Trastuzumab Subcutaneous (Herceptin™)
Metastatic Breast Cancer

**Background:** Trastuzumab monotherapy (NICE TA 34) is recommended for people with tumours expressing HER 2 scored at levels of 3+ who have received at least two chemotherapy regimens for metastatic breast cancer. Prior chemotherapy must have included at least an anthracycline and a taxane where these treatments are appropriate. It should also have included hormonal therapy in suitable oestrogen receptor positive patients.

**Patient Group:**

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<th>HER 2 positive metastatic breast cancer (3+ by IHC or CISH/FISH+)</th>
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Monotherapy in patients who have received at least two chemotherapy regimens for metastatic disease. Prior chemotherapy will generally have included at least an anthracycline and a taxane unless patients are unsuitable for these treatments.

**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).
Regimen Details:

**Day 1**

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

Cycles are repeated every 21 days until 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 trastuzumab subcutaneous formulation 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 Herceptin 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.

**Pre-Meds:** Paracetamol 1g PO if required.

**Anti-emetics:** Low emetogenicity

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<tbody>
<tr>
<td>Tracy Parry-Jones</td>
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<td>Dr Cath Bale</td>
<td>Jun 14</td>
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**CONTROLLED DOCUMENT- ONLY VALID ON DATE OF PRINTING**
**Additional Medication:** Chlorphenamine IV and Hydrocortisone IV for administration related reactions.

**Monitoring and Assessment:**
- Blood pressure - prior to each cycle
- Clinical Assessment – prior to each cycle or if well every 6 weeks
- Tumour markers- maximum 3 weekly
- U&E, LFT creatinine clearance (calculated) – every 6 weeks
- Echocardiogram (LVEF) at 4 months and then as clinically indicated

**Dose Modifications:**

*Haematological toxicity*

Dose modifications are not recommended.

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

*Non Haematological Toxicity*

**Cardiac toxicity**

Congestive heart failure (NYHA II-IV) is a common adverse reaction to Herceptin. 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 ≥ 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.
Pulmonary events
Severe pulmonary adverse events have been reported with the use of the intravenous 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.

Renal Impairment
Dedicated pharmacokinetic studies have not been carried out.

Hepatic Impairment
Dedicated pharmacokinetic studies have not been carried out.

Pharmaceutical Care:

- 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 Herceptin subcutaneous formulation administrations should not be less than three weeks.

Most Common Toxicities:
- Cardiac toxicity
- Administration-related reactions
- Hypertension
- Weight gain/loss
- Nausea and/or vomiting
- Neutropenia +/- infection
- Lip and/or facial swelling
- Pulmonary toxicity
- Diarrhoea
- Erythema, Rash
- Headache, dizziness, tremor
- Tumour site pain
- Hot flushes
- Fatigue
- Arthralgia, myalgia
• Conjunctivitis, excessive lacrimation and dry eyes
• Hepatotoxicity (rare)

References:

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