Trastuzumab S/C + Capecitabine
Metastatic Breast Cancer

**Background:** Trastuzumab in combination with capecitabine is an option for patients with HER2 positive metastatic breast cancer.

2nd-line treatment
A phase III randomised clinical trial (GBG 26/BIG 03-05) in patients with HER2 positive advanced breast cancer that had progressed on previous trastuzumab, compared the combination of trastuzumab plus capecitabine versus capecitabine alone (von Minckwitz 2009, von Minckwitz 2011). Compared with capecitabine alone, trastuzumab plus capecitabine was associated with a statistically significant improvement in time to progression (the trial's primary end point) but not overall survival.

1st-line treatment
Although trastuzumab plus capecitabine is not a standard 1st-line regimen for patients with advanced HER2 positive advanced breast cancer, it is an option for patients who are unable to receive a standard 1st-line regimen.

Neither trastuzumab or capecitabine are licensed for use in combination.

**Patient Group:**

| First or second line for HER2 positive metastatic breast cancer patients who have failed or cannot tolerate first line anthracycline or taxane containing chemotherapy. |
| >6 months gap after anthracycline therapy |
| ECOG PS 0-2 |

**Pre-treatment Assessment:**
Confirmed Her-2 positive on histology
Tumour markers (CA 15-3)
Weight, FBC, U&E, LFTs and Creatinine clearance
Blood Pressure
Appropriate staging e.g. CT thorax, abdomen and pelvis if visceral disease

**Cardiac assessment**
All patients for treatment with trastuzumab, but especially those with prior anthracycline and cyclophosphamide exposure, should undergo baseline cardiac assessment including history and physical examination and electrocardiogram (ECG), echocardiogram, and/or multigated acquisition (MUGA) scan.
Trastuzumab is contraindicated in patients with a history of documented congestive heart failure, coronary artery disease with previous Q-wave myocardial infarction or evidence of transmural infarction on ECG, angina pectoris requiring medication, poorly controlled hypertension, clinically significant valvular disease, or high risk of uncontrolled arrhythmias.

A left ventricular ejection fraction (LVEF) above the lower limit of normal (> 50%) is required for the treatment to go ahead (measured on ECHO or MUGA).

**Treatment Threshold**
- WBC $\geq 3.0 \times 10^9$/L
- ANC $\geq 1.5 \times 10^9$/L
- Platelets $\geq 100 \times 10^9$/L
- Cr Cl $> 50$ ml/min

**Regimen Details:**

**Day 1**

Trastuzumab 600mg (flat dose) by subcutaneous injection over 2-5 minutes

Capecitabine 1250mg/m$^2$ orally BD on days 1 to 14

**Cycles are repeated every 21 days until unacceptable toxicity or disease progression.**

**Administration:**

- The 600 mg dose should be administered as a subcutaneous injection only over 2-5 minutes. The injection site should be alternated between the left and right thigh. New injections should be given at least 2.5 cm from the old site and never into areas where the skin is red, bruised, tender, or hard. During the treatment course with subcutaneous trastuzumab, other medicines for subcutaneous administration should preferably be injected at different sites. Patients should be observed for six hours after the first injection and for two hours after the second injection for signs or symptoms of administration-related reactions. The observation time in subsequent doses may be reduced at local clinician's discretion.
• Although serious administration-related reactions (ARRs), including dyspnoea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation and respiratory distress, were not reported in the clinical trial with the trastuzumab subcutaneous formulation, caution should be exercised as these have been associated with the intravenous formulation. ARRs can be treated with an analgesic/antipyretic such as Paracetamol, or an antihistamine such as chlorphenamine. Serious reactions to intravenous trastuzumab have been treated successfully with supportive therapy such as oxygen, beta-agonists, and corticosteroids. In rare cases, these reactions were associated with a clinical course culminating in a fatal outcome. Patients experiencing dyspnoea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of a fatal ARR.

• Capecitabine film-coated tablets should be swallowed with water within 30 minutes after a meal and given 12 hourly.

Pre-Meds: None

Anti-emetics: Low emetogenicity

Additional Medication: Loperamide 4mg stat then 2mg PRN (maximum 16mg/24 hours)

Monitoring and Assessment:
Blood pressure – prior to each trastuzumab dose
Clinical Assessment (medical review) – prior to each cycle
Tumour markers – maximum 3 weekly
FBC, U&E, LFT creatinine clearance (calculated) – prior to each cycle
Echocardiogram (LVEF) at 4 months and then as clinically indicated
Dose Modifications:

Standard and reduced dose calculations according to body surface area for a starting dose of capecitabine of 1250 mg/m$^2$.

<table>
<thead>
<tr>
<th>Body surface area (m$^2$)</th>
<th>Dose per administration (mg)</th>
<th>150 mg</th>
<th>500 mg</th>
<th>Reduced dose (75 %)</th>
<th>Reduced dose (50 %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1.26</td>
<td>1500</td>
<td>-</td>
<td>3</td>
<td>1150</td>
<td>800</td>
</tr>
<tr>
<td>1.27 - 1.38</td>
<td>1650</td>
<td>1</td>
<td>3</td>
<td>1300</td>
<td>800</td>
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<tr>
<td>1.39 - 1.52</td>
<td>1800</td>
<td>2</td>
<td>3</td>
<td>1450</td>
<td>950</td>
</tr>
<tr>
<td>1.53 - 1.66</td>
<td>2000</td>
<td>-</td>
<td>4</td>
<td>1500</td>
<td>1000</td>
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<td>2150</td>
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<td>4</td>
<td>1650</td>
<td>1000</td>
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<td>4</td>
<td>1800</td>
<td>1150</td>
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<td>1.93 - 2.06</td>
<td>2500</td>
<td>-</td>
<td>5</td>
<td>1950</td>
<td>1300</td>
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<tr>
<td>2.07 - 2.18</td>
<td>2650</td>
<td>1</td>
<td>5</td>
<td>2000</td>
<td>1300</td>
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<tr>
<td>≥ 2.19</td>
<td>2800</td>
<td>2</td>
<td>5</td>
<td>2150</td>
<td>1450</td>
</tr>
</tbody>
</table>

**Haematological Toxicity**

Patients with baseline neutrophil counts of < 1.5 x 10$^9$/L and/or platelet counts of < 100 x 10$^9$/L should not be treated with capecitabine. Treatment should be delayed until the haematological parameters are ANC >1.5 x 10$^9$/L and platelets >100 x 10$^9$/L

Patients may continue trastuzumab therapy during periods of reversible, chemotherapy-induced myelosuppression but monitor closely for complications of neutropenia.

**Non Haematological Toxicity**

Toxicity due to capecitabine administration may be managed by symptomatic treatment and/or modification of the dose (treatment interruption or dose reduction). Once the dose has been reduced, it should not be increased at a later time. For those toxicities considered by the treating physician to be
unlikely to become serious or life-threatening, e.g. alopecia, altered taste, nail changes, treatment can be continued at the same dose without reduction or interruption. Patients taking capecitabine should be informed of the need to interrupt treatment immediately if moderate or severe toxicity occurs. Doses of capecitabine omitted for toxicity are not replaced. The following are the recommended dose modifications for toxicity:

<table>
<thead>
<tr>
<th>Toxicity grades*</th>
<th>Dose changes within a treatment cycle</th>
<th>Dose adjustment for next cycle/dose (% of starting dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Grade 1</td>
<td>Maintain dose level</td>
<td>Maintain dose level</td>
</tr>
<tr>
<td>• Grade 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-1st appearance</td>
<td>Interrupt until resolved to grade 0-1</td>
<td>100%</td>
</tr>
<tr>
<td>-2nd appearance</td>
<td></td>
<td>75%</td>
</tr>
<tr>
<td>-3rd appearance</td>
<td></td>
<td>50%</td>
</tr>
<tr>
<td>-4th appearance</td>
<td>Discontinue treatment permanently</td>
<td>Not applicable</td>
</tr>
<tr>
<td>• Grade 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-1st appearance</td>
<td>Interrupt until resolved to grade 0-1</td>
<td>75%</td>
</tr>
<tr>
<td>-2nd appearance</td>
<td></td>
<td>50%</td>
</tr>
<tr>
<td>-3rd appearance</td>
<td>Discontinue treatment permanently</td>
<td>Not applicable</td>
</tr>
<tr>
<td>• Grade 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-1st appearance</td>
<td>Discontinue permanently or</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>If physician deems it to be in the patient's best interest to continue, interrupt until resolved to grade 0-1</td>
<td></td>
</tr>
<tr>
<td>-2nd appearance</td>
<td>Discontinue permanently</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>
Cardiac toxicity
Congestive heart failure (NYHA II-IV) is a common adverse reaction to trastuzumab. It has been associated with a fatal outcome. Signs and symptoms of cardiac dysfunction such as dyspnoea, orthopnoea, increased cough, pulmonary oedema, S3 gallop, or reduced ventricular ejection fraction, have been observed in patients treated with trastuzumab.

Cardiac monitoring is carried out at baseline and at 4 months. Beyond this, LVEF should be monitored as clinically indicated (See North Wales Guidelines).

If left ventricular ejection fraction (LVEF) drops $\geq 10$ ejection fraction (EF) points from baseline AND to below 50 %, treatment should be suspended and a repeat LVEF assessment performed within approximately 6 weeks with initiation of e.g. ACE inhibitor (with monitoring of renal function and blood pressure) to improve cardiac function. If LVEF has not improved, or declined further, or symptomatic congestive heart failure (CHF) has developed, discontinuation of trastuzumab should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks. All such patients should be referred for assessment by a cardiologist and followed up.

Cardiotoxicity has been associated with fluoropyrimidine therapy, including myocardial infarction, angina, dysrhythmias, cardiogenic shock, sudden death and electrocardiographic changes (including very rare cases of QT prolongation). These adverse reactions may be more common in patients with a prior history of coronary artery disease. Cardiac arrhythmias (including ventricular fibrillation, torsade de pointes, and bradycardia), angina pectoris, myocardial infarction, heart failure and cardiomyopathy have been reported in patients receiving capecitabine. Caution must be exercised in patients with history of significant cardiac disease, arrhythmias and angina pectoris.

Pulmonary events
Severe pulmonary adverse events have been reported with the use of the intravenous trastuzumab formulation. Fatal events have been reported and may occur as part of an infusion-related reaction or with delayed onset. In addition, cases of interstitial lung disease including lung infiltrates, acute respiratory distress syndrome, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary oedema and respiratory insufficiency have been reported with the intravenous preparation. Patients experiencing dyspnoea at rest due to advanced malignancy or requiring supplementary oxygen therapy may be at increased risk of a fatal administration-related reaction and should only be treated with trastuzumab with extreme caution.

Skin Reactions
The Medicines and Healthcare products Regulatory Agency (MHRA) issued drug safety advice about capecitabine. Severe skin reactions such as Stevens-Johnson syndrome and toxic epidermal necrosis have been reported.
during treatment with capecitabine. Some cases were fatal. Capecitabine should be discontinued if a serious skin reaction occurs, and the reaction should be treated promptly.

**Diarrhoea**
Patients with severe diarrhoea should be carefully monitored and given fluid and electrolyte replacement if they become dehydrated. Standard anti-diarrhoeal treatments (e.g. loperamide) may be used. NCIC CTC grade 2 diarrhoea is defined as an increase of 4 to 6 stools/day or nocturnal stools, grade 3 diarrhoea as an increase of 7 to 9 stools/day or incontinence and malabsorption. Grade 4 diarrhoea is an increase of ≥10 stools/day or grossly bloody diarrhoea or the need for parenteral support. Dose reduction should be applied as necessary.

**Hand-Foot Syndrome**
Grade 1 hand-foot syndrome is defined as numbness, dyseaesthesia /paresthesia, tingling, painless swelling or erythema of the hands and/or feet and/or discomfort which does not disrupt the patient's normal activities.

Grade 2 hand-foot syndrome is painful erythema and swelling of the hands and/or feet and/or discomfort affecting the patient's activities of daily living.

Grade 3 hand-foot syndrome is moist desquamation, ulceration, blistering and severe pain of the hands and/or feet and/or severe discomfort that causes the patient to be unable to work or perform activities of daily living. If grade 2 or 3 hand-foot syndrome occurs, administration of capecitabine should be interrupted until the event resolves or decreases in intensity to grade 1. Following grade 3 hand-foot syndrome, subsequent doses of Capecitabine should be decreased.

**Renal Impairment**

<table>
<thead>
<tr>
<th>Cr Cl (ml/min)</th>
<th>Capecitabine Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>51-80</td>
<td>100%</td>
</tr>
<tr>
<td>30-50</td>
<td>75%</td>
</tr>
<tr>
<td>&lt;30</td>
<td>CI</td>
</tr>
</tbody>
</table>

**Hepatic Impairment**
There is no recommendation for dose adjustment in hepatic impairment.

**Pharmaceutical Care:**
- Capecitabine tablets are available in 150mg and 500mg.
- Tablets will disperse in water.
- No loading dose is required with subcutaneous trastuzumab.
• If the patient misses a dose of trastuzumab subcutaneous formulation, it is recommended to administer the next 600 mg dose (i.e. the missed dose) as soon as possible. The interval between consecutive trastuzumab subcutaneous formulation administrations should not be less than three weeks.
• Clinically significant interactions with capecitabine include: coumarin anticoagulants, and phenytoin,
• Avoid co-administration of allopurinol and antacids
• **DPD deficiency:** Rarely, unexpected, severe toxicity (e.g. stomatitis, diarrhea, neutropenia and neurotoxicity) associated with 5-FU has been attributed to a deficiency of DPD activity. A link between decreased levels of DPD and increased, potentially fatal toxic effects of 5-FU therefore cannot be excluded. Patients with known DPD deficiency should not be treated with capecitabine.
• **Diabetes mellitus or electrolyte disturbances.** Caution must be exercised in patients with diabetes mellitus or electrolyte disturbances, as these may be aggravated during capecitabine treatment.
• **Hypo- or hypercalcaemia.** Hypo- or hypercalcaemia has been reported during capecitabine treatment.
• Dehydration should be prevented or corrected at the onset. Patients with anorexia, asthenia, nausea, vomiting or diarrhoea may rapidly become dehydrated. If Grade 2 (or higher) dehydration occurs, capecitabine treatment should be immediately interrupted and the dehydration corrected. Treatment should not be restarted until the patient is rehydrated and any precipitating causes have been corrected or controlled.

**Most Common Toxicities:**
• Cardiac toxicity
• Administration-related reactions
• Hypertension
• Neutropenia +/- infection
• Thrombocytopenia
• Pulmonary toxicity
• Weight loss/gain
• Nausea and/or vomiting
• Mucositis
• Diarrhoea
• Abdominal pain
• Hypo/hypercalcaemia
• Hand-foot syndrome
• Lip and/or facial swelling
• Alopecia
• Erythema, Rash
• Headache, dizziness, tremor
• Tumour site pain
• Hot flushes
• Fatigue
• Anorexia
• Insomnia
• Depression
• Arthralgia, myalgia
• Conjunctivitis, excessive lacrimation and dry eyes
• Hepatotoxicity (rare)

References:


2. SPC Herceptin 600mg/5mL solution for injection™ Roche Products Limited. www.medicines.org.uk [accessed 20th May 2014]


