

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

Protocol Code

BRAJDCARBT

Tumour Group

Breast

Contact Physician

Dr. Susan Ellard

ELIGIBILITY:

- ECOG 0-1
- Node positive or high risk node negative, including patient with T1b disease (T1a still requires CAP approval)
- HER-2 over-expression defined as either IHC3+, or FISH amplification ratio greater than or equal to 2 per BC Cancer central laboratory
- Adequate renal and hepatic function
- Adequate hematological parameters (ANC greater than $1.5 \times 10^9/L$ and platelets greater than $100 \times 10^9/L$)
- No signs or symptoms of 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
- Stage IV disease (please refer to advanced regimens)
- Significant hepatic dysfunction, contraindicating DOCEtaxel
- 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

TESTS:

- Baseline: CBC & diff, platelets, bilirubin, GGT, ALT, LDH, alkaline phosphatase, creatinine, (see Precaution #5 for guidelines regarding hepatic dysfunction and DOCEtaxel), suggested: nuclear renogram for GFR (if available locally, and not previously done)
- Before each treatment cycle: CBC & diff, platelets, creatinine
- 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 #2 for adjustment of trastuzumab based on changes in LVEF)
- If clinically indicated: bilirubin, GGT, ALT, LDH, alkaline phosphatase, creatinine, MUGA scan or echocardiogram

PREMEDICATIONS:

- 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.

- Additional antiemetics not usually required.
- For CARBOplatin: ondansetron 8 mg PO 30 minutes pre-CARBOplatin.
- For trastuzumab: 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:

Cycle 1 only

Drug	Dose	BC Cancer Administration Guideline
trastuzumab	8 mg/kg	IV in 250 mL NS over 1 hour 30 min for Cycle 1 Observe for 1 hour post-infusion* then start DOCEtaxel infusion
DOCEtaxel	75 mg/m ²	IV in 250 to 500 mL NS over 1 hour (use non-DEHP bag and non-DEHP)
CARBOplatin	Dose = AUC 6 x (GFR + 25)	In 100 to 250 mL NS over 30 minutes

Cycle 2 to 6

Drug	Dose	BC Cancer Administration Guideline
trastuzumab	6 mg/kg	<ul style="list-style-type: none"> • IV in 250 mL NS over 1 hour on the second dose, observe for 30 minutes post infusion* • IV IN 250 ml NS over 30 min on all subsequent doses if no adverse reactions, observe for 30 min post infusion**
DOCEtaxel	75 mg/m ²	IV in 250 to 500 mL NS over 1 hour (use non-DEHP bag and non-DEHP)
CARBOplatin	Dose = AUC 6 x (GFR + 25)	In 100 to 250 mL NS over 30 minutes

*observation period not required after 3 consecutive treatments with no reaction

Measured GFR (e.g. nuclear renogram) is preferred whenever feasible, *particularly* in circumstances of co-morbidity that could affect renal function (third-space fluid accumulations, hypoproteinemia, potentially inadequate fluid intake, etc.). The lab reported GFR (MDRD formula) may be used as an alternative to the Cockcroft-Gault estimate of GFR; the estimated GFR reported by the lab or calculated using the Cockcroft-Gault equation should be capped at 125 mL/min when it is used to calculate the initial CARBOplatin dose. When a nuclear renogram is available, this clearance would take precedence.

Cockcroft-Gault Formula

$$\text{GFR} = \frac{\text{N}^* \times (140 - \text{age in years}) \times \text{wt (kg)}}{\text{serum creatinine (micromol/L)}}$$

Note: The same method of estimation should be used throughout the treatment course (i.e. if lab reported GFR was used initially, this should be used for dosing in all subsequent cycles and not the Cockcroft-Gault estimate).

For males N = 1.23, For females N = 1.04

- DOCEtaxel and CARBOplatin to be given every 21 days x 6 cycles.
- trastuzumab to be given every 21 days x 6 cycles, followed by single agent trastuzumab (see BC Cancer protocol **BRAJTR**) to complete further 11 treatments (total 51 weeks or 17 doses)

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 and previous cycle febrile neutropenia. No dose reduction for nadir counts. **No reduction of trastuzumab dose for hematologic toxicity.**

1. Hematological – DOCEtaxel and CARBOplatin

ANC (x 10 ⁹ /L)		Platelets (x 10 ⁹ /L)	All Chemotherapy Drugs % Dose of Previous Cycle	Filgrastim (G-CSF) Option
greater than or equal to 1.5	and	greater than or equal to 100	100%	
1.0 to less than 1.5	and	greater than or equal to 100	75%	100% regimen with G-CSF 300 mcg sc daily on Days 3-10 (adjust as needed)
less than 1.0	or	less than 100	Delay until ANC greater than or equal to 1.5 and platelets greater than or equal to 100 then give 75%	Delay until ANC greater than or equal to 1.5 and platelets greater than or equal to 100 then give 100% regimen with filgrastim 300 mcg sc daily on Days 3-10 (adjust as needed)

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 100	100% regimen with filgrastim 300 mcg sc daily on Days 3-10 (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 100	75% regimen with filgrastim 300 mcg sc daily on Days 3-10 (adjust as needed)
3 rd episode	Discontinue protocol or switch to Filgrastim (G-CSF) Option	50% regimen with filgrastim 300 mcg sc daily on Days 3-10 (adjust as needed)
4 th episode	N/A	Discontinue protocol

2. 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 *
1-5 points below LLN	Continue	Hold *	Hold *
greater than or equal to 6 points below LLN	Continue *	Hold *	Hold *

- *Repeat LVEF assessment after 3-4 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.

- 3. Stomatitis:** For Grade 3 or 4 stomatitis (painful erythema, edema or ulcers and cannot eat; mucosal necrosis and/or requires enteral support; dehydration), delay chemotherapy until

recovered then give 75% dose of Day 1 of previous cycle. Maintain dose reduction for all subsequent cycles. **Continue trastuzumab without dose change** even if DOCEtaxel/CARBOplatin held.

- 4. Renal Dysfunction** Use nuclear renogram or predictive formula to calculate cycle 1 dose, as detailed above. Consider re-calculation of dose if serum creatinine changes \pm 20% from baseline.

5. 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:** DOCEtaxel causes 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 filgrastim. Febrile neutropenia rates with prophylactic filgrastim are lower (5-7%) 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 if cardiac function is equivocal at baseline, or if symptoms of possible CHF develop on trastuzumab, and recommended at any time if clinically indicated with a formal evaluation of LVEF (MUGA scan or ECHO).
- 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 signaled by 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. See Cancer Drug Manual.
- 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. 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. For serious reactions, discontinue the trastuzumab infusion and provide supportive therapy such as oxygen, beta-agonists and corticosteroids.

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 8-10 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.
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.

Contact Dr. Susan Ellard or tumour group delegate at (250) 712-3900 or 1-888-563-7773 with any problems or questions regarding this treatment program.

References:

1. Slamon D, Eiermann W, Robert N, et al. Phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (AC→T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC→TH) with docetaxel, carboplatin and trastuzumab (TCH) in HER2 positive early breast cancer patients: BCIRG 006 study. San Antonio Breast Cancer Symposium 2005. Available at: http://www.abstracts2view.com/sabcs05/view.php?nu=SABCS05L_921. Accessed 31 July 2007.
2. Perez A, Rodeheffer R. Clinical Cardiac Tolerability of Trastuzumab. *J Clin Oncol* 2004;22:322-329.
3. 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 April; 17(2):2-3.
4. Soong, D et al. High rate of febrile neutropenia in patients with operable breast cancer receiving docetaxel and cyclophosphamide. *JCO* 2009, 27(26): 101-2.
5. 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.
6. 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. *JCO* 2009, 27(8):1177-83.