Capecitabine and RT – 7 day

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement status
Locally advanced pancreatic cancer after induction chemotherapy	C25	00523a	CDS

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Capecitabine is administered twice daily on day 1-5 of each cycle (one cycle is equal to 7 days). Radiotherapy is given concurrently on day 1-5 of each cycle up to a maximum of 5-6 cycles.

Day	Drug	Dose	Route	Cycle
1-5	Capecitabine	830mg/m^2 Twice Daily[1, 2, 3]	PO with food	Every 7 days for up to 6 cycles with radiotherapy
[1] The dose to be administered should consider the available tablet strengths.Reference to the NCCP DOSE BANDING TABLES for dosing of capecitabine here. Capecitabine tablets should be swallowed whole with plenty of water with food or within 30 minutes of eating. The tablets should not be crushed or cut. [2] (total daily dose = 1660mg/m^2)				
[3] See dose modifications section for patients with identified partial DPD deficiency.				

ELIGIBILITY:

- Indications as above
- ECOG status 0-2

EXCLUSIONS:

- Hypersensitivity to capecitabine or any of the excipients
- Known complete DPD deficiency
- History of severe and unexpected reactions to fluoropyrimidine therapy
- Pregnancy and lactation
- Severe hepatic or renal impairment
- Recent or concomitant treatment with brivudine

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist.

TESTS:

Baseline tests:

- FBC, renal and liver profile
- DPD testing prior to first treatment with capecitabine using phenotype and/or genotype testing unless patient has been previously tested

Regular tests:

- FBC, renal and liver profile prior to each cycle.

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Consider a reduced starting dose in patients with identified partial DPD deficiency.
  - Initial dose reduction may impact the efficacy of treatment. In the absence of serious toxicity, subsequent doses may be increased with careful monitoring.
- Any dose modification should be discussed with a Consultant.

Haematological:

Table 1: Dose modification of capecitabine based on haematological toxicity

ANC (x 10^9/L)		Platelets(x 10^9/L)	1st Event Dose	2nd Event Dose	3rd Event Dose	4th Event Dose
≥ 1.5	and	≥ 75	100%	100%	100%	100%
1-1.49	or	50 – 74.9	Delay* then 100%	Delay* then 75%	Delay* then 50%	Discontinue
0.5-0.99	or	25- 49.9	Delay* then 75%	Delay* then 50%	Discontinue	Discontinue
< 0.5	or	< 25	Discontinue or delay* then 50%	Discontinue	Discontinue	Discontinue

*Delay until ANC ≥ 1.5x 10^9/L and platelets ≥ 75x10^9/L

Renal and Hepatic Impairment:

Table 2: Dose modification of capecitabine in renal and hepatic impairment

Renal Impairment		Hepatic Impairment
Cr Cl (ml/min)	**Dose**	In the absence of 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**.**
≥ 30	100% dose	
<30	Discontinue treatment	
Reference Table 6 for dose modification of capecitabine in treatment related hepatotoxicity.		

Management of adverse events:

Table 3 shows the recommended dose modifications of capecitabine for those toxicities which are not individually specified:

Table 3: Capecitabine dose reduction schedule based on toxicity (Any)

Toxicity grades*	Dose changes within a treatment cycle	Dose adjustment for next cycle/dose (% of starting dose)
Grade 1	Maintain dose level	Maintain dose level
Grade 2		
• 1st appearance	Interrupt until resolved to grade 0-1	100%
• 2nd appearance		75%
• 3rd appearance		50%
• 4th appearance	Discontinue permanently	
Grade 3		
• 1st appearance	Interrupt until resolved to grade 0-1	75%
• 2nd appearance		50%
• 3rd appearance	Discontinue permanently	
Grade 4		
• 1st appearance	Discontinue permanently or If consultant deems it to be in patient's best interest to continue, interrupt until resolved to grade 0-1	50%
• 2nd appearance	Discontinue permanently	

*Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Table 4: Dose modification of capecitabine for diarrhoea

Grade	Diarrhoea	Dose changes within a treatment cycle	Dose adjustment for next cycle/dose (% of starting dose)
0-1	Increase of 2 to 3 stools/day or nocturnal stools	Maintain dose level	Maintain dose level
2	Increase of 4 to 6 stools/day or nocturnal stools		
	• 1st appearance	Interrupt until resolved to grade 0-1	100%
	• 2nd appearance		75%
	• 3rd appearance		50%
	• 4th appearance	Discontinue permanently	
3	Increase of 7 to 9 stools/day or incontinence and malabsorption		
	• 1st appearance	Interrupt until resolved to grade 0-1	75%
	• 2nd appearance		50%
	• 3rd appearance	Discontinue permanently	
4	Increase of 10 or more stools/day or grossly bloody diarrhoea; may require parenteral support		
	• 1st appearance	Discontinue permanently or If consultant deems it to be in patient's best interest to continue, interrupt until resolved to grade 0-1	50%
	• 2nd appearance	Discontinue permanently	

Hand foot syndrome:

Table 5: Dose modification of capecitabine in hand foot syndrome

Toxicity Grade		Dose Modification
Grade 1	Skin changes (eg, numbness, dysesthesia, paresthesia, tingling, erythema) with discomfort not disrupting normal activities.	100% Dose
Grade 2	Skin changes (eg, erythema, swelling) with pain affecting activities of daily living.	Withhold treatment until event resolves or decreases in intensity to grade 1.
Grade 3	Severe skin changes (eg, moist desquamation, ulceration, blistering) with pain, causing severe discomfort and inability to work or perform activities of daily living.	Withhold treatment until event resolves or decreases in intensity to grade 1. Subsequent doses of capecitabine should be decreased.

Treatment related hepatotoxicity

Table 6: Dose modification of capecitabine in treatment related hepatotoxicity

Bilirubin		ALT, AST	Dose Modification
> 3.0 x ULN	**or**	> 2.5 x ULN	Withhold treatment until bilirubin decreases to ≤ 3.0 x ULN or ALT, AST decrease to ≤ 2.5 x ULN.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Minimal to Low (**Refer to local policy)**

PREMEDICATIONS: Not usually required

OTHER SUPPORTIVE CARE:

Medication may be required for management of diarrhoea, e.g. loperamide (4mg at first onset followed by 2mg after each loose stool (max 16 mg /day) or see local policy.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Diarrhoea and dehydration:** This may be dose limiting. Patients with severe diarrhoea should be carefully monitored and given fluid and electrolyte replacement if they become dehydrated.
- **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated appropriately.
- **Cardiotoxicity:** Angina-like chest pain, tachycardia, arrhythmias, heart failure, myocardial infarction and cardiac arrest may occur with capecitabine especially in patients with a prior history of coronary artery disease.
- **Dihydropyrimidine dehydrogenase (DPD) deficiency:** DPD is an enzyme encoded by the DPYD gene which is responsible for the breakdown of fluoropyrimidines. Patients with DPD deficiency are therefore at increased risk of fluoropyrimidine-related toxicity, including for example stomatitis, diarrhoea, mucosal inflammation, neutropenia and neurotoxicity. Treatment with 5-Fluorouracil, capecitabine or tegafur-containing medicinal products is contraindicated in patients with known complete DPD deficiency. Consider a reduced starting dose in patients with identified partial DPD deficiency. Initial dose reduction may impact the efficacy of treatment. In the absence of serious toxicity, subsequent doses may be increased with careful monitoring. Therapeutic drug monitoring (TDM) of fluorouracil may improve clinical outcomes in patients receiving continuous 5-fluorouracil infusions.
- **Hand-foot syndrome (HFS**): HFS, also known as palmar-plantar erythrodysaesthesia (PPE) is a common side effect associated with capecitabine/5-fluorouracil (see Table 5 for dose modification of capecitabine for HFS).

DRUG INTERACTIONS:

- Capecitabine enhances the anticoagulant effect of warfarin. Patients taking coumarin derivative anticoagulants should be monitored regularly for alterations in their coagulation parameters and the anticoagulant dose adjusted accordingly.

- Brivudine must not be administered concomitantly with capecitabine. Brivudine inhibits dihydropyrimidine dehydrogenase which can lead to increased fluoropyrimidine toxicity. Fatal cases have been reported following this drug interaction. There must be at least a 4 week waiting period between end of treatment with brivudine and start of capecitabine therapy.
- Patients taking phenytoin or fosphenytoin concomitantly with capecitabine should be regularly monitored for increased phenytoin plasma concentrations.
- Current drug interaction databases should be consulted for more information.

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Version	Date	Amendment	Approved By
1	07/11/2018		Prof Maccon Keane
2	30/01/2019	Updated dosing recommendations in renal impairment.	Prof Maccon Keane
3	20/08/2020	Updated exclusion criteria, baseline testing, dose modifications and adverse events with respect to DPD deficiency as per DHPC from HPRA June 2020 Updated Adverse events regarding palmar-plantar erythrodysesthesia.	Prof Maccon Keane
4	10/02/2021	Added to exclusion criteria, amended emetogenic potential and added to drug interactions.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.