Regimen Monograph

A - Regimen Name

CISPDOXO Regimen

CISplatin-DOXOrubicin

Disease Site	Sarcoma Osteogenic / Bone
Intent	Adjuvant Neoadjuvant 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	Neoadjuvant/adjuvant treatment for resectable osteogenic sarcoma; palliative treatment for advanced osteogenic sarcoma

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B - Drug Regimen

DOXOrubicin[1] (Round to nearest 1 mg)	75 mg /m²	IV	Day 1
CISplatin[1] (Round to nearest 1 mg)	100 mg /m²	IV	Day 1 (over 2, 4, or 24 hours)

[1] Various doses and schedules have been used in clinical trials. Doxorubicin total dose may be split over 2 to 3 days. Alternate regimens administered doxorubicin as a bolus or a 4 hour infusion or cisplatin over 2, 4, or 24 hours on Day 1.

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C - Cycle Frequency

REPEAT EVERY 21 DAYS

For a usual total of 6 cycles unless disease progression or unacceptable toxicity occurs

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D - Premedication and Supportive Measures

Antiemetic Regimen: High

Febrile Neutropenia Risk: Moderate

Other Supportive Care:

Also refer to CCO Antiemetic Recommendations.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

Standard regimens for Cisplatin premedication and hydration should be followed. Refer to local guidelines.

For curative regimens, growth factors were used prophylactically.

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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.

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 or dose reduction. 75% dose if > 1 week delay despite G-CSF
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. Cisplatin: 75% dose if further episodes despite G-CSF.
Cardiotoxicity**			OMIT doxorubicin
Grade 3 or 4 mucositis or typhilitis			Hold*; ↓ doxorubicin to 80% dose
Grade 2 neurotoxicity			↓ cisplatin to 75% dose
Grade 3 or 4 neurotoxicity or symptomatic ototoxicity			Discontinue cisplatin
Grade 3 related other organ /			*75% for suspect drug(s)

non-hematologic			
Grade 4 related other organ / non-hematologic			Discontinue

*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	Doxorubicin (% Usual Dose)	Cisplatin
1-2x ULN			50%	No change
2-4x ULN	±	5-10 x ULN	25%	No change
4-10xULN	±	> 10 x ULN	OMIT	No change

Renal Impairment

Creatinine Clearance (mL/min)	cisplatin (% previous dose)	doxorubicin (% previous dose)
>60	100%	No change
>30-60	Delay x 1 week; Omit if does not improve to > 60 mL/min	No change
10-30		No change
<10		No change

Dosage in the Elderly

- Geriatric patients may be at higher risk of developing nephrotoxicity, ototoxicity/neurotoxicity or hematologic adverse effects with cisplatin.
- Use doxorubicin with caution.

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F - Adverse Effects

Refer to CISplatin, DOXOrubicin 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, vomiting (may be severe) • Alopecia • Mucositis • Diarrhea • ↑LFTs • Rash • Nephrotoxicity (may be severe) • Electrolyte abnormalities • Neurotoxicity and ototoxicity (may be severe) • Reproductive risk • Urine discolouration	• Arterial thromboembolism • Venous thromboembolism • Cardiotoxicity • Arrhthmyia • Secondary malignancies • Photosensitivity • Hypersensitivity • Radiation recall reaction • Hemolytic uremic syndrome • Hemolysis • Optic neuritis • Vasculitis • SIADH • Thrombotic microangiopathy • Phlebitis (vesicant)

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G - Interactions

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

- Avoid nephrotoxic and ototoxic drugs (i.e. aminoglycosides) due to additive effects.
- Concomitant use of renally excreted drugs (i.e. methotrexate) may decrease renal clearance and enhance toxicities of these drugs. Avoid use, if possible. If not possible, modify doses as necessary.
- Barbiturates can decrease the therapeutic effects of doxorubicin.
- Doxorubicin can cause decreased digoxin absorption; monitor patient and levels.
- May need to modify doses of quinolones due to decreased absorption with concomitant doxorubicin.
- Doxorubicin causes zidovudine and stavudine to be less effective; avoid the combination.

- Doxorubicin and cisplatin may decrease phenytoin levels; monitor levels and patient.
- Avoid sorafenib while on doxorubicin due to increased doxorubicin toxicity.
- Avoid calcium channel blockers due to additive cardiotoxicity with doxorubicin.
- P-glycoprotein inhibitors (cyclosporine, verapamil, quinidine) should be used with caution as they increase doxorubicin exposure and toxicity.

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H - Drug Administration and Special Precautions

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

Administration

Cisplatin:

- Cisplatin is physically incompatible with any IV set, needle or syringe containing aluminum.
- Dilute in NS and administer IV according to local guidelines.
- All patients should receive adequate hydration and premedication for emesis, according to local guidelines.
- Oral hydration with 8 glasses of fluid per day is strongly encouraged on treatment day and for 1-2 days after cisplatin; if nausea and vomiting prevent oral hydration, the patient may need to return for more IV hydration.
- Hydration and diuresis for patients with pre-existing renal, cardiac, or diabetic history at discretion of physician.
- Adequate hydration and urinary output must be maintained for 24 hours following cisplatin treatment.
- Store unopened vials between 15°C to 25°C and protect from light. Do not refrigerate or freeze since precipitation will occur.

Doxorubicin:

- Slow push through sidearm of free flowing IV (5% Dextrose, Normal Saline). Depending on the dose volume and vein condition, administer the dose between 3 to 10 minutes to minimize thrombosis risk or extravasation.
- Do not admix with other drugs unless data are available; precipitates with fluorouracil and heparin.
- Avoid contact with alkaline solutions as this can lead to hydrolysis of doxorubicin
- Slow down injection rate if erythematous streaking or facial flushing occurs.
- If any signs or symptoms of extravasation occur, the injection or infusion should be immediately terminated and restarted in another vein. Any known or suspected extravasation should be managed promptly as per local guidelines.
- Store vials under refrigeration (2 to 8ºC) and protect from light.

Contraindications:

- patients with known hypersensitivity to platinum-containing compounds
- patients who have severe myelosuppression
- patients with pre-existing renal impairment and hearing impairment, unless the possible benefits of treatment outweigh the risks.
- Doxorubicin is contraindicated in patients with a hypersensitivity to this drug or any of its components, other anthracyclines or anthracenediones (i.e. epirubicin, daunorubicin, mitoxantrone or mitomycin C), severe hepatic impairment, severe myocardial insufficiency, arrhthymias, history of cardiac disease or recent myocardial infarction, previous treatment with maximum cumulative doses of doxorubicin, other anthracyclines (or anthracenediones)

Other Warnings/Precautions:

- Avoid the use of live vaccines; use may result in serious infections in immunocompromised patients.
- Patients with pre-existing neuropathy or prior treatment with other neurotoxic drugs may have increased potential for neurotoxicity

Pregnancy/Lactation

- This regimen is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners while on treatment and after the last treatment dose. Recommended methods and duration of contraception may differ depending on the treatment. Refer to the drug monograph(s) for more information.
- Male patients should not donate semen while using cisplatin and up to 2 years after the last dose.
- Breastfeeding is not recommended during this treatment and after the last treatment dose. Refer to the drug monograph(s) for recommendations after the last treatment dose (if available).

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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.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

- CBC; baseline and before each cycle
- Liver function; baseline and before each cycle
- Renal function and electrolytes, (including magnesium, sodium, potassium, phosphate and calcium); baseline and before each cycle
- Audiogram; baseline and as clinically indicated
- Cardiac examination especially with risk factors (including prior therapy with epirubicin, mitoxantrone, or other cardiotoxic drug), or a cumulative doxorubicin dose of > 450 mg/m2; baseline and as clinically relevant
- Clinical toxicity (including infection, bleeding, nausea/vomiting, stomatitis, thromboembolism, neurotoxicity, ototoxicity, cardiotoxicity, skin or local toxicity) assessment; 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	3.5-7 hours
Pharmacy Workload (average time per visit)	49.167 minutes
Nursing Workload (average time per visit)	61.667 minutes

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K - References

Bramwell VH, Burgers M, Sneath R, et al. A comparison of two short intensive adjuvant chemotherapy regimens in operable osteosarcoma of limbs in children and young adults: the first study of the European Osteosarcoma Intergroup. J Clin Oncology 1992; 10: 1579-91.

Bramwell VH, Steward WP, Nooij M, et al. Neoadjuvant chemotherapy with doxorubicin and cisplatin in malignant fibrous histiocytoma of bone: an European Osteosarcoma Intergroup Study. J Clin Oncology 1999; 17(10): 3260-69.

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EURAMOS-1 protocol. Children's Oncology Group, 2011.

Souhami RL, Craft AW, Van der Eijken JW, et al. Randomised trial of two regimens of chemotheray in operable osteosarcoma: a study of the European Osteosarcoma Intergroup. Lancet 1997; 350: 911-17.

Lewis IJ, Nooij, MA, Whelan J, et al. Improvement in histologic response but not survival in osteosarcoma patients treated with intensified chemotherapy: a randomized phase III trial of the European Osteosarcoma Intergroup. J Natl Cancer Inst 2007; 99: 112-28.

Lewis MJ, Dubois SG, Fligor B, et al. Ototoxicity in Children Treated for Osteosarcoma. Pediatr Blood Cancer 2009;52:387–91.

Zalupski MM, Rankin C, Ryan JR, et al. Adjuvant Therapy of Osteosarcoma—A Phase II Trial (SWOG 9139). Cancer 2004; 100(4): 818-25.

November 2023 Modified Drug Administration/Special Precautions and Pregnancy/breastfeeding sections

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L - Other Notes

Sarcomas are rare tumours and as such benefit from referral to specialized centres where there will be access to multidisciplinary expertise including good radiology, orthopedic and thoracic surgery, medical oncology, radiation oncology, pathology, and other supportive care disciplines.

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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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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.

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