Regimen Monograph

A - Regimen Name

VAC Regimen

VinCRIStine-DOXOrubicin-Cyclophosphamide (may be part of IE-VAC)

Disease Site

Sarcoma - Ewing's
Sarcoma - Soft Tissue

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

- Ewing's sarcoma
- Rhabdomyosarcoma
- Other primitive neuroectodermal tumours, small round blue cell undifferentiated sarcoma, CIC-DUX4, BCOR sarcoma

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B - Drug Regimen

vinCRIStine	1.5 mg /m²	IV (maximum 2 mg)	Day 1
DOXOrubicin[1]	75 mg /m²	IV	Day 1
cyclophosphamide[2]	1200 mg /m²	IV	Day 1

[1]Doxorubicin is omitted during radiation therapy. Some studies split the dose of doxorubicin over 2 days. Give for a maximum of 5-6 cycles and then VC thereafter.

[2] Prophylactic diuresis to reduce the incidence of cystitis is recommended. Consider usage of Mesna, especially for younger patients or those with risk factors (e.g. previous radiation to the pelvic area).

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C - Cycle Frequency

VAC*/ VC: Repeat every 3 weeks

IE-VAC*/VC: Used in an alternating schedule with ETOPIFOS for a total of 14 cycles given every 3 weeks (7 of each) in the absence of progression or unacceptable toxicity.

Intensified IE-VAC*/VC† (for Ewing's sarcoma): Used in an alternating schedule with ETOPIFOS for a total of 14 cycles (7 of each) given every 2 weeks. GCSF Prophylaxis is recommended with this regimen

*VAC for a maximum of 5-6 cycles then VC
† Note that only patients less than 50 years old were included in the clinical trial by Womer et al.

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D - Premedication and Supportive Measures

Antiemetic Regimen: High

Other Supportive Care:

Also refer to CCO Antiemetic Summary

- All patients should receive an appropriate hydration protocol according to local guidelines.

- Consider G-CSF prophylaxis for patients at high risk of febrile neutropenia

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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 have been adapted from clinical trials or product monographs and could be considered.

More aggressive protocols, for example, those used with curative intent may allow re-treatment when ANC ≥ 0.75 x 10^9/L and platelets ≥75 x 10^9/L.

Dosage with toxicity

Worst Toxicity / Counts (x10^9/L) in previous cycle		**Worst Toxicity / Counts (x 10^9/L) in previous cycle**	**Action (% previous dose)**
ANC <1.5	OR	Platelet < 100	Hold *; consider G-CSF if repeated delay. If recurs, may consider reducing doxorubicin and cyclophosphamide by 25%
Febrile Neutropenia OR ANC < 0.5 for ≥ 5-7 days	OR	Thrombocytopenic bleeding OR Platelets < 25	Hold *, then 75% or consider GCSF if isolated neutropenia. If recurs despite GCSF, reduce doxorubicin and cyclophosphamide by 25%
Cardiotoxicity**			OMIT doxorubicin (may substitute dactinomycin)
Neurotoxicity: Areflexia only			100% vincristine dose
Neurotoxicity: Abnormal buttoning, writing, moderate motor neuropathy (± cranial)			Hold until recovery then restart at 50% vincristine dose
Severe motor neuropathy			OMIT vincristine
Pneumonitis			Hold, investigate and if confirmed, discontinue regimen

Grade 3 related organ / non-hematologic			Hold until recovery* then 75% for suspect drug(s)
Grade 4 related organ / non-hematologic			Discontinue
Cystitis			Hold cyclophosphamide for macroscopic hematuria – consider mesna for next dose

*Do not start new cycle until toxicities have recovered to ≤ grade 2, 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

Doxorubicin is contraindicated in patients with severe hepatic impairment, and doses should be modified for mild-moderate impairment.

Bilirubin (µmol/L)		**AST/ALT**	**Vincristine (% usual dose)**	**Doxorubicin (% Usual Dose)**	**Cyclophosphamide (% Usual dose)**
1-2x ULN			50%	50%	100%
2-4x ULN	±	5-10 x ULN	25%	25%	Caution
4-10xULN	±	> 10 x ULN	25% or OMIT	OMIT	Caution

Renal Impairment

Creatinine Clearance (mL/min)	**Vincristine**	**Doxorubicin**	**Cyclophosphamide (% of Dose)**
> 50	No adjustment needed	No adjustment needed	100%
10 - 50			75%
< 10			Use with extreme caution or discontinue

Dosage in the elderly:

- Older patients may have more neurotoxicity with vincristine. No dose modification is routinely required with doxorubicin and cyclophosphamide, but they should be used with caution.

Children:

- Dose adjustment of cyclophosphamide may be required.
- At higher risk of secondary leukemia from doxorubicin. Children and adolescents are at an increased risk of developing delayed cardiotoxicity (up to 15 years after treatment). Females may have a higher risk than males. Increased monitoring is required.

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F - Adverse Effects

Refer to vinCRIStine, DOXOrubicin, cyclophosphamide drug monograph(s) for additional details of adverse effects

Most Common Side Effects	Less Common Side Effects, but may be Severe or Life-Threatening
• Myelosuppression ± infection/bleeding (may be severe) • Nausea and vomiting • Alopecia • Constipation (may be severe) • Mucositis, diarrhea • Dysgeusia • Abdominal pain • Increased LFTs (may be severe) • Hand foot syndrome; rash • Skin hyperpigmentation • Neurotoxicity (may be severe) • Flu-like symptoms • Fatigue • Urine discolouration	• Arterial thromboembolism • Venous thromboembolism • Cardiotoxicity • Arrhthymia • Secondary malignancies • Vesicant (vincristine, doxorubicin) • Photosensitivity • Hypersensitivity • Radiation recall reaction • Nephrotoxicity • SIADH • Pneumonitis • Pancreatitis • Cystitis

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G - Interactions

Refer to vinCRIStine, DOXOrubicin, cyclophosphamide drug monograph(s) for additional details

- All drugs in regimen may decrease absorption and effectiveness of digoxin and verapamil; use with caution and monitor levels
- Avoid nifedipine as it may decrease vincristine excretion
- Vincristine and doxorubicin may decrease phenytoin levels; monitor levels and adjust phenytoin dose as needed
- CYP3A4 inducers may increase clearance and decrease efficacy of vincristine
- Use ototoxic drugs with extreme caution due to an increased ototoxicity risk with vincristine
- Avoid nephrotoxic drugs due to additive effects with cyclophosphamide
- Barbiturates can decrease the therapeutic effects of doxorubicin.
- Decreased absorption of quinolones is possible with doxorubicin and vincristine; caution with Ciprofloxacin as it may decrease efficacy of cylclophophamide
- Doxorubicin causes zidovudine and stavudine to be less effective; avoid the combination
- Avoid calcium channel blockers due to additive cardiotoxicity with doxorubicin
- P-glycoprotein inhibitors should be used with caution as they increase doxorubicin exposure and toxicity
- Lovastatin may cause increased rhabdomyolysis and renal failure with cyclophosphamide; avoid
- Drugs that induce hepatic microsomal enzymes (especially 2B6, 2C9 and 3A4) decrease the activation of cyclophosphamide. Drugs that inhibit hepatic microsomal enzymes increase the activation. Use with caution and monitor for toxicity/efficacy
- Increased and decreased warfarin effects have been reported with cyclophosphamide; monitor INR closely
- Acute encephalopathy has been reported with metronidazole and cylcophosphamide

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H - Drug Administration and Special Precautions

Refer to vinCRIStine, DOXOrubicin, cyclophosphamide drug monograph(s) for additional details

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

- CBC; baseline and prior to each cycle
- Liver function tests; baseline and prior to each cycle
- Renal function tests; baseline and prior to each cycle
- Urinalysis; baseline and regular
- Cardiac function tests (Echo, RNA and/or MUGA scans) for all patients with cardiac risk factors; baseline and periodic
- Clinical assessment of neurotoxicity, GI (stomatitis, nausea/vomiting), infusion site reactions, cystitis, infection, bleeding, thromboembolism, skin, cardiac or pulmonary adverse effects; at each visit

- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Administrative Information

Approximate Patient Visit	2 hours
Pharmacy Workload (average time per visit)	36.054 minutes
Nursing Workload (average time per visit)	66.667 minutes

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K - References

Arndt CA, Nascimento AG, Schroeder G, et al. Treatment of intermediate risk rhabdomyosarcoma and undifferentiated sarcoma with alternating cycles of vincristine/doxorubicin/cyclophosphamide and etoposide/ifosfamide. Eur J Cancer 1998;34:1224–1229.

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Cyclophosphamide, doxorubicin, and vincristine drug monographs, Cancer Care Ontario.

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ifosfamide and etoposide to standard chemotherapy for Ewing's sarcoma and primitive neuroectodermal tumor of bone. N Engl J Med. 2003 Feb 20;348(8):694-701.

Miser JS, Krailo MD, Tarbell NJ, Link MP, Fryer CJ, Pritchard DJ, Gebhardt MC, Dickman PS, Perlman EJ, Meyers PA, Donaldson SS, Moore S, Rausen AR, Vietti TJ, Grier HE. Treatment of metastatic Ewing's sarcoma or primitive neuroectodermal tumor of bone: evaluation of combination ifosfamide and etoposide--a Children's Cancer Group and Pediatric Oncology Group study. J Clin Oncol. 2004 Jul 15;22(14):2873-6.

Womer RB, West DC, Krailo MD, Dickman PS, Pawel BR, Grier HG, Marcus K, Sailer S, Healey JH, Dormans JP, Weiss AR. Randomized controlled trial of interval-compressed chemotherapy for the treatment of localized Ewing sarcoma: a report from the Children's Oncology Group. J Clin Oncol. 2012 Nov 20; 30(33): 4148-54.

July 2019 Updated hyperlink to vincristine drug monograph

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M - Disclaimer

Regimen Abstracts

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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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