Regimen Monograph

A - Regimen Name

MTRX Regimen

Methotrexate

Disease Site	Head and Neck
Intent	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	Treatment for recurrent and/or metastatic head and neck cancer

back to top

B - Drug Regimen

methotrexate	40 mg /m²	IV	Day 1

(If no toxicity at 40mg/m^2, may increase by 10mg/m^2 q2weeks (maximum 60 mg/m² IV on Day 1)

back to top

C - Cycle Frequency

REPEAT EVERY 7 DAYS
Until evidence of disease progression or limited by toxicity to chemotherapy

back to top

D - Premedication and Supportive Measures

Antiemetic Regimen: Low

back to top

E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated.

Evaluate any pre-existing hepatitis B and C before starting treatment.

Dosage with toxicity

Toxicity	Action
Grade 4 neutropenia or thrombocytopenia, febrile neutropenia or thrombocytopenic bleeding	Hold until recovery* and then reduce by 25%
Grade 3 non-hematologic/organ	Hold until recovery* and then reduce by 25%
Grade 4 non-hematologic/organ	Discontinue
Suspected pneumonitis	Hold, investigate appropriately and discontinue of confirmed
Leukoencephalopathy, hepatic fibrosis, viral reactivation	Discontinue
* until ANC ≥ 1.5 x 10^9/L, platelets ≥ 100 x 10^9/L and other toxicity ≤ grade 2	

Hepatic Impairment

Bilirubin (µmol/L)		Transaminases	% usual dose
2.5 - 4 x ULN	or	> 3 x ULN	75%
> 4 x ULN			DISCONTINUE

Renal Impairment

Methotrexate is **contraindicated** in patients with severe renal impairment. The following are recommended starting doses in patients with renal impairment. May require further dose adjustment due to wide inter-subject variability in pharmacokinetics.

Creatinine clearance (mL/min)	Starting dose (% usual dose)
>80	100%
80	75%
60*	60%
50	55%
<50	Use alternative therapy

Dosage in the Elderly

Methotrexate has not been well studied in the elderly. It should be used with extreme caution because of likely renal and hepatic impairment and reduced folate stores in the elderly. Monitor closely.

back to top

F - Adverse Effects

Refer to methotrexate drug monograph(s) for additional details on adverse effects.

More Common Side Effects (≥ 10%)	Less Common Side Effects, but may be Severe or Life-Threatening
• Nausea and vomiting • Mucositis • Anorexia • Dyspepsia • ↑ LFTs (may be severe)	• Myelosuppression ± bleeding, infection (including opportunistic infection, viral reactivation) • Nephrotoxicity/proteinuria • Encephalopathy • Pneumonitis • Arterial thromboembolism • Venous thromboembolism • DRESS • Stevens-Johnson syndrome • Toxic epidermal necrolysis • Erythema multiforme • Radiation skin reaction • Hypersensitivity • GI perforation • Pancreatitis • Tumour lysis syndrome • Vasculitis • Secondary malignancies

back to top

G - Interactions

Refer to methotrexate drug monograph(s) for additional details

- Contraindicated with concomitant use of nitrous oxide anesthesia or acitretin.
- Avoid concurrent use with hepatotoxic drugs (e.g. leflunomide, retinoids, azathioprine, sulfasalazine).
- Consider adjusting methotrexate dose if used together with cyclosporine or theophylline; monitor for toxicity.
- Caution with concomitant use or proton pump inhibitors and low-dose methotrexate, due to reduced renal elimination of methotrexate or its metabolite; consider use of H2 antagonists.

- Thiazide diuretics, including triamterene, may increase the risk of myelosuppression; consider alternative antihypertensive therapy.

back to top

H - Drug Administration and Special Precautions

Refer to methotrexate drug monograph(s) for additional details

Administration

- Do not admix with 5FU, prednisolone, KCl or other drugs unless compatibility data are available.
- Avoid contact with acidic solutions since methotrexate precipitation may occur.
- May be given by IV push.
- Store unopened vials between 15 to 25ºC. Protect from light

Contraindications

- Patients who are hypersensitive to methotrexate or any components of the formulation or container
- Patients with severe renal impairment including end stage renal disease with and without dialysis
- Women of childbearing potential until pregnancy is excluded
- Breastfeeding women
- Concomitant use with nitrous oxide anesthesia
- Formulations containing benzyl alcohol are contraindicated for use in intrathecal, intracerebroventricular, high-dose therapy, or neonates (less than one month of age)

Refer to the product monograph for contraindications related to the treatment of psoriasis or rheumatoid arthritis.

Warning / Precautions

- Use with extreme caution in patients with a history of peptic ulceration or ulcerative colitis and in patients with poor performance status, with active infection, impaired bone marrow function, prior or current wide field radiation, chronic liver disease, cirrhosis or with mild or moderate renal impairment.
- Avoid the use of live vaccines.
- Immunization may be ineffective when given during methotrexate treatment.
- Rare hypogammaglobulinemia has been reported.
- Not recommended in patients with active or chronic hepatitis B or C infection.
- Folate deficiency states may increase methotrexate toxicity.
- Patients with relevant third space fluid collections have prolonged excretion of methotrexate

levels and a resulting increase in toxicity. Evacuation of fluid collections and close monitoring of serum levels are recommended in such patients.
- There may be an increased risk of tissue necrosis or osteonecrosis when methotrexate is given concurrently with radiotherapy

Pregnancy/ lactation

- Methotrexate is **contraindicated** in pregnancy and breastfeeding. It has been reported to cause fetal death and/or congenital anomalies. Abortion is likely when administered to a pregnant woman.
- Adequate contraception should be used in both sexes, during treatment and for at least for 6 **months** after the last dose.
- Effects on fertility: Yes

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 dose
- Liver function tests; baseline and as clinically indicated
- Renal function tests; baseline and as clinically indicated
- Chest x-ray; baseline and as clinically indicated
- Clinical assessment of infection, bleeding, GI (stomatitis, diarrhea), skin, pulmonary or CNS toxicity; 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	0.5 hour
Pharmacy Workload (average time per visit)	15.714 minutes
Nursing Workload (average time per visit)	36.667 minutes

back to top

K - References

Forastiere AA, Metch B, Schuller DE, et al, Randomized comparison of cisplatin plus fluorouracil and carboplatin plus fluorouracil versus methotrexate in advanced squamous-cell carcinoma of the head and neck: A Southwest Oncology Study. J Clin Oncol, 1992; 10: 1245-51.

Hong WK, Schaefer S, Issell B, et al. A prospective randomized trial of methotrexate versus cisplatin in the treatment of recurrent squamous cell carcinoma of the head and neck. Cancer 1983;52(2):206-10.

Methotrexate drug monograph, Ontario Health (Cancer Care Ontario).

Stewart JS, Cohen EE, Licitra L, et al. Phase III study of gefitinib compared with intravenous methotrexate for recurrent squamous cell carcinoma of the head and neck. J Clin Oncol 2009;27(11):1864-71.

November 2022 Updated Antiemetic category, Dosage in renal impairment, Adverse effects, Interactions, Drug administration and special precautions, Clinical monitoring sections

back to top

L - Other Notes

Methotrexate regimen is associated with low toxicity risks and response rates of about 10-15% but no difference in survival when compared against 5FU and Cisplatin.

In patients with adequate performance status where standard chemotherapy would unlikely yield a good therapeutic index, consideration should be made for enrollment into a clinical trial of novel agent(s).

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,

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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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back to top