

CISplatin, Methotrexate and vinBLASstine Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Neoadjuvant treatment of muscle invasive transitional cell carcinoma (TCC) of the urothelium	C67	00337a	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 patient's individual clinical circumstances.

Treatment is administered as described below every 21 days for a maximum of **3** cycles or until disease progression or unacceptable toxicity develops.

Facilities to treat anaphylaxis **MUST** be present when the chemotherapy is administered.

Admi n Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1,8	Methotrexate	30mg/m ²	IV Bolus		Every 21 days for up to 3 cycles
2	1,8	^a VinBLASstine	4mg/m ²	IV infusion	50ml 0.9% NaCl over 15 min	Every 21 days for up to 3 cycles
3	2	^b CISplatin	100mg/m ²	IV infusion	500ml 0.9% NaCl over 120mins	Every 21 days for up to 3 cycles
4	2,9	Folinic acid	15mg	PO or IV	Every 6 hrs (total 4 doses) to start 24hr after methotrexate on day 1 and day 8	Every 21 days for up to 3 cycles

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

^b Pre and post hydration therapy required for CISplatin

See local hospital policy recommendations.

Suggested prehydration for CISplatin therapy:

1. Administer 10mmol magnesium sulphate (MgSO₄) ((+/-KCl 20mmol/L if indicated) in 1000 mL 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 (3,4).

ELIGIBILITY:

- Indications as above
- ECOG 0-1

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EXCLUSIONS:

- Hypersensitivity to methotrexate, vinBLASTine, CISplatin or any of the excipients
- 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
- Audiology and creatinine clearance if clinically indicated

Regular tests:

- FBC, renal and liver profile prior to each cycle
- FBC and renal profile Day 8

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 ($\times 10^9$ /L)		Platelets ($\times 10^9$ /L)	Dose
≥1.5	and	≥100	100% Dose
<1.5	or	<100	Hold* until recovery
Febrile neutropenia or ANC < 0.5	or	< 50	Hold *until recovery then 75% of previous dose
*Do not start a new cycles until ANC ≥1.5 x 10 ⁹ /L and platelets ≥100 x10 ⁹ /L			

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Renal and Hepatic Impairment:

Table 2: Dose modifications in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment			
	Cr Cl (ml/min)	Dose	Bilirubin(micromol/L)		AST (Units)	Dose
Methotrexate	>80	100%	<50	and	<180	100%
	60-80	65%	51-85	or	>180	75%
	45-60	50%	>85			Contra-indicated
	30-45	Clinical decision	Contraindicated in severe hepatic impairment			
	<30	Contra-indicated				
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
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 CMV 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:

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

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.

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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 is a vesicant which may cause pain and tissue necrosis if extravasated. (Refer to local extravasation guidelines).
- **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.
- CISplatin may potentiate the nephrotoxic and ototoxic effects of loop diuretics and aminoglycosides so concurrent use should be avoided.
- Current drug interaction databases should be consulted for more information.

ATC CODE:

Methotrexate	-	L01BA01
vinBLASTine	-	L01CA01
CISplatin	-	L01XA01

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REFERENCES:

1. International Collaboration of Trialists. International phase III trial assessing neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: long-term results of the BA06 30894 trial. *J Clin Oncol*. 2011;29(16):2171-2177.
2. Neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: a randomised controlled trial. International collaboration of trialists. *Lancet*. 1999;354(9178):533
3. Nephrotoxicity Associated with CISplatin EviQ ID: 184 v.3
<https://www.eviq.org.au/clinical-resources/side-effect-and-toxicity-management/prophylaxis-and-prevention/184-nephrotoxicity-associated-with-CISplatin>
4. Portilla D et al. CISplatin nephrotoxicity. UptoDate Accessed Oct 2017
https://www.uptodate.com/contents/CISplatin-nephrotoxicity?source=search_result&search=CISplatin%20hydration&selectedTitle=1~150
5. Methotrexate Summary of Product Characteristics. Last updated 19/12/2019. Accessed June 2020 Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA0822-206-006_19122019123254.pdf
6. Vinblastine Sulfate 1mg/ml Solution for Injection. Last updated: 30/10/2018. Accessed Dec 2019. Available at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA0822-208-001_31102018125148.pdf
7. Cisplatin 1mg/ml Concentrate for Solution for Infusion. Summary of Product Characteristics. Last updated: 11/03/2019. Accessed Dec 2019. Available at <https://www.hpra.ie/img/uploaded/swedocuments/Final%20approved%20SPC%20PA0822.199.001.pdf>
8. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V1 2018. Available at: <https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp%20antiemetic%20classification%20document%20v1%202018.pdf>

Version	Date	Amendment	Approved By
1	20/06/2016		Prof Maccon Keane
2	20/06/2018	Updated with new NCCP regimen format, standardisation of treatment table updated with revised CISplatin hydration regimen recommendations	Prof Maccon Keane
3	10/06/2020	Reviewed. Standardisation treatment table and dose modifications in hepatic and renal impairment.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

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