REGIMEN TITLE: Trastuzumab in Gastric cancer

Indications:
NICE eligibilities:
First line treatment: Confirmed HER2-positive (3+ or FISH+) metastatic adenocarcinoma of the stomach or gastro-oesophageal junction.
In combination with Cisplatin 80mg/m² and Capecitabine 1000mg/m² BD D1-14 or Cisplatin 80mg/m² and Fluorouracil 800mg/m² D1-5 based chemotherapy (refer to separate protocols for Cisplatin/Capecitabine or Cisplatin/Fluorouracil).

Note:
If Trastuzumab is being given following anthracycline based treatment, there should be a gap of 3 weeks from finishing the last course of anthracycline chemotherapy.

Cardiac contra-indications: History of documented congestive heart failure, coronary artery disease with previous Q-wave myocardial infarction, angina pectoris requiring medication, uncontrolled hypertension, clinically significant valvular disease, or unstable arrhythmias.

Regimen details:
3-weekly regimen
Loading dose: Trastuzumab 8mg/kg IV D1 (1.cycle)
Maintenance dose: Trastuzumab 6mg/kg IV D1 (2. cycle onwards)

For the first cycle only, Trastuzumab is recommended to be administered on Day 1., initiating Cisplatin based chemotherapy from D2 onwards. Administer Trastuzumab before Cisplatin based chemotherapy (after hydration) for subsequent cycles.

Missed doses: 3-weekly schedule- If the patient misses a dose by more than one week, a re-loading dose of trastuzumab should be given.

Administration: Trastuzumab in 250ml Sodium Chloride 0.9% IV over 90 minutes (see below)

Reduced infusion times:
If the loading and the first dose are well tolerated, the infusion time can be reduced to 60 minutes, and then to 30 minutes in subsequent infusions. Emergency equipment must be available. If the shortened infusion time is not tolerated, increase back to 90 minutes.

Patients should be observed for at least 6 hours after the start of the first infusion and for 2 hours after the start of subsequent infusions for symptoms like fever and chills or other infusion-related symptoms. Interruption of the infusion may help control such symptoms and infusion may be resumed when symptoms abate. If the patient has tolerated the infusion well during the first 3 occurrences, the observation time can be decreased to 30 minutes for the subsequent infusions.
Infusion related and pulmonary symptoms may rarely occur more than 6 hours after the start of a trastuzumab infusion. Patients should be warned about this and instructed to contact the hospital if any such symptoms occur.

Frequency: 3- weekly cycle, until progression

Anti- emetics: Low emetogenicity

Regular investigations:
- FBC: Baseline and 3 monthly
- LFTs: Baseline and 3 monthly
- U&Es: Baseline and 3 monthly
- MUGA/ ECHO, LVEF: Baseline and 3 monthly

(see monitoring of toxicities section - cardiac function assessment)

Post chemotherapy follow up cardiac monitoring if requested

Comments: The dose is calculated on patient’s actual weight and should be re-calculated if actual weight changes by more than 10%. The weight should be measured at least once every 3 months during treatment, or if the patient reports weight change between treatments.

Supportive medication:
- Hydrocortisone and chlorphenamine can be given for chills / fever during the infusion
- Pethidine for rigors during the infusion if required

Extravasation: Non vesicant

Toxicities:
- Infusion related symptoms (mild to moderate in severity): fever, chills, headache, nausea, rash, arthalgia, myalgia (occur mainly with first dose)
- Infusion related symptoms (serious but rare): dyspnoea, hypotension, bronchospasm, tachycardia, angioedema, anaphylaxis (occur mainly with first dose)
- Cardiotoxicity, diarrhoea, rash, hepatotoxicity (rare)

Infusion related reactions
Majority occur during the first infusion. Symptoms include fever and chills that often resolve following interruption of the infusion and administration of the necessary supportive medication (see above).

More severe infusion-related symptoms manifest as dyspnoea, hypo/ hypertension, wheezing, bronchospasm, anaphylaxis, rigors, respiratory distress, urticaria and angioedema. Patients experiencing dyspnoea 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.

Pulmonary events
Serious pulmonary events, occasionally fatal, have been reported rarely. Trastuzumab is contra-indicated in patients with severe dyspnoea at rest due to complications of advanced malignancy or co-morbidities.
Cardiotoxicity

An LVEF (left ventricular ejection fraction) above the lower limit of normal (above 50%) is required for the treatment to go ahead (measured on echocardiography or multiple gated acquisition, ECHO or MUGA) Cardiac monitoring is carried out at baseline and 3 monthly intervals.

The risk of developing heart failure is greatest when trastuzumab is used in combination with anthracyclines, and they should not be used concurrently. Patients who have previously received anthracyclines are also at risk of cardiotoxicity. The half-life of trastuzumab is approximately 28.5 days, and it may persist in the circulation for up to 24 weeks after stopping treatment. Therefore, if possible, anthracyclines should be avoided for up to 24 weeks after stopping trastuzumab. Patients who receive anthracyclines after stopping trastuzumab may be at increased risk of cardiotoxicity and should have cardiac function monitored carefully. Trastuzumab following anthracycline therapy should not be given until 3 weeks of finishing anthracycline.

A guideline for stopping treatment in the event of reduced cardiac function:
If LVEF has fallen 10 ejection points or more from baseline and below 50% trastuzumab should be suspended and
a) if patient is symptomatic start anti heart-failure medication including, where appropriate, ACE inhibitor and inform consultant.
b) If patient is asymptomatic a repeat LVEF should be performed in 3-4 weeks. If there is no improvement discuss with consultant and seek cardiology opinion.

Discuss with consultant before re-starting trastuzumab.

Dose Modifications

Haematological Toxicity
It is recommended to perform full blood count at the same time as the cardiac monitoring (4-monthly).
Patients may continue trastuzumab therapy during periods of reversible, chemotherapy induced myelosuppression.

Renal Impairment
It is recommended to perform renal function tests at the same time as the cardiac monitoring (3-monthly).

Hepatic Impairment
It is recommended to perform liver function tests at the same time as the cardiac monitoring (3-monthly).

Drug interactions:  Monitor INR levels carefully if on concomitant warfarin

References:
www.medicines.org.uk,
www.micromedex.com
NICE TA208, Nov 2010
Bang et al.(2010) Lancet; 376: 687-697