



Singe Institutional Experiences With Intravenous Viscum Album

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Disclosure & Thanks

- I am an owner of a healthcare center that provides supportive naturopathic care for cancer patients including viscum album treatment with Helixor
- I have no other relevant relationships to disclose
- Thank you to Dr. Ashley Chauvin Co-author



Naturopathic Oncology Centre

MARSDEN CENTRE FOR NATUROPATHIC EXCELLENCE

- I am the clinic director for MCNE
- MCNE is an integrative cancer center near Toronto, Canada providing:
 - Advanced applications of viscum album including intravenous and intralesional
 - Intravenous infusion therapies with Vitamin C, Artesunate, Dichloroacetate, Alpha lipoic Acid, Glycyrrhizic Acid, etc.
 - Locoregional Hyperthermia (Capacitive)
 - Clinical Nutrition
 - Asian Medicine and Acupuncture
 - Diet therapy: Carbohydrate restriction, mucositis diet, therapeutic fasting
- MCNE offers the only Naturopathic Oncology residency program in Canada



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Institutional Experiences With Intravenous Viscum Album at MCNE

QUALITY ASSURANCE ANALYSIS WITH CASE HIGHLIGHTS

- We reviewed all treatments of intravenous viscum at our centre from May 1, 2011 through July 31, 2014
- Treatment data was collected for each intervention recorded in our electronic record system QHR
- QA study design had inclusion criterion of:
 - All intravenous viscum treatments over the study period
 - All treatments where patients had clearly documented diagnosis
 - All treatments where patients had follow up to assess for tolerance



Institutional Experiences MCNE

QA STUDY DESIGN

- Treatments excluded:
 - Patients with incomplete patient data (Diagnosis, date of birth, etc.)
 - Patients lost to follow-up
- ADR recording and assessment
 - All suspected ADRs were recorded and classified using MedDRA hierarchy and graded using the CTCAE 4.0
 - All ADRs were reviewed by study doctors and assessed for causality
- Limitations due to the need for spontaneous reporting and potential documentation omission (trend will be lower ADR than actual)



Intravenous Viscum Treatment

TREATMENT PROTOCOL

- Patients are given an intradermal provocation dosage to rule out severe allergy to viscum
- Patients are rarely pretreated to a certain dosage tolerance level of subcutaneous mistletoe first (larger number of ADRs using that method)
- Incremental dose escalation after each treatment to prescribed dosage, maximum dosage or ADR occurs
- Intravenous Viscum is administered in NS or concurrently with high dose Ascorbic Acid over 2 hour period



Intravenous Viscum Treatment

TREATMENT PROTOCOL

- Patients undergoing intravenous viscum treatments also receive subcutaneous viscum
- Principle here is that IV viscum is cleared more quickly while the subcutaneous viscum is cleared more slowly giving the patient a bolus and sustained release medicament
- I have found patients on IV viscum can escalate subcutaneous viscum dosages much quicker.
- This is likely due to a stronger induction of anti-mistletoe lectin antibodies with IV administration

R. J.Wills, S.Dennis, H. E. Spiegel, "Interferon kinetics and adverse reactions after intravenous, intramuscular, and subcutaneous injection," *Clinical Pharmacology and Therapeutics*, vol. 35, no. 5, pp. 722–727, 1984.

Huber, R., Eisenbraun, J., Miletzki, B., Adler, M., Scheer, R., Klein, R., & Gleiter, C. H. (2010). Pharmacokinetics of natural mistletoe lectins after subcutaneous injection. *European Journal of Clinical Pharmacology*, 66(9), 889–97. doi:10.1007/s00228-010-0830-5



Reason for concurrent treatment with AA

- Studies of viscum album direct cytotoxic effect has shown great apoptotic effect with increased ROS
- High dose administration of Ascorbic Acid increases ROS within the intra and extracellular space by generating hydrogen peroxide

Kim, W., Park, W. B., Gao, B., & Jung, M. H. (2004). Critical Role of Reactive Oxygen Species and Mitochondrial Membrane Potential in Korean Mistletoe Lectin-Induced Apoptosis in Human Hepatocarcinoma Cells. *Molecular Pharmacology*, 66(6), 1383–1396. doi:10.1124/mol.104.001347.

Chen, Q., Espey, M. G., Sun, A. Y., Lee, J.-H., Krishna, M. C., Shacter, E., ... Levine, M. (2007). Ascorbate in pharmacologic concentrations selectively generates ascorbate radical and hydrogen peroxide in extracellular fluid in vivo. *Proceedings of the National Academy of Sciences of the United States of America*, 104(21), 8749–54. doi:10.1073/pnas.0702854104



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Treatment Goals Intravenous Viscum

- Stronger cancer inhibition
- Increased immune activation to augment subcutaneous administration
- Stronger QOL improvements (most notably pain)
- Poor tolerance of subcutaneous viscum administration

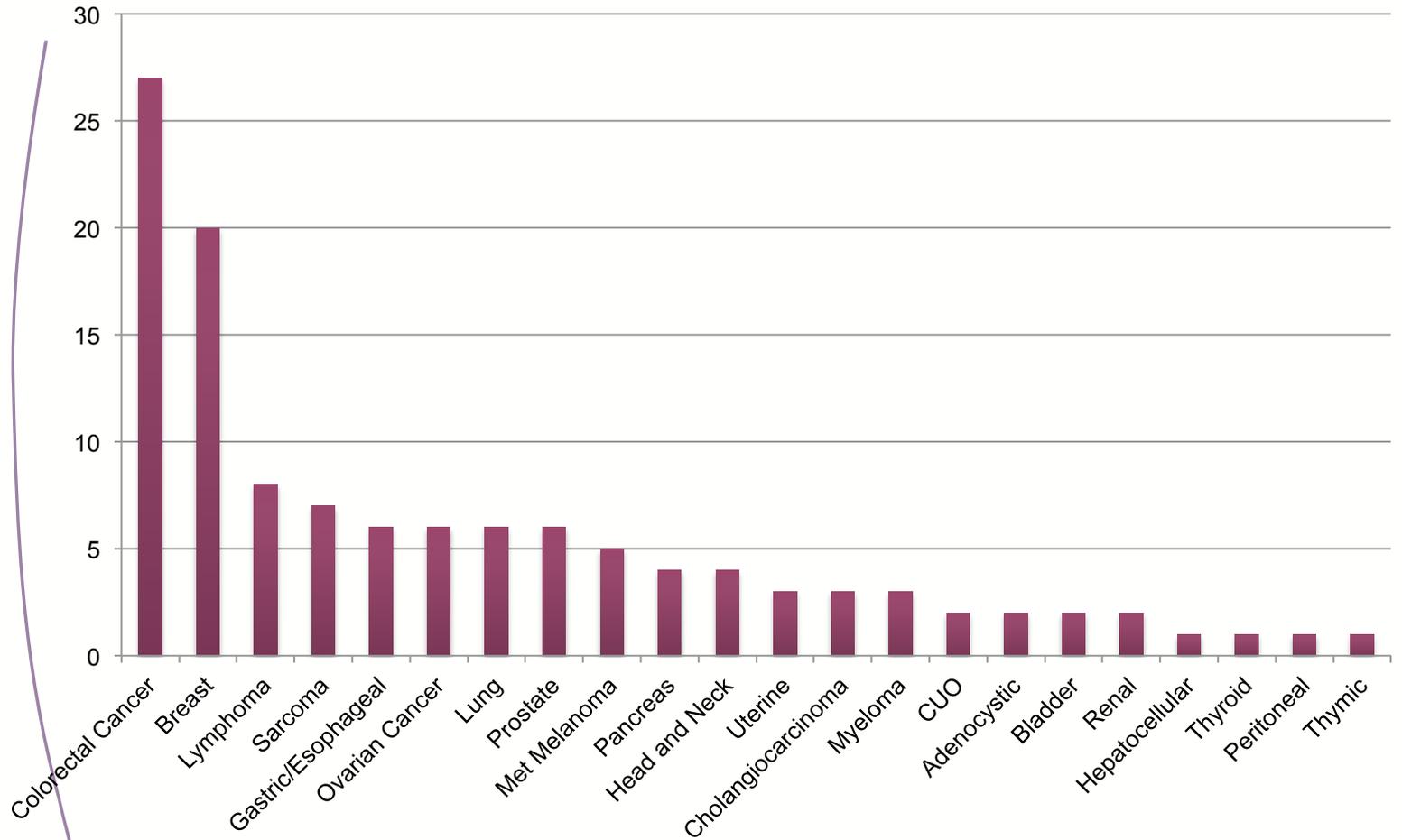


QA Study Summary Results

- Total number of intravenous viscum treatments delivered during the study period: 1,747
- Total number of patients treated: 120
- Average number of intravenous treatments of viscum album a patient received: 14 ranging from 1 treatment to a maximum of 87



Cancer Types



ADRs

- All suspected (unlikely, somewhat likely and likely) ADRs recorded
- Total number of ADRs: 38 = 2.2%
- ADRs consisted of Grade 1 and 2 Cytokine Release Syndrome
- Symptoms consisted of:
 - Urticaria
 - Reactivation of prior sub-cutaneous injection sites
 - Fever (greater than 38⁰C)
 - Angioedema
 - Bronchospasm
 - Tumor Pain
- Successfully treated with discontinuation of infusion or administration of benadryl



Treatment of Cytokine Release in Viscum

- Grade 1 (urticaria)
 - In the case of reactivation of injection sites no alteration in treatment necessary
 - in case of fever greater than 38⁰C observe patient, if well tolerated continue treatment, but if poorly tolerated stop treatment and/or administer antiphlogistic
 - With generalized urticaria discontinue infusion, run normal saline to keep vein open (KVO)
 - Observe and administer anti-histamine if reaction does not subside



Treatment of Cytokine Release in Viscum cont'd

- Grade 2 & 3
 - Angioedema, bronchospasm, etc.
 - discontinue infusion, run normal saline to keep vein open (KVO)
 - Administer benadryl IV 20-50 mg as needed to stop reaction and observe for 2-4 hours



ADR Clustering

- ADRs appeared to have the following patient characteristics:
 - Dose related in sensitive patients
 - Sensitization occurring after multiple infusions (>40)



Case Report: Angiosarcoma

- 41 year old man
- Dx with Osteosarcoma (knee) in 1995 treated with surgery and 3 rounds of chemotherapy
- 2007 had a sore knee (contralateral side) diagnosed as an angiosarcoma
- Had neoadjuvant chemotherapy and surgery thought to be curative
- During chemotherapy he developed c.difficile, was given vancomycin and developed acute renal injury



Angiosarcoma cont'd

- Patient was treated with subcutaneous helixor for 3 years alongside other naturopathic therapies with no evidence of disease and good QOL
- In 2011 he developed epigastric pain, imaging revealed pancreatic metastasis
- He was treated with radiation, but had progression and was no longer a candidate for chemotherapy given reduced renal function



Angiosarcoma cont'd

- Patient was treated with intravenous viscum and vitamin C (titrated to 75g)
- Had partial response and the stable disease for 1 year
- Developed new skeletal metastasis for which he received radiation followed by insulin potentiated chemotherapy with WBHT and LRHT
- Continued IV viscum and vitamin c PR with combined therapy but became sensitized to viscum (large cutaneous reaction near insertion site) and had to discontinue therapy resulting in more rapid disease progression
- Patient currently lost to follow up



Case Report: T Cell Lymphoma

- 38 year old man
- Dx with T Cell Lymphoma
- Failed R CHOP and ASCT
- Had leukopenia, fatigue and leptomenigeal disease on presentation to clinic prognosis 3-6 months
- Given gemcitabine and bortoziemib
- Failed treatment with bortoziemib
- Began supportive treatments with subcutaneous and intravenous viscum, vitamin c, DCA and botanical adaptogens



T Cell Lymphoma cont'd

- Patient had improving constitutional symptoms, reduced lymph nodes inguinal, lower LDH over
- Over next several months had lymph nodes in both cervical and inguinal areas variably reduce and increase in size with blood counts stable
- Lumbar puncture after 1 year showed CSF clear of disease, but bone marrow still 75% affected



T Cell Lymphoma Cont'd

- Continued IV viscum, vitamin C and DCA for another 7 months
- He struggles with infections due to leukopenia and has been on multiple antibiotics
- Had to discontinue viscum due to reactions (unclear causality) and DCA because of clear allergic reaction
- He is still alive no current treatment for lymphoma, but managing infections with various anti microbials



Case Report: B Cell Lymphoma

- 46 year old woman Dx with T Cell Lymphoma
- Failed R CHOP and ASCT
- During ASCT developed severe myelosuppression resulting in twice weekly transfusions of blood product and chronic leukopenia
- Was then diagnosed with both NHL and HL
- Had received viscum subcutaneously but was not positively impacting myelosuppression



B Cell Lymphoma cont'd

- Began IV viscum had tolerance issues at high doses, but was able to tolerate moderate doses
- After 3 months of treatment on IV viscum was receiving transfusions once monthly and had improved energy and leukocyte counts
- Patient lived 2 years post failed ASCT with good QOL

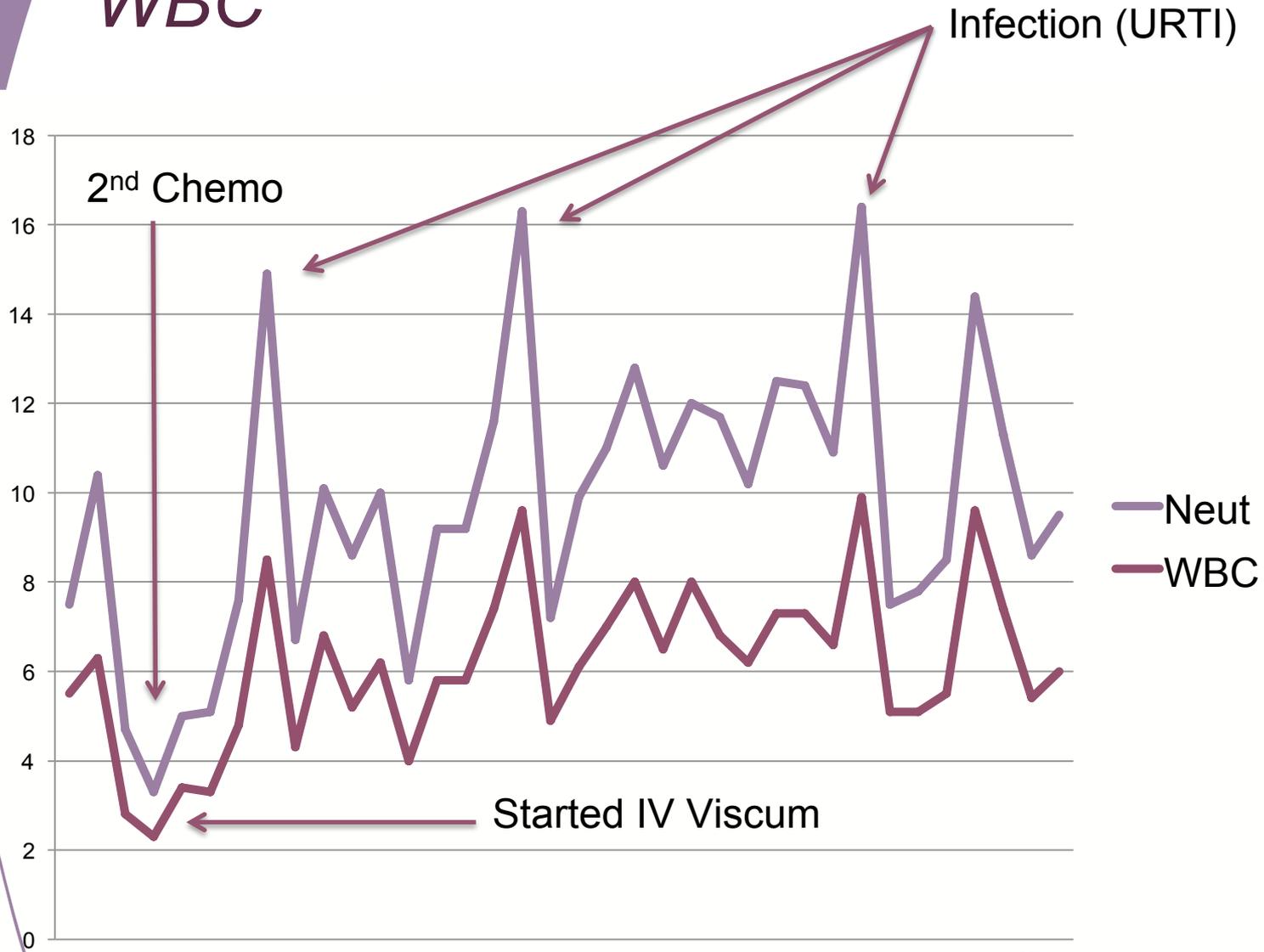


Case Report: Colorectal Cancer

- 59 year old man dx with metastatic colorectal cancer 2013
- Treated with FOLFIRI protocol
- Experienced significant leukopenia during chemotherapy
- Treated with both subcutaneous and intravenous viscum (since patient was already neutropenic and was unable to escalate subcutaneous doses quickly)
- Also treated with lower dose intravenous vitamin c and locoregional hyperthermia



WBC



Ovarian Cancer

- Female 47 years old ovarian cancer (Stage IV)
- Multiple bone metastasis given 6 weeks to live
- Goal to make it to Christmas and young son's birthday
- Severe pain that was not really touched by pain meds
- Given high dose AA initially
- Felt more energy, but no change in pain/mild impact in QOL
- Added viscum IV and noticed immediate improvement
- Patient lived 4.5 months with significantly improved QOL



Lung Cancer (NSCLC)

- 60 year old woman
- NSCLC Stage IV pleural effusion treated with pleurodesis
- Given Iressa in March 2011
- Had OR with moderate regression
- Still experienced severe pain with nausea and vomiting resistant to opiates
- Treated with infused viscum and homeopathic complexes twice weekly
- Within 3 weeks was pain free and had nausea and vomiting 1-2 times max per week tumor still stable to date has a hip fracture but is relatively well with no pain and relatively good QOL



Conclusion

- IV Viscum in an outpatient setting is:
 - Very safe with a low rate of ADR easily manageable with minimal interventions
 - May increase therapeutic response in cancer patients beyond simple SC viscum administration
 - May provide increased immune activation when compared to SC viscum alone
 - May provide increased QOL improvements (especially with pain)



Thank You For Your Attention