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

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved Reimbursement Status*
Locally advanced or metastatic transitional cell carcinoma (TCC) of the urothelium.	C67	00333a	N/A

*This is for post 2012 indications

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 and 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 minutes	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 minutes	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 Available on the NCCP website

[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 NaCl 0.9% over 60 – 120 minutes. Refer to relevant local hospital policy for advice on administration of electrolyte infusions).

Administer CISplatin as described above
Post hydration: Administer 1000mL 0.9% NaCl over 60 minutes
Mannitol 10% may be used 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
- Pre-existing renal impairment
- Pregnancy and breastfeeding
- 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 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**	No need for dose adjustment is expected	
			Bilirubin(micromol/L)	
			>86	Avoid use
	≥50	No dose adjustment is needed		
	20-50	50% of the original dose		
	<20	Not recommended. If unavoidable, consider haemodialysis		
	Haemodialysis	Not recommended, if unavoidable 50% of the original dose, can be dialysed with daily high flux dialysis.		
vinBLAStine	No dose adjustment is needed. Haemodialysis: No need for dose adjustment is expected		**Bilirubin(micromol/L)**	**Dose**
			>51	50% of original dose
DOXOrubicin	**CrCl (mL/min)**	**Dose**	**Bilirubin (micromol/L)**	**Dose**
	> 10	No dose adjustment is needed	20-50	50% of the original dose
			51-86	25% of the original dose
	< 10	No need for dose adjustment is expected	>86 or Child Pugh C	Not recommended
	Haemodialysis	75% of the original dose may be considered		
CISplatin	**CrCl (mL/min)**	**Dose**	No need for dose adjustment is expected.	
	50-59	75% of original dose		
	40-49	50 of original dose%		
	<40	Not recommended		
	Haemodialysis	50% of the original dose may be considered		

Methotrexate: Renal and hepatic dose modifications from Giraud et al 2023
vinBLAStine: Renal and hepatic dose modifications from Giraud et al 2023
DOXOrubicin: Renal and hepatic dose modifications from Giraud et al 2023
CISplatin: Renal and hepatic dose modifications from Giraud et al 2023

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:

- As outlined in NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting- Available on the NCCP website

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.

Within NCIS regimens, antiemetics have been standardised by Medical Oncologists and Haemato-oncologists and information is available in the following documents:

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) - Available on the NCCP website
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - Available on the NCCP website

PREMEDICATIONS:

- Hydration pre and post CISplatin administration (Refer to local policy or see recommendations above).

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:

- Please refer to the relevant Summary of Product Characteristics (SmPC) for details.

REGIMEN SPECIFIC COMPLICATIONS:

- **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.

DRUG INTERACTIONS:

- Current SmPC and drug interaction databases should be consulted for information.

REFERENCES:

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9. Methotrexate 1g/10mLSummary of Product Characteristics. Last updated 05/08/2022. Accessed February 2025. Available at:https://www.medicines.ie/medicines/methotrexate-1-g-10-ml-injection-32833/spc

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11. CISplatin 1mg/mL Concentrate for Solution for Infusion. Summary of Product Characteristics. Last updated: 06/09/2022. Accessed February 2025. Available at: https://www.medicines.ie/medicines/cisplatin-1-mg-ml-concentrate-for-solution-for-infusion-latex-free-vial-stopper--35271/spc

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	15/05/2023	Updated CISplatin infusion time. Amended renal impairment table. Updated emetogenic potential and drug interactions section. Removed ATC codes.	Prof Maccon Keane
5	14/05/2025	Regimen reviewed. Updated exclusions. Updated renal and hepatic dose modifications in line with Giraud et al (2023). Updated regimen in line with NCCP standardisation.	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.