Systemic Anti Cancer Treatment Protocol

Mitomycin-C and Fluorouracil Chemoradiation Regimen Urothelial Bladder Cancer

PROTOCOL REF: MPHAUROMMF
(Version No: 1.1)

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/m^2 (max 20mg)**	IV	Bolus via fast running infusion of 0.9% Sodium chloride
1 to 5	**Fluorouracil**	**500mg/m^2/24hours**	IV	LV 2 yellow ambulatory infusion device (2ml/hr) Over 5 days
22 to 26	**Fluorouracil** *corresponds to fractions 16-20 of radiotherapy	**500mg/m^2/24hours**	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 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.
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 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. Sensitivity of the skin to sunlight
Cardiovascular	**Cardiac disorders** Angina, Ischemic ECG abnormalities <u>Uncommon</u> - Arrhythmia, myocardial infarction, myocardial ishchemia myocarditis, dilative cardiomyopathy, cardiac shock.

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	
Dihydropyrimidine dehydrogenase (DPD) deficiency test	X			This test is normally only required if a patient has not had capecitabine, or fluorouracil in the past. However a consultant may still request this test if capecitabine or fluorouracil was not tolerated previously. The result must be available before administration of chemotherapy unless clear documentation from the consultant is available to the contrary. Treatment with capecitabine and fluorouracil is contraindicated in patients with known complete DPD deficiency.

Dose Modifications and Toxicity Management:

Refer to consultant oncologist for advice regarding any toxicity ≥ 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

Haematological Toxicity:

Proceed on day 1 and day 22 if-

ANC ≥ 1.0 x 10^9/L	Plt ≥ 100 x 10^9/L

Discuss with consultant oncologist if blood results are below these recommended limits

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

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 baldder 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.

Fluorouracil 50 mg/ml Solution for Injection or Infusion, Summary of Product Characteristics, Hospira, Warwickshire. 19/07/2004. Available from https://www.medicines.org.uk/emc Last updated 24/07/14.

Mitomycin C, Summary of Product Characteristics, Kyowa Kirin Ltd Galashiels. 26/11/1992. Available from https://www.medicines.org.uk/emc 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)