Gemcitabine and Capecitabine (pancreas)

Indication
First line palliative therapy for locally advanced or metastatic or relapsed pancreatic cancer.

ICD-10 codes
Codes prefixed with C25.

Regimen details

Day	Drug	Dose	Route
1, 8, 15	Gemcitabine	1000mg/m^2	IV infusion
1-21	Capecitabine	830mg/m^2 BD*	PO

*followed by a 7 day rest

Cycle frequency
28 days

Number of cycles
Until disease progression

Administration
Gemcitabine is administered in 250-500mL sodium chloride 0.9% over 30 minutes.

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

Doses should be prescribed as per the following table:

Body surface area (m^2)	Dose level 830mg/m^2 BD
	Dose to be prescribed (mg)
≤1.26	1000mg BD
1.27-1.38	1150mg BD
1.39-1.52	1150mg morning and 1300mg evening
1.53-1.66	1300mg BD
1.67-1.78	1450mg BD
1.79-1.92	1500mg BD
1.93-2.06	1650mg BD
2.07-2.18	1800mg BD
≥2.19	1950mg BD

Pre-medication
Nil

Emetogenicity
This regimen has a low emetogenic potential

Additional supportive medication

Mouthwashes as per local policy.
Proton pump inhibitor or H_2 antagonist if required.
Topical emollients for PPE

Extravasation

Gemcitabine is neutral (Group 1).

Investigations – pre first cycle

Investigation	**Validity period** (or as per local policy)
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days

Investigations – pre subsequent cycles

Investigation	**Validity period** (or as per local policy)
FBC	96 hours
U+E (including creatinine)	7 days
LFTs	7 days

Additional FBC is required prior to gemcitabine on days 8 and 15 (valid for 24 hours).

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	> 100 x 10^9/L
Bilirubin	≤ 1.5 x ULN
Creatinine Clearance (CrCl)	> 50mL/min

Dose modifications

- **Haematological toxicity**

Neutrophils (x10^9/L)		**Platelets** (x10^9/L)	**Gemcitabine dose** (days 1,8, and 15)	**Capecitabine dose**
> 1.0	and	> 100	100%	100%
0.5-1.0	or	50-100	75%*	Delay 1 week (or until recovery)
<0.5	or	<50	Day 1 – delay 1 week Days 8 or 15 - omit	Delay 1 week (or until recovery)

*dose reduction for day of treatment only, subsequent doses can return to 100%.

In the case of febrile neutropenia (neutrophils < 0.5 × 10^9/L and fever > 38.5°C requiring IV antibiotics) delay until FBC recovers.
Restart gemcitabine at 75% dose.

- **Renal impairment**

CrCl (mL/min)	**Gemcitabine dose**	**Capecitabine dose**
> 50	100%	100%
30-50	100%	75%
< 30	Consultant decision	contraindicated

- **Hepatic impairment**

Capecitabine:
Lack of information available. In patients with mild to moderate hepatic dysfunction due to liver metastases (bilirubin < 3 x ULN and/or AST/ALT < 5 x ULN). Probably no dose reduction necessary (consultant decision).

Gemcitabine:
Lack of information available on the use of gemcitabine in patients with hepatic impairment, therefore, used with caution. If bilirubin > 1.5 x ULN, consider reducing dose to 800mg/m^2 (consultant decision).

- **Other toxicities**

Capecitabine:
Other toxicities should be managed by symptomatic treatment and/or dose modification. Capecitabine should be omitted and treatment delayed until the toxicity has resolved to grade 0-1. Once the dose has been reduced, it should not be increased at a later time.

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.

Gemcitabine:
Mucositis/stomatitis or diarrhoea:

- Grade 2 (3rd occurrence) – 75% dose
- Grade 3 (2nd occurrence) – 75% dose
- Grade 4 – discontinue or 50% dose

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

- **Serious side effects**

Myelosuppression
Infertility
Cardiotoxicity
Hepatotoxicity
Peripheral neuropathy
Interstitial pneumonitis, ARDS
Secondary malignancy
Severe toxicity due to DPD deficiency (see comments below)

- **Frequently occurring side effects**

Myelosuppression
Nausea and vomiting
Diarrhoea
Stomatitis and mucositis
Palmar-plantar erythema
Haematuria
Fatigue
Rash

- **Other side effects**

Taste disturbance
Anorexia
Headache

Alopecia (mild)

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.

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.

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.

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.

References

- Summary of Product Characteristics Gemcitabine (Hospira) accessed 25 June 2014 via www.medicines.org.uk
- Summary of Product Characteristics Capecitabine (Roche) accessed 25 June 2014 via www.medicines.org.uk
- Allwood M, Stanley A, Wright P, editors. The cytotoxics handbook. 4th ed. Radcliffe Medical Press. 2002.
- Cunningham D, Chau I, Stocken DD, Valle JW, Smith D, Steward W, et al. Phase III Randomized Comparison of Gemcitabine Versus Gemcitabine Plus Capecitabine in Patients With Advanced Pancreatic Cancer. J Clin Oncol 2009 27 (33): 5513-5518

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