ELIGIBILITY:
- HER-2 over-expression defined as either IHC 3+, or FISH amplification ratio greater than or equal to 2 per BC Cancer central laboratory
- High risk, node negative or node positive patients, not otherwise considered best treated with a longer standard 6 to 8 cycle anthracycline or anthracycline plus taxane regimen (e.g. BRAJFECDT, BRAJACTT, BRAJDCARBT, etc) as decided by their treating physician
- ECOG 0 to 1
- Adequate renal and hepatic function
- Adequate hematological parameters (ANC greater than 1.5 x 10^9/L and platelets greater than 90 x 10^9/L)
- No clinically significant 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 to 4
- Pregnancy or lactation
- Significant hepatic dysfunction
- Greater than or equal to grade 2 sensory or motor neuropathy
- 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

TESTS:
- Baseline: CBC & diff, platelets, bilirubin, ALT, creatinine (see Precaution #5 for guidelines regarding hepatic dysfunction and DOCEtaxel). If clinically indicated: GGT, LDH, Alk Phos
- MUGA scan or echocardiogram: prior to first treatment with trastuzumab, 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 #3 for adjustment of trastuzumab based on changes in LVEF)
- Before each treatment (Day 1): CBC & diff, platelets
- If clinically indicated: creatinine, bilirubin, albumin, GGT, LDH, ALT, Alk Phos, urea, MUGA scan or echocardiogram
PREMEDICATIONS:

- Antiemetic protocol for High/Moderate emetogenic chemotherapy (see protocol SCNAUSEA)
- 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.
  - 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:

Administer cyclophosphamide prior to DOCEtaxel to reduce hypersensitivity response to DOCEtaxel.

Cycle 1 only

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>BC Cancer Administration Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>trastuzumab</td>
<td>8 mg/kg</td>
<td>IV in 250 mL NS over 1 hour 30 min Observe for 1 hour post-infusion</td>
</tr>
<tr>
<td>cyclophosphamide</td>
<td>600 mg/m²</td>
<td>IV in 100 to 250 mL* NS over 20 min to 1 hour</td>
</tr>
<tr>
<td>DOCEtaxel</td>
<td>75 mg/m²</td>
<td>IV in 250 to 500 mL NS over 1 hour (use non-DEHP equipment)</td>
</tr>
</tbody>
</table>

Cycle 2 to 4

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>BC Cancer Administration Guideline</th>
</tr>
</thead>
</table>
| trastuzumab   | 6 mg/kg         | • Cycle 2: IV in 250 mL NS over 1 hour. Observe for 30 minutes post infusion.  
                    • Cycles 3 and 4: IV in 250 mL NS over 30 min. Observe for 30 min post infusion** |
| cyclophosphamide | 600 mg/m²    | IV in 100 to 250 mL* NS over 20 min to 1 hour                          |
| DOCEtaxel     | 75 mg/m²        | IV in 250 to 500 mL NS over 1 hour (use non-DEHP equipment)            |

* Cyclophosphamide – If less than or equal to 1000 mg, use 100 mL bag; if greater than 1000 mg use 250 mL bag
** Trastuzumab – 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/cyclophosphamide/trastuzumab for a total of 1 year of trastuzumab treatment (maximum of 17 cycles of trastuzumab). 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

<table>
<thead>
<tr>
<th>ANC (x 10^9/L)</th>
<th>Platelets (x10^9/L)</th>
<th>Dose (DOCEtaxel and cyclophosphamide)</th>
<th>Filgrastim (G-CSF) Option</th>
</tr>
</thead>
<tbody>
<tr>
<td>greater than or equal to 1.5 and greater than or equal to 90</td>
<td>100%</td>
<td>100 % regimen with filgrastim 300 mcg SC daily on Days 5 to 12 (adjust as needed)</td>
<td></td>
</tr>
<tr>
<td>1.0 to less than 1.5 or 70 to less than 90</td>
<td>75%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>less than 1.0 or less than 70</td>
<td>Delay until ANC greater than 1.5 and Plts greater than 90, then give 75% of previous cycle doses</td>
<td>Delay until ANC greater than 1.5 and Plts greater than 90, then give 100 % regimen with filgrastim 300 mcg SC daily on Days 5 to 12 (adjust as needed)</td>
<td></td>
</tr>
</tbody>
</table>
### Febrile Neutropenia

<table>
<thead>
<tr>
<th>Event</th>
<th>Dose Reduction Option (DOCEtaxel and cyclophosphamide)</th>
<th>Filgrastim (G-CSF) Option</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; episode</td>
<td>75% of previous cycle dose if Day 1 ANC greater than or equal to 1.5 and Plts greater than or equal to 100</td>
<td>100% regimen with filgrastim 300 mcg SC daily on Days 5 to 12 (adjust as needed)</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; episode</td>
<td>50% of original cycle dose if Day 1 ANC greater than or equal to 1.5 and Plts greater than or equal to 100</td>
<td>75% regimen with filgrastim 300 mcg SC daily on Days 5 to 12 (adjust as needed)</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; episode</td>
<td>Discontinue protocol or switch to Filgrastim (G-CSF) Option</td>
<td>50% regimen with filgrastim 300 mcg SC daily on Days 5 to 12 (adjust as needed)</td>
</tr>
<tr>
<td>4&lt;sup&gt;th&lt;/sup&gt; episode</td>
<td>N/A</td>
<td>Discontinue protocol</td>
</tr>
</tbody>
</table>

### Hepatic

<table>
<thead>
<tr>
<th>Alkaline Phosphatase</th>
<th>AST or ALT</th>
<th>DOCEtaxel Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>less than 2.5 x ULN</td>
<td>less than or equal to 1.5 x ULN</td>
<td>100%</td>
</tr>
<tr>
<td>2.5 to 5 x ULN</td>
<td>1.6 to 5 x ULN</td>
<td>75%</td>
</tr>
<tr>
<td>greater than 5 x ULN</td>
<td>greater than 5 ULN</td>
<td>discuss with contact physician</td>
</tr>
</tbody>
</table>

ULN = upper limit of normal
3. Cardiac Dysfunction

Asymptomatic Patients – Trastuzumab continuation based on serial LVEFs

<table>
<thead>
<tr>
<th>Relationship of LVEF to LLN</th>
<th>Absolute Decrease Of Less Than 10 Points From Baseline</th>
<th>Absolute Decrease Of 10 to 15 Points From Baseline</th>
<th>Absolute Decrease Of Greater Than or Equal to 16 Points From Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within Normal Limits</td>
<td>Continue</td>
<td>Continue</td>
<td>Hold *</td>
</tr>
<tr>
<td>1 to 5 points below LLN</td>
<td>Continue</td>
<td>Hold *</td>
<td>Hold *</td>
</tr>
<tr>
<td>Greater than or equal to 6 points below LLN</td>
<td>Continue *</td>
<td>Hold *</td>
<td>Hold *</td>
</tr>
</tbody>
</table>

* 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:


4. Treatment Interruptions – Trastuzumab

If an interruption in treatment of greater than 6 weeks occurs (i.e. 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. 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% to 7%) making this the safer option. Fever or other evidence of infection must be assessed promptly and treated aggressively.

2. Extravasation: DOCEtaxel causes pain and tissue necrosis if extravasated. Refer to BC Cancer Extravasation Guidelines.

3. Renal Dysfunction: Dose modification may be required for cyclophosphamide if creatinine clearance less than 0.3 mL/sec, i.e. less than 18 mL/minute (see 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 (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.

6. Interstitial pneumonitis (DOCEtaxel) may occur. Risk may be increased with radiation
therapy.

7. 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.

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.

8. 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 BRAVITR regimen) due to concern for
occult systemic metastases is at the discretion of the treating oncologist and dependent on
the individual circumstances.

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

References: