TRASTUZUMAB CISPLATIN CAPECITABINE

INDICATION (ICD10) C16

1. HER2+ve metastatic adenocarcinoma of stomach or gastro-intestinal oesophageal junction (TA208) (unlicensed) PS 0, 1, 2

REGIMEN

Cycle 1

Day 1	TRASTUZUMAB	8mg/kg in 250ml sodium chloride 0.9% IV infusion
Day 2	Prehydration	
	CISPLATIN	80mg/m^2 in 1000ml sodium chloride 0.9% IV infusion over 2 hours
	Posthydration	
Days 1 to 14	CAPECITABINE	1000mg/m^2 twice daily (2000mg/m^2/day) oral followed by a 7 day rest

Cycles 2 to 6

Day 1	Prehydration	
	TRASTUZUMAB	6mg/kg in 250ml sodium chloride 0.9% IV infusion
	CISPLATIN	80mg/m^2 in 1000ml sodium chloride 0.9% IV infusion over 2 hours
	Posthydration	
Days 1 to 14	CAPECITABINE	1000mg/m^2 twice daily (2000mg/m^2/day) oral followed by a 7 day rest

Cycle 7 onwards

Day 1	TRASTUZUMAB	6mg/kg in 250ml sodium chloride 0.9% IV infusion

NB Trastuzumab SPC states patients need to be monitored for 6 hours after the start of the first dose and 2 hours after the start of subsequent doses.
Cycle 1 - administer trastuzumab over 90 minutes. Monitor for 3.5 hours post start of infusion (2 hours after completion) of the first dose,
Subsequent cycles - if the initial loading dose was well tolerated (no signs of hypersensitivity), the 2nd dose can be administered as a 30 minute infusion (otherwise to continue to be administered over 90 minutes), and subsequent infusions can be administered over 30 minutes.
If the first cycle was well tolerated, following the 2nd and 3rd cycles patients should be observed on the ward / day unit for 30 minutes after the completion of trastuzumab infusion.
If the 2nd and 3rd cycles were well tolerated, after the 4th and subsequent cycles patients do not need to be observed following completion of trastuzumab infusion.
Patients should be warned of the possibility of delayed reactions and instructed to seek medical advice immediately should this occur.

CYCLE FREQUENCY AND NUMBER OF CYCLES

Combination every 21 days for 6 cycles
Trastuzumab monotherapy every 21 days from cycle 7 until disease progression

ADMINISTRATION

Tablets should be taken 12 hours apart.
Swallowed with water within 30 minutes after a meal.

ANTI-EMETICS

Highly emetogenic day 1 cycles 1 to 6
Low emetogenic risk days 2 to 14 cycles 1 to 6
Minimal risk day 1 cycle 7 onwards

CONCURRENT MEDICATION REQUIRED

Capecitabine	Mouth and bowel support eg Loperamide, benzydamine mouthwash
Cisplatin	Ensure adequate pre and post hydration. If urine output is <100ml/hour or if patient gains >2kg in weight during IV administration post cisplatin give 20-40mg furosemide PO/IV.
Trastuzumab	Infusion related chills and/or fevers – treat with paracetamol and chlorphenamine.

EXTRAVASATION AND TYPE OF LINE / FILTERS

Cisplatin – exfoliant
Trastuzumab IV – neutral

Peripheral line

INVESTIGATIONS

Blood results required before SACT administration
FBC, U&E and LFTs cycles 1 to 6
FBC, U&E and LFTs every 3 months cycle 7 onwards
Neutrophils x 10^9/L ≥1.0
Platelets x 10^9/L ≥75 day 2
Ideally EDTA GFR should be used
Creatinine clearance (GFR) calculated, at the Consultants discretion
Serum creatinine
Monitor cardiac function according to network guidelines
DPD test
Baseline weight and every cycle for cycles 1 to 6, then 3 monthly weight.

MAIN TOXICITES AND ADVERSE REACTIONS

Capecitabine	Palmar plantar (handfoot syndrome) causing red palms and soles – treat with pyridoxine 50mg tds Diarrhoea – treat with loperamide or codeine Cardiotoxicity – monitor cardiac function. To minimise risk of anthracycline induced cardiac failure signs of cardiotoxicity e.g. cardiac arrhythmias, pericardial effusion, tachycardia with fatigue. All patients should be told to report any cardiac symptoms immediately and should be told to stop the medication immediately if any suspicion of cardiac problems. Stomatitis
Cisplatin	Nephrotoxicity – ensure adequate pre and post hydration is prescribed. Ototoxicity – assess patient for tinnitus or hearing abnormalities.
Trastuzumab	Cardiotoxicity - monitor cardiac function. Trastuzumab infusion related chills and/or fevers are commonly observed during the first infusion (but infrequently with subsequent infusions). Other symptoms may include nausea, hypertension, vomiting, pain, rigors, headache, cough, dizziness, rash, and asthenia. Some adverse reactions to trastuzumab infusion including dyspnoea, hypotension, wheezing, bronchospasm, supraventricular tachyarrhythmia, reduced oxygen saturation and respiratory distress can be serious and potentially fatal. If symptoms of back ache, nausea or vomiting, do a set of obs. Give hydrocortisone 100mg IV, chlorphenamine 10mg IV.

INTERACTIONS WHICH MAY REQUIRE DOSE MODIFICATIONS
(not exhaustive list check SPC/BNF/Stockleys)

Capecitabine	Brivudine and analogues should be avoided Warfarin Phenytoin Allopurinol
Cisplatin	Aminoglycosides increased risk of nephrotoxicity and ototoxicity. Renal function should be well monitored and audiometric tests as required. Cisplatin can cause a decrease in phenytoin serum levels. This may lead to reappearance of seizures and may require an increase of phenytoin dosages.

DOSE MODIFICATIONS
Haematological
ANC ≥1x10^9/L and/or platelets ≥75x10^9/L give 100% dose
ANC 0.5-0.99x10^9/L and/or platelets 50-74x10^9/L OR any episode of neutropenic sepsis during the previous cycle. Stop chemotherapy until recovery. Restart with 75% dose cisplatin and capecitabine.
ANC <0.5x10^9/L and/or platelets <50x10^9L. Stop chemotherapy until recovery. Restart with 50% dose cisplatin and capecitabine

Trastuzumab
No dose reduction or cessation of trastuzumab is required if patient has acute reversible neutropenia.

Non-haematological
Capecitabine
Dose limiting toxicities include diarrhoea, abdominal pain, nausea, stomatitis and handfoot syndrome.
Toxicity can 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.
When capecitabine is stopped for toxicity, the doses are omitted and not delayed.

Toxicity Grades	Dose changes within a treatment cycle	Dose adjustment for next cycle/dose (% of starting dose)
Grade 2 - 1st appearance	Interrupt until resolved to grade 0-1	100%
Grade 2 - 2nd appearance	Interrupt until resolved to grade 0-1	75%
Grade 2 - 3rd appearance	Interrupt until resolved to grade 0-1	50%
Grade 2 - 4th appearance	Discontinue treatment permanently	Not applicable
Grade 3 - 1st appearance	Interrupt until resolved to grade 0-1	75%
Grade 3 - 2nd appearance	Interrupt until resolved to grade 0-1	50%
Grade 3 - 3rd appearance	Discontinue treatment permanently	Not applicable
Grade 4 - 1st appearance	Discontinue permanently OR if physician deems it to be in the patient's best interest to continue, interrupt until resolved to grade 0-1	50%
Grade 4 - 2nd appearance	Discontinue treatment permanently	Not applicable

Cisplatin
If patient complains of tinnitus, tingling of fingers and/or toes, discuss with SpR or Consultant before administration.

Trastuzumab
Continuation and discontinuation of trastuzumab based on interval LVEF assessment as per network guidelines

Hepatic impairment

Bilirubin of >3xULN or ALT/AST >2.5xULN	Interrupt Capecitabine Treatment may be resumed when bilirubin decreases to <3xULN or hepatic aminotransferases decrease to <2.5xULN.

Renal impairment

Capecitabine

CrCl (ml/min) >50	give 100% dose
CrCl (ml/min) 30-50	give 75% dose
CrCl (ml/min) <30	contraindicated

Cisplatin

GFR >60ml/min	give 100% dose
GFR 45-60ml/min	give 75% dose
GFR <45ml/min	not recommended

REFERENCES