PROTOCOL

Systemic Anti Cancer Therapy Protocol

# Methotrexate and Vinblastine
## Sarcoma

PROTOCOL REF: MPHAMETVIN
(Version No. 1.1)

## Approved for use in:

Fibromatosis or desmoid tumours

## Dosage:

| Drug | Dose | Route | Frequency |
|---|---|---|---|
| **Methotrexate** | **50mg** | IV infusion | Day 1 |
| **Vinblastine** | **10mg** | IV infusion | Day 1 |
| Cycles lengths vary – 7 or 14 or 21 or 28 days<br>Given until disease progression or unacceptable toxicity | | | |

In the presence of unacceptable neurotoxicity

| **Alternative regimen should neurotoxicity occur** | | | |
|---|---|---|---|
| **Drug** | **Dose** | **Route** | **Frequency** |
| **Methotrexate** | **50mg** | IV infusion | Day 1 |
| **Vinorelbine capsules** | **30mg** | Oral | Day 1 |

## Administration:

- Caution with vinblastine in patients with cachexia and ulcerated skin.

## Emetogenic risk:

Mild emetogenic.

## Supportive treatments:

Metoclopramide 10mg tablets taken orally up to three times a day if required

## Extravasation risk:

Vinblastine- vesicant
Methotrexate- non vesciant
Refer to the CCC policy for the 'Prevention and Management of Extravasation Injuries'

## Dosing in renal and hepatic impairment:

| | | | |
|---|---|---|---|
| **Renal** | Methotrexate | **CrCl (mL/min)** | **Dose** |
| | | Above 50 | 100% |
| | | 20-50 | 50% |
| | | Below 20 | Do not administer |
| | Vinblastine | No dose adjustment is needed | |
| | Vinorelbine | No dose adjustment is needed | |

| | | | |
|---|---|---|---|
| **Hepatic** | Methotrexate | **Bilirubin (micromole/L)** | **Dose** |
| | | >86 | Omit |
| | Vinblastine | **Bilirubin (micromole/L)** | **Dose** |
| | | >51 | 50% |
| | | >180 | Omit |
| | Vinorelbine | **Bilirubin (micromole/L)** | **Dose** |
| | | >63 | Omit |

## Interactions:

### Methotrexate

Concomitant use of other drugs with nephrotoxic or hepatotoxic potential (including alcohol) should be avoided.

Vitamin preparations containing folic acid or its derivatives may decrease the effectiveness of methotrexate.

Caution should be used when NSAIDs and salicylates are administered concomitantly with methotrexate. These may enhance its toxicity and concomitant use of NSAIDs and salicylates has been associated with fatal methotrexate toxicity.

A potential interaction may exist between methotrexate and proton-pump inhibitors (e.g. omeprazole, pantoprazole). Omeprazole may inhibit methotrexate clearance resulting in potentially toxic methotrexate levels.

Concomitant application of methotrexate and theophylline can reduce theophylline clearance.

Methotrexate

## Vinblastine

Erythromycin may increase the toxicity of vinblastine.

Serum levels of anticonvulsants may be reduced by cytotoxic drug regimes, which include vinblastine.

Caution should be exercised in patients concurrently taking drugs known to inhibit drug metabolism by hepatic cytochrome P450 isoenzymes in the CYP 3A subfamily, or in patients with hepatic dysfunction. Concurrent administration of vinblastine sulfate with an inhibitor of this metabolic pathway may cause an earlier onset and/or an increased severity of side-effects.

## Vinorelbine

Interactions common to all cytotoxics

Warfarin / live attenuated vaccines / yellow fever vaccine contraindicated / Phenytoin

Ciclosporine, tacrolimus: Excessive immunosuppression with risk of lymphoproliferation is to be taken into consideration.

Itraconazole should not be administered concomitantly because of the risk of increased neurotoxicity due to the decrease of their hepatic metabolism.

Vinorelbine is a P-glycoprotein substrate and concomitant use with inhibitors (e.g. **verapamil**, **ciclosporin** and **quinidine**) or inducers of this transport protein can affect the concentration of vinorelbine.

As CYP 3A4 is mainly involved in the metabolism of vinorelbine, combination with strong inhibitors of this isoenzyme (e.g. **itraconazole, ketoconazole, clarithromycin, erythromycin and ritonavir**) could increase blood concentrations of vinorelbine and combination with strong inducers of this isoenzyme (e.g. **rifampicin, phenytoin, phenobarbital, carbamazepin** and St. John's wort) could decrease blood concentrations of vinorelbine.

**For more detailed interactions please refer to the SPC.**

## Treatment schedule:

| Day | Drug | Dose | Route | Diluent and rate |
|---|---|---|---|---|
| 1 | **Methotrexate** | **50mg** | **IV** | Over 5 minutes as IV bolus |
| | **Vinblastine** | **10mg** | **IV** | In 50mL 0.9% sodium chloride over 10 minutes |

## Main toxicities:

| **Methotrexate** | |
|---|---|
| **Blood** | Bone marrow depression, leukopenia, thrombocytopenia, anaemia, hypogammaglobulinaemia, haemorrhage from various sites, septicaemia |
| **Alimentary system** | Gingivitis, pharyngitis, stomatitis, mucositis, anorexia, vomiting, diarrhoea, haematemesis, melaena, gastrointestinal ulceration and bleeding, pancreatitis, enteritis, hepatic toxicity resulting in active liver atrophy, necrosis, fatty metamorphosis, periportal fibrosis, or hepatic cirrhosis |
| **Hepatic** | Hepatic toxicity resulting in significant elevations of liver enzymes, acute liver atrophy, necrosis, fatty metamorphosis, hepatitis, periportal fibrosis or cirrhosis or death may occur, usually following chronic administration |
| **Central nervous system** | Headaches, drowsiness, blurred vision, aphasia, cognitive disorder, hemiparesis and convulsions have occurred possibly related to haemorrhage or to complications from intra arterial catheterization. |
| **Vinblastine** | |
| **Nervous system disorders** | Numbness, paraesthesia's, peripheral neuritis, mental depression, loss of deep tendon reflexes, headache, convulsions, Treatment with vinca alkaloids has resulted rarely in both vestibular and auditory damage to the eighth cranial nerve. |
| **Cardiac disorders** | Myocardial infarction |
| **Vascular disorders** | Hypertension |
| **Gastrointestinal disorders** | Nausea, vomiting, constipation, oral mucosal blistering, diarrhoea, anorexia, abdominal pain, rectal bleeding, pharyngitis, haemorrhagic enterocolitis, bleeding from an old peptic ulcer, ileus, stomatitis |
| **Musculoskeletal and connective tissue disorders** | Myalgia, bone pain, jaw pain, tumour pain |

Please refer to SPC for more detailed information.

## Investigations and treatment plan:

| | Pre | Cycle 1 | Cycle 2 | Cycle 3 | Cycle 4 | Ongoing |
|---|---|---|---|---|---|---|
| Informed Consent | X | | | | | |
| Clinical Assessment | X | | | X | | Every 6 weeks |
| SACT Assessment (to include PS and toxicities) | X | X | X | X | X | Every cycle |
| FBC | X | | X | X | X | Every cycle |
| U&E & LFTs & Magnesium | X | | X | X | X | Every Cycle |
| CrCl (Cockcroft and Gault) | X | | X | X | X | Every cycle |
| CT scan** | X | | | | | Every 3-6 months or if clinically indicated |
| Main observations (Blood pressure measurement, resp rate, O2 sats etc) | X | X | X | X | X | Every cycle |
| Height Rate | X | | | | | If clinically indicated |
| Weight recorded | X | X | X | X | X | Every cycle |
| Blood glucose | X | | | | | Repeat if clinically indicated |

## Dose Modifications and Toxicity Management:

Complete this guidance in line with SPC/ other protocols or trial protocols

## Haematological toxicity:

Proceed on day 1 if-

| | |
|---|---|
| ANC ≥ 1.0 x $10^9$/L | Plt ≥ 100 x $10^9$/L |

Delay 1 week on day 1 if-

| | |
|---|---|
| ANC ≤ 0.9 x $10^9$/L | Plt ≤ 99 x $10^9$/L |

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

## Non- Haematological toxicity:

**GI toxicity**
For stomatitis not related to haematological toxicity - institute appropriate mouthcare measures. Check renal function and adjust methotrexate dose if necessary. Consider folinic acid (calcium folinate tablets) with subsequent cycles starting 24 hours after methotrexate injection, giving 15mg orally every 6 hours for 6 doses.

**Neurotoxicity**
Refer to consultant if any neurotoxicity > grade 2 or if persistent troubling symptoms – may switch to vinorelbine

## References:

Summary of Product Characteristics. *Methotrexate 100mg/ml Injection.* Hospira UK Ltd. Electronic medicines compendium. [accessed on: 09/08/2023] Last updated 29/06/2023

Summary of Product Characteristics. *Vinblastine Sulphate 1 mg/ml Injection.* Hospira UK Ltd. Electronic medicines compendium. [accessed on: 09/08/23] Last updated 09/06/2023

Summary of Product Characteristics. Vinorelbine. *Navelbine 20mg soft capsule.* Pierre Fabre Ltd. Electronic medicines compendium. [accessed on: 09/08/23] Last updated 26/07/2023

Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Lancet Oncol 2019;20: e201–08

Nishida et al. Desmoid with biweekly methotrexate and vinblastine shows similar effects to weekly administration: A phase II clinical trial. Cancer Science Weekly. 2020. 111:4187–4194.

## Circulation/Dissemination

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|---|---|
| Date added into Q-Pulse | 16th February 2024 |
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## Version History

| Version | Date | Author name and designation | Summary of main changes |
|---|---|---|---|
| 1.1 | 06/09/23 | Rob Challoner (Pharmacist) | Reviewed with Dr Ali. Updated doses to flat dose as per Meditech. Added info oral vinorelbine alternative to vinblastine. Added reference. |
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