

BC Cancer Protocol Summary for Treatment of Locally Advanced Breast Cancer using DOXOrubicin and Cyclophosphamide followed by DOCEtaxel and Trastuzumab

Protocol Code

BRLAACDT

Tumour Group

Breast

Contact Physician

Dr. Karen Gelmon

ELIGIBILITY:

- locally advanced and inflammatory breast cancer with the invasive cancer showing overexpression of HER-2 less than or equal to 60 years of age or fit greater than 60 years of age.
- HER-2 overexpression defined as either IHC3+, or FISH amplification ratio greater than or equal to 2 per BC Cancer central laboratory
- ECOG 0-2
- No clinically significant cardiac disease
- LVEF greater than or equal to 55%* after the AC portion of chemotherapy
- Adequate marrow, renal, and hepatic function
- Anticipated survival of greater than 5 years

*If the LVEF is greater than LLN for the institution but less than 55%, the oncologist may decide to treat based on clinical assessment.

EXCLUSIONS:

- Pregnancy
- Significant cardiovascular disease and/or LVEF less than 55%; if initial reading after AC is less than 55%, physician may consider repeating for validity, or assessing LVEF by the other modality, ie. Echo instead of MUGA

TESTS:

- Baseline: CBC & diff, platelets, bilirubin, GGT, ALT, LDH, Alk Phos
- Before each treatment: CBC & diff, platelets
- Prior to **cycle #5**: bilirubin, ALT, Alk Phos (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 #4 for adjustment of trastuzumab based on changes in LVEF)
- If clinically indicated at any time: creatinine, protein level, albumin, bilirubin, GGT, Alk Phos, LDH, ALT, MUGA scan or echocardiogram

PREMEDICATIONS:

- For the 4 cycles of DOXOrubicin and cyclophosphamide: Antiemetic protocol for highly emetogenic chemotherapy (see protocol SCNAUSEA)
- For the 4 cycles of 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 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:

- 4 consecutive cycles of DOXOrubicin and cyclophosphamide

Drug	Dose	BC Cancer Administration Guideline
DOXOrubicin	60 mg/m ²	IV push
cyclophosphamide	600 mg/m ²	IV in NS 100 to 250* mL over 20 min to 1 hour

*Use 250 mL for dose greater than 1000 mg

- Repeat every 21 days x 4 cycles
- Followed by 4 consecutive cycles of DOCEtaxel concurrent with trastuzumab to start **21 days after** final cycle of DOXOrubicin and cyclophosphamide

Cycle 5

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

Cycle 6, 7, and 8

Drug	Dose	BC Cancer Administration Guideline
trastuzumab	6 mg/kg	<ul style="list-style-type: none">• IV in NS 250 mL over 1 hour on the second dose (Cycle 6). Observe for 30 minutes post infusion*• IV IN NS 250 mL over 30 min on all subsequent doses (Cycle 7, 8), if no adverse reactions. Observe for 30 min post infusion**
DOCEtaxel	100 mg/m ²	IV in NS 250 to 500 mL over 1 hour (use non-DEHP equipment)

*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/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:

1. Hematological

For cycles of DOXOrubicin and cyclophosphamide only:

ANC (x10 ⁹ /L)		Platelets (x10 ⁹ /L)	Dose (both drugs)
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%
less than 1.0	or	less than 70	delay

For cycles of DOCEtaxel only:

ANC (x 10 ⁹ /L)		Platelets (x10 ⁹ /L)	Dose	Dose after Neutropenic Sepsis on DOCEtaxel
greater than or equal to 1.5	and	greater than or equal to 90	100%	75%
1.0 to less than 1.5	or	70 to less than 90	75%	delay
less than 1.0	or	less than 70	delay	delay

2. **Renal dysfunction:** Dose modification may be required for **cyclophosphamide**. Refer to BC Cancer Drug Manual.

- Hepatic dysfunction:** Dose modification required for **DOXOrubicin** and **DOCEtaxel**. Refer to BC Cancer Drug Manual for DOXOrubicin and BC Cancer chemotherapy protocol BRAVDOC for DOCEtaxel.

4. 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.

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:

- 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 (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.
- Extravasation (DOXOrubicin and DOCEtaxel):** DOXOrubicin and DOCEtaxel cause pain and tissue necrosis if extravasated. Refer to BC Cancer Extravasation Guidelines.

3. **Cardiac Toxicity (DOXOrubicin):** DOXOrubicin is cardiotoxic and must be used with caution, if at all, in patients with severe hypertension or cardiac dysfunction. Cardiac assessment recommended if lifelong dose of 450 mg/m² to be exceeded. Refer to BC 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 (eg, 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 judgement 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. **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

9. **CNS Metastases on Adjuvant Trastuzumab:** Patients with her2/neu overexpression 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. In various cancer settings, some individuals who develop isolated metastases, who are managed with aggressive local therapy and systemic treatment as appropriate, may yet obtain durable remissions. In view of this, the Breast Tumour Group members would propose that, if a patient develops limited and isolated CNS metastases while on an adjuvant trastuzumab regimen, resection of metastases and CNS radiation should proceed if feasible. If all visible

disease has been resected, providing a chance of long-term remission, then it would be up to the discretion of the treating oncologist whether to continue to complete the intended year of adjuvant trastuzumab. Alternately, patients could suspend therapy with trastuzumab at that time, and resume it at the time that non-CNS metastases were detected. If, at the time of presentation with CNS metastases on therapy, there were metastases also found outside the CNS, trastuzumab therapy should be discontinued and not restarted.

10. **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.

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

References:

1. Wolmark, N et al. The effect on primary tumor response of adding sequential Taxotere to Adriamycin and cyclophosphamide: preliminary results from NSABP Protocol B-27. [Abstract 5] *Breast Cancer Res and Treat* 2001;69(3):210.
2. Perez A, Rodeheffer R. Clinical Cardiac Tolerability of Trastuzumab. *J Clin Oncol* 2004;22:322-329. 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.
3. 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.
4. 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.
5. 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.