IJCIM

International Journal of Complementary and Internal Medicine

CASE REPORT

Clinical Regression of Chondrosarcoma Applying High Doses of Viscum album extracts (VAE) by Intratumoral Injection: A Case Report

Joon Beom (John) Park,[1] Inmyung Oh,[2] Sunjoo Chung,[2] Taek Joon Yoon,[3] JongBae Kim[1]

[1]*Mistletoe Research Center, New Breath Hospital, Seoul*
[2]*Mistletoe Cancer Clinic, New Breath Hospital, Seoul*
[3]*DoGenBio, Independent Researcher & Consultant, Seoul*

Corresponding Author: Joon Beom (John) Park, Mistletoe Research Center, New Breath Hospital, KD70 Jeungui-ro 8-gil 4, Songpa-gu, Seoul, Korea. E-mail: gdjbpark1106@gmail.com.

Received: April 12, 2024 **Published:** April 30, 2024

Citation: Joon Beom Park. Clinical Regression of Chondrosarcoma Applying High Doses of Viscum album extracts (VAE) by Intratumoral Injection: A Case Report. Int J Complement Intern Med. 2024;6(1):246–253. DOI: 10.58349/IJCIM.1.6.2024.00138

Copyright: ©2024 Park. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and build upon your work non-commercially.

Abstract

Mistletoe lectins (ML/VAL) are known to induce apoptotic cell death. Intratumoral applications of Viscum album extract (VAE) have induced local tumor response in various cancer entities for variant carcinomas. A 46-year-old male patient suffering from chondrosarcoma had two large-sized masses (40 cm x 25 cm x 17 cm) and a satellite tumor (8 cm x 14 cm x 3 cm). The patient was treated with by 24 times Abnobaviscum F (fraxini) 20 mg intratumoral injections and concomitant administration of 19 times Helixor A (abietis) 100 mg IV infusions weekly. 32 weeks after treatment the tumoral parenchyma showed a significant regression (>70% of the tumor size) These treatments aimed to improve survival and QoL by reducing tumor burden and symptoms, such as shortness of breath, coughing, hemoptysis, and cachexia.

Retrospectively, on average, the lectin amount in one ampoule of Abnobaviscum F 20 mg was 205.2 ng/ml. As eight ampoules of Abnobaviscum F 20 mg (total 160 mg) were injected into the patient a day by intratumoral application, up to 1,642 ng/ml of mistletoe lectin (ML) was injected as the extending maximum high-dose in safety. The concentration of VAL was determined by ELISA. Reference mistletoe lectin was isolated using an immunoaffinity column with lectin-specific monoclonal antibodies.

Keywords: mistletoe, chondrosarcoma, intratumoral mistletoe injection, Viscum album, lectin

Introduction

Chondrosarcomas are malignant tumors, comprise an estimated 20 % of primary malignant bone tumors, second only to osteosarcoma. Chondrosarcoma is a type of bone cancer that starts in cartilage cells. Cartilage is the smooth connective tissue that protects the ends of bones and lines most joints. Chondrosarcoma mainly affects the cartilage cells of the thighbone (femur), shoulder, or pelvis. Less often, it starts in the knee, ribs, skull, and trachea. Björnsson and colleagues (1998) found a 5-year survival rate of 89 % for grade 1 chondrosarcoma and 57 % for the combined group of patients with Grade 2 and Grade 3 tumors. Chondrosarcomas frequently grow slowly, and can be present for several years before a patient consults a doctor. Pain in the absence of a pathologic fracture can be important in helping to differentiate an enchondroma from a low-grade chondrosarcoma.[6]

Intralesional curettage with adjuvant local therapy (i.e., intralesional cryotherapy, phenol, liquid nitrogen, or argon-beam laser) has emerged as an effective treatment for tumors of the long bones classified as Grade 1 chondrosarcomas or atypical/borderline tumors, provided the tumors show no radiologic evidence of aggression (*i.e.*, cortical permeation or soft tissue extension).[3,8] In patients with higher grade chondrosarcomas of the extremities or chondrosarcoma of any grade involving the axial skeleton the tumors are usually resected.[4] Chondrosarcomas do not respond to standard chemotherapy, and local recurrence rates vary from 15 % to 28 %, depending on the type of surgical procedure. Occasionally, recurrent tumors are of a higher histologic grade.[10]

We here studied whether *Viscum album* would show tumoral cell death and necrosis effects when injected into tumors of connective tissue cancer such as chondrosarcoma, and what would be the highest dose of lectin that could safely be used in a patient.

Material and Methods

A 46-year-old male patient was diagnosed with chondrosarcoma with pleural and lung metastasis in the lower and posterior parts of the 7th and 8th ribs in the left chest in September 2016. In October 2016, the chest wall resection of the 7th & 8th ribs was performed. Histological findings were 7.4 x 7.0 x 6.6 cm sized mass, grade 2, resection margin <0.1 cm involvement, parietal pleural invasion positive, necrosis and lymphovascular invasion were negative. Postoperative radiation therapy for the left chest wall was performed 30 times at 45 GY/25 fx.

After 14 months, exploratory thoracotomy and mass excision were performed again due to recurrence at the previous operative site. After the second operation, chemotherapy with ifosfamide and doxorubicin for six cycles was applied, and some adverse effects of chemotherapy were seen. Surgery and subsequent chemotherapy was effective and tumor growth was retarded as demonstrated by CT.

However, in the following 11 months, the tumor mass grew, and the invasion of the left lung's pleural and metastatic infiltration in the pulmonary parenchyma further expanded significantly. As a result, the additional chemotherapy was performed again with VIP (etoposide + ifosfamide + cisplatin) twice, followed by palliative chemotherapy with adriamycin and dacarbazine four times and palliative radiation therapy to the large left chest wall and pleural mass in 52 Gy/13fx.

Patient Pathway

In July 2020, the patient underwent his final chemotherapy. Following this, the patient was transferred to a hospice ward because of the advancement of tumor extension and correlated general symptoms in resisting the effect of conventional treatments. One week after the end of the conventional treatments, the patient came to the mistletoe clinic at New Breath Hospital. We conducted our intratumoral injection and simultaneous intravenous injection treatment using VAE.

Tumor characteristics

When the patient first came to New Breath Hospital, he had two tumor masses. Masses of the same nature were located somewhat close to each other. The very large external tumoral mass that had grown out of the chest wall occupied from just below the left shoulder joint to the 8th rib laterally, back neck and lateral and posterior chest walls were invaded by enlarged tumoral mass from the middle of posterior triangle with left trapezius muscle to the entire left scapula and surrounding soft tissues posteriorly. The anterior wall of the chest protruded into a diffuse lump from the left sub-clavicular point to 3rd to 6th intercostal level of left anterior chest wall. The large tumoral tissue connected between anterior, lateral, and posterior wall was 400 mm[A] x 250 mm[B] x170 mm[C] in size. The depth of mass from the chest wall was 150 mm. The smaller tumor was 180 mm[D] x 140mm[E] x 20mm(depth). Both masses were palpably hard in-depth and more little soft in the dermal and epidermal layers (Figure 1). Inside the thoracic cavity, the tumor had extensively invaded the lung parenchyma of all three lobes (Figure 2).

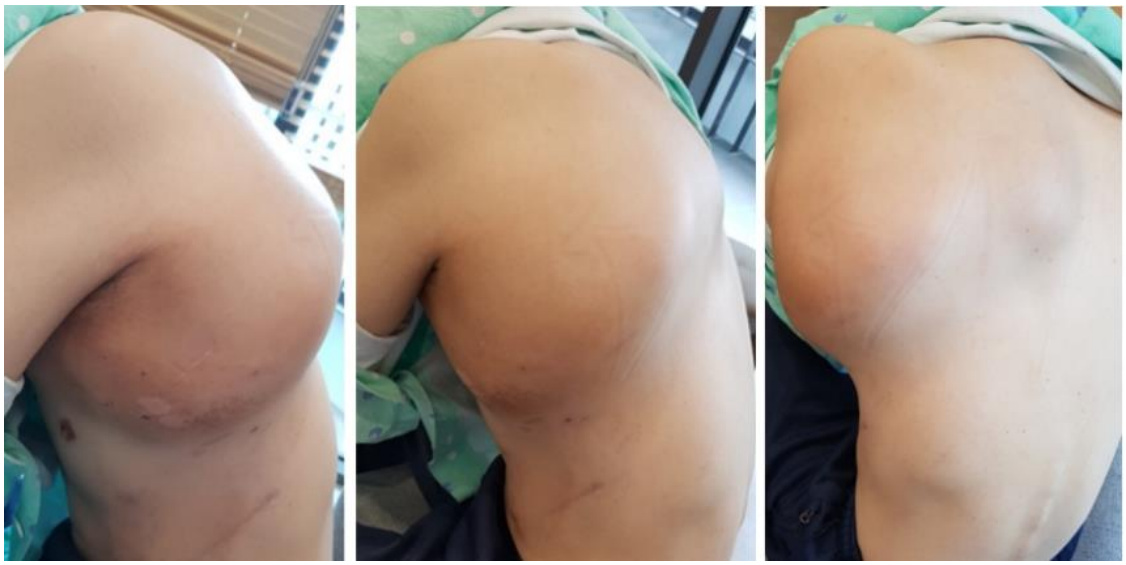

Figure 1. External appearance of the patient's advanced large chondrosarcoma

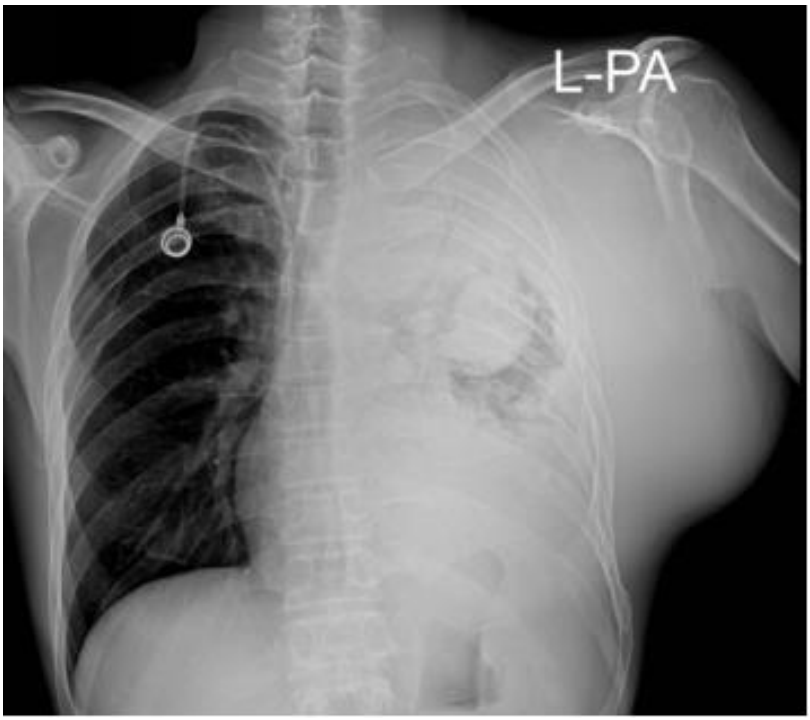

Figure 2. Chest X-Ray showing chondrosarcoma invaded to left lung cavity.

Viscum album intratumoral and intravenous injections We initiated a set of continual treatments with intratumoral injection of Abnobaviscum F 20 mg (Abnoba GmbH) preparation into the large tumor mass and intravenous administrations of Helixor A 100 mg (Helixor Heilmittel) mixed with saline solution.

First, to induce the patient's immune physiology and sensitize the mistletoe component, Abnobaviscum F 0.02 mg, the smallest unit, was injected subcutaneously. At the same time, Abnobaviscum F 0.2 mg was injected into the tumor mass. Three days after this first injection, another dose of Abnobaviscum F 0.02 mg was applied Abnobaviscum F 2 mg was carried out (Table 1).

Strong immediate drug adverse effects were not observed in the patient, but there were three time pyrexia over 38.5 °C at the nights at home in the following weeks. We proceeded the intratumoral injections according to the following protocol: 1) one time 20 mg injection, followed by 5 times 40 mg , 3 times 60 mg, 6 time 80 mg 5 times 100 mg, and 5 times 120 mg a week mostly while this treatment protocol confronted actively to the tumor burden with vigorous intensity, and was continued two weeks interval when the tumor size was decreased significantly after three months later. Finally, the intratumoral injection dose reached 160 mg of Abnobaviscum F (Table 2).

Table 1. Intratumoral & intravenous treatments with Viscum album preparation on the patient (1 to 17 week)

Week of treatment	Abnoba F® intratumoral injection	Abnoba F® Subcutaneous	Helixor A® IV mixing with n/s	Clinical remarks
1	0.2mg (Tues), 2mg(Fri)	0.02mg	100mg	Starting Tx under Off-Label agreement Existed hemoptysis
2	20mg	0.2mg		
3	40mg	2mg		decresed hemoptysis
4	-		200mg	more soften on sarcoma mass
5	40mg	2mg		fever 37.3, chilling after one day
6	40mg			No aggravated tumor extension
7	40mg	2mg		tolerable to increased VAE aount
8	40mg (Fri)	2mg	200mg (Tue)	dark sanguneous mucid fluid aspirated. fever 37.7
9	120mg (Mon)		200mg (Tue)	starting decreased tumor mass locally
10	40mg (Fri)		200mg (Tue)	
11	60mg (Fri)		200mg (Tue)	significantly decreased external(lat & post) tumor contour
12	60mg (Fri)		250mg (Tue)	after one time injection on ant. upper chest, decreased tumor contour and size
13	80mg (Fri)		250mg (Tue)	decresed hemoptysis and pain on injected tumor site
14	80mg (Fri)		250mg (Tue)	more exercise and diet
15	120mg (Fri)		-	tolerable to increased VAE aount
16	-		250mg (Tue, Thur)	
17	-		250mg (Tue)	

Table 2. Intratumoral & intravenous treatments with Viscum album preparation on the patient (18to 34 week)

Week of treatment	Abnoba F® intralesional injection/week	Helixor A® IV mixing with n/s 250ml	Abnoba F® IV with n/s 250ml	Clinical remarks
18	80mg (Mon)	200mg (Fri)		
19	120mg (Thur)	200mg (Tue)		
20	100mg	250mg (Tue)		
21	-	250mg		
22	100mg	250mg		
23	120mg (Tue), 40mg (Fri)	250mg	40mg	
24	160mg		-	tolerable to increased VAE aount
25	100mg (Tue)		60mg (Thur)	
26	120mg (Mon)		60mg (Thur)	
27	120mg (Mon)		80mg (Thur)	
28	120mg (Tue)		80mg (Thur)	
29	140mg		80mg (Thur)	
30	-		80mg (Thur)	Hematochezia d/t stercoral colitis on colonoscopy. No evidence of active bleesing on abd CT angio
31	-		40mg	
32	-		80mg (Thur)	
33	160mg		100mg (Thur)	torable to the amount of VAE
34	160mg		100mg (Thur)	
TOTAL	**29 times**	**18 times**	**11 times**	

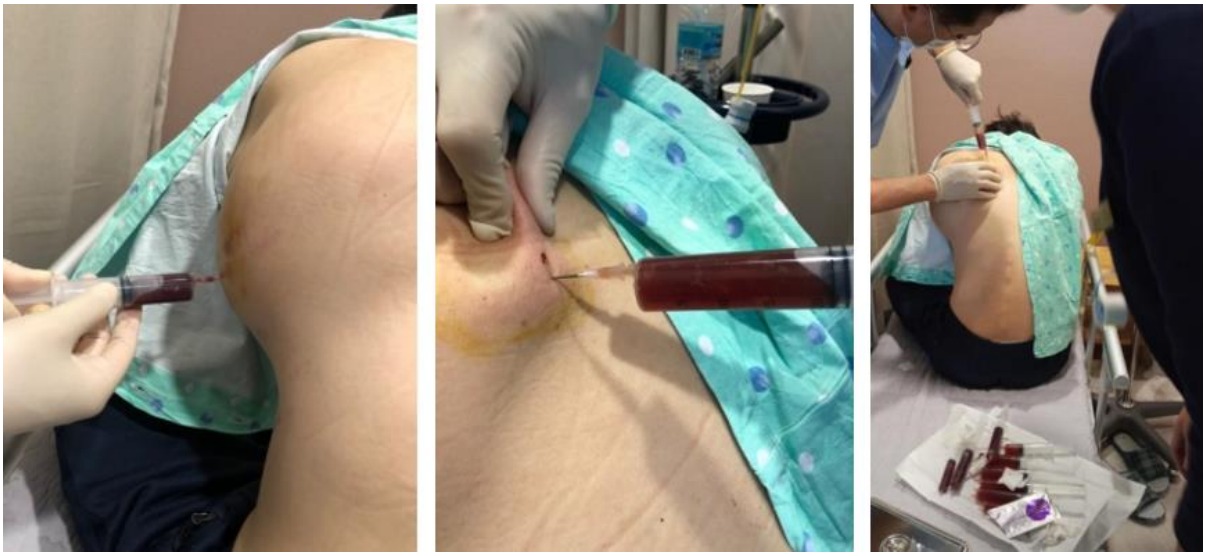

Figure 3. Intratumoral Injections with VA & aspirating the necrotic tumor weekly.

In parallel with intratumoral injection for resolution of a large tumor mass, intravenous Helixor therapy was administered to stop the aggravation of various cancerous complications at the terminal stage of the patient, maintain the equilibrium of cells and immune system, and raise QoL. Starting with Helixor A 100mg, from the second injection, we infused Helixor A 200mg mixed with 500ml of normal saline solution once regularly at weekly intervals.

One week after the second time injection of mistletoe, the mass of the tumor started to fluctuate without any added manipulation, and when the lesion formed was aspirated with 18 gauge needles, the aspirated content was bloody sanguineous color containing necrotic tissues which was of mucoid nature and the amount was about 140 to 200 ml weekly. For example, when 5 mL of Abnobaviscum F 20 mg (corresponding to 100 mg) were injected, approximately 200 ml +/- 20 ml of tissue fluid was removed by syringe aspirations. When 8 ampoules were injected, approximately 300 ml of tissue fluid was aspirated (Figure 3).

Measuring maximum dose and safety of VAE intratumoral injection

The lectin component found in *Viscum album* preparation has been shown to cause cancer cell necrosis.[5,6] The aim of our study was to determine the safe dosage of VAE that can be directly injected into tumors. The safety criteria used in this study for assessing the effects of VAE injection were as follows:

1. Absence of anaphylactic symptoms, i.e., diastolic BP less than 60mmHg or tachycardia exceeding 100/min.
2. No systemic allergic reactions.
3. No respiratory distress.

However, the cases of manageable pyrexia occurring within two days after injection were not considered part of the safety evaluation criteria.

To achieve this, we reviewed our clinical experience in this case to determine the maximum usable dose of VAE that we have safely administered through intratumoral injection into solid chondrosarcoma tumor. To find out the highest possible dose of VA lectin that can be administered intratumorally to the patient using Abnobaviscum F 20 mg once, we measured the lectin content in Abnobaviscum F 20 mg. For this purpose, we conducted a test on five ampoules (labeled N1 to N5) of Abnobaviscum F 20 mg. We conducted a Sandwich ELISA analysis using a polyclonal antibody as a capture antibody and a monoclonal antibody (8b11-2C5) that responded well to the lectin antigen (Figure 4). The standard material used for this analysis was a previous lectin, and we determined the lectin antigen concentration in the samples (Figure 5). The amount of lectin in Abnobaviscum F 20 mg and Helixor A 100 mg was measured using the Bradford[6] assay. We measured an average amount of 205.2 ng/ml of lectin from blind-tested five ampoules of Abnobaviscum F 20 mg (Table 4).

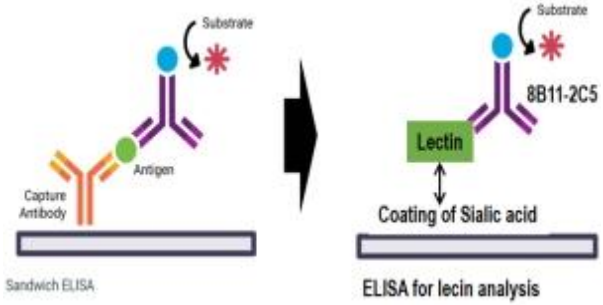

Figure 4. ELISA Analysis Measuring Lection of VAE, Abnoba 20 mg.

Based on this finding, we assumed that the maximum safe amount of lectin that can be administered to a patient on the day eight ampoules of Abnobaviscum F 20 mg are injected for intratumoral injection is 1642 ng/ml.

Table 3. The lectin amount concentration after 54-fold dilution of one ample of Abnoba 20mg (Two-Site Sandwich ELISA, Bradford Assay) by Park & Yoon (2023)

AbnobaViscum 20mg® Sample	N1	N2	N3	N4	N5
Mean Lectin (ng/ml)	201.8	214.8	195.0	201.2	213.2
SD	+/- 0.1	+/- 6.7	+/- 2.8	+/- 1.3	+/- 19.8

Results

We share the outcomes of our study that involved multiple intratumoral injections of *Viscum album* into a large chondrosarcoma mass. Our primary goals were to improve the patient's life expectancy, enhance their quality of life by decreasing tumor burden, and examine the direct antitumoral impact of *Viscum album* on connective tissue cancers, such as chondrosarcoma. We conducted our intratumoral injection and simultaneous intravenous injection treatments using VAE so that we could evaluate VAE therapies' effectiveness independently, excluding chemotherapy and other therapeutic factors.

We observed clinical effectiveness in the large tumor of advanced chondrosarcoma through treatments with intratumoral injections with VAE, reducing tumor mass by over 70%. Certainly, there was a remarkable decrease in the externally grown tumor mass where we performed intratumoral injections, but not until internal increased tumor extension in the lung cavity.

The patient well tolerated a dose of up to 160mg of Abnoba F 20 mg. This treatment increased the patient's life expectancy from less than a month to 11 months. It was demonstrated that intratumoral injection treatment with VAE for chondrosarcoma may be a viable option during the course of treatment from the beginning. To the best of our knowledge, this is the first report about treating chondrosarcoma and even large chest wall chondrosarcoma with VAE intratumoral injections experiencing partial regression.

Discussion

Lectin-inducing apoptosis of *Viscum album* is well known.[1] Several case reports about intratumoral applications of VAE showed durable remission in different types of cancer (cutaneous squamous cell carcinoma, adenoid cystic carcinoma, breast cancer, Merkel-cell carcinoma, cutaneous B-cell lymphoma, and malignant melanoma.[12] Many authors reported that the high cytotoxic, apoptotic, and immunologic properties of VAE may have been pivotal in inducing the remissions in intratumoral injections.[9,11,13]

This case of chondrosarcoma tumor was reduced significantly by VAE intratumoral injections and aspirations weekly. We suppose that the entire amount of lectin and viscotoxin injected into a large tumor mass may contribute to destroying cancer cells and vessels in connective tissues and that the amount of those is not absorbed wholly into the bloodstream. Further research on the blood concentration of lectin and viscotoxin, while we do intratumoral injections to large malignant tumors, is needed to set a tolerated maximum dose of *Viscum album* intratumorally.

The declined tumor induced improving this patient's general symptoms, chronic inflammation, malignant cachexia, and breathing difficulty. Clearly, the patient's survival period was extended. The patient's cause of death was an acute respiratory failure at home due to acute respiratory and cardiac failure in the cardio-pulmonary system by extensive tumor invasion into the pericardiac space, mediastinum, and main bronchus of this aggressive chondrosarcoma.

Surgical resection is undoubtedly necessary as a first-line treatment for chondrosarcoma. However, it is essential to note that even in cases where there is chondrosarcoma, regardless of first diagnosis or recurrence and tumor size, intralesional VAE therapy is supposed to affect tumor mass necrosis and provide a higher potential of curing when used in conjunction with resection and chemotherapy and radiation.

Conclusion

We observed the tumor cell necrosis and death of chondrosarcoma by intratumoral injections high-dose AVE. It was demonstrated that intratumoral injection treatment with VAE for chondrosarcoma may be a viable option for treating this kind of tumor. Even chondrosarcoma, a very resistant to conventional therapies, was observed to cause significant tumor regression due to the dose-dependent effects of VAE with up to 1,642 ng/ml of lectin amount of VAE at once for intratumoral injection. The quantified lectin content of Abnobaviscum F 20 mg is to contribute to setting the standard for maximum usage of intratumoral injection for achieving tumoral regression by apoptosis-induced cell death and clinical safety.

Acknowledgement

We remember and express our gratitude to this patient, who showed courage and love for living beautifully until the end of his life. We are deeply grateful to Nam Sang-Ok, Chairman of LB Bridge Co. Ltd., for his encouragement and cooperation in completing this study and presenting it at the 8th Mistletoe Symposium.

Funding

None

Conflicts of Interest

This study has no conflict of interest with the German manufacturers of the mistletoe products (Abnoba GmbH and Helixor Heilmittel GmbH), nor with the pharmaceutical companies in South Korea (LB Bridge and Dalim Biotech). The choice of Abnobaviscum F and Helixor A as therapeutic drugs was made based on the doctor's clinical judgment.

References

1. Büssing A, Schietzel M. Apoptosis-inducing properties of *Viscum album* L. extracts from different host trees, correlate with their content of toxic mistletoe lectins. *Anticancer Res*. 1999 Jan-Feb;19(1A):23-28.
2. Carrie Y Inwards, Jodi M. Carter and André M. Oliveira Diagnostic Histopathology of Tumors, Chapter 25, 2002-2066.
3. Dierselhuis EF, Gerbers JG, Ploegmakers JJW, et al. Local treatment with adjuvant therapy for central atypical cartilaginous tumors in the long bones. *Journal of Bone and Joint Surgery*. 2016;98(4):303-313.
4. Gelderblom H, Hogendoorn PCW, Dijkstra SD, et al. The clinical approach towards chondrosarcoma. *The Oncologist*. 2008;13(3):320-329.
5. Hajtó T, Hostanska K, Berki T, et al. Oncopharmacological perspectives of a plant lectin (viscum albumagglutinin-I): Overview of recent results fromin vitroexperiments andin vivoanimal models, and their possible relevance for clinical applications. *Evidence Based Complementary and Alternative Medicine*. 2005;2(1):59-67.
6. Majeed M, Hakeem KR, Rehman RU. Mistletoe lectins: From interconnecting proteins to potential tumour inhibiting agents. *Phytomedicine Plus*. 2021;1(3):100039.
7. Mavrogenis AF, Angelini A, Drago G et al. Survival analysis of patients with chondrosarcomas of the pelvis. *Journal of Surgical Oncology*. 2013;108(1):19-27.
8. Meftah M, Schult P, Henshaw RM. Long-term results of intralesional curettage and cryosurgery for treatment of low-grade chondrosarcoma. *The Journal of Bone and Joint Surgery-American Volume*. 2013;95(15):1358-1364.
9. Orange M, Fonseca M, Lace A et al. Durable tumour responses following primary high dose induction with mistletoe extracts: two case reports. *Eur J Integr Med*. 2010;2:63-69.
10. Schwab JH, Wenger D, Unni K et al. Does local recurrence impact survival in low-grade chondrosarcoma of the long bones? *Clin Orthop Relat Res*. 2007;462:175-80.
11. Werthmann PG, Helling D, Heusser P et al. Tumour response following high-dose intratumoural application of *Viscum album* on a patient with adenoid cystic carcinoma. *BMJ Case Rep*. 2014;31:2014:bcr2013203180.
12. Werthmann PG, Huber R, Kienle GS. Durable Clinical Remission of a Skull Metastasis under Intralesional *Viscum album* Extract Therapy: Case Report. *Head & Neck*. 2018;40(7):E79.
13. Werthmann PG, Sträter G, Friesland H, et al. Durable response of cutaneous squamous cell carcinoma following high dose peri-lesional injections of *Viscum album* extracts -- a case report. *Phytomedicine*. 2013;20:324-327.