Regimen Monograph

A - Regimen Name

DOXOIFOS Regimen

DOXOrubicin-Ifosfamide

Disease Site	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	Neoadjuvant and adjuvant treatment for patients with high-risk soft tissue sarcoma. Patients with symptomatic, locally-advanced, or inoperable soft tissue sarcoma, in whom tumour response might potentially result in reduced symptomatology or render a tumour resectable.

back to top

B - Drug Regimen

Multiple regimens exist with various dosing and schedules. The following regimen is from Judson, et al.

DOXOrubicin	25 mg /m²/day	IV	Days 1 to 3
ifosfamide	2500 mg /m²/day	IV	Days 1 to 4
mesna			

Dosing schedules can vary. Use mesna table below as an example:

Mesna	Route	Timing
20% of Ifosfamide dose	IV	Bolus at hour 0 of Ifosfamide
40% of Ifosfamide dose	PO	4 hours and 8 hours post-Ifosfamide

back to top

C - Cycle Frequency

REPEAT EVERY 21 DAYS

For a usual total of 4 to 6 cycles, or until evidence of disease progression or limited by drug toxicity

back to top

D - Premedication and Supportive Measures

Antiemetic Regimen: Moderate

Febrile Neutropenia Risk: High

Other Supportive Care:

- Oral hydration is strongly encouraged; poorly hydrated patients may need more IV hydration
- Inadequate total hydration may result in dose-related hemorrhagic cystitis

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

Also refer to CCO Antiemetic Summary

back to top

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 if repeated delay. If recurs, may consider reducing ifosfamide dose by 25%
Febrile Neutropenia OR ANC < 0.5 for ≥ 5-7 days	OR	Thrombocytopenic bleeding OR Platelets < 25	Hold *, then 75% or consider G-CSF if isolated neutropenia. If recurs despite G-CSF, reduce dose by 25%
Cardiotoxicity**			OMIT doxorubicin. Consider discontinuing ifosfamide when LVEF ≤ 45%
Grade 2 peripheral neuropathy or ototoxicity			↓ cisplatin to 75% dose; consider discontinuing ifosfamide for peripheral neuropathy

Somnolence or other signs of encephalopathy			Hold ifosfamide; methylene blue 50mg IV q4h until resolution. Consider prophylactic methylene blue for subsequent cycles. For Grade 1-2 consider discontinuing or dose reduce for ifosfamide for next cycle. Discontinue for Grade 3 or 4 symptoms
Grade 3 or 4 neurotoxicity or symptomatic ototoxicity			Discontinue cisplatin and ifosfamide
Grade 3 related other organ / non-hematologic			*75% for suspect drug(s)
Grade 4 related other organ / non-hematologic			Discontinue

**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%.

Management of Urotoxicity

Finding	Action
Microscopic hematuria	Hold ifosfamide until resolves. Consider increasing mesna dose (e.g. double) in subsequent cycle.
Macroscopic hematuria	Discontinue or reduce ifosfamide dose

Hepatic Impairment

Doxorubicin is contraindicated in patients with severe hepatic impairment, especially with elevated bilirubin. Consideration should be given to dose modification for patients with severe increases in transaminases

Bilirubin		AST/ALT	Doxorubicin (% previous dose)	Ifosfamide* (% previous dose)
1-2 x ULN	and/ or	<2 x ULN	50%	100%
2-4 x ULN		2-5 x ULN	25%	75%
> 4 x ULN		> 5 x ULN	Discontinue	Discontinue

*Based on clinical judgment – less conservative adjustments can be considered if hepatic changes are secondary to metastases rather than hepatic cirrhosis or hepatitis.

Renal Impairment

Creatinine Clearance (mL/min)	Doxorubicin	Ifosfamide (% previous dose)
> 60	No change	100%
40-60		75%
20-40		50%
< 20		Discontinue

Dosage in the elderly:

Exercise caution as the elderly population may have decreased hepatic, renal, cardiac or hematopoietic function. Increases in ifosfamide half-life has been observed with advancing age; however, no significant changes in clearance were reported. No dose modification is routinely required with doxorubicin, but it should be used with caution.

Children:

Safety and efficacy have not been fully established. Refer to treatment protocol for details. Side effects of ifosfamide in children were reported to be similar to those in adults. Children 5 years of

age or younger may be more susceptible to ifosfamide- induced renal toxicity than older children and adults.

Children are 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.

back to top

F - Adverse Effects

Refer to DOXOrubicin, ifosfamide, mesna, drug monograph(s) for additional details of adverse effects

Most Common Side Effects	Less Common Side Effects, but may be Severe or Life-Threatening
• Dysgeusia (oral mesna) • Alopecia • Myelosuppression +/- infection, bleeding (may be severe) • Nausea, vomiting (may be severe) • Hemorrhagic cystitis (may be severe) • Abdominal pain • Mucositis • Diarrhea (may be severe) • Flu-like symptoms • Neurotoxicity (may be severe) • Nephrotoxicity (may be severe) • Increased LFTs • Hand foot syndrome • Urine discolouration • Edema • Fatigue • Weight Loss • Headache • Cough, dyspnea	• Cardiotoxicity • Arrhythmia • Arterial thromboembolism • Venous thromboembolism • Hemolysis • Pancreatitis • Pneumonitis • Rhabdomyolysis • SIADH • Hypersensitivity • Secondary malignancies • Vesicant (doxorubicin) • Photosensitivity • Radiation recall reaction • Vision changes • Renal tubular acidosis • Hemolytic uremic syndrome • Disseminated intravascular coagulation

back to top

G - Interactions

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

Administration

- Increased neurotoxicity has been reported with ifosfamide and aprepitant; caution and monitor closely if used together
- Doxorubicin may decrease absorption and effectiveness of digoxin and verapamil
- Doxorubicin may decrease phenytoin levels
- Barbiturates can decrease the therapeutic effects of doxorubicin.
- 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
- Avoid calcium channel blockers due to additive cardiotoxicity with doxorubicin
- P-glycoprotein inhibitors increase doxorubicin exposure and toxicity
- Ifosfamide is a major substrate of CYP3A4 and a minor substrate of 2A6, 2B6, 2C8, 2C19 and 2C9. Inhibitors or inducers of these isoenzymes may decrease or increase the metabolism of ifosfamide.
- Ifosfamide is also a weak inhibitor of CYP3A4 and a weak inducer of CYP2C8 and 2C9.
- Drugs acting on the CNS have additive CNS effects with ifosfamide
- Hepatic-enzyme inducing drugs may increase ifosfamide toxicity
- Nephrotoxic, ototoxic and cardiotoxic drugs may increase ifosfamide toxicity; caution and monitor

back to top

H - Drug Administration and Special Precautions

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

Administration

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 perivenous extravasation.
- 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.

Ifosfamide

- May give bolus dose of mesna before ifosfamide infusion, with or without mesna admixed in ifosfamide solution, then followed by 2 doses of mesna by IV bolus or PO, see mesna monograph.
- Add reconstituted drug to NS or D5W for infusion; the final concentration should be between 0.6 to 20 mg/mL.
- May mix doses ≤2000mg in 100mL bag; Infuse over 30-60 minutes.
- May mix doses >2000mg in 500-1000mL bag; Infuse over 1-4 hours.
- May be admixed with mesna.
- Oral hydration is strongly encouraged; poorly hydrated patients may need more IV hydration.
- Inadequate total hydration may result in dose-related hemorrhagic cystitis.

Ifosfamide and Mesna Admixture

- May be diluted in larger volumes for continuous infusion over 6-24 hours; May be infused using a CADD ambulatory infusion pump over longer periods.

Contraindications

- Doxorubicin is contraindicated in patients with severe hepatic impairment, severe myocardial insufficiency, arrhthymias or history of cardiac disease or recent myocardial infarction
- Ifosfamide is contraindicated in patients with known hypersensitivity to the drug, with severe myelosuppression, severe renal and/or hepatic impairment, cystitis, obstructive uropathy, active infections/severe immunosuppression, or cerebral arteriosclerosis.
- Avoid the use of live vaccines

Other warnings/precautions

- Mesna must be coadministered with ifosfamide.
- Use with caution in patients with prior radiotherapy or anticancer therapy, concomitant aprepitant usage, hepatic or renal impairment, risk factors for cardiotoxicity, hypoalbuminemia, pre-existing cardiac disease, brain or extensive bone marrow metastases, concurrent or prior use of nephrotoxic agents or prior nephrectomy. Do not use within 10 to 14 days of surgery or within 3 months after nephrectomy.
- Electrolytes imbalances must be corrected before treatment.
- Alcohol can increase the risk of nausea/vomiting or neurotoxicity; avoid
- Doxorubicin and ifosfamide are not recommended for use in pregnancy or breastfeeding. Effective contraception must be used by both sexes during ifosfamide treatment and for at least 12 months after treatment cessation. Fertility is usually affected.

back to top

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 before each cycle
- Liver function tests; baseline and before each cycle
- Renal function tests, including electrolytes; baseline and before each cycle
- Urinalysis, for RBCs and specific gravity; before each dose and as clinically indicated
- Cardiac function tests (Echo, RNA and/or MUGA scans) for all patients with cardiac risk factors (including prior trastuzumab or patients at or above threshold dose levels); baseline and as clinically indicated
- Clinical assessment of neurotoxicity (especially in patients with increased risk), infection, bleeding,stomatitis, nausea, vomiting, injection-site reactions, cystitis, skin and cardiac symptoms; at each visit

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

back to top

J - Administrative Information

Approximate Patient Visit	4.5 hours (Ifosfamide and Doxorubicin split into Days 1 to 3)
Pharmacy Workload (average time per visit)	36.865 minutes
Nursing Workload (average time per visit)	56.667 minutes

back to top

K - References

Davis EJ, Chugh R1, Zhao L, et al. A randomised, open-label, phase II study of neo/adjuvant doxorubicin and ifosfamide versus gemcitabine and docetaxel in patients with localised, high-risk, soft tissue sarcoma. Eur J Cancer 2015 Jun 9 pii: S0959-8049(15)00441-4.

Doxorubicin and Ifosfamide drug monographs, Cancer Care Ontario.

EURAMOS-1 protocol.

Grobmyer SR, Maki RG, Demetri GD, et al. Neo-adjuvant chemotherapy for primary high-grade extremity soft tissue sarcoma. Ann Oncol 2004 Nov;15(11):1667-72.

Judson I, Verweij J, Gelderblom H, et al. Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial. Lancet Oncol 2014 Apr;15(4):415-23.

Santoro A, Tursz T, Mouridsen H, et al. Doxorubicin versus CYVADIC versus doxorubicin plus ifosfamide in first-line treatment of advanced soft tissue sarcomas: a randomized study of the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. J Clin Oncol. 1995;13:1537-45.

March 2021 modified dosing section

back to top

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.

back to top

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.

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