

Systemic Anti Cancer Treatment Protocol

**Mitomycin-C and Fluorouracil
Chemo-radiation regimen
Urothelial bladder cancer**

**PROTOCOL REF: MPHAUROMMF
(Version No: 1.0)**

Approved for use in:

Muscle-invasive transitional cell urothelial bladder cancer in patients where radical therapy is suitable.

Dosage:

A single cycle only (with concurrent radiotherapy)

Drug	Dose	Route	Frequency
Mitomycin-C	12mg/m ²	IV Infusion	Day 1 only
Fluorouracil	500mg/m ²	IV Infusion	Days 1 to 5 and 16 to 20

Supportive treatments:

Dexamethasone 4mg oral tablets twice daily for 3 days

Ondansetron 8mg oral tablets twice daily for 3 days

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

Administration

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

Day	Drug	Dose	Route	Diluent and rate
1	Dexamethasone 30 mins before treatment	16mg	PO	
1	Ondansetron 30 mins before treatment	16mg	PO	
1	Mitomycin-C	12mg/m² (max 20mg)	IV	Bolus via fast running infusion of 0.9% Sodium chloride
1 to 5	Fluorouracil	500mg/m²/24hours	IV	LV 2 yellow ambulatory

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				infusion device (2ml/hr) Over 5 days
22 to 26	Fluorouracil *corresponds to fractions 16-20 of radiotherapy	500mg/m²/24hours	IV	LV 2 yellow ambulatory infusion device (2ml/hr) Over 5 days

Extravasation risk:

Mitomycin C is a vesicant

Fluorouracil is an inflammitant

Main Toxicities:

Mitomycin-C	
Gastrointestinal	Diarrhoea, constipation, stomatitis
Haematological	Neutropenia, anaemia, *haemolytic uraemic syndrome, thrombocytopenic purpura, *Haemolytic Uraemic Syndrome consists of microangiopathic haemolytic anaemia, renal failure thrombocytopenia, 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.
Hepatobiliary disorders	Cholecystitis, jaundice
Renal and urinary disorders	Acute renal failure, haematuria, proteinuria,
Fluorouracil	
Gastrointestinal	Stomatitis/Mucositis Diarrhoea: Patients presenting with diarrhoea must be carefully monitored until the, a rapid (sometimes fatal) deterioration can occur.
Hepatobiliary	Liver cell damage, liver necrosis, biliary sclerosis, cholecystitis
Haematological	Myelosuppression (leucopenia, pancytopenia and thrombocytopenia); agranulocytosis, anaemia
Dermatological	Palmar – plantar syndrome (hand-foot syndrome), on the palms of the hands and soles of the feet

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	<p>Alopecia (hair may thin unlikely to cause total hair loss) Brittle, chipped and ridged nails –blue tinge or darkening or the nails, flaking of the nails, or pain and thickening of the nail bed.</p> <p>Sensitivity of the skin to sunlight</p>
Cardiovascular	<p>Cardiac disorders Angina, Ischemic ECG abnormalities</p> <p><u>Uncommon</u> - Arrhythmia, myocardial infarction, myocardial ishchemia myocarditis, dilative cardiomyopathy, cardiac shock.</p>

Investigations and Treatment Plan:

	Pre	Day 1	Day 22	Ongoing
Medical Assessment	X		X	Repeat investigations when clinically indicated
Nursing Assessment		X	X	
FBC	X	X	X	
U&E & LFT	X	X	X	
CT scan	X			
Informed Consent	X			
ECG	X			
Blood pressure measurement	X	X	X	
PS recorded	X	X	X	
Toxicities documented	X	X	X	
Weight recorded	X	X	X	

Dose Modifications and Toxicity Management:

Refer to consultant oncologist for advice regarding any toxicity \geq grade 2

Recommended dose reduction	Fluorouracil
Grade 2	Reduce all subsequent doses of fluorouracil by 25%
Grade 3	Discontinue chemotherapy; consider interruption in radiotherapy.
Grade 4	Discontinue treatment

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Haematological Toxicity:

Proceed on day 1 and day 22 if-

ANC $\geq 1.0 \times 10^9/L$	Plt $\geq 100 \times 10^9/L$
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Discuss with consultant oncologist if blood results are below these recommended limits

Hepatic impairment:

Mitomycin-C
Clinical decision when AST levels $> 2 \times$ ULN. Clearance is primarily by metabolism in the liver, with approximately 10% of a dose excreted unchanged in the urine.

Fluorouracil		
Bilirubin /$\mu\text{mol/L}$	AST/ALT /units	Dose
<85	and <180	No dose modification
>86	or >181	Contra indicated

Renal impairment:

CrCl (mL/min)	Mitomycin-C
> 60	100% dose
10 to 60	75% dose
<10	50% dose

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

References:

Intermediate-risk non-muscle-invasive bladder cancer. Bladder cancer: diagnosis and management. NICE. 02/2015.

Available from www.nice.org.uk/guidance/NG2

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 bladder cancer (MIBC) (BC2001 CRUK/01/004), J Clin Oncol 2010 28:15s, abstr 4517

Hussain SA, Stocken DD, Peake DR, Glaholm JG, Zarkar A, Wallace DMA, and James ND Long-term results of a phase II study of synchronous chemoradiotherapy in advanced muscle invasive bladder cancer. Br J Cancer 2004; 90 (11): 2106-2111.

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Mitomycin C, Summary of Product Characteristics, Kyowa Kirin Ltd Galashiels. 26/11/1992. Available from www.medicines.org.uk/emc/medicine. Last updated 26/09/2016.

Dosage Adjustment for Cytotoxics in Hepatic Impairment. January 2009 UCLH (Version 3 - updated January 2009)

Dosage Adjustment for Cytotoxics in Renal Impairment. January 2009 UCLH (Version 3 - updated January 2009)

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