Regimen Monograph

A - Regimen Name

MVAC(HD) Regimen

Methotrexate-VinBLAStine-ADRIAMYCIN ® (DOXOrubicin)-CISplatin (high dose / dose dense)

Disease Site	Genitourinary Bladder / Urothelial
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

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B - Drug Regimen

methotrexate (Round to nearest 2.5 mg)	30 mg /m²	IV	Day 1
vinBLAStine (Round to nearest 0.1 mg)	3 mg /m²	IV	Day 2

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

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C - Cycle Frequency

REPEAT EVERY 14 DAYS

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

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D - Premedication and Supportive Measures

Antiemetic Regimen: Minimal (D1)
High (D2)

Febrile Neutropenia Risk: High

Primary prophylaxis with G-CSF is indicated. Refer to the Febrile Neutropenia Guideline.

Other Supportive Care:

Also refer to CCO Antiemetic Recommendations.

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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 (x 10^9/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 Platelets < 25	Hold *, then 75%			
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)			

Worst Toxicity / Counts (x 10^9/L) in previous cycle		**Worst Toxicity / Counts (x 10^9/L) in previous cycle**	**methotrexate (% previous dose)**	**vinBLAStine (% previous dose)**	**DOXOrubicin (% previous dose)**	**Cisplatin (% previous dose)**
Grade 4 related organ / non-hematologic Leucoencephalopathy, hepatic fibrosis, viral reactivation, Hemolysis, optic neuritis, arterial thromboembolism, severe hypersensitivity			Discontinue			

reactions			
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 ≥ $100x10^9$/L, and ANC≥ $1.5x10^9$/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)			

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F - Adverse Effects

Refer to methotrexate, vinBLAStine, DOXOrubicin, CISplatin, filgrastim 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 thromboembolism • Venous thromboembolism • Hypersensitivity • GI perforation • Pancreatitis • Secondary malignancies • Cardiotoxicity • Vesicant • SIADH • Photosensitivity • Pneumonitis • Arrhythmia • Hemolytic uremic-syndrome, vasculitis • Raynaud's • Hemolysis

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G - Interactions

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

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H - Drug Administration and Special Precautions

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

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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

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J - Administrative Information

Approximate Patient Visit	Day 1: 0.5 hour, Day 2: 4-5 hours
Pharmacy Workload (average time per visit)	22.93 minutes
Nursing Workload (average time per visit)	49.167 minutes

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K - References

Blick C, Hall P, Pwint T, et al. Accelerated methotrexate, vinblastine, doxorubicin, and cisplatin (AMVAC) as neoadjuvant chemotherapy for patients with muscle-invasive transitional cell carcinoma of the bladder. Cancer 2012;118(16):3920-7

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.

Sternberg CN, de Mulder PHM, 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.

PEBC Advice Documents or Guidelines

- Systemic Therapy for Metastatic Urothelial Cancer: Endorsement of a Portion of the European Association of Urology Guideline on Muscle-Invasive and Metastatic Bladder Cancer

September 2022 added PEBC guideline

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M - Disclaimer

Regimen Abstracts

A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. 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, and Cancer Care Ontario disclaims all liability for the use of this information, and for any claims, actions, demands or suits that arise from such use.

Information in regimen abstracts is accurate to the extent of the ST-QBP regimen master listings, and has not undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.

Regimen Monographs

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

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