Mitomycin-C and Fluorouracil (bladder)

Indication
Radical treatment of transitional call cancer of the bladder with concurrent radiotherapy.

ICD-10 codes
Codes with a prefix C67

Regimen details

Day	Drug	Dose	Route
1	Mitomycin C	12mg/m^2	IV bolus
1-5	Fluorouracil	500mg/m^2/24 hours	IV infusion
22-26*	Fluorouracil	500mg/m^2/24 hours	IV infusion

*corresponds to fractions 16-20 of radiotherapy

Cycle frequency
1 cycle only. Mitomycin C on day 1 only.

Number of cycles
1 cycle

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 5 days, via CVC and ambulatory infusion device.

If patient not suitable for central line:
Fluorouracil is to be given as a continuous peripheral IV infusion over 5 days (as an in-patient) in 5 x 1000mL Sodium Chloride 0.9%.

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	Weekly during radiotherapy (and within 72 hours of chemotherapy)
U+E (including creatinine)	Weekly during radiotherapy (and within 7 days of chemotherapy)
LFT	Within 7 days of chemotherapy

Patient to be pre-assessed prior to day 22, including investigations as above and clinical and toxicity assessment.

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
Haemoglobin	>12g/dL
Creatinine clearance (CrCl)	>60mL/min
Bilirubin	≤1.5 x ULN

Dose modifications

- **Haematological toxicity**

Haemoglobin must be maintained above 12g/dL. If below this discuss with consultant.

- **Renal impairment**

CrCl (mL/min)	**Mitomycin C (day 1 only)**	**Fluorouracil**
>60	100% dose	100% dose
10-60	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	Discontinue chemotherapy, interrupt radiotherapy
	Grade 4	Discontinue all treatment
Diarrhoea*	Grade 2	Reduce all subsequent fluorouracil to 75% dose
	Grade 3	Discontinue chemotherapy, interrupt radiotherapy
	Grade 4	Discontinue all treatment
Palmer Plantar Erythrodysthesia (PPE)	Grade 3	Reduce all subsequent fluorouracil to 75% dose
	Grade 4	Discuss with consultant. If to proceed reduce all subsequent fluorouracil to 75-50% 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

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.
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.
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

- James ND, Hussain SA, Hall E, Jenkins P, Tremlett J,Rawlings C et al. Results of a phase III randomized trial of synchronous chemoradiotherapy (CRT) compared to radiotherapy (RT) alone in muscle invasive baldder cnacer (MIBC) (BC2001 CRUK/01/004), J Clin Oncol 2010 28:15s,
- Allwood M, Stanley A, Wright P, editors. The cytotoxics handbook. 4th ed. Radcliffe Medical Press. 2002.
- Summary of Product Characteristics Fluorouracil (Hospira) accessed 2 Apr 2014 via www.emc.medicines.org.uk
- Summary of Product Characteristics Mitomycin-C (Kyowa Kirin) accessed 2 Apr 2014 via www.emc.medicines.org.uk

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