Mitomycin-C and Fluorouracil (anal)

Indication
Treatment of anal cancer with concurrent radiotherapy.

ICD-10 codes
Codes with a prefix C21

Regimen details

Day	Drug	Dose	Route
1 (cycle 1 only)	Mitomycin C	12mg/m^2 (max 20mg)	IV bolus
1-4	Fluorouracil	1000mg/m^2/24 hours*	IV infusion

*reduce dose to 75% if patient is ≥ 75 years.

Cycle frequency
28 days

Number of cycles
2 cycles. Mitomycin C for cycle 1 only.

Administration
Mitomycin C is administered by IV bolus via fast running infusion of sodium chloride 0.9%.

Fluorouracil is to be started at least 2 hours prior to first fraction of radiotherapy.

For patients with central line:
Fluorouracil is given as a continuous IV infusion over 4 days (96 hours), via CVC and ambulatory infusion device.

If patient not suitable for central line:
Fluorouracil is given as a peripheral IV infusion over 4 days (as an in-patient) in 4 x 1000mL sodium chloride 0.9% each administered over 22 hours.

Pre-medication
Nil

Emetogenicity
This regimen has low emetogenic potential.

Additional supportive medication
Mouthwashes if required.
Loperamide if required.

Extravasation
Mitomycin C is a vesicant (Group 5).
Fluorouracil is an inflammatant (Group 2).

Investigations – pre first cycle

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

Investigations – pre subsequent cycles

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

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
Creatinine clearance (CrCl)	≥ 60mL/min
Bilirubin	≤1.5 x ULN
AST/ALT	≤1.5 x ULN

Dose modifications

- **Haematological toxicity**

Delay for 1 week if neutrophils < 1.0 x 10^9/L or platelets < 100 x 10^9/L.

- **Renal impairment**

CrCl (mL/min)	**Mitomycin C (cycle 1)**	**Fluorouracil**
≥ 60	100% dose	100% dose
10-59	75% dose	100% dose
< 10	50% dose	Consider dose reduction

- **Hepatic impairment**

Bilirubin (x ULN)		**AST (x ULN)**	**Mitomycin C (day 1 only)**	**Fluorouracil**
≤1.5	and	≤1.5	100% dose	100% dose
1.5 - ≤ 3	or	1.5 - ≤3	100% dose	67% dose*
3 - ≤ 5	or	3 - ≤5	100% dose	50% dose*
> 5	or	>5		contraindicated

* Fluorouracil doses may be increased to 100% if no further toxicity

- **Other toxicities**

Toxicity	Definition	Dose adjustment
Stomatitis/Mucositis	Grade 2	Reduce all subsequent fluorouracil to 75% dose
	Grade 3	Reduce all subsequent fluorouracil to 50% dose
	Grade 4	Discontinue all treatment
Diarrhoea*	Grade 2	Reduce all subsequent fluorouracil to 75% dose
	Grade 3	Reduce all subsequent fluorouracil to 50% dose
	Grade 4	Discontinue all treatment
Palmer Plantar Erythrodysthesia (PPE)	Grade 2	Reduce all subsequent fluorouracil to 75% dose
	Grade 3/4	Reduce all subsequent fluorouracil to 50% dose
Haemolytic Uraemic Syndrome (HUS)	Microangiopathic haemolytic anaemia, renal failure, thrombocytopaenia and hypertension. More common with cumulative doses of mitomycin C (>36mg/m^2). If suspected test for red cell fragmentation. Discuss with renal team. Consider prednisolone 30mg OD for 7 days to prevent worsening haemolysis.	

* Monitor patients with diarrhoea until symptoms completely resolved as rapid (sometimes fatal) deterioration may occur.

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

- **Rare or serious side effects**

Myelosuppression
Thrombocytopenia
Cardiac toxicity
Occular toxicity
Interstitial lung disease
HUS

- **Frequently occurring side effects**

Myelosuppression
Mucositis and stomatitis
Diarrhoea and Constipation
Alopecia (mild)
Nausea and vomiting
PPE
Fatigue

- **Other side effects**

Transient cerebellar syndrome
Tremor
Confusion
Thrombophlebitis

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

Oral coumarin anticoagulants including warfarin**:** increased or fluctuating anticoagulant effects. Avoid if possible: in the first instance, consider switching patient to a low molecular weight heparin during treatment or if the patient continues taking an oral anticoagulant monitor the INR at least once a week and adjust dose accordingly.

Mitomycin-C:
Tamoxifen: increased risk of haemolytic uraemic syndrome with mitomycin-C.

Fluorouracil:
Allopurinol: may potentiate cytotoxic effect - avoid concomitant use.
Clozapine: increased risk of agranulocytosis - avoid concomitant use.
Digoxin tablets: fluorouracil may reduce digoxin absorption - give digoxin in liquid form.
Metronidazole and Cimetidine: inhibit metabolism of fluorouracil, increased exposure and risk of toxicity.
Phenytoin: reduced absorption of phenytoin (especially if patient had gastrointestinal toxicity from the radiation-sensitisation effects of fluorouracil).

Additional comments

Dihydropyrimidine dehydrogenase (DPD) deficiency can result in severe toxicity secondary to reduced fluorouracil metabolism – avoid use in patients with known DPD deficiency. Consider possibility of DPD deficiency in patients who experience severe toxicity.

Cardiotoxicity has been associated with fluoropyrimidine therapy, with adverse events being more common in patients with a prior history of coronary artery disease. Caution must be taken in patients with a history of significant cardiac disease, arrhythmias or angina pectoris.

Congestive heart failure has been reported with mitomycin-C.

Mitomycin-C maximum cumulative dose=36mg/m^2.

References

- Rich T. Infusional chemoradiation for rectal and anal cancer. Oncology 1999; 13 (10 Suppl 5): 131-4
- Allwood M, Stanley A, Wright P, editors. The cytotoxics handbook. 4th ed. Radcliffe Medical Press. 2002.
- Summary of Product Characteristics Fluorouracil (Hospira) accessed 10 Sept 2014 via www.emc.medicines.org.uk
- Summary of Product Characteristics Mitomycin-C (Kyowa Kirin) accessed 10 Sept 2014 via www.emc.medicines.org.uk

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