Pembrolizumab Cisplatin Capecitabine

Indication

First-line treatment of patients with locally advanced unresectable or metastatic carcinoma of the oesophagus or HER-2 negative gastroesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 10

Untreated HER2-negative advanced gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1

Regimen details

Cycle 1 to 6

Day	Drug	Dose	Route
1	Pembrolizumab	200mg	IV infusion
		Or 395mg	Subcutaneous
1	0.9% sodium chloride + 20mmol potassium chloride + 10mmol magnesium sulphate	1000mL	IV infusion
1	Cisplatin	80mg/m^2	IV infusion
1	0.9% sodium chloride + 20mmol potassium chloride + 10mmol magnesium sulphate	1000mL	IV infusion
1-21	Capecitabine	625 mg/m^2 bd	PO

Cycle 7 onward

Day	Drug	Dose	Route
1	Pembrolizumab	400mg	IV infusion
		Or 790mg	Subcutaneous

Cycle frequency

Cycles 1-6: 21 days
Cycle 7 onwards: 42 days

Number of cycles

Cisplatin and capecitabine should be stopped after 6 cycles.
Pembrolizumab is continued until radiological or clinical progression, unacceptable toxicity or after 2 years of treatment.

Administration

Intravenous pembrolizumab

Pembrolizumab is administered in 100ml 0.9% sodium chloride over 30 minutes prior to chemotherapy.
The infusion must be administered through a sterile, non-pyrogenic, low protein binding in-line filter with a pore size of 0.2-5 µm.

Subcutaneous pembrolizumab

Inject into the subcutaneous tissue of the thigh or abdomen, avoiding the 5 cm area around the navel. Do not inject into skin that is damaged, sore, bruised, scarred, scaly, or has red patches. Rotate injection sites for subsequent injections.

- Inject 395mg over 1 minute
- Inject 790mg over 2 minutes

Cisplatin

Cisplatin is administered in 1 litre 0.9% sodium chloride over 2 hours.

Pre and post hydration consists of 20mmol potassium chloride and 10mmol magnesium sulphate given in 1 litre 0.9% sodium chloride over 2 hours.
All patients must be advised to drink at least 2 litres of fluid over the following 24 hours.

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

Pre-medication
Hydration regimen as above.

Emetogenicity
High Risk (Category A)

Additional Supportive Medication
None required routinely

Extravasation
Cisplatin is an exfoliant (group 4).
Pembrolizumab is neutral (group 1)

Investigations – pre first cycle
See standard list of pre-SACT bloods

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

Investigations – pre subsequent cycles

Investigation	**Validity period** (or as per local policy)
FBC	48 hours
U+E (including creatinine)	48 hours
LFTs (including AST)	48 hours*
Magnesium	48 hours
Calcium	48 hours
Thyroid function	Every 6 weeks unless otherwise clinically indicated
Glucose	As clinically indicated
Cortisol	At consultant discretion

*LFTs may be reviewed retrospectively (i.e. after the chemotherapy treatment) unless known to be deranged, in which case must be reviewed within the 48 hour pre-treatment period.

Standard limits for administration to go ahead
If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant.

Investigation	**Limit**
Neutrophil count	≥ 1.0 x 10^9/L
Platelet count	≥ 100 x 10^9/L (75-100 may go ahead at discretion of consultant)
Creatinine clearance	≥ 60 mL/min If serum creatinine raised >20% repeat bloods
Bilirubin	≤ 1.5 x ULN
AST, ALT	< 2.5 x ULN
TSH	Outside normal range to contact consultant

Dose modifications

- **Renal impairment**

CrCl (mL/min)	Cisplatin dose	Capecitabine dose	Pembrolizumab dose
>60	100%	100%	100%
50-55	80%	100%	100%
30-50	Contraindicated*	75%	100%
<30	Contraindicated	Contraindicated	100% (use with caution <15mL/min)

Consultant to consider a change to carboplatin for patients with a creatinine clearance <50mL/min.

- **Hepatic impairment**

Capecitabine: Limited safety and efficacy data in patients with hepatic impairment, capecitabine use should be carefully monitored in patients with mild to moderate liver dysfunction, regardless of the presence or absence of liver metastasis. Administration of capecitabine should be interrupted if treatment-related elevations in bilirubin of >3.0 x ULN or treatment-related elevations in hepatic aminotransferases (ALT, AST) of >2.5 x ULN occur. Treatment with capecitabine monotherapy may be resumed when bilirubin decreases to ≤ 3.0 x ULN or hepatic aminotransferases decrease to ≤ 2.5 x ULN.

Cisplatin: Limited data in patients with hepatic impairment. Discuss with consultant.

Pembrolizumab: Limited data in patients with hepatic impairment. Discuss with consultant.

- **Haematological toxicity**

Delay treatment until count recovery
Reduce cisplatin and capecitabine doses by 25% following febrile neutropenia or more than 2 x delays due to haematological toxicity. Consider other options.

- **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 util the toxicity has resolved to grade 0-1.

Cisplatin:
Neurotoxicity or ototoxicity:

- ≥ Grade 2: permanently stop cisplatin and switch to carboplatin AUC 5.

Diarrhoea: reduce doses as follows:

- Grade 2: 75% dose
- Grade 3: 50% dose
- Grade 4: discontinue or 50% dose (consultant decision)

Immune related adverse events (IRAEs)
Consult network guidance for management of IRAEs
https://www.healthierlsc.co.uk/application/files/8916/8744/0377/ESMO_IO_Toxicity_Treatment_Guidance.pdf

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

5% - 10% incidence of precipitation of angina, chest pain must be taken seriously

- **Serious side effects**

Immune related adverse events (IRAEs)
Myelosuppression
Infertility
Nephrotoxicity
Ototoxicity
Cardiomyopathy
Secondary malignancy
Severe toxicity due to DPD deficiency

- **Frequently occurring side effects**

Myelosuppression
Reduced appetite
Headache
Dizziness
Dry eyes
Cough
Diarrhoea
Nausea
Rash
Fatigue
Stromatitis and mucositis
Palmar-planar erythema

- **Other side effects**

Arthralgia

Significant drug interaction – 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.

Allopurinol and antigout agents: interactions have been observed between allopurinol and fluorouracil with possible decreased efficacy of fluorouracil. Concomitant use of allopurinol with capecitabine should be avoided. Cisplatin may increase the concentration of blood uric acid. Thus, in patients concurrently receiving **antigout agents** such as allopurinol, colchicine, probenecid or sulfinpyrazone, dosage adjustment of these drugs may be necessary to control hyperuricemia and gout.

Cisplatin: Avoid ototoxic and nephrotoxic agents (including aminoglycosides, loop diuretics and amphotericin B) as these may increase toxicity of cisplatin.

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.

Antacids – the use of antacids with capecitabine can decrease absorption – avoid.

Additional comments

Women of child bearing potential should use effective contraception during treatment and for at least 4 months after the last dose.

References

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