IV administration of Viscum album alongside myelosuppressive chemotherapy and/or targeted therapy may reduce incidence of febrile neutropenia in solid tumor malignancies: a single-centre pilot study

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Background

Febrile neutropenia (FN) is defined by the National Comprehensive Cancer Network (NCCN) as the presence of an oral temperature of >38.3°C (or >38.0°C for 1 hour duration) with an absolute neutrophil count (ANC) of <500/mcL (or <1000/mcL with an expected decline to <500 within 48 hours) (1). Despite advances in its prevention and treatment, FN remains a serious complication and dose-limiting toxicity of myelosuppressive chemotherapy that often results in costly interventions including hospitalization and prolonged antimicrobial use, as well as impaired treatment outcomes and early death (1). Risk for FN in solid tumor malignancies receiving myelosuppressive chemotherapy is estimated at ~0.7-40% for chemotherapy-naïve patients (2,3). Risk stratification for FN is complicated, with both treatment- and patient-related factors involved in risk assessment (Table 1, (1)), and many national organizations lack firm consensus on accurate risk stratification due to disparities in degree of each risk factor's impact, and encourage clinical judgment on a case-by-case basis. To complicate risk stratification further, newer regimens that include targeted therapies can alter FN risk. For these reasons, it is estimated that true risk for FN and grade 3-4 neutropenia may be under-reported (1). NCCN and Cancer Care Ontario (CCO) recommend use of primary prophylactic myeloid growth factors (MGFs) to reduce risk of FN for myelosuppressive regimens whose risk of FN is high at >20%, and strong consideration based on patient risk factors for regimens with moderate FN risk of 10-20% (1,4). MGF costs often prevent widespread use despite these recommendations, and they are not without adverse effects, with some reports of associated fatality (1).

Table 1 - Cancer Care Ontario Risk Factors for FN

Risk Factors	Clinical Factors
High level of supporting evidence	• ≥85% relative intensity • Extensive prior chemotherapy • Prior radiation to bone marrow • Age greater than 65 years • Bone marrow involvement with tumor
Intermediate level of supporting evidence	• Poor performance status • Low albumin/high LDH • Pulmonary disease • Cardiovascular disease • Liver disease • Diabetes mellitus
Low level of supporting evidence	• Open wounds or active infection • Poor nutritional status • Hgb < 120 g/L • Female sex (smaller BSA)
Other/unclear level of supporting evidence	• Preexisting neutropenia • Advanced cancer • Leukemia • Lymphoma • Lung cancer • Decreased immunity

Viscum album has been used as an adjunctive cancer therapy for many years for the purposes of reducing chemotherapy-related adverse events (including myelosuppression), improving quality of life parameters, and offering immunomodulatory benefit (5-9) (Fig 1 (_____). While research on subcutaneous administration of Viscum album suggests positive benefit to reducing ANC nadir during myelosuppressive chemotherapy (9), there are no trials to date describing rates of FN during myelosuppressive chemotherapeutic/targeted agent regimens in solid tumor malignancies with concomitant intravenous (IV) Viscum album administration.

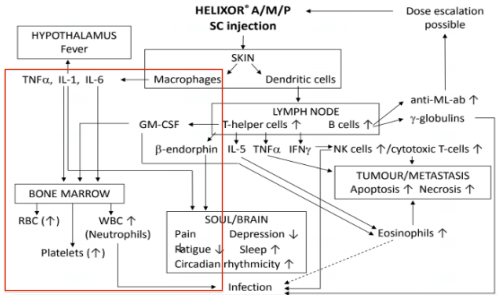


Figure 1 - Summary of Subcutaneous Viscum MOA

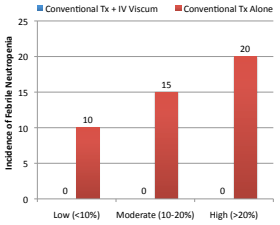
Methods

A retrospective, single-centre pilot study was conducted to assess the incidence of FN in all patients with solid tumor malignancies receiving IV Viscum album (Helixor®) alongside conventional myelosuppressive regimens at the Marsden Centre for Excellence in Integrative Medicine in the years 2016-2017. Exclusion factors included hematological malignancies, total # of Viscum infusions <8, and use of MGFs as primary prophylaxis of FN. Patients at our centre received IV Helixor® Viscum album based on clinic protocol of 100-1000mg 1-2x/wk, alongside other adjunctive naturopathic care.

Results

	Cancer type	Total # of Patients	CCO GCSF Chemotherapy Regimen Risk Stratification	Grade 3-4 Neutropenia	FN
FEC-D	BR	1	High	1	0
Palbociclib	mBR	3	High	1	0
Sorafenib	mHCC	1	High	0	0
Total		**5**		**2**	**0**
Paclitaxel/Tras + Pert	BR	1	Moderate	0	0
Sunitinib	mGIST	1	Moderate	0	0
Carboplatin/Taxol/Avastin	mCERV	2	Moderate	0	0
Paclitaxel	ENDO	1	Moderate	0	0
Gemcitabine	SARC	1	Moderate	0	0
Cisplatin/Capecitabine/Tras	mESO	1	Moderate	0	0
ECX	GASTRIC	1	Moderate	1	0
FOLFIRINOX	mPANC	2	Moderate	0	0
FOLFOX/Avastin	mCRC	1	Moderate	1	0
FOLFIRINOX	mCRC	1	Moderate	0	0
FOLFIRI	PANC	1	Moderate	0	0
FOLFIRI/Avastin	mCRC	2	Moderate	0	0
Total		**15**		**2**	**0**
Paclitaxel	GASTRIC	1	Low	0	0
Cabecitabine	mBR	1	Low	0	0
Abraxane	mBR	2	Low	0	0
Afatinib	mLUNG	1		0	0
Pemetrexed	mLUNG	1	Low	0	0
Cisplatin/Pemetrexed	mLUNG	1	Low	0	0
Carboplatin/Taxol	CUP	1	Low	1	0
Carboplatin	OV	1	Low	0	0
Carboplatin/Taxol	ENDO	2	Low		0
Carboplatin/Taxol	OV	2	Low	1	0
Caelyx	OV	1	Low	0	0
Regorafenib (mCRC)	mCRC	1	Low	0	0
Total		**15**		**2**	**0**

During 2016-2017, the incidence of FN in patients at our centre with solid tumor malignancies receiving myelosuppressive chemo- and/or targeted therapy without MGFs, but with concomitant IV Viscum album, was 0%.

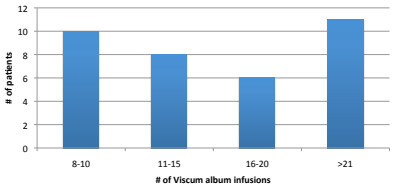


Conclusions & Discussion

Considering many of the patients were heavily pre-treated (not chemotherapy-naïve), with moderate-high risk regimens, this preliminary data suggests administration of IV Viscum album alongside such regimens may reduce the incidence of FN, alongside other immune and quality of life benefits that adjunctive Viscum album administration offers. Adjunctive IV Viscum album may be a more cost-effective, better-tolerated primary prophylactic measure for prevention of FN than MGFs for moderate-high risk regimens in solid tumor malignancies. However, larger, prospective, more vigorously standardized, randomized studies are needed to confirm these results.

Limitations of this study include a) neutropenic episodes in relation to Viscum infusions and ANC nadir not commented upon, b) patients present to clinic for supportive care at different stages of conventional treatment, c) all patients were receiving additional adjunctive Naturopathic care, d) difficult to evaluate each individual's specific risk for FN with aforementioned compounding factors, and e) number of Viscum album infusions not standardized (Fig 2).

Figure 2 – Number of patients receiving IV Viscum album



Information has not been presented at another conference to date (though discussed in oral presentation at Helixor® event in Brazil in Nov 2017). Study was entirely self-funded, with no conflicts of interest to declare.

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