Systemic Anti Cancer Treatment Protocol

Mitomycin-C 5FU and Folinic Acid (MMC+MdG)

PROTOCOL REF: MPHAMCFAGA
(Version No: 1.0)

Approved for use in:

Advanced colorectal cancer second or third line

Dosage:

Drug	Dosage	Route	Frequency
Mitomycin C	7mg/m^2	IV	Every 42 days
Folinic Acid	350mg	IV	Every 14 days
Fluorouracil	400mg/m^2	IV	Every 14 days
Fluorouracil	2400mg/m^2 over 46 hours	IV	Every 14 days

For a maximum of 4 cycles

Supportive treatments:

Domperidone 10mg oral tablets, up to 3 times a day or as required

Loperamide 4mg initially, then 2mg after each loose stool (maximum 16mg in 24hrs)

Extravasation risk:

Mitomycin-C – vesicant – follow trust / network extravasation policy.

Fluorouracil - Irritant – follow trust/network extravasation policy.

Administration:

Day	Drug	Dosage	Route	Diluent and Rate
1	Dexamethasone	8mg	Oral	N/A
1	Mitomycin C	7mg/m^2	IV	IV bolus in sodium chloride 0.9% over 10 mins
1	Folinic Acid	350mg	IV	IV infusion in glucose 5% over 2 hours
1	Fluorouracil	400mg/m^2	IV	IV bolus in sodium chloride 0.9% over 5 minutes
1	Fluorouracil	2400mg/m^2	IV	Via LV5 burgundy ambulatory infusion device in 230ml sodium chloride 0.9% over 46hrs at 5ml/hr
15	Folinic Acid	350mg	IV	IV infusion in glucose 5% over 2 hours
15	Fluorouracil	400mg/m^2	IV	IV bolus in sodium chloride 0.9% over 5 minutes
15	Fluorouracil	2400mg/m^2	IV	In 230ml sodium chloride 0.9% over 46hrs at 5ml/hr via LV 5 burgundy ambulatory infusion device
29	Folinic Acid	350mg	IV	IV infusion in glucose 5% over 2 hours
29	Fluorouracil	400mg/m^2	IV	IV bolus in sodium chloride 0.9% over 5 minutes
29	Fluorouracil	2400mg/m^2	IV	In 230ml sodium chloride 0.9% over 46hrs at 5ml/hr via LV 5 burgundy ambulatory infusion device

Repeat for a maximum of 4 cycles.

Notes:

Maximum cumulative Mitomycin dose is 28mg/m^2 or 56mg total

Care with patients on coumarin anticoagulants – monitor INR closely, consider LMWH

Sorivudine and analogues – Potentially fatal interaction – avoid completely

Caution in patients with pre-existing coronary heart disease, angina pectoris, arrhythmias.

Medical/Nursing review as per patient management plan

For severe reactions, discuss with Consultant before continuing with treatment.

Main Toxicities:

Mitomycin-C – myelosuppression, haemolytic uremic syndrome, pulmonary toxicity, diarrhoea, constipation, stomatitis, cholecyctitis, jaundice, acute renal failure and proteinuria. Haemolytic Uraemic Syndrome consists of microangiopathic haemolytic anaemia, renal failure thrombocytopaenia, and hypertension. Patients are at greater risk if they have renal failure, evidence of red cell fragmentation and if they have received several courses of treatment with cumulative doses of Mitomycin-C >36mg/m^2. Where suspected, test for red cell fragmentation. HUS may be treated with Prednisolone 30mg once daily for one week to prevent worsening haemolysis.
Patient should be discussed with renal team.

Fluorouracil - Diarrhoea, Nausea and vomiting, conjunctivitis / sore eyes, skin rashes, Palmar Plantar Erythema (PPE or hand foot syndrome), stomatitis, chest pain (myocardial ischaemia or angina), ovarian failure / infertility, nail ridges, taste changes DPD deficiency leads to severe early 5FU toxicity, affects approximately 3% of population, may be life threatening.

Investigations and treatment plan

		Cycle 1			Subsequent cycles		
	Pre	**Day 1**	**Day 15**	**Day 29**	**Day 1**	**Day 15**	**Day 29**
Clinical Assessment	x				x		
SACT Assessment	x	x	x	x	x	x	x
FBC	x		x	x	x	x	x
U&E & LFT	x		x	x	x	x	x
CT scan	x						Check CT ordered on last cycle
Informed Consent	x						
Weight recorded	x	x	x	x	x	x	x
Urine dipstick for protein / RBC	x				x		

Dose Modifications and Toxicity Management:

Haematological toxicity

Proceed on day 1 if:-

ANC ≥ 1.0 x 10^9/L	Platelets ≥ 100 x 10^9/L

Delay 1 week on day 1 if:-

ANC ≤ 0.9 x 10^9/L	Platelets ≤ 100 x 10^9/L

If platelets or ANC still below required levels for treatment for a second week, delay treatment again and patient will need to be assessed and consideration given for a chemotherapy dose reduction. Refer to consultant if in doubt.

Renal impairment:

CrCl (mL/min)	Fluorouracil
Above 30	100% dose
Below 30	Consider reduction

CrCl (mL/min)	Mitomycin-C
Above 10	100% dose
Below 10	75% dose

Calculate Creatinine clearance (CrCl) using Cockcroft and Gault equation below:

Male patients $\frac{1.23 \times (140 - \text{age}) \times \text{weight (kg)}}{\text{Serum Creatinine (micromol/L)}}$

Female patients $\frac{1.04 \times (140 - \text{age}) \times \text{weight (kg)}}{\text{Serum Creatinine (micromol/L)}}$

Hepatic impairment:

Mitomycin-C		
Clinical decision when AST levels > 2 x ULN. Clearance is primarily by metabolism in the liver, with approximately 10% of a dose excreted unchanged in the urine.		
Fluorouracil		
Bilirubin /µmol/L	**AST/ALT /units**	**Dose**

<85	and	<180	No dose modification
>86	or	>181	Contra indicated

Non-haematological toxicity

Mitomycin

Haemolytic Uremic Syndrome	This is a complication of mitomycin-C. Monitor renal function / urine dipstick carefully and request red cell fragments on peripheral blood films if in doubt. It is associated with prolonged course lengths and cumulative doses above 50mg/m^2 and can occur several months after treatment. Has been known at shorter and lower doses

Fluorouracil	
Chest pain, coronary artery spasm	Stop fluorouracil, standard angina investigations, refer to consultant, if symptoms persist stop permanently
Stomatitis	If mouth ulcers or > grade 2 symptoms develop treat symptomatically as per UKONS guide Delay treatment until resolved to grade 1 and reduce fluorouracil doses by 20%.
Diarrhoea	Monitor increase of bowel/stoma output over pre-treatment normal. Treat diarrhoea between cycles symptomatically as per UKONS guide. If diarrhoea remains troublesome reduce dose by 20%
PPE	Treat symptomatically, delay treatment until resolved to grade 1. Reduce fluorouracil dose by 20% for subsequent doses if persistent troublesome PPE. Refer to dose fluorouracil dose reduction table for non-haematological toxicity.

Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
None or no change from normal	Increase of up to 3 bowel movements a day over pre-treatment normal or mild increase in ostomy output	Increase of up to 4-6 episodes a day or moderate increase in ostomy output or nocturnal movement or moderate cramping	Increase of up to 7-9 episodes a day or severe increase in ostomy output or incontinence / severe cramping / bloody diarrhoea	Increase >10 episodes a day or grossly bloody diarrhoea

Fluorouracil dose reductions for non-haematological toxicity

	Non haematological toxicities (diarrhoea, stomatitis, PPE)			
grade	0-1	2	3	4
1st occurrence	100%	80%	50%	Stop treatment
2nd occurrence	80%	70%	50%	Stop treatment
3rd occurrence	50%	50%	50%	Stop treatment

References:

Summary of Product Characteristics, Electronic Medicines Compendium, Mitomycin, www.medicines.org.uk/emc/medicine/26917 [accessed 20/12/18]

Summary of Product Characteristics, Electronic Medicines Compendium, Fluorouracil, https://www.medicines.org.uk/emc/medicine/636 [accessed 20/12/18]