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말기 유방암 환자에 대한 다기관 공개적 임상시험 (ABNOBAviscum Fraxini®)

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초록

말기 유방암 환자 26명을 대상으로 9개 이집트 종양학 센터에서 Viscum Fraxini 2 치료를 시행하였다. 대상 환자들은 표준 항암치료 방법 (외과적, 방사선 요법, 화학요법, 호르몬 치료)으로 치료가 되지 않은 환자들로서 다양한 정도의 증상을 가지고 있었다. 그리고 이 환자들은 모두 6개월 이상의 생존 예후를 가지고 있었다.

Viscum Fraxini 2 (30,000ng)을 원발성 및 재발성 유방암 병소 내와 종양 주위 부위에 피하주사 하였다. 임상검사와 이학적 검사를 매주 1회 시행하였으며 치료 기간동안 진통제나 수면제 투여를 하지 않았다. 일반적인 임상평가 종료시기는 16주이었으나 18명 환자에서는 18-136주간 장기 치료를 시행하였다. 16주 치료 후에 총 26명 환자 중 16명에서 반응이 관찰되었다 (61.5%). 반면 최대 136주까지 16주 이상 투여한 환자 18명중 14명에서 치료에 대한 반응이 관찰되었다 (77.8%). 그리고 여성의 폐경기를 전후한 두 연령군 사이에 치료효과의 유의한 차이가 발견되지 않았다.

Key words: Viscum Fraxini, 후기와 말기 유방암 환자에서 고식적 치료 임상효과

서론

지구상의 모든 형태의 생명체는 자연자원 및 환경과 평형을 이루고 존재한다. 고대 이집트 시절 이미 인간과 동물의 건강유지에 유용한 자연산물과 그 역할에 대하여 많은 발견이 되었으며 많은 정보가 축적되어 있었다.

최근 빈카 알칼로이드와 다른 많은 식물들로부터 현재 사용되는 악성 종양 치료 요법의 기본이 되는 많은 항암 약물들이 개발되었다. 이 분야에서 새로이 각광을 받고 있는 약물이 Viscum album이다.

Viscum album은 다양한 종류의 숙주나무에서 성장하는 반기생 (半寄生)식물로서 유럽에서 자생하는 미슬토과(科)에 속하는 속(屬) 중 가장 잘 알려진 식물이다[1]. 1920년에 Steiner는 미슬토의 항암효과를 처음으로 보고하였다[51]. Viscum Album은 미슬토의 수용성 추출물로서 순수한 막성분 (엽록체 세망 내피계, 골지체 등의

막성분)으로 이루어진 소포체(小胞體; vesicle)를 추출하기 위해 고도의 정밀기술을 이용하여 제조된다[11,29].

약리학적 고찰

조성:

- **렉틴 (lectin)**은 당단백질로서 수용성 미슬토 추출물에는 3가지 렉틴 성분이 존재하며 (ML-1, ML-2, ML-3) 각기 A 사슬 (독성을 지닌 구조)과 B 사슬 (당결합 구조)로 구성되며 2개 사슬의 분자량은 각각 62 kd, 86 kd 이다. 렉틴은 RNA-N-glycosidase 활성에 의해 단백질 합성을 억제한다.
- **다당류**와 **올리고당**은 D-galactouronane의 유도체이다. 미슬토 다당류는 NK 세포를 활성화한다[21,26,33,34,35,59].
- **Viscotoxin**은 분자량이 5 kd인 크기가 작은 염기성 단백질이다[37-39,45-47]. Scheller 등 (1995)은 막파괴 기전으로 세포독성을 유도하는 5가지 viscotoxin을 서술하였다[37,38,39, 40,45,46,47].
- **소포체**는 리포좀 (liposome)과 유사한 구조물로서 순수한 막으로 구성되며 직경이 150 nm이다[41]. 소포체는 T 세포, 특히 helper 세포의 증식을 촉진하며 또한 활성화 한다[2].

작용기전:

- **면역조절 효과**: 미슬토 추출물은 시험관 내 및 생체 내에서 모두 면역조절 효과를 나타낸다. 렉틴과 미슬토 추출물이 IL-1, IL-6, TNF-α , IFN-γ 및 IL-2 등의 cytokine들의 분비를 촉진하는 것이 보고되어 있다[2,3,6,15-20,32,34]. 올리고당 및 다당류는 시험관 내에서 NK 세포 활성을 향상시키는 효과를 나타낸다[21,24,33,35,59]. 미슬토 추출물 처리를 한 암환자의 B 임파구는 미슬토 렉틴에 대한 항체를 형성하여 렉틴에 의해 유도되는 세포독성을 중화할 수 있다[52,57]. 또한 Viscum album은 시험관 내에서 미슬토 치료를 받는 암환자에서 채취한 임파구의 증식을 자극한다[4,10,48,49,50,58]. 미슬토의 전추출물과 소포체는 올리고클론성 T-helper 세포 증식을 유도한다[12,59]. 그리고 T-helper 세포 증식과 관련하여 렉틴과 소포체 사이에 상승효과가 관찰된다[10,44].
- Viscum Fraxini는 백혈병 환자에서 채취한 배양 T-ALL 세포와 B-CLL 세포를 억제하지만 저친화성 (low affinity) interleukin 2 수용체나 트랜스페린 수용체 (transferrin receptor)의 발현을 유도하지 않는다[6]. 이러한 사실은 미슬토 렉틴이 인체 중성구에서 superoxide 분비를 유도하는 것을 의미한다[53].
- 숙주 방어 기전에 중요한 역할을 하는 superoxide 생성 감소는 대부분의 암환자에서 관찰된다[54].
- **β-엔돌핀 분비**: 미슬토 추출물로 21주간 치료한 유방암 환자에서 β-엔돌핀

분비가 관찰된다[22]. 미슬토 추출물 투여 후에 관찰되는 β-엔도르핀의 혈장농도 증가는 암환자의 통증 감소와 생활의 질 향상과 연관되어 있다. 면역학적 효과와 직접적인 종양세포 독성효과는 인체에서도 증명된 바 있다[22,28,30,43,56].

- **세포독성효과**: 미슬토 추출물은 종양세포의 성장을 (용량 의존성으로) 정지시킨다[6,13,14,23,30,31,36,42,55]. 이러한 성장 억제는 렉틴에 의한 세포소멸[5,7,25]과 viscotoxin에 의한 세포괴사의 유도에 기인한다. 직접적인 세포독성 효과가 생체 내에서 증명된 바 있다[8,43,56].

연구목적:

본 연구는 공개적 다기관 임상시험으로서 Viscum Fraxini 2의 임상적 평가를 주요 목적으로 하였다:

1. 유방암 (원발성, 재발 및 전이성)에 대한 암세포 제거 효과
2. 16주 치료 후의 임상 반응과 일부 환자에서 16주에서 136주간 투여한 후의 임상반응

실험 방법

유방암 환자 26명을 대상으로 하였으며 이중 11명은 폐경기 전 여성이며 15명은 폐경기를 지난 여성으로 구성되었다. 상기 환자군중 11명은 간, 폐, 골격, 임파절 및 피부 부위로 암 전이를 가지고 있었다 (표 1).

환자 선정:

1. KPS 가 70% 이상인 환자
2. 예상 생존일이 6개월 이상인 환자
3. 표준 항암요법 (수술요법, 방사선 치료, 화학요법 및 호르몬 요법)으로 치료가 되지 않은 환자
4. 모든 연령군
5. 임상검사, 암의 단계 결정, 흉부 X-ray 촬영, 혈액학적 및 생화화적 검사를 포함하는 완전한 임상 평가와 병리조직학적 확진을 받은 증례로서 매주 임상검진을 받는 환자

용량과 투여 방법:

Viscum Fraxini 2단계 3ml (30,000 ng)를 피하 주사하여 원발성 유방종양 부위 내와 주위에 피하주사 또는 종양 내 직주로 매주 일회 투여하였다.

진정제, 마약성진통제, 비스테로이드 소염제 (NSAIDs), 아스피린 및 항생제를 임상시험 기간 중 투여하지 않았다. 치료와 연관되어 발생하는 24-48시간 지속되는 발열 (38-39℃)을 환자가 견디지 못할 경우에는 paracetamol을 저용량 투여하였다.

국소부위 반응을 조절하기 위해 냉습포를 처방하였다.

표준 평가 종료점은 16주이었으나 18증례에서는 치료를 계속하여 18주에서 136주간 치료를 계속하였다.

결과와 고찰

치료군중 26명은 16주간 투여 후 치료효과를 평가하였으며 이중 11명은 폐경기 전 여성이고 15명은 폐경기가 지난 여성이었다. 폐경기 전 환자에서 17-90%의 종양 크기 감소가 관찰되었으며 그 반응 정도가 다양하였다. 그러나 완전 관해 (complete regression)는 관찰되지 않았으며 6명에서 부분관해, 4명은 변화가 없었으며 1명에서 종양이 더 진행되었다 (표 2).

폐경기 후 환자에서는 17-100%의 종양 크기 감소가 관찰되었다. 그러나 2명에서 완전관해가 관찰되었으며 8명에서 부분관해, 5명은 변화가 없었으며 종양이 더 진행된 환자는 한 명도 없었다. (표 3).

상기 결과로부터 Viscum Fraxini 치료의 임상효과가 폐경기 전 여성 (6/11; 54.5%)과 폐경기 후 여성 (10/15; 66.67%) 사이에 유의한 차이가 존재하지 않는 것을 알 수 있다.

즉 종양의 특성은 폐경기와 무관하며 Viscum의 면역조절 효능이 폐경기에 의해 영향을 받지 않는다고 추론할 수 있다.

16주 치료 후에 상기 환자군을 종합한 총 반응률은 61.53% (16/26)이었다 (표 1). 그러나 16주 이상 치료를 지속하여 18주에서 136주에 걸치는 치료를 받은 환자군에서 총 반응률은 77.78% (14/18)이었다 (표 4). 장기 치료군 환자들에서 2명은 원발암의 완전관해, 12명은 부분관해, 4명은 변화가 없고 종양이 더 진행된 환자는 한 명도 없었다.

장기 치료군 환자 18명 모두에서 치료기간이 18주에서 136주까지 큰 차이에도 불구하고 다소간의 질병의 관해가 관찰되었다. 그러므로 Viscum의 면역조절 및 세포독성 효과는 16주 이상의 장기 투여를 하여야 발현되는 것으로 판단된다. 또한 이러한 실험결과는 Viscum의 면역조절 및 세포독성 효과를 보여주는 것으로서 다른 표준 항암요법의 보조약물로서의 Viscum의 가능성을 부여한다.

16주 이상 투여한 장기 치료군 환자 중 11명은 이미 다른 장기로의 암 전이가 관찰된 환자였다 (표 5). 폐 전이암 환자 3명은 모두 폐경기 전 여성으로서 1명은 완전관해, 2명은 부분관해가 관찰되었다.

골 전이암 환자중 3명은 폐경기 전 여성으로 Viscum 치료 효과가 나타나지 않았지만 폐경기를 지난 1명의 환자에서 골 전이암이 소멸되었다.

폐경기가 지난 2명에서 간 전이암이 완전 소멸되었다. 임파절 전이가 발견되는 폐경기가 지난 5명 환자에서 전이암이 완전히 소멸되었다. 1명의 환자는 66주의 치료 후에 뇌전이가 나타났다.

본 연구의 대상환자 수가 적음에도 불구하고 상술한 결과는 Viscum의 암세포 박멸효과가 골 전이암보다는 연체조직 전이암에 대해 더 효과적인 것을 시사하며 이러한 치료효과가 폐경기 전 여성보다 폐경기를 지난 여성에서 더 현저한 것을 알 수 있다.

증례 4는 70세를 넘은 고령 환자로서 $T_4N_2M_0$ 궤양성 선암 (腺癌; adeno-carcinoma)을 가졌으며 Viscum 치료 전에는 수술을 시행할 수 없는 상황이었다. 16주간 Viscum 투여를 시행한 결과 $T_2N_2M_0$ (궤양의 완전한 치료; 그림 1)으로 전환되었으나 여전히 수술이 불가능한 상태이었다. Viscum 치료 28주 후에 $T_2N_0M_0$ 으로 전환되었으며 수술을 성공적으로 시행할 수 있었다 (그림 2). 유감스럽게도 수술 후 절제조직의 조직병리학적 검사가 시행되지 않았다. 이 환자는 주당 유지용량으로 1 ml Viscum (10,000 ng) 피하주사를 136주간 계속하며 생존하고 있다.

치료에 따른 생활의 질 향상은 1998년 4월 30일에 시행된 다양한 말기 암환자 30명을 대상으로 한 이전 연구 결과와 동일한 양상을 나타내었다 (행동 능력, 통증, 식욕 및 수면의 10-30% 향상).

주의사항: 치료환자에서 WHO가 규정한 어떠한 독성 부작용도 관찰되지 않았다.

결론

이상의 임상적 및 이학적 검사 결과로 보아 Viscum이 종양세포 소멸 효과를 보이는 것을 확인할 수 있었으며 유방암 환자의 총 반응률이 폐경기 후 여성에서 54.5%(6/11)이었다. 이러한 연령에 따른 총 반응률의 차이는 통계적으로 유의하지 않았으며 이는 Viscum의 치료효과가 호르몬 상태와 관련이 없음을 의미한다.

16주 치료 후 상기 2개 연령군의 총 반응률은 61.53% (16/26)이었으며 16주 이상 (18-136주) 장기 치료를 계속한 환자군에서 77.78% (14/18)이었다. 이것은 치료 기간이 16주 이상일 경우 면역조절 효과와 세포독성 효과가 증가하는 것을 시사한다.

이상의 결과를 종합하면 Viscum을 표준 항암 치료 방법에 대한 보조 요법으로 사용할 수 있다고 사료된다.

표 1. Viscum Fraxini® 2의 16주간 투여 시 26명 환자의 유방암 병소 (원발성 및 잔재성) 반응

환자	반 응				종양 크기 변화율%
	총반응		무변	진행	
	완전관해	부분관해			
1		+			67
2		+			89
3		+			67
4		+			89
5		+			98
6		+			87
7		+			96
8		+			73
9		+			56
10			+		44
11			+		40
12			+		17
13			+		34
14				+	진행
15			+		17
16			+		44
17		+			73
18	+				100
19		+			94.5
20			+		무변
21		+			53
22		+			82
23			+		무변
24	+				100
25		+			97.5
26			+		44
합계	2	14	9	1	
16/26=61.53%					

총반응율 : 61.53% = 16/26명(완전관해 2명, 부분관해 14명)
무변 : 34.70% = 9/26명, 진행 : 3.77% = 1/26명

표 2. Viscum Fraxini 2 투여로 16주 치료한 폐경기 전 유방암 환자 11명의 원발성 유방암 병소 혹은 잔류질병의 치료 반응

환자	크기 변화율 (%)	종양 반응			
		전체 반응		무변	진행
		완전관해	부분관해		
1	67		+		
2	89		+		
6	87		+		
7	96		+		
8	73		+		
13	34			+	
14	증가				+
15	17			+	
20	무변			+	
21	53		+		
26	44			+	
총합		0	6	4	1
총반응률 6/11 = 54.5%					

총반응 : 54.5% = 6/11명(부분관해 6명)

무변 : 36.5% = 4/11명, 진행 : 9.0% = 1/11명

표 3. Viscum Fraxini 2 투여로 16주 치료한 폐경기 후 유방암 환자 15명의 원발성 유방암 병소 혹은 잔류질병의 치료 반응

환자	종양 반응			
	전체 반응		무변	진행
	완전관해	부분관해		
3		+		
4		+		
5		+		
9		+		
10			+	
11			+	
12			+	
16			+	
17		+		
18	+			
19		+		
22		+		
23			+	
24	+			
25		+		
총합	2	8	5	0
총반응률 10/15 = 66.5%				

총반응 : 54.5% = 6/11명(부분관해 6명)
무변 : 36.5% = 4/11명, 진행 : 9.0% = 1/11명

표 4. Viscum Fraxini 2 투여로 16주 이상 (18-136주) 치료한 유방암 환자 18명의 원발성 유방암 병소 혹은 잔류질병의 치료 반응

환자	환자군	치료 기간 (주)	크기 변화율 (%)	종양 반응			
				전체 반응		무변	진행
				완전관해	부분관해		
1	폐경기전	23	67		+		
2	폐경기전	23	56		+		
3	폐경기후	132	98.8		+		
4	폐경기후	132	96		+		
5	폐경기후	136	99.4		+		
6	폐경기전	64	94.5		+		
7	폐경기전	38	98		+		
8	폐경기전	18	73		+		
9	폐경기후	24	72		+		
10	폐경기후	20	44			+	
11	폐경기후	27	40			+	
18	폐경기후	62	100	+			
21	폐경기전	22	53		+		
22	폐경기후	25	81		+		
23	폐경기후	29	무변			+	
24	폐경기후	48	100	+			
25	폐경기후	32	98.75		+		
26	폐경기전	134	44			+	
총합	18			2	12	4	0
총반응률 14/18 = 77.78%							

총반응 : 77.78% = 14/18명(완전관해 2명,부분관해 8명)

무변 : 22.22% = 4/18명, 진행 : 없음

표 5. Viscum Fraxini 2를 16주 이상 (18-136주) 투여한 11명 유방암 환자에서의 전이암 병소 치료반응

환자 #	환자군	연령	치료기간 (주)	전이부위	치료결과
1	폐경기전	32	23	폐	소실
2	폐경기전	45	23		골 전이 출현
3	폐경기후	60	132	임파절 종괴	소실
4	폐경기후	70	132	임파절 종괴	소실
5	폐경기전	60	136	임파절 종괴	소실
7	폐경기전	43	38	폐	크기 감소 골 전이 출현
11	폐경기후	48	27	뼈,간	소실
18	폐경기후	54	62	간	감소 골 전이 출현
21	폐경기전	48	22	폐	감소 골 전이 출현
24	폐경기후	55	48	임파절 종괴	소실
25	폐경기후	70	38	임파절 종괴	소실

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Multicenter Open Labeled Clinical Study in Advanced Breast Cancer Patients. A Preliminary Report

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ABSTRACT

26 patients of advanced breast cancer from 9 Egyptian oncology centers received Viscum Fraxini 2 (V.F.2).

All patients had exhausted all other lines of treatment (surgical, radiotherapy, chemotherapy, and hormonal therapy). And were complaining of various degrees of severity of symptoms. Those patients had a life expectancy not less than 6 months.

V.F 2 was given through subcutaneous injection of 30,000 ngm around or/and intralesional in the site of the primary or recurrent breast lesions.

The clinical and laboratory examinations were conducted once weekly. During the treatment trial no pain controlling or sleeping drugs were used. The end point of assessment was 16 weeks, however 18 cases continued treatment by Viscum for different periods (18-136 weeks). The total response rate (TRR) at the end of 16 weeks of treatment was 16/26 (61.5%) while TRR of cases that continued the treatment more than 16 weeks up to 136 weeks showed an average of 14/18 (77.8%). No TRR difference was noted between pre-and post-menopausal cases.

Key words : *Viscum Fraxini – Advanced breast cancer – Palliation.*

INTRODUCTION

All forms of life on our planet have been in equilibrium between natural resources and environment.

The ancient Egyptian, the Arab's of the medieval ages have contributed a lot of in-formation about the use of natural products and their role in maintaining health of man and animal.

In recent times, Winka alkaloids and many other plants provided the therapeutic list of anticancer compounds with series of drugs that are the basis of many protocols of treatment in malignant diseases. A new comer in this field is Viscum album.

Viscum album is a semiparasitic plant growing on different host trees. It is the best known genus of mistletoe family growing in Europe [1]. In 1920, Steiner recommended the mistletoe as a remedy against cancer [51]. Viscum Fraxini is an aqueous extract of mistletoe (Viscum album L. growing on the ash tree) prepared with a highly sophisticated technology using a machine to get vesicles of genuine membrane systems (Membranes of the chloroplasts, endoplasmic reticulum, golgi apparatus, etc) in the extract [11,29].

Pharmacological Aspects:

Composition:

- Lectins are glycoproteins, aqueous mistletoe extract contains 3 lectins (ML-1, ML-2 and ML-3). Lectins inhibit the protein synthesis because of their RNA-N-glycosidase activity [9].

- Polysaccharides oligosaccharides are essentially derivatives of D-galactouronanes. Mistletoe polysaccharides activate NK cells [21,26, 33,34,35,59].

- Viscotoxins are small basic protein with a molecular weight of 5KD [37-39,45-47]. Scheller et al. (1995) showed five different viscotoxins [37,38,39.40,45,46,47] which induce cytotoxicity by membranolysis.

- Vesicles are liposome-like bodies with a diameter of about 150 mm formed by genuine

membrane systems [41]. They enhance T-cell proliferation especially helpr cells [2]. and their activation.

Mode of action:

Immunomodulatory Effects: Mistletoe extract is immunemodulating in vitro and in vivo. It was demonstrated that lectins and mistletoe extract induced the release of cytokines like IL-1, IL-6, TNF-α, INF-γ and IL2 [2,3,6,15-20, 32,34]. Oligo- and polysaccharides activate the NK in vitro [21,24,33,35,59]. B-cells lymphocytes of cancer patients treated with mistletoe extract produce antibodies against mistletoe lectins, neutralizing lectininduced cytotoxicity [52, 57].Viscum Fraxini stimulates in vitro the proliferation of lymphocytes from mistletoe-treated cancer patients [4,10,48,49,50,58]. The whole extract and the vesicles induce an oligoclonal T-helper cell prolifiration [12,59]. Synergistic effects were measured with lectins and vesicles in relation to T-helper cell proliferation [10,44].

Viscum Fraxini inhibits cultured leukemic T-ALL cells and B-CLL cells with no induction of low affinity interleukin 2 receptor or transferrin receptor expression [6]. This indicates that mistletoe lectin induces superoxide release from human neutrophils [53]. Decreased superoxide production was found in most cancer patients and superoxide is important in host defense [54].

β-endorphins release: Breast cancer patients teated with mistletoe extract for 21 weeks showed increase in β-endorphin realease [22]. The increased levels of plasma β-endorphin after mistletoe administration are correlated with decreased pain and improved quality of life. The immunological and direct tumor cytotoxic data were also verified in humans [27,28,30,43, 56].

- Cytotoxic Effects: Mistletoe extract stops (dose dependent) the growth of tumor cells [6,13,14,23,30,31,36,42,55]. This growth inhibition is caused by the induction of apoptosis due to lectins [5,7,25] and necrosis by viscotocxins. A direct cytotoxic effect was also shown in vivo [8,43,56].

Aim of the study:

The main objectives of this open labeled clinical multicenter trial on V.F.$_2$® is to continue the clinical evalutation of viscum on:

1- The clinical effects on the primary cancer breast lesions, recurent or metastatic lesions.

2- The clinical response at 16 weeks end- point as well as to report on some cases who received the drug for more than 16 weeks up to 136 weeks.

PATIENTS AND METHOD:

26 breast cancer patients, 11 patients were premenopausal and 15 patients were postmenopausal as well as 11 patients of this group presented with hepatic, pulmonary, osseous, lymph nodes and skin metastasis (Table 1).

Table (1): The response of primary breast lesions or residual disease in 26 breast cancer patient treated with VISCUM Fraxini® 2 for 16 weeks.

Pat. S. No.	Tumor Response: Total Response C.R.	Total Response P.R.	Stationary	Progression	*Tu. size change ratio%
1		+			67
2		+			89
3		+			67
4		+			89
5		+			98
6		+			87
7		+			96
8		+			73
9		+			56
10			+		44
11			+		40
12			+		17
13			+		34
14				+	Prog.
15			+		17
16			+		44
17		+			73
18	+				100
19		+			94.5
20			+		Stationary
21		+			53
22		+			82
23			+		Stationary
24	+				100
25		+			97.5
26			+		44
T. No.	2	14	9	1	
	16/26=61.53%				

TRR : 61.53% = 16/26 Patients (2 CR, 14 PR)
STATIONARY : 34.70% = 9/26 Patients
PROGRESSION :3.77% = 1/26 Patient
* Tumor Size change: tumor size before treatment with Viscum and at wk 16 treatment.

Criteria of eligibility:

1- Patients should have more than 70% Karnofisky Peroformonce scale.

2- Expected life span is not less than 6 months.

3- Patients who exhausted all othe lines of orthodox treatment (surgery, radiotherapy, chemotherapy, and hormonal therapy).

4- Any age group.

5- All patients had pathological verification of their disease as well as a complete clinical work-up including clinical examination, staging, X-Ray chest, blood, biochemical profiles and frequent weekly clinical assessments

Dose and method of administration:

Three ml. (30.000 ngm) of V.F. $_2$® were injected subcutaneously around the site of the primary breast tumor, intratumorally or both, once a week.

No sedatives, narcotics, NSAIDs, acetylsalicylic acid preparations or antibiotics were given during the trial period. Paracetamol was given only in low dose if the patients could not bear the associated pyrexia (38-39°C) for 24-48 hrs. Local cold foments were also prescribed to control local cutaneous reaction.

The assessment end point was 16th week. Eighteen patients continued treatment to longer periods from 18 to 136 weeks.

RESULTS AND DISCUSSION

26 patients, who were assessed at the 16th week treatment, 11 were premenopausal and 15 were postmenopausal. The premenopausal patients showed regession at different degrees of the tumor size from 17-90 % However, none showed complete regression (C.R.), 6 patients showed partial regression (P.R.), 4 patients were stationary and 1 patient showed progression (Table 2).

The postmenopausal patients showed regression at different degrees of the tumor size from 17-100%. However 2 patiens showed C.R., 8 patients showed P.R., 5 patients were stationary and none showed progression (Table 3).

Comparing the clinical response (TRR) of Viscum on premenopausal (6/11= 54.5%) and postmenopausal (10/15- 66.67%) patients, one has to admit that these results showed no appreciable difference between the response rates of the two groups.

It is possible to deduce that the biological behavior of the tumor being pre- or postmenopausal does not affect the efficacy of the immunomodulatory function of Viscum.

All patients were assessed at the 16th week of treatment with TRR 16/26 (51.53%), (Table 1), however 18 patients continued treatment for longer periods and were assessed at intervals ranging between 18 to 136 weeks showed TRR 14/18 (77.78%), (Table 4). The results of observation of this group of patients were: 2 patients showed C.R in the primary tumor, 12 patients showed P.R, 4 patients stationary and none showed progression.

In spite of the different observation intervals, all the 18 patients showed regression of the disease. It seems most probably that the immunomodulatory and cytotoxic effects of Viscum need a longer treatment period than 16 weeks. Furthermore , this observation indicates the immunomodulatory and cytotoxic effects of Viscum, which would suggest its adjuvant role if added to other classical methods of treatment.

Out of this particular group, who continued treatment after 16 weeks, 11 patients were suffering from metastasis in different organs (Table 5). Lung metastasis 3 patients: 1 patient showed complete resolution and the other 2 patients, lung deposits decreased in size, all 3 patients were premenopausal.

Bone metastasis did not resolve, in the contrary other lessons appeared under Viscum treatment in 3 premenopausal patients. However, bone metastasis disappeared in one postmenopausal patient.

Hepatic metastasis was found in 2 patients who were postmenopausal and completely disappeared under treatment. Lymph nodes metastasis were found in 5 patients who were postmenopausal and completely disappeared. One postmenopausal patient had had brain metastasis after 66 weeks of Viscum injection.

In spite of this small number of patients in the series, this observation may lead to the assumption that the efficacy of Viscum cancericidal effect is more efficient in soft tissue metastasis than bone metastasis, and this efficacy is more apparent in postmenopausal than in premenopausal patients.

It is noteworthy that patients No. 4, who was over 70 years and had $T_4N_2M_0$ ulcerative adenocarcinoma was inoperable before Viscum treatment, rendered after 16 weeks of treatment by Viscum $T_2N_2M_0$ (ulcer heald completely, Fig. 1), however still inoperable, after 28 weeks of Viscum treatment became $T_2N_0M_0$ and operated upon successfully (Fig. 2). This patient is still living after 136 weeks on mintenance dose 1 ml. (10.000 ngm) Viscum sc. weekly.

Quality of life (QOL) has followed the same patteren observed in 9 previous study (improvement 10 - 30% of performance status, pain, ap-

petite, and sleep), of 30 cases of different advanced malignancy, done on 30/4/1998.

N.B.: No toxic side effects had been reported in the treated patients.

Table (2): The response of primary breast lesions or residual disease in 11 premenopausal breast cancer patients treated with VISCUM Fraxini® 2 for 16 weeks.

Pat. S. No.	Tumor Response: Total Response C. R.	Total Response P. R.	Stationary	Progression	*Tu. Size change Ratio%
1		+			67
2		+			89
6		+			87
7		+			96
8		+			73
13			+		34
14				+	Prog
15			+		17
20			+		Stationary
21		+			53
26			+		44
T. No.	0	6	4	1	
	6/11=54.5%				

TRR : 54.5% = 6/11 Patients (no CR, 6 PR)
STATIONARY : 36.5% = 4/11 Patients
PROGRESSION : 9.0% = 1/11 Patient
* Tumor Size change: Tumor size before treatment with Viscum and at wk 16 treatment.

Table (3): The response of primary breast lesions or residual disease in 15 postmenopausal breast cancer patients treated with VISCUM Fraxini® 2 for 16 weeks.

Pat. S. No.	Tumor Response: Total Response C. R.	Total Response P. R.	Stationary	Progression	*Tu. Size change Ratio%
3		+			67
4		+			89
5		+			98
9		+			56
10			+		44
11			+		40
12			+		17
16			+		44
17		+			73
18	+				100
19		+			94.5
22		+			82
23			+		Stationary
24	+				100
25		+			97.5
T. No.	2	8	5	0	
	10/15=66.5%				

TRR : 66.6% = 10/15 Patients (2 CR, 8 PR)
STATIONARY : 33.33% = 5/15 Patients
NO PROGRESSION
* Tumor Size change: Tumor size before treatment with Viscum and wk 16 treatment.

Table (4): The response of primary breast lesions or residual disease in 18 postmenopausal breast cancer patients treated with VISCUM Fraxini® 2 for more than 16 weeks (18 - 136 wks).

Pat. S. No.	Group	Treat. interv. in weeks	Tumor response: Total response C. R.	Total response P. R.	Stationary	Progression	*Tu. Size change ratio%
1	Pre	23		+			67
2	Pre	23		+			56
3	Post	132		+			98.8
4	Post	132		+			96
5	Post	136		+			99.4
6	Pre	64		+			94.5
7	Pre	38		+			98
8	Pre	18		+			73
9	Post	24		+			72
10	Post	20			+		44
11	Post	27			+		40
18	Post	62	+				100
21	Pre	22		+			53
22	Post	25		+			81
23	Post	29			+		Stationary
24	Post	48	+				100
25	Post	32		+			98.75
26	Pre	134			+		44
T. No.	18		2	12	4	0	
			14/1.8=77.78%				

TRR : 77.78% = 14/18 Patients (2 CR, 8 PR) STATIONARY: 22.22% = 4/18 Patients NO PROGRESSION
*Tumor Size change: Tumor size before treatment with Viscum and for than 16 wks treatment.

Table (5): The response of metastatic lesions in 11 breast cancer patients treated with VISCUM Fraxini® 2 for more than 16 wks (18 - 136 wks).

Pat. S. No.	Group	Age	Treat. interv. in weeks	Metastatic site	Results in metastasis
1	Pre-menop.	32	23	Lung	Disappeared
2	Pre-menop.	45	23	-	Bone met. appeared
3	Post-menop.	60	132	L.N. masses	Disappeared
4	Post-menpo	70	132	L.N. masses	Disappeared
5	Pre -menop.	60	136	L.N. masses	Disappeared
7	Pre-menop.	43	38	Lung	Decreased in size but bone met. appeared
11	Post-menop.	48	27	Bone, Hep.	Disappeared
18	Post menop.	54	62	Hepatic	Decreased, but brain met appeared
21	Pre-menop.	48	22	Lung	Lung decreased & Bone met. appeared
24	Post-menop.	55	48	L.N. mass	Disappeared
25	Post-menop.	70	38	L.N. masses	Disappeared

Fig. (1): 70 years old female patient with inoperable carcinoma of left breast.

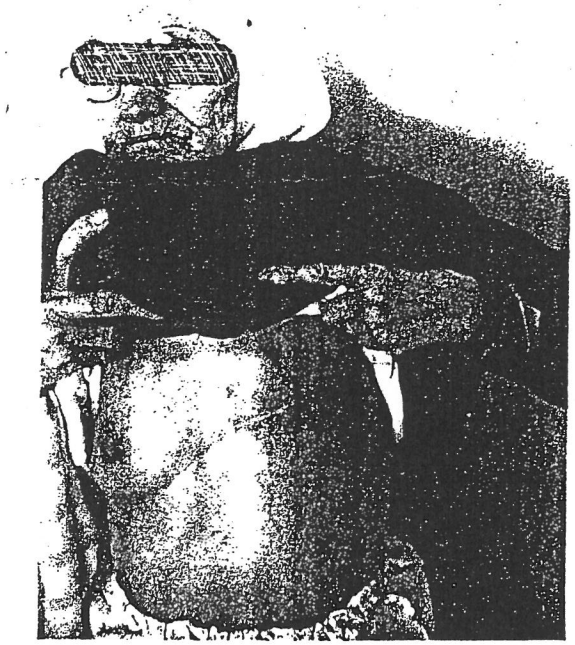

Fig. (2): Same patient after treatment by viscum for 28 weeks rendered operable.

Conclusion:

The clinical and laboratory results presented suggest that VISCUM may have a tumoricidal effect on the breast cancer patients with total response rate of 6/11 = 54.5% in postmenopausal patients. Such a difference in the total response of the low age groups indicates that hormone dependence had modest effect on Viscum action.

The total response rate of both groups at 16 weeks end point was 16/26 = 61.53% and in patients who continued the trial for more than 16 weeks (18-136 weeks), TRR was 14/18 = 77.78. This indicates that the immunomodulatory and cytotoxic effects of VISCUM is increased when the treatment period is longer than 16 weeks.

Accordingly VISCUM therapy has still to be examined for the possibility of its use as an adjuvant therapy to the classical therapeutic protocols.

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