**REGIMEN TITLE:** Trastuzumab single agent in Adjuvant Breast cancer

**Indications:**
NICE eligibilities:
Adjuvant treatment
Early-stage confirmed HER2-positive (3+ or FISH+) breast cancer after surgery and chemotherapy (neo-adjuvant or adjuvant), (and sometimes radiotherapy).

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

Single agent sequential trastuzumab adjuvant chemotherapy is recommended to be started up to 6 months after finishing the last course of 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)

**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.

Trastuzumab is prescribed on multi-dose proformas, sequenced so that a new prescription is required coinciding with 3 monthly MUGA/ECHO monitoring.

**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 60minutes, and then to 30minutes in subsequent infusions. Emergency equipment must be available. If the shortened infusion time is not tolerated, increase back to 90 minutes.

**Note:** Shortened infusion times in adjuvant setting are outside current license recommendation (unlicensed use), but have been used successfully in clinical practise. See references for further data.

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

Adjuvant treatment Total of 12 months (18 doses including the loading dose)

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, arthralgia, 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
Mostly 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 (i.e. before cycles 1, 5, 9, 13 and 17)

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 (3-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, accessed June 08
GSTT protocol, Trastuzumab adjuvant therapy. Revised Jan 06.
SWHCN Protocols. Adjuvant Trastuzumab. Revised March 08.
BCCA Protocol Summaries. BRAJTR. Revised June 07.
UK Clinical Guidelines for the use of Adj. Trastuzumab with or following chemotherapy in HER2 positive Early breast cancer. NCRI Breast Clinical Studies Group. Dec 05