

BCCA Protocol Summary for Adjuvant Therapy for Breast Cancer Using Dose Dense Therapy: Doxorubicin and Cyclophosphamide Followed by Paclitaxel and Trastuzumab

Protocol Code

BRAJACTTG

Tumour Group

Breast

Contact Physician

Dr. Karen Gelmon

ELIGIBILITY:

- 1 or more axillary lymph node metastasis(es), or node negative but with high risk of recurrence (see Cancer Management Guidelines for categories of risk), including patient with T1b disease (T1a still requires CAP approval)
- HER-2 overexpression defined as either IHC3+, or FISH amplification ratio greater than or equal to 2 per BCCA central laboratory
- ECOG 0-2
- No clinically significant cardiac disease
- LVEF greater than or equal to 55%* after the AC portion of chemotherapy (*If the LVEF is greater than LLN for the institution but less than 55%, the oncologist may decide to treat based on clinical assessment)
- Adequate marrow, renal, and hepatic function
- Anticipated survival of greater than 5 years
- A "Class II Drug Registration Form" must be submitted at the time of initiation of treatment. For other indications, a BCCA "Compassionate Access Program" request must be approved.
- Filgrastim (G-CSF) is not covered as a benefit at the BCCA

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
- Known hypersensitivity to E. coli derived products

TESTS:

- Baseline: CBC & diff, platelets, bilirubin, AST (AST and bilirubin should be measured prior to first cycle of AC and first cycle of paclitaxel)
- Before each treatment: CBC & diff, platelets
- MUGA scan or echocardiogram: prior to first treatment with trastuzumab and every 12 weeks during treatment and at completion of therapy (see dose modification #7 for adjustment of trastuzumab based on changes in LVEF)
- If clinically indicated: creatinine; MUGA scan or echocardiogram, bilirubin, AST

PREMEDICATIONS:

- For the 4 cycles of doxorubicin and cyclophosphamide: Antiemetic protocol for High/Moderate emetogenic chemotherapy (see protocol SCNAUSEA)
- For the 4 cycles of paclitaxel: **Paclitaxel must not be started unless the following drugs have been given:**
 - 45 minutes prior to paclitaxel give dexamethasone 20 mg IV in 50 mL NS over 15 minutes
 - 30 minutes prior to paclitaxel give diphenhydramine 50 mg IV and ranitidine 50 mg IV in 50 mL over 20 minutes (compatible up to 3 hours when mixed in bag)
 - additional anti-emetics are not usually required
- For trastuzumab: not usually required

TREATMENT:

4 consecutive cycles of doxorubicin and cyclophosphamide

Drug	Dose	BCCA Administration Guideline
doxorubicin	60 mg/m ²	IV push
cyclophosphamide	600 mg/m ²	IV in 100 to 250* mL NS over 20 min to 1 hour
filgrastim (G-CSF)	5 mcg/kg/day Days 3-10 (or adjust as needed**)	SC

*Use 250 mL for dose \geq 1000 mg

reduce filgrastim treatment duration if ANC greater than 10 or intolerable bone pain. Filgrastim **should not be stopped before the time of the predicted nadir from chemotherapy.

Repeat every 14 days x 4 cycles.

- 4 consecutive cycles of Paclitaxel concurrent with trastuzumab to start **14 or 21 days after** final cycle of Doxorubicin and Cyclophosphamide (physician may use their discretion to choose the interval between AC and paclitaxel/trastuzumab—reference 4 and 5 below)
- Cardiac status must be assessed prior to initiating paclitaxel/trastuzumab

Cycle 5 - DAY 1

Drug	Dose	BCCA Administration Guideline
Trastuzumab (HERCEPTIN®)	8 mg/kg Day 1 only	IV in 250 mL NS over 1 hour 30 minutes Observe for 1 hour post-infusion**

Cycle 5 – DAY 2

Drug	Dose	BCCA Administration Guideline
Paclitaxel	175 mg/m ² Day 2 only	IV in 500 mL* NS over 3 hours (use non-PVC equipment, in-line filter)

*use 250 mL for doses less than 150 mg

Cycle 6, 7, and 8

Drug	Dose	BCCA Administration Guideline
Trastuzumab (HERCEPTIN®)	6 mg/kg	<ul style="list-style-type: none">• IV in 250 mL NS over 1 hour, on second dose. Observe for 30 minutes post-infusion**• IV in 250 mL NS over 30 minutes, on all subsequent doses, if no adverse reactions. Observe for 30 minutes post-infusion** then start Paclitaxel premedications
Paclitaxel	175 mg/m ²	IV in 500 mL* NS over 3 hours (use non-PVC equipment, in-line filter)

*use 250 mL for doses less than 150 mg

**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 paclitaxel/trastuzumab for a total of 1 year of trastuzumab treatment (maximum of 17 cycles of trastuzumab). Start BCCA 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 Day 1 counts)

For cycles of Doxorubicin and Cyclophosphamide only:

ANC (x 10 ⁹ /L)		Platelets (x 10 ⁹ /L)	Dose (all drugs)
greater than or equal to 1	and	greater than or equal to 100	100%
less than 1	and	greater than or equal to 100	delay for 1 week (or longer if needed), then give 100% dose if ANC greater than 1 and platelets greater than or equal to 100. Give filgrastim days 3-13 for remaining cycles.
greater than or equal to 1	and	less than 100	delay for 1 week (or longer if needed), then give 75% if ANC greater than 1 and platelets greater than or equal to 100
less than or equal to 1		less than 100	delay for 1 week (or longer if needed), then give 75% if ANC greater than 1 and platelets greater than or equal to 100

For cycles of Paclitaxel only:

ANC (x10 ⁹ /L)		Platelets (x10 ⁹ /L)	Dose (Paclitaxel)
greater than or equal to 1.5	and	greater than 90	175 mg/m ²
1 -1.49	or	70-90	150 mg/m ²
less than 1	or	less than 70	delay

- Febrile neutropenia:** 75% of dose for current and subsequent cycles.
- Renal dysfunction:** Dose modification may be required for cyclophosphamide. Refer to BCCA Cancer Drug Manual.
- Hepatic dysfunction:** Dose modification required for doxorubicin and for paclitaxel. Refer to BCCA Cancer Drug Manual.
- Arthralgia and/or myalgia:** If arthralgia and/or myalgia from paclitaxel of grade 2 (moderate) or higher is not relieved by adequate doses of NSAIDs or acetaminophen with codeine (TYLENOL #3®) a limited number of studies report a possible therapeutic benefit from the following:
 - Prednisone 10 mg PO BID x 5 days starting 24 hours post paclitaxel
 - Gabapentin 300 mg PO on day prior to paclitaxel, 300 mg PO BID on treatment day and then 300 mg PO TID x 7-10 days
- Neuropathy:** Dose modification or discontinuation for paclitaxel may be required. Refer to BCCA Cancer Drug Manual.

7. 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.

8. 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. **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively.
2. **Extravasation:** Doxorubicin and paclitaxel may cause pain and tissue necrosis if extravasated. Refer to BCCA Extravasation Guidelines.
3. **Cardiac Toxicity:** 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 BCCA Cancer Drug Manual.

4. **Hypersensitivity:** Reactions are common with paclitaxel. Refer to BCCA Hypersensitivity Guidelines.

<i>Mild</i> symptoms (e.g. mild flushing, rash, pruritus)	<ul style="list-style-type: none"> ▪ complete Paclitaxel infusion. Supervise at bedside ▪ no treatment required
<i>moderate</i> symptoms (e.g. moderate rash, flushing, mild dyspnea, chest discomfort, mild hypotension)	<ul style="list-style-type: none"> ▪ stop Paclitaxel infusion ▪ give IV Diphenhydramine 25-50 mg and Hydrocortisone IV 100 mg ▪ after recovery of symptoms resume Paclitaxel infusion at 20 mL/h for 5 minutes, 30 mL/h for 5 minutes, 40 mL/h for 5 minutes, then 60 mL/h for 5 minutes. If no reaction, increase to full rate. ▪ if reaction recurs, discontinue Paclitaxel therapy
<i>severe</i> symptoms (i.e. <i>one</i> or more of respiratory distress requiring treatment, generalised urticaria, angioedema, hypotension requiring therapy)	<ul style="list-style-type: none"> ▪ stop Paclitaxel infusion ▪ give IV antihistamine and steroid as above. Add Epinephrine or bronchodilators if indicated ▪ discontinue Paclitaxel therapy

5. **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

6. **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.

7. 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.

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.

Date activated: 11 Jul 2005 (as BRJACTTG)

Date revised: 01 June 2011 (Infusion section revised)

References:

1. Citron ML, Berry DA, Cirincione C et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of nod-positive primary breast cancer: first report of intergroup trial C9741/cancer and leukemia group b trial 9741. *J Clin Oncol* 2003; 21:1431-1439.
2. 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.
3. Perez A, Rodeheffer R. Clinical Cardiac Tolerability of Trastuzumab. *J Clin Oncol* 2004;22:322-329.
4. Dang C et al. The safety of dose-dense doxorubicin and cyclophosphamide followed by paclitaxel with trastuzumab in HER-2/neu overexpressed/amplified breast cancer. *J Clin Oncol* 2008;26:1216-1222
5. Mayer EL, Burstein, HJ. Weighing a dose-dense option for adjuvant chemotherapy and trastuzumab in Early-Stage Breast Cancer. *J Clin Oncol* 2008;26:1198-1200.