Regimen Monograph

A - Regimen Name

MVAC Regimen

Methotrexate-VinBLAStine-ADRIAMYCIN ® (DOXOrubicin)-CISplatin

Disease Site	Genitourinary - Bladder
Intent	Neoadjuvant Adjuvant Palliative
Regimen Category	**Evidence-Informed :** Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.
Rationale and Uses	For the treatment of transitional cell carcinoma of the bladder or urothelium

back to top

B - Drug Regimen

methotrexate (Round to nearest 2.5 mg)	30 mg /m²	IV	Days 1, 15, 22
vinBLAStine (Round to nearest 0.1 mg)	3 mg /m²	IV	Days 2, 15, 22

DOXOrubicin (Round to nearest 1 mg)	30 mg /m²	IV	Day 2
CISplatin (Round to nearest 1 mg)	70 mg /m²	IV	Day 2

back to top

C - Cycle Frequency

REPEAT EVERY 28 DAYS

Until disease progression or unacceptable toxicity or 3 to 4 cycles in adjuvant/neoadjuvant settings

back to top

D - Premedication and Supportive Measures

Antiemetic Regimen: Minimal (Days 1, 15, 22); High (Day 2)

Febrile Neutropenia Risk: High

back to top

E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated. The following recommendations are in use at some centres.

Dosage with toxicity

Worst Toxicity / Counts (x 10^9/L) in previous cycle		Worst Toxicity/ Counts (x10^9/L) in previous cycle	methotrexate (% previous dose)	vinBLAStine (% previous dose)	DOXOrubicin (% previous dose)	Cisplatin (% previous dose)
ANC <1.5	Or	Platelet < 100	Hold *			
Febrile Neutropenia Or ANC < 0.5 for ≥ 5-7 d	Or	Thrombocytopenic bleeding Or	Hold *, then 75%			

		Platelets < 25				
ANC ≥ 1.5	And	Platelet ≥ 100	100%			
Cardiotoxicity**			No change	No change	Discontinue	No change
Grade 2 neurotoxicity /ototoxicity			No change	Consider dose reduction	No change	↓ 25%
Grade 3 or 4 neurotoxicity/ototoxicity			No change	Discontinue	No change	Discontinue
Grade 3 related organ / non-hematologic			*75% for suspect drug(s)			
Grade 4 related organ / non-hematologic Leucoencephalopathy, hepatic fibrosis, viral reactivation Hemolysis, optic neuritis, arterial thromboembolism, severe hypersensitivity reactions			Discontinue			
Suspected Pneumonitis			Hold, investigate appropriately and discontinue if confirmed			

*Do not start new cycle until toxicities have recovered to ≤ grade 2 (grade 1 for neurotoxicity), platelets ≥ 100 x 10^9/L, and ANC ≥ 1.5 x 10^9/L.
**including any signs and symptoms of heart failure, greater than 10% decline in LVEF to below the lower limit of normal, a greater than 20% decline in LVEF from any level, or LVEF ≤ 45%.

Hepatic Impairment

Bilirubin		**AST/ALT**	**methotrexate (% previous dose)**	**vinBLAStine (% previous dose)**	**DOXOrubicin (% previous dose)**	**Cisplatin (% previous dose)**
1-2 x ULN			Caution	50%	50%	No adjustment required
>2-4 x ULN	OR	2-4 x ULN	75%	25%	25%	
>4 x ULN	OR	>4 x ULN	Discontinue	Discontinue	Discontinue	

Renal Impairment

Creatinine clearance (mL/min)	Methotrexate (% usual dose)	Cisplatin (% previous dose)	Vinblastine and Doxorubicin
80	75%	100%	No change
60	60%*	75%	
50	50%*	75%	
30-50	Discontinue	50%	
<30	Discontinue	Discontinue	
* Less conservative dose modifications could be considered for low dose regimens (<50mg/m^2)			

back to top

F - Adverse Effects

Refer to methotrexate, vinBLAStine, DOXOrubicin, CISplatin drug monograph(s) for additional details of adverse effects

Most Common Side Effects	Less Common Side Effects, but may be Severe or Life-Threatening
• Mucositis • Diarrhea • Myelosuppression ± infection, bleeding (may be severe) • Nausea, vomiting • Rash (may be severe) • ↑ LFTs (may be severe) • Alopecia • Nephrotoxicity (may be severe) • Electrolyte abnormalities • Neurotoxicity and ototoxicity (may be severe)	• Arterial/venous thromboembolism • Hypersensitivity • GI perforation • Pancreatitis • Secondary malignancies • Cardiotoxicity • Vesicant • SIADH • Photosensitivity • Pneumonitis • Arrhythmia • Hemolytic uremic-syndrome, vasculitis • Raynaud's • Hemolysis

back to top

G - Interactions

Refer to methotrexate, vinBLAStine, DOXOrubicin, CISplatin drug monograph(s) for additional details

back to top

H - Drug Administration and Special Precautions

Refer to methotrexate, vinBLAStine, DOXOrubicin, CISplatin drug monograph(s) for additional details

back to top

I - Recommended Clinical Monitoring

Recommended Clinical Monitoring

- CBC; baseline and regular
- Electrolytes, including magnesium, phosphate and calcium; baseline and regular
- Liver function tests; baseline and regular
- Renal function tests; baseline and regular
- Clinical toxicity assessment (infection, bleeding, nausea/vomiting, mucositis, neurotoxicity, cardiotoxicity, ototoxicity, local toxicity, pulmonary, skin, CNS); at each visit
- Cardiac function tests (Echo, RNA and/or MUGA scans) for all patients with cardiac risk factors; baseline
- Cardiac tests for all patients with cardiac risk factors (including prior trastuzumab or patients at or above the threshold doxorubicin cumulative dose levels (400mg/m^2 for q21 day schedules and 550mg/m^2 for weekly schedules); periodic
- Audiogram; as clinically indicated
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

back to top

J - Administrative Information

Approximate Patient Visit	Day 1, 15, 22: 0.5 hour; Day 2: 4 hours
Pharmacy Workload (average time per visit)	25.086 minutes
Nursing Workload (average time per visit)	47.917 minutes

back to top

K - References

Lehmann J, Franzaring L, Thüroff J, et al. Complete long-term survival data from a trial of adjuvant chemotherapy vs control after radical cystectomy for locally advanced bladder cancer. BJU Int 2006;97(1):42-7.

Loehrer PJ Sr, Einhorn LH, Elson PJ, et al. A randomized comparison of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: a cooperative group study. J Clin Oncol, 1992;10:1066-73.

Logothetis CJ, Dexeus FH, Finn L et al. A prospective randomized trial comparing M-VAC and CISCA chemotherapy for patients with metastatic urothelial tumors. J Clin Oncol, 1990;8:1050-5.

Roberts JT, von der Maase H, Sengeløv L, et al. Long-term survival results of a randomized trial comparing gemcitabine/cisplatin and methotrexate/vinblastine/doxorubicin/cisplatin in patients with locally advanced and metastatic bladder cancer. Ann Oncol 2006;17 Suppl 5:v118-22.

Sternberg CN, de Mulder PH, Schornagel JH, et al. Randomized phase III trial of high-dose-intensity methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy and recombinant human granulocyte colony-stimulating factor versus classic MVAC in advanced urothelial tract tumors: European Organization for Research and Treatment of Cancer Protocol no. 30924. J Clin Oncol 2001;19(10):2638-46.

Sternberg CN, de Mulder P, Schornagel JH, et al. Seven year update of an EORTC phase III trial of high-dose intensity M-VAC chemotherapy and G-CSF versus classic M-VAC in advanced urothelial tract tumours. Eur J Cancer. 2006;42(1):50-4.

von der Maase H, Sengelov L, Roberts JT, et al. Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. J Clin Oncol 2005;23(21):4602-8.

von de Maase H, Hansen SW, Roberts JT, et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, Phase III Study. J Clin Oncol 2000;18(17):3068-77.

April 2016 Replaced regimen category with evidence-informed

back to top

M - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare

providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

The format and content of the drug monographs, regimen monographs, appendices and symptom management information contained in the Formulary will change as they are reviewed and revised on a periodic basis. The date of last revision will be visible on each page of the monograph and regimen. Since standards of usage are constantly evolving, it is advised that the Formulary not be used as the sole source of information. It is strongly recommended that original references or product monograph be consulted prior to using a chemotherapy regimen for the first time.

Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

While care has been taken in the preparation of the information contained in the Formulary, such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability.

CCO and the Formulary's content providers shall have no liability, whether direct, indirect, consequential, contingent, special, or incidental, related to or arising from the information in the Formulary or its use thereof, whether based on breach of contract or tort (including negligence), and even if advised of the possibility thereof. Anyone using the information in the Formulary does so at his or her own risk, and by using such information, agrees to indemnify CCO and its content providers from any and all liability, loss, damages, costs and expenses (including legal fees and expenses) arising from such person's use of the information in the Formulary.

back to top