BC Cancer Protocol Summary for Palliative Therapy for Metastatic Breast Cancer using Trastuzumab and Capecitabine

Protocol Code	*BRAVTCAP*
Tumour Group	*Breast*
Contact Physician	*Dr. Stephen Chia*

ELIGIBILITY:
Patients must have:
- HER2-positive advanced breast cancer
  - HER-2 overexpression defined as either IHC3+, or FISH amplification ratio greater than or equal to 2 per BC Cancer central laboratory, and
- Previously treated with one prior trastuzumab-based protocol in the advanced setting.

Patients should have:
- ECOG status 0 to 2
- No signs or symptoms of cardiac disease. For patients with equivocal cardiac status, a MUGA scan or ECHO should be done and reveal a normal left ventricular ejection fraction.
- Ability to report any severe toxicity such as diarrhea, hand/foot syndrome, severe nausea, stomatitis

EXCLUSIONS:
Patients must not have:
- Clinically significant cardiac disease (history of symptomatic ventricular arrhythmias, congestive heart failure or myocardial infarction within previous 12 months)
- Severe renal impairment (calculated creatinine clearance less than 30 mL/min, see Cockcroft-Gault equation under **DOSE MODIFICATIONS**)
- suspected dihydropyrimidine dehydrogenase (DPD) deficiency (see **PRECAUTIONS**)

CAUTION:
- Severe hepatic dysfunction (total bilirubin greater than 50 micromol/L)

TESTS:
- Baseline: CBC & diff, platelets, creatinine. bilirubin, ALT, Alk phos, *DPYD* test (not required if previously tested, or tolerated fluorouracil or capecitabine)
- Baseline if clinically indicated: cardiac function (ECG, echocardiogram or MUGA scan)
- Prior to each cycle: CBC & diff, platelets, creatinine
- For patients on warfarin, weekly INR until stable warfarin dose established, then INR prior to each cycle.
- If clinically indicated at anytime: cardiac function, protein level, albumin, bilirubin, GGT, Alk Phos, ALT, LDH, urea, creatinine, CA15-3
- Consider weekly nursing assessment for capecitabine toxicity in first two cycles and when increasing capecitabine dose.

PREMEDICATIONS:
- Not usually required for trastuzumab or capecitabine

SUPPORTIVE MEASURES

- all patients should be advised to obtain an adequate supply of loperamide (IMODIUM®) with directions for management of diarrhea; proactive management of diarrhea is very important.
- topical emollients (eg, Bag Balm®, Udderly Smooth®) applied liberally and frequently to the hands and feet to reduce the symptoms hand-foot syndrome, sunscreen for all sun exposed areas

TREATMENT:

- patients must start treatment **within 6 weeks** of last trastuzumab cycle (no need to re-load trastuzumab)

Drug	Dose	BC Cancer Administration Guideline
trastuzumab	6 mg/kg	IV in 250 ml NS over 30 min
capecitabine*	1000 to 1250 mg/m^2 BID x 14 days (d 1 to 14) (Total daily dose = 2000 to 2500 mg/m^2/day)	PO

*Starting dose of 1000 mg/m^2 BID recommended. Capecitabine is available as 150 mg and 500 mg tablets (refer to Capecitabine Suggested Tablet Combination Table for dose rounding).

Repeat every 21 days x 6 to 8 cycles. Responding patient may be continued on treatment at the discretion of the treating physician. If capecitabine is discontinued for any reason other than progressive disease or trastuzumab related toxicity, can continue trastuzumab till evidence of progression. Discontinue if no response after 2 cycles or unacceptable toxicity. **Note: further combining trastuzumab with any other chemotherapy drugs would require a separate CAP approval.**

DOSE MODIFICATIONS:

Capecitabine Dosing Based on DPYD Activity Score (DPYD-AS)

Refer to "Fluorouracil and Capecitabine Dosing Based on DPYD Activity Score (DPYD-AS)" on www.bccancer.bc.ca/health-professionals/clinical-resources/cancer-drug-manual.

- Dose modifications for capecitabine may occur independently of trastuzumab
- Maximum treatment delay of 2 weeks is allowed for resolution of toxicity. If delay of more than 2 weeks due to toxicity, treatment should be discontinued
- Trastuzumab treatment can be continued while capecitabine is being held for toxicity resolution at the discretion of the ordering physician

1. Hematological – for Capecitabine

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	1st Event Dose	2nd Event Dose	3rd Event Dose	4th Event Dose
greater than or equal to 1.5	and	greater than or equal to 75	100%	100%	100%	100%
1 to 1.49	or	50 to 74.9	delay* then 100%	delay* then 75%	delay* then 50%	discontinue
0.5 to 0.99	or	25 to 49.9	delay* then 75%	delay* then 50%	discontinue	discontinue
less than 0.5	or	less than 25	discontinue or delay* then 50%	discontinue	discontinue	discontinue

*delay until ANC greater than or equal to 1.5 x 10^9/L and platelets greater than or equal to 75 x 10^9/L

2. Other Non-Hematologic Toxicity: for capecitabine

- if treatment is interrupted due to toxicity, retain the original stop and start dates (i.e. do not make up for missed doses when treatment is resumed)

Toxicity Criteria

Grade	Diarrhea	Nausea and Vomiting	Stomatitis
0 to 1	Increase of 2 to 3 stools/day or nocturnal stools	1 vomit/day but can eat	Painless ulcers, erythema or mild soreness
2	Increase of 4 to 6 stools/day or nocturnal stools	2 to 5 vomits/day; intake decreased but can eat	Painful erythema, edema or ulcers but can eat
3	Increase of 7 to 9 stools/day or incontinence, malabsorption	6 to 10 vomits/day and cannot eat	Painful erythema, edema or ulcers and cannot eat
4	Increase of 10 or more stools/day or grossly bloody diarrhea; may require parenteral support; dehydration	10 vomits or more per day or requires parenteral support; dehydration	Mucosal necrosis, requires parenteral support

Toxicity Grade	1st Event Dose	2nd Event Dose	3rd Event Dose	4th Event Dose
0 to 1	100%	100%	100%	100%
2	delay* then 100%	delay* then 75%	delay* then 50%	discontinue
3	delay* then 75%	delay* then 50%	discontinue	discontinue
4	discontinue or delay* then 50%	discontinue	discontinue	discontinue

*stop treatment immediately and delay until toxicity resolved to grade 0 to 1

3. Hand-Foot Skin Reaction: for capecitabine

- If treatment is interrupted due to toxicity, retain the original stop and start dates (i.e. do not make up for missed doses when treatment is resumed)

Grade	**Hand-Foot Skin Reaction**	**1st Event Dose**	**2nd Event Dose**	**3rd Event Dose**	**4th Event Dose**
1	Skin changes (eg, numbness, dysesthesia, paresthesia, tingling, erythema) with discomfort not disrupting normal activities	100%	100%	100%	100%
2	Skin changes (eg, erythema, swelling) with pain affecting activities of daily living	delay* then 100%	delay* then 75%	delay* then 50%	discontinue
3	Severe skin changes (eg, moist desquamation, ulceration, blistering) with pain, causing severe discomfort and inability to work or perform activities of daily living	delay* then 75%	discontinue or delay* then 50%	discontinue	discontinue

*Stop treatment immediately and delay until resolved to grade 0 to 1

4. Renal dysfunction: for capecitabine

Creatinine Clearance mL/min	**Capecitabine Dose only**
greater than 50	100%
30 to 50	75%
less than 30	Discontinue

Cockcroft-Gault Equation:

$$\text{Estimated creatinine clearance (mL/min)} = \frac{N\,(140 - \text{age})\,\text{wt (kg)}}{\text{serum creatinine (micromol/L)}}$$

N = 1.23 male
N = 1.04 female

5. **Hepatic dysfunction**: Dose modification may be required. Capecitabine has not been studied in severe hepatic dysfunction.

PRECAUTIONS:

1. **Neutropenia (uncommon):** Fever or other evidence of infection must be assessed promptly and treated aggressively.

Trastuzumab

2. **Cardiac toxicity**: Trastuzumab can produce ventricular dysfunction and congestive heart failure in about 2% of patients. The majority of patients who develop cardiac dysfunction are symptomatic. Regular monitoring of asymptomatic patients is not routinely necessary but may be ordered within 4 to 6 months of treatment with trastuzumab. If no significant decline in cardiac function 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. Most patients who develop cardiac dysfunction respond to appropriate medical therapy and in some cases (where the benefit outweighs the risk) may continue trastuzumab under close medical supervision.
3. **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.
4. **A possible interaction with 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 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.[1]

Capecitabine

5. **Dihydropyrimidine dehydrogenase (DPD) deficiency** can result in severe and unexpected toxicity – stomatitis, diarrhea, neutropenia, neurotoxicity - secondary to reduced drug metabolism of capecitabine. This deficiency is thought to be present in about 3% of the population.
6. **Myocardial ischemia and angina occurs rarely in patients receiving fluorouracil or capecitabine.** Development of cardiac symptoms including signs suggestive of ischemia or of cardiac arrhythmia is an indication to discontinue treatment. If there is development of cardiac symptoms patients should have urgent cardiac assessment. Generally re-challenge with either fluorouracil or capecitabine is not recommended as symptoms potentially have a high likelihood of recurrence which can be severe or even fatal. Seeking opinion from cardiologists and oncologists with expert knowledge about fluorouracil or capecitabine toxicity is strongly advised under these circumstances. The toxicity should also be noted in the patient's allergy profile.

7. **Possible drug interactions with capecitabine and warfarin, phenytoin or fosphenytoin** have been reported and may occur at any time. Close monitoring is recommended (eg, for warfarin, monitor INR weekly during capecitabine therapy and for 1 month after stopping capecitabine).

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

References:

1. Nissenblatt MJ. Karp GI. Bleeding risk with trastuzumab (Herceptin) treatment.
2. JAMA 1999;282:2299-301.
3. Slamon D, Leyland-Jones B, Shak S, Paton V et al. Addition of Herceptin™ (humanized anti-HER2 antibody) to first line chemotherapy for HER2 overexpressing metastatic breast cancer (HER2 +/MBC) markedly increases anticancer activity: a randomized, multinational controlled phase III trial. Proc Am Soc Clin Oncol 1998;17:98a.
4. 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.
5. Perez A, Rodeheffer R. Clinical Cardiac Tolerability of Trastuzumab. J Clin Oncol 2004;22:322-329.
6. von Minckwitz et al. Trastuzumab beyond progression in human epidermal growth factor receptor 2-positive advanced breast cancer: a German Breast Group 26/Breast International Group 03-05 Study. J Clin Oncol 2009;27:1999-2006.