Methotrexate, vinBLAStine, DOXOrubicin, CISplatin (MVAC) -14 Days Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Locally advanced or metastatic transitional cell carcinoma (TCC) of the urothelium	C67	00333a	Hospital

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Methotrexate is administered on day 1 and vinBLAStine, DOXOrubicin and CISplatin on day 2 once every 14 days until disease progression or unacceptable toxicity develops**.**

Granulocyte-Colony stimulating factor (G-CSF) is administered on day 3, 4, 5, 6 & 7 of every 14 day cycle.

Facilities to treat anaphylaxis MUST be present when systemic anti cancer therapy (SACT) is administered.

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	Methotrexate	30mg/m^2	IV Bolus		Every 14 days
2	2	[a]vinBLAStine	3mg/m^2	IV infusion	50ml 0.9% NaCl over 15 min	Every 14 days
3	2	[b]DOXOrubicin	30mg/m^2	IV Bolus		Every 14 days
4	2	[c]CISplatin	70mg/m^2	IV infusion	500ml 0.9% NaCl over 60 min	Every 14 days

[a]vinBLAStine is a neurotoxic chemotherapeutic agent. Refer to NCCP Guidance on the Safe Use of Neurotoxic drugs (including Vinca Alkaloids) in the treatment of cancer Link

[b]Lifetime cumulative dose of DOXOrubicin is 450mg/m^2
In establishing the maximal cumulative dose of an anthracycline, consideration should be given to the risk factors outlined below and to the age of the patient.[i]

[c] **Pre and post hydration therapy required for CISplatin**
See local hospital policy recommendations.
Suggested prehydration for CISplatin therapy:

1. Administer 10mmol magnesium sulphate ($MgSO_4$) (+/-KCl 10-20mmol/L if indicated) in 1000mL sodium chloride 0.9% over 60 minutes.

Administer CISplatin as described above
Post hydration: Administer 1000 ml 0.9% NaCl over 60mins
Mannitol 10% may be used to as per local policy to induce diuresis, although there is no conclusive evidence that this is required. The routine use of furosemide to increase urine flow is not recommended unless there is evidence of fluid overload.

ELIGIBILITY:

- Indications as above
- ECOG 0-1

EXCLUSIONS:

- Hypersensitivity to methotrexate, vinBLAStine, DOXOrubicin, CISplatin or any of the excipients
- Congestive heart failure (LVEF < 50%) or other significant heart disease
- Moderate/severe renal impairment (creatinine clearance < 60 mL/min)
- Pregnancy and Lactation
- Pre existing neuropathies ≥ grade 2
- Significant hearing impairment/tinnitus

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist.

TESTS:

Baseline tests:

- FBC, Renal and liver profile
- ECG
- MUGA or ECHO (LVEF > 50% to administer doxorubicin) if >65 years or if clinically indicated.
- Audiology and creatinine clearance if clinically indicated

Regular tests:

- FBC, Renal and liver profile prior to each cycle
- If clinically indicated MUGA scan or ECG

Disease monitoring:
Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.

Haematological:

Table 1: Dose modification for haematological toxicity

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Dose
≥1.5	and	≥100	100% Dose
<1.5	or	<100	Hold*
Febrile neutropenia or ANC < 0.5 for 5-7 days	or	Thrombocytopenic bleeding or platelets < 25	Hold *then 75% of previous dose
*Do not start a new cycles until ANC ≥1.5x10^9/L and platelets ≥100x10^9/L			

Renal and Hepatic Impairment:

Table 2: Dose modifications in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment			
Methotrexate	**CrCl (ml/min)**	**Dose**	**Bilirubin(micromol/L)**		**AST (Units)**	**Dose**
	≥50	100%	<50	and	<180	100%
	20-50	50%	51-85	or	>180	75%
	<20	Not recommended. If unavoidable, consider haemodialysis	>85			CI
			Contraindicated in severe hepatic impairment			
vinBLAStine	No dose reduction necessary		**Bilirubin(micromol/L)**		**AST/ALT(Units)**	**Dose**
			26-51	or	60-180	50%
			>51	and	Normal	50%
			>51	and	>180	Omit
DOXOrubicin	No dose reduction required. Clinical decision in severe impairment.		**Bilirubin (micromol/L)**		**Dose**	
			20-51		50%	
			51-85		25%	
			>85		Omit	
			If AST 2-3 x normal, give 75% dose.			
			If AST >3x ULN, give 50% dose			
CISplatin	**CrCl (ml/min)**	**Dose**	No dose reduction necessary			
	≥60	100%				
	45-59	75%				
	<45	Consider CARBOplatin				

Management of adverse events:

Table 3: Dose Modification of MVAC Therapy for Adverse Events

Adverse reactions	Recommended dose modification
Neurotoxicity	
Grade 2 present at start of next cycle	Reduce dose of CISplatin and vinBLAStine by 25% dose.
Grade 3	Discontinue CISplatin and vinBLAStine

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Methotrexate – Low **(Refer to local policy)**.
vinBLAStine – Minimal **(Refer to local policy)**.
DOXOrubicin – Moderate **(Refer to local policy)**.
CISplatin – High **(Refer to local policy)**.

Consider increased risk of vinca alkaloid-induced adverse effects due to inhibition of CYP3A4 by aprepitant.

PREMEDICATIONS: None usually required

OTHER SUPPORTIVE CARE:

- Hydration prior and post CISplatin administration **(Reference local policy or see recommendations above)**. Patient should be encouraged to drink large quantities of liquids for 24 hours after the CISplatin infusion to ensure adequate urine secretion.
- Prophylactic laxatives may be required to prevent constipation related to the use of vinca alkaloids.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated appropriately.
- **Pleural effusion or ascites**: Methotrexate should be used with caution in patients with pleural effusions or ascites, as methotrexate may accumulate in third space fluid compartments.
- **Extravasation:** vinBLAStine and DOXOrubicin are vesicants which may cause pain and tissue necrosis if extravasated (Refer to local extravasation guidelines).
- **Cardiac Toxicity:** DOXOrubicin is cardiotoxic and must be used with caution, if at all, in patients with severe hypertension or cardiac dysfunction.
- **Hypersensitivity:** Hypersensitivity reactions have been reported with CISplatin.
- **Renal Toxicity:** Nephrotoxicity is common with CISplatin. Strongly encourage oral hydration. If oral hydration is not possible (e.g. excessive nausea), IV hydration is indicated. Avoid nephrotoxic drugs such as aminoglycoside antibiotics where possible. Where treatment with nephrotoxic drugs must be used, monitor renal function.
- **Ototoxicity and sensory neural damage:** These are associated with CISplatin therapy. They should be assessed by history prior to each cycle

DRUG INTERACTIONS:

- NSAIDs may decrease the clearance of methotrexate by decreasing its renal perfusion and tubular secretion thus increasing its toxicity.
- Sulphonamides and penicillins may displace bound methotrexate from plasma protein increasing serum methotrexate levels and its toxicity.
- Concomitant administration of drugs that cause folate deficiency may lead to increased methotrexate toxicity.
- Ciprofloxacin may inhibit renal tubular transport of methotrexate, increasing serum methotrexate levels and its toxicity.
- Probenecid may inhibit renal excretion of methotrexate, increasing serum methotrexate levels and its toxicity.
- Co-administration of CISplatin has been reported to cause higher plasma concentrations of vinBLAStine.

- Erythromycin may increase the toxicity of vinBLAStine.
- Concurrent administration of calcium channel blockers with DOXOrubicin should be avoided as they may decrease the clearance of DOXOrubicin.
- CISplatin may potentiate the nephrotoxic and ototoxic effects of loop diuretics and aminoglycosides so concurrent use should be avoided.
- Consider increased risk of vinca alkaloid-induced adverse effects due to inhibition of CYP3A4 by aprepitant.
- Current drug interaction databases should be consulted for more information.

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Version	Date	Amendment	Approved By
1	20/06/2016		Prof Maccon Keane
2	11/12/2017	Updated with new NCCP regimen format, updated with revised CISplatin hydration regimen recommendations	Prof Maccon Keane
3	08/01/2020	Reviewed. Standardisation of treatment table and renal dose modifications. Update of emetogenic potential	Prof Maccon Keane
4	15/5/2023	Updated CISplatin infusion time. Amended renal impairment table. Updated emetogenic potential and drug interactions section. Removed ATC codes.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] Cardiotoxicity is a risk associated with anthracycline therapy that may be manifested by early (acute) or late (delayed) effects.

Risk factors for developing anthracycline-induced cardiotoxicity include:
- high cumulative dose, previous therapy with other anthracyclines or anthracenediones
- prior or concomitant radiotherapy to the mediastinal/pericardial area
- pre-existing heart disease
- concomitant use of other potentially cardiotoxic drugs

In establishing the maximal cumulative dose of an anthracycline, consideration should be given to the risk factors above and to the age of the patient.