# MCNE Treatment Protocol:
# Intravenous Viscum Album

## Rationale

Viscum Album is the most commonly used non-conventional treatment in Germany. VA has other historical applications including hypertension, epilepsy, osteoarthritis, etc. Its first recorded use in cancer patients was in 1916 in Leukemic patients. The traditional mode of application of viscum album is via subcutaneous injection beginning with low doses and gradually escalating dose in a methodical way based on patient constitution and tolerance. In this manner it can be an effective supportive therapy for cancer patients helping improve conventional treatment tolerance and efficacy, enhancing quality of life, and potentially positively affect survival.

Many in-vitro studies have shown a significant cytotoxic effect and endorphin induction with VA at higher lectin concentrations. While many components of VA have cytotoxic effects, Lectins are the main phytochemical agent responsible for the greatest direct cytotoxicity of VA. Lectins are also the component of VA with the strongest immunostimulatory properties. It is the component that is responsible for the dose limiting local erythematous reaction seen with sub-cutaneous injections of VA. Anti-Lectin antibodies are induced in every patient on VA and lead to eventual neutralization of the lectin effect within 6-12 months in most patients. VA delivered via intravenous route can avoid local reactions and allow for faster dose escalation and greater maintenance dose. This may lead to increased tumor specific response and pain control in wide spread disease. There are some case studies published showing partial and complete responses of breast and pancreatic cancers using IV VA in combination with Intra lesional VA.

## Clinical Indication for use (not approved)

- Tumor response in patients on 2$^{nd}$ line or beyond conventional treatment protocols
- Palliative treatment of metastatic disease (especially bone mets) for pain control and other QOL measures
- Primary treatment in patients who have refused conventional care with the known caveat that there have been only 2 published cases of CR in IV and intra-lesional VA. Therefore patients need to be advised that this is not a likely curative treatment

## Contraindication for use

- Tumor location where significant swelling (100-200% of pretreatment size) might lead to dangerous complications. Examples include:

    - Head and neck tumors
    - Prostate tumors
    - Lung tumors
- Patients where strong immune stimulation may lead to a worsening of comorbid conditions or may lead to allergic type reactions
    - Patients with Auto-immune conditions
    - Atopic Patients

## Side Effects and their treatment

This is a list of the most common (5% plus) ADRs reviewed specific to VA infusion based on patient data within our centre.

**Cytokine Release Syndrome –** Signs and symptoms similar to allergy, but this should have been ruled out by prior provocation testing.

*Treatment:*

Grade 1 – finish treatment observing every 15 minutes for worsening of CRS

Grade 2 – discontinue treatment initiate slow drip of 250 ML normal saline bag for 60 minutes and discharge patient once reaction has subsided

Grade 3 – discontinue treatment, initiate slow drip of 250 mL normal saline, give patient oral diphenhydramine 25-50 mg unless swallowing is effected. If swallowing affected give intravenous diphenhydramine 25-50 mg. Observe for 2 hours and discharge if no reaction is present and give patient two 25 mg diphenhydramine capsules as a delayed prescription to take as needed if CRS recurs, and advise patient to go to local emergency room if reaction is not fully corrected by delayed prescription.

Grade 4 – same as in grade 3 include immediate activation of EMS and referral of care to hospital as patient will likely need prednisone.

**Tumor Swelling and Pain –** this is caused by combination of moderate tumor lysis and a tumor specific immune response leading to tumor information.

*Treatment:*

Mild – Moderate – patient to use current painkiller if already prescribed or use paracetamol/NSAID as needed.

Severe – referral for assessment for tumor lysis syndrome and for more significant pain control likely need for temporary opiates as pain of treatment origin should subside within 2-3 days.

Phlebitis – rates of phlebitis in VA infusions seem higher in patients who also experience a CRS when compared with other infusions.

Treatment:

Discontinuation of infusion and re-initiated at alternate site. Advise patient to apply heat or cold depending on comfort and for grade 2+ give hamamaelis/aesulus/pau d'arco cream 2-3 applications for 5-7 days.

## Treatment/Dose Strategies

For patients with solid tumors our centre uses VA type - Abnobaviscum F
For patients with systemic cancers our centre uses VA type - Helixor M

Patients need to first be evaluated for hypersensitivity then give rapidly escalating doses of VA until max dose or they get an intolerance reaction. An intolerance reaction for VA includes CRS or Tumor Swelling or Pain.

### Pre-treatment Sensitivity Evaluation

Patient to be given 0.1 mg of either preparation intra-dermally at least 72 hours prior to first intravenous VA treatment. The injection site should be marked with 2" diameter circle and patient to be asked to observe if they develop a skin erythema reaction outside of this or if they develop urticarial or hive-like reaction.

If they have a erythematous reaction outside the 2-inch mark we will escalate the patient's dose at a 50% velocity.

If the patient develops and urticarial type reaction – this patient likely has a hypersensitivity to VA and is not a candidate to IV VA.

### Standard Dose Escalation Strategy

IV VA (either type) should be done 2-3 times weekly. If an intolerance reaction occurs, subsequent treatment should be delayed until symptoms subside.

### Abnobaviscum F

*1st treatment* – 20 mg delivered in 250 mL normal saline over 2 hours.

*2nd treatment* – 40 mg delivered in 250 mL normal saline over 2 hours

*Subsequent treatments* – each subsequent treatment can be done at a 20 mg increase until the patient reaches the maximum dose of 200 mg per treatment.

Subcutaneous Abnobaviscum F should also be given subcutaneously at each visit beginning with 1 mg and increasing to 3, 5, 10, 20 until local tolerance is met. Maximal maintenance dose is 40 mg.

**Helixor M**

*1st treatment* – 50 mg delivered in 250 mL normal saline over 2 hours

*2nd treatment* – 100 mg delivered in 250 mL normal saline over 2 hours

*Subsequent treatments* – each subsequent treatment can be done at a 100 mg increase until the patient reaches the maximum dose of 1,000 mg per treatment. Subcutaneous Helixor P should also be given subcutaneously at each visit beginning with 1 mg and increasing to 3 mg, 5 mg, 10 mg, 20 mg, 30 mg, 50 mg, 100 mg, 200 mg until local tolerance is met. Maximal maintenance dose is 200 mg.

**Monitoring During Treatment**

Patients will be monitored for the following during IV VA treatment:

| | Frequency of Monitoring | |
|---|---|---|
| Monitoring | Induction/Escalation Phase | Maintenance Phase |
| Patient Temperature | Each treatment | Each treatment |
| CBC with differential | Bi weekly | Monthly |
| VA cutaneous reaction | Each treatment | Monthly |
| Tumor Markers Level | Not during this phase | 4-8 weeks |
| Imaging | Not during this phase | Every 3-6 months |

**Duration of Treatment**

All patients receiving VA express neutralizing mistletoe lectin anti-bodies after 6-12 months. This leads to a negation of lectin based effects of VA. Patients need to be assessed for the continued presence of local reactions to ensure reactivity to mistletoe lectin. Generally IV VA will last for 6-12 months and terminate once cutaneous reactions (regardless of dose) cease to occur.