

BCCA Protocol Summary for Palliative Therapy for Metastatic Breast Cancer using Trastuzumab (HERCEPTIN®) and Docetaxel as First-Line Treatment for Advanced Breast Cancer

Protocol Code: BRAVTRAD

Tumour Group: Breast

Contact Physician: Dr. Susan Ellard

ELIGIBILITY:

- Overexpression of HER-2 neu
- HER-2 overexpression defined as either IHC3+, or FISH amplification ratio greater than or equal to 2 per BCCA central laboratory
- Life expectancy greater than 3 months
- ECOG status 0-2
- No signs or symptoms of cardiac disease. For patients with equivocal cardiac status, a MUGA scan or cardiac ECHO should be done and reveal a normal left ventricular ejection fraction.
- A "Class II Drug Registration Form" must be submitted for at the time of initiation of treatment.

EXCLUSIONS:

- Clinically significant cardiac disease (history of symptomatic ventricular arrhythmias, congestive heart failure or myocardial infarction within previous 12 months)

TESTS:

- Baseline: CBC & diff, platelets, total bilirubin, liver enzymes
 - Baseline if clinically indicated: cardiac function (ECG, echocardiogram or MUGA scan)
 - Before each treatment: CBC & diff, platelets
 - At cycle 4 or if clinically indicated before each docetaxel treatment*: total bilirubin, liver enzymes
- *See Precaution #7 for guidelines regarding hepatic dysfunction
- If clinically indicated at any time: cardiac ECHO or MUGA scan

PREMEDICATIONS:

- Not usually required for trastuzumab
- 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.
- 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

Drug	Dose	BCCA Administration Guideline
Trastuzumab (HERCEPTIN®)	8 mg/kg	IV in 250 mL NS over 1 hour 30 min Observe for 1 hour post-infusion**
Docetaxel	100 mg/m ²	IV in 250 to 500 mL* NS over 1 hour (use non-PVC equipment)

*use 250 mL for doses 74-185 mg, use 500 mL for doses greater than 185 mg

Cycles 2 – 6

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 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	100 mg/m ²	IV in 250 to 500 mL* NS over 1 hour (use non-PVC equipment)

* use 250 mL for doses 74-185 mg, use 500 mL for doses greater than 185 mg

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

Repeat every 21 days x 6 cycles in responding patients

Note: To continue single agent trastuzumab after completion of cycle 6, see protocol BRAVTR.

DOSE MODIFICATIONS:

1. Trastuzumab:

None required. Discontinue if unacceptable toxicity occurs.

2. Docetaxel

2a. Hematological

ANC (x 10 ⁹ /L)		Platelets (x 10 ⁹ /L)	Dose	Dose after neutropenic sepsis on Docetaxel
greater than or equal to 1.5	and	greater than 90	100%	75%
1.0 - 1.4	or	70-90	75%	75%
less than 1.0	or	less than 70	delay	delay

2b. Hepatic Dysfunction

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

ULN = upper limit of normal

PRECAUTIONS:

- Cardiac toxicity:** Trastuzumab can produce declines in ventricular dysfunction and congestive heart failure (CHF). The incidence of CHF on this protocol is approximately 2%. Regular monitoring of asymptomatic patients is not routinely necessary but may be ordered within 4-6 months of treatment with trastuzumab. If no significant decline in LVEF is apparent, repeated testing is not generally necessary, unless the patient's medical condition changes. Discontinue treatment for symptomatic congestive heart failure or serious cardiac arrhythmias/events. Most patients who develop congestive heart failure respond to appropriate medical therapy and in some cases (where the benefit outweighs the risk) may continue trastuzumab under close medical supervision.
- 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.

3. **Docetaxel Hypersensitivity:** Reactions 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 BCCA Hypersensitivity Guidelines
4. **Fluid retention:** Dexamethasone premedication must be given to reduce incidence and severity of fluid retention.
5. **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively.
6. **Extravasation:** Docetaxel causes pain and tissue necrosis if extravasated. Refer to BCCA Extravasation Guidelines.
7. **Hepatic Dysfunction:** Docetaxel undergoes hepatic metabolism. Hepatic dysfunction (particularly 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 (eg, repeat liver enzymes prior to each treatment if liver enzymes are elevated, liver metastases are present or there is severe toxicity such as neutropenia). If liver enzymes are normal and there is no evidence of liver metastases or severe toxicity, check liver enzymes after 3 cycles (ie, at cycle 4). Note: this information is intended to provide guidance but physicians must use their clinical judgment when making decisions regarding monitoring and dose adjustments
8. **A possible interaction between trastuzumab and warfarin** 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 weekly 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. (JAMA 1999;282:2299-301)

Call 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.

Date activated: 01 July 2005

Date last revised: 1 June 2011 (Infusion section revised)

References:

1. Marty M, Cagnetti F, Maraninchi D et al, Efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2 – positive metastatic breast cancer administered as first-line treatment: results of a randomized phase II trial by the M77001 study group. *J Clin Oncol* 23:1-10, 2005
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. Esteva FJ, Valero V, Booser D, et al. Phase II study of weekly docetaxel and trastuzumab for patients with HER-2-overexpressing metastatic breast cancer. *JCO*. 2002; 20:1800-1808.
5. Tedesco KL, Thor AD, Johnson DH, et al. Docetaxel combined with trastuzumab is an active regimen in HER-2 3+ overexpressing and fluorescent in situ hybridization-positive metastatic breast cancer: A multi-institutional phase II trial. *JCO*. 2004; 22:1071-1077.
6. Raff JP, Rajdev L, Malik U et al. Phase II study of weekly docetaxel alone or in combination with trastuzumab in patients with metastatic breast cancer. *Clin Breast Cancer*. 2004; 4:420-427.
7. Montemurro F, Choa G, Faggiuolo R, et al. A phase II study of three-weekly docetaxel and weekly trastuzumab in HER-2-overexpressing advanced breast cancer. *Oncology*. 2004; 66:38-45.