HOX – Trastuzumab, Oxaliplatin and Capecitabine (oesophagus)

Indication

First line palliative treatment for locally advanced, inoperable oesophago-gastric cancer for patients unsuitable for radical therapy. And have tumours expressing high levels of HER2 as defined by a positive immunohistochemistry score of 3

Regimen details

Day	Drug	Dose Level A	Dose Level B	Dose Level C	Route
1	Trastuzumab	8mg/kg – 6mg/kg from cycle 2	-	-	IV infusion
1	Oxaliplatin	130mg/m^2	80% Level A	60% Level A	IV infusion
1-21	Capecitabine	625mg/m^2 BD	80% Level A	60% Level A	Oral

Reduced-intensity chemotherapy should be considered for older and/or frail patients.

Cycle frequency

21 days.

Number of cycles

Continued until radiological or clinical progression, unacceptable toxic effects, or patient choice.
Generally, 6 cycles in locally advanced or metastatic disease followed by maintenance IV trastuzumab until progression.

Administration

Trastuzumab is administered in 250ml 0.9% NaCl over 90 minutes for cycle 1 and then over 30minutes from cycle 2.

Trastuzumab is contraindicated in patients with severe dyspnoea at rest due to complications of advanced malignancy or requiring supplementary oxygen therapy.
Risk of infusion reactions, hypersensitivity and anaphylaxis, particularly on first cycle. The majority of these events occur during or within 2.5 hours of the start of the first infusion. May not need to stop trastuzumab for minor hypersensitivity e.g. reactions, flushing, localised rash. Must be stopped for major reactions, e.g. hypotension, dyspnoea, angioedema or generalised urticaria. Antihistamines, paracetamol and hydrocortisone can be used to treat reactions and should be available if required but must not be used prophylactically. If patient has hypersensitivity reaction, follow manufacturers re-challenge guidelines before continuing with treatment.

Oxaliplatin is administered in 250-500mL glucose 5% over 2 hours. If patients experience laryngo-pharyngeal dyaesthesia (see below), subsequent infusions should be should be given over 4-6 hours.
Oxaliplatin is not compatible with sodium chloride 0.9%. **Line must only be flushed with glucose 5% after infusion**.
Lines must not be piggybacked or flushed with sodium chloride 0.9%.

Patients should be observed closely for platinum hypersensitivity reactions, particularly during the first and second infusions. Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of oxaliplatin. Facilities for the treatment of hypotension and bronchospasm must be available.
If hypersensitivity reactions occur, minor symptoms such as flushing or localised cutaneous reactions do not require discontinuation of therapy: the infusion may be temporarily interrupted and when symptoms improve re- started at a slower infusion rate. Chlorphenamine 10mg IV may be administered.
Severe reactions, such as hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of oxaliplatin and appropriate therapy.

Oxaliplatin may cause transient paraesthesia of hands and feet and laryngopharyngeal dysaesthesia (unpleasant

sensations in the throat). Onset is during or within hours of infusion and resolves within minutes to a few days. Symptoms are exacerbated by cold, so patients should be well advised on precautions to be taken. This does not require treatment or dose reduction but subsequent infusions should be given over 6 hours.

Capecitabine is available as 150mg and 500mg tablets.
Tablets should be taken after food and swallowed whole with a glass of water.

Pre-medication

Paracetamol 1g 30-60 minutes before treatment, and regularly for 24 hours after treatment

Emetogenicity

This regimen has a moderate emetogenic potential

Additional supportive medication

None required routinely

Extravasation

Oxaliplatin is an exfoliant (Group 4).

Investigations – pre first cycle

Dihydropyrimidine dehydrogenase (DPD) deficiency can result in severe toxicity secondary to reduced fluorouracil metabolism (this can present as severe diarrhoea and/or severe stomatitis early in the first cycle). Patients require DPD testing prior to administration. Dose adjustments should be made in accordance with local DPD policy.

Investigation	**Validity period** (or as per local policy)
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days
Magnesium	14 days
Calcium	14 days
MUGA scan or ECHO	28 days

Investigations – pre subsequent cycles

Investigation	**Validity period** (or as per local policy)
FBC	48 hours
U+E (including creatinine)	48 hours
LFTs	48 hours
Magnesium	48 hours
Calcium	48 hours
MUGA scan or ECHO	6 months as per cardiorespiratory pathway

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant.

Investigation	**Limit**
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥ 75 x 10^9/L
Bilirubin	< 1.5 x ULN
Creatinine Clearance (CrCl)	> 50mL/min
Congestive heart failure	LVEF <50%

Dose modifications

- **Haematological toxicity**

Neutrophils (x 10^9/L)		**Platelets** (x 10^9/L)	**Oxaliplatin Dose**	**Capecitabine dose**
≥ 1.0	and	≥ 75	100% original dose	100% original dose

0.5 - < 1.0	or	50-74	Delay treatment until count recovery 80% original dose on restart.	Stop and delay until count recovery.

- **Renal impairment**

CrCl (mL/min)	**Oxaliplatin dose**	**Capecitabine dose**	**Trastuzumab dose**
> 50	100% original dose	100% original dose	No dose reduction necessary
30-49	75%	75%	
< 30	omit	contraindicated	

- **Hepatic impairment**

Capecitabine:

Bilirubin	**Oxaliplatin dose**	**Capecitabine dose**
1.5 – x2 ULN	Little information available. Probably no dose reduction necessary, consultant decision	75% original dose
>x2 ULN		Omit

- **Other toxicities**

Capecitabine:

Other toxicities should be managed by symptomatic treatment and/or dose modification (i.e. by treatment interruption or undertaking a dose reduction).
Once the dose has been reduced, it should not be increased at a later time.

Dose modifications should be made as per the following table:

Toxicity grade	**1st occurrence**	**2nd occurrence**	**3rd occurrence**	**4th occurrence**
0-1	100%	100%	100%	100%
2	Delay then 100%	Delay then 75%	Delay then 50%	Discontinue
3	Delay then 75%	Delay then 50%	Discontinue	
4	Delay then 50%	Discontinue		

Any delays should be until the toxicity has resolved to grade 0-1.

Oxaliplatin:

Neurological toxicity:

If neurological symptoms occur, use the following oxaliplatin dose adjustments:

Toxicity grade	**Oxaliplatin dose**
1	100%
2 (persisting until next cycle)	100mg/m^2
3 (>7 days but resolved before next cycle)	100mg/m^2
3 (persisting until next cycle) or 4	Discontinue

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Infertility
Allergic reactions
Neurotoxicity
Nephrotoxicity
Severe toxicity due to DPD deficiency (see comments below)

- **Frequently occurring side effects**

Myelosuppression
Nausea and vomiting
Diarrhoea
Stomatitis and mucositis

Palmar-plantar erythema
Fatigue

- **Other side effects**

Dysguesia
Headache
Dizziness

Significant drug interactions – for full details consult product literature/ reference texts

Warfarin/coumarin anticoagulants: Avoid use due to elevations in INR. Switch to low molecular weight heparin during treatment.

Oxaliplatin:
Avoid nephrotoxic agents as these may increase toxicity of oxaliplatin.

Capecitabine:
Folinates: Avoid concomitant use of folinic and folic acid – enhanced toxicity of capecitabine.
Co- trimoxazole/trimethoprim: Avoid if possible – enhances antifolate effect. If essential, monitor FBC regularly.
Phenytoin and fosphenytoin – toxicity has occurred during concomitant capecitabine therapy – monitor levels regularly.
Sorivudine and its analogues – co-administration causes increased toxicity which may be fatal.
Allopurinol – A decrease in capecitabine activity as been shown when taken in combination of allopurinol. Avoid if possible.
Antacids – the use of antacids with capecitabine can decrease absorption – avoid.

Additional comments

This regimen is contraindicated if known or suspected dihydropyrimidine dehydrogenase (DPD) deficiency

Dose related peripheral sensory neuropathy can occur with oxaliplatin. It usually occurs after a cumulative dose of 800mg/m2. It can occur after treatment with oxaliplatin is completed, and is usually reversible, taking approximately 3 – 5 months to recovery.

Caution if history of ischaemic heart disease Raised bilirubin or AST

Contra-indication
Patients experiencing dyspnoea at rest due to either co-morbidities or complications of advanced malignant disease should not receive trastuzumab.

References

- Summary of Product Characteristics Oxaliplatin via www.medicines.org.uk
- Summary of Product Characteristics Capecitabine via www.medicines.org.uk
- Allwood M, Stanley A, Wright P, editors. The cytotoxics handbook. 4th ed. Radcliffe Medical Press. 2002.
- GO2 trial - Efficacy of Reduced-Intensity Chemotherapy With Oxaliplatin and Capecitabine on Quality of Life and Cancer Control Among Older and Frail Patients With Advanced Gastroesophageal Cancer The GO2 Phase 3 Randomized Clinical Trial *JAMA Oncol.* Published online May 13, 2021. doi:10.1001/jamaoncol.2021.0848

THIS PROTOCOL HAS BEEN DIRECTED BY DR MITCHELL, DESIGNATED LEAD CLINICIAN FOR UPPER GI CANCER

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE