Trastuzumab S/C + Oral Vinorelbine
Metastatic Breast Cancer

**Background:** Trastuzumab in combination with Vinorelbine is a first or second line treatment option for patients with HER 2 positive metastatic breast cancer (NICE CG81),

**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 ≥ $3.0 \times 10^9/L$
ANC ≥ $1.5 \times 10^9/L$
Platelets ≥ $100 \times 10^9/L$
Regimen Details:

**Day 1**
Trastuzumab 600mg (flat dose) by subcutaneous injection over 2-5 minutes
Vinorelbine 60mg/m² orally as a single dose (maximum 120mg)

**Day 8**
Vinorelbine 60mg/m² orally as a single dose (maximum 120mg)

Cycles are repeated every 21 days for up to 6 cycles, trastuzumab continues 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 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 subcutaneous trastuzumab, 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.

- Vinorelbine capsules should be taken orally as a single dose, swallowed with water without chewing or sucking the capsule. Take with food.

**Pre-Meds:** Ondansetron 8mg PO 30-60 minutes prior to each vinorelbine dose.

**Anti-emetics:** Moderately emetic

**Additional Medication:** None

**Monitoring and Assessment:**
- Blood pressure – prior to each trastuzumab dose
- Clinical Assessment (medical review) – prior to each cycle
- Tumour markers – maximum 3 weekly
- FBC – prior to D1 and D8
- U&E, LFT creatinine clearance (calculated) – prior to each cycle
- Echocardiogram (LVEF) at 4 months and then as clinically indicated

**Dose Modifications:**

*Haematological toxicity*

If the neutrophil count is below \(1.5 \times 10^9/L\) and/or the platelet count below \(100 \times 10^9/L\), then the treatment should be delayed until recovery.

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 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 ≥ 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.

**Constipation**
Patients receiving concomitant morphine or opioid analgesics with vinorelbine: laxatives and careful monitoring of bowel mobility are recommended. Prescription of laxatives may be appropriate in patients with prior history of constipation.

*Renal Impairment*

No dose modifications are necessary in renal impairment.

*Hepatic Impairment*

In patients with moderate liver impairment (bilirubin from 1.5 to 3 x ULN, whatever the levels of ALT), Vinorelbine should be administered at a dose of 50 mg/m²/week. The administration of Vinorelbine in patients with severe hepatic impairment is contra-indicated.
Pharmaceutical Care:

- Vinorelbine capsules are available as 20mg, 30mg and 80mg
- 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.
- Oral vinorelbine is associated with a higher incidence of nausea and vomiting than the intravenous formulation. Primary prophylaxis with anti-emetics and administration of the capsules with some food is recommended as this has also been shown to reduce the incidence of nausea and vomiting. If the patient vomits within a few hours of administration, re-administration is not recommended.
- If the patient chews or sucks the capsule by error, the liquid is an irritant. Advise patient to rinse mouth with water or preferably a normal saline solution.
- Drug interactions (Vinorelbine)
  - Phenytoin: risk of exacerbation of convulsions resulting from the decrease of phenytoin digestive absorption by cytotoxic drug or risk of toxicity enhancement or loss of efficacy of the cytotoxic drug due to increased hepatic metabolism by phenytoin
  - Itraconazole: as with all vinca-alkaloids, increased neurotoxicity of vinca-alkaloids due to the decrease of their hepatic metabolism.
The following table gives the dose required for appropriate ranges of body surface area (BSA).

<table>
<thead>
<tr>
<th>BSA (m²)</th>
<th>Dose (mg)</th>
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<tbody>
<tr>
<td>0.95 to 1.04</td>
<td>60</td>
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<tr>
<td>1.05 to 1.14</td>
<td>70</td>
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<tr>
<td>1.15 to 1.24</td>
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<tr>
<td>1.25 to 1.34</td>
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<tr>
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<tr>
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<tr>
<td>1.65 to 1.74</td>
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<tr>
<td>1.75 to 1.84</td>
<td>110</td>
</tr>
<tr>
<td>1.85 to 1.94</td>
<td>110</td>
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<tr>
<td>≥ 1.95</td>
<td>120</td>
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</tbody>
</table>

**Most Common Toxicities:**
- Cardiac toxicity
- Administration-related reactions
- Hypertension
- Neutropenia +/- infection
- Thrombocytopenia
- Weight loss/gain
- Nausea and/or vomiting
- Pulmonary toxicity
- Neurotoxicity
- Constipation
- Mucositis
- Diarrhoea
- Lip and/or facial swelling
- Alopecia
- Erythema, Rash
- Headache, dizziness, tremor
• Tumour site pain
• Hot flushes
• Fatigue
• 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](http://www.medicines.org.uk) [accessed 20th May 2014]

