDH, alkaline phosphatase
- MUGA scan or echocardiogram: prior to first treatment with trastuzumab, every 3 to 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
- If clinically indicated: creatinine, total bilirubin, albumin, GGT, LDH, ALT, alkaline phosphatase, urea

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:**Cycle 1 only**

Drug	Dose	BC Cancer Administration Guideline
trastuzumab	8 mg/kg*	IV in 250 mL NS over 90 minutes Observe for 1 hour post-infusion
cyclophosphamide	600 mg/m ²	IV in 100 to 250 mL NS over 20 to 60 minutes
DOCEtaxel	75 mg/m ²	IV in 250 to 500 mL NS over 60 minutes (use non-DEHP equipment)
filgrastim (G-CSF)	5 mcg/kg/day starting on Day 3, for 5 to 7 doses (adjust as needed**)	subcutaneously

Cycle 2 to 4

Drug	Dose	BC Cancer Administration Guideline
trastuzumab	6 mg/kg*	<ul style="list-style-type: none"> • Cycle 2: IV in 250 mL NS over 60 minutes. Observe for 30 minutes post infusion. • Cycles 3 and 4: IV in 250 mL NS over 30 minutes Observe for 30 minutes post infusion***
cyclophosphamide	600 mg/m ²	IV in 100 to 250 mL NS over 20 to 60 minutes
DOCEtaxel	75 mg/m ²	IV in 250 to 500 mL NS over 60 minutes (use non-DEHP equipment)
filgrastim (G-CSF)	5 mcg/kg/day starting on Day 3, for 5 to 7 doses (adjust as needed**)	subcutaneously

* [Select dose per Dose Banding Table \(appendix\)](#)

** [Reduce filgrastim treatment duration if ANC greater than 10 x 10⁹/L or intolerable bone pain.](#)

Filgrastim should not be stopped before the time of the predicted nadir from chemotherapy.

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

Repeat every 21 days for 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)
Greater than or equal to 1.0	and	Greater than or equal to 100	100%
Less than 1.0	and	Greater than or equal to 100	Delay for 1 week (or longer if needed), then give 100% dose if ANC greater than 1.0 and platelets greater than or equal to 100. Increase the filgrastim treatment duration per provider discretion.
Greater than or equal to 1.0	and	Less than 100	Delay for 1 week (or longer if needed), then give 75% if ANC greater than 1.0 and platelets greater than or equal to 100
Less than 1.0	and	Less than 100	Delay for 1 week (or longer if needed), then give 75% if ANC greater than 1.0 and platelets greater than or equal to 100

Febrile Neutropenia

Event	Dose (DOCEtaxel and cyclophosphamide)
1 st episode	75% if Day 1 ANC greater than or equal to 1.0 and platelets greater than or equal to 100
2 nd episode	50% if Day 1 ANC greater than or equal to 1.0 and platelets greater than or equal to 100
3 rd episode	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:** Risk of febrile neutropenia is greater than 20% without the use of filgrastim. Mandatory filgrastim reduces the risk of febrile neutropenia. Febrile neutropenia can result in patient harm, treatment delays and hospitalization. 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 AST or 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 SCDRUGRX protocol.

Alternative therapy with protocol BRAJPNT is available for moderate to severe hypersensitivity reaction that occurs despite premedications, or in those patients who cannot be managed with premedications due to a strong contraindication.

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 cyclophosphamide chemotherapy in early breast cancer: discrepancy between published reports and community practice – a retrospective analysis. *Curr Oncol* 2010;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.

Appendix. Dose Bands

TRASTUZUMAB DOSE BANDING TABLE

Ordered Dose (mg)		Rounded dose (mg)
From:	To:	
Less than 58		Pharmacy prepares specific dose
58	68.49	63
68.5	76.49	71.4
76.5	84.49	79.8
84.5	94.49	88.2
94.5	104.49	100.8
104.5	117.49	109.2
117.5	127.49	117.6
127.5	144.49	130.67
144.5	162.49	147
162.5	185.49	168
185.5	208.49	189
208.5	230.49	210
230.5	251.49	231
251.5	276.49	252
276.5	323.49	294
323.5	369.49	336
369.5	415.49	378
415.5	463.49	420
463.5	550.49	504
550.5	647.49	588
647.5	740.49	672
740.5	822.49	756
822.5	928.49	840
928.5	1046.49	966
1046.5	1150.49	1050
1150.5	1258.49	1176
1258.5	1390.5	1260
More than 1390.5		Pharmacy prepares specific dose