



Breast Tumor Regression using Mistletoe Extract: An evidence from an Indian Clinic

*Sandeep Roy

MD (Practice of Medicine), AEMT (Germany), Rishikesh Hospital, Nashik

Email: dr_roysandeep@yahoo.com

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Abstract:

Mistletoe extract use in cancer patients is widely increasing with the upsurge of cancer incidence rates and reduction in survival time of patients. This study was designed to assess the tumor regression in breast cancer patients with the mistletoe extract. Subjects were designated from outpatient clinic at Rishikesh Hospital, Nashik, INDIA. After giving written informed consent, participants completed a self-administered questionnaire. Twelve patients with histologically confirmed breast cancer tumors of at least 2 cm in diameter received mistletoe extract in an ascending dosage. The tumour was again measured after six months to assess the therapeutic potential of mistletoe extract. The median size of the tumour decreased significantly, from 3.8 cm (range, 1 to 8 cm) to 2 cm (range, 0.1 to 4.8 cm; $P < 0.001$) on physical examination. Sonographic measurement revealed that, the tumour median size was significantly decreased from 3 cm (range, 0 to 8 cm) to 1.5 cm (range, 0 to 4 cm; $P < 0.001$). The area of tumour was significantly decreased on physical measurement and sonographic measurement ($P < 0.001$). The positive nodal status decreased from 66.6 to 41.6 percentages of patients. Mistletoe extract is highly effective and provides a feasible therapeutic option to the clinical oncologist in tumour regression of breast cancer.

Introduction:

Breast cancer is one of the most extensively prevalent cancer in women, which accounts almost 30 % of all cancers (Ries *et al.*, 2001). Breast cancer is the most common type of non-cutaneous malignancy in women in the United States (Greene *et al.*, 2002). Globally, US, India and China accounts almost one third of the breast cancer burden. In India, the incidence rate of breast cancer increasing rampantly. A statistical trend of breast cancer was compared in India with western nations like the US and with neighbour, China. In year 2012, the incidence to mortality ratio was high in India, almost three times higher than US and two times higher than China. The breast cancer burden in India has almost

reached about two third of that of the US and is steadily rising (IARC, 2012). Breast cancer survival is robustly associated with tumour size detection at initial stages of the disease (Okugawa *et al.*, 2005; Michaelson *et al.*, 2002; Jayasinghe *et al.*, 205). Taking into an account of various factors like physical, emotional, and financial impacts allied with disease, it is prudent to diagnose with greatest accuracy. Tumour size pivots a major role in determining disease-free and cause-specific survival in invasive breast cancer particularly, in cases of node-negative breast cancers.

Breast tumours are pathologically classified into groups for staging purpose, because accurate measurement of the tumour is decisive for management of best outcomes. Measuring tumour size is one of the most conventional technique for monitoring cancer development with response to treatment in oncology. Tumour size is measured by various methods including palpation on physical examination and breast-imaging studies such as mammography, sonography and MRI. In this present study, tumour size of patients before and after treatment was measured by physical examination and sonography.

Mistletoe extract is also known as European mistletoe (*Viscum album*) and used as cancer therapy based on anthroposophy (Steiner *et al.*, 1985). However, mistletoe extract is considered as complementary medicine, it is most commonly used in oncological medicine (Schwabe *et al.*, 1998). Mistletoe extract management in cancer is evidenced from a plethora of clinical studies. Quality of life and survival of cancer patients significantly increased with mistletoe in cancer patients was reported in various studies (Sandeep roy, 2014; Semiglazov *et al.*, 2006; Piao *et al.*, 2004; Kim *et al.*, 2012; Semiglazov *et al.*, 2004). The present investigation was carried out to determine the effects of mistletoe extract in breast cancer patients.

Materials and Methods:

Patients with newly diagnosed breast cancer who met all of the following eligibility criteria were included in the study: histologically confirmed diagnosis by a core-cut or incisional biopsy with a maximum tumour diameter of at least 2 cm; two dimensional measurable tumour on ultrasonogram; age 26 to 65 years; and written informed consent and presumed compliance of the patient. Specific criteria for exclusion were as follows: previous treatment for breast cancer, including surgery, chemotherapy, radiation, and cytotoxic and endocrine treatments (except surgical diagnostic procedures); previous malignancy other than breast cancer; non-invasive breast lesions, if the disease-free interval was less than 10 years; metastatic, locally inoperable, bilateral, or inflammatory breast cancer; previous cytotoxic treatment for any condition; pre-existing neurotoxicity greater than grade 2 (National Cancer Institute of Canada [NCIC] grading); active infection or other significant illness that could affect toleration of treatment; current treatment with sex hormones (treatment had to have been discontinued before the start of systemic therapy); and psychiatric illness or drug addiction that would preclude obtaining informed consent. Patients were recruited from outpatient clinic from Hrishikesh hospital, Nashik, India. Eligible patients received mistletoe extract. A physical and sonographic assessment of the primary tumour in the breast had carried out before the start of therapy. Both measurements had to be repeated. The response to therapy was assessed physically and sonographically. Response was considered complete if there was no evidence of the primary breast tumour by the assessment method concerned. Response rate was considered partial if there was a reduction of 50% or more in the product of the two largest perpendicular diameters of the tumour. If the tumour shows a reduction of less than 50% or an increase of less than 25%, no change was considered to have occurred.

Statistics:

A paired t test was used to compare tumour sizes before and after chemotherapy; measurements during physical and sonographic examinations. The significance level for all tests was assumed to be 5%.

Results and Discussion:

Twelve patients were recruited onto this study (Table 1). All patients were evaluated for tumour size before and after therapy. The median age of the patients was 50 years (range, 26 to 65 years).

Half of the patients had clinical stage II disease, and a quarter of them had stage IIIA disease. The median tumour size on physical examination was 3.8 cm (range, 1 to 8 cm)

for the largest diameter and 20 cm² (range, 2 to 90 cm²) by two-dimensional measurements. Sonographic measurements yielded a median diameter of 3 cm (range, 0 to 8 cm) and an area of 8 cm² (range, 0 to 56 cm²) (Table No.2). The nodal status was determined negative and positive in 33 % and 66 % of patients respectively (Table No.3).

The overall response rate as assessed by physical evaluation was 83.3 %. Three out of twelve patients (25 %) had complete remission of the tumour i.e. reduction of tumour size was more than 50 % after physical examination. The reduction of tumour area less than 50 % was found in only two patients (16 %). The initial measurement, largest diameter of tumour median size was 3.8 cm (range, 1-8 cm) decrease to 2 cm (range, 0.1-4.8 cm) after mistletoe therapy. The median area of the tumour was found 20 cm² (range, 2-90 cm²) in initial measurement, and decreased to 8 cm² (range, 0-22 cm²).

A similar trend was exhibited with sonographically. The overall response rate was found 50%, with complete remission in one patient (8.33 %) (Table No. 4). The largest diameter of the tumour decreased from 3 cm (range, 0 to 8 cm), as observed in the initial physical examination, to 1.5 cm (range, 0 to 4 cm) after mistletoe therapy (*P* < 0.001). The median area of the tumour was decreased from 8 cm² (range, 0-56 cm²) to 3 cm² (range, 0-44 cm²).

The positive nodal status was decreased from 66 % to 41 % of patients. Tumour stage was significantly decreased after mistletoe therapy. Whereas as half of the patients had disease of at least stage II at the start of treatment, remaining were found to have stage 0 or I disease on histologic evaluation.

Table: 1 Base line characteristics of patients:

	No of patients	% of Patients
Assessment for efficacy	12	100
Treatment	12	100
Age (in years)		
< 45	5	41
> 45	7	58

Table:2 Down staging effect of mistletoe therapy

	Before (n = 12)			After (n = 12)			P
	Median	Range	Mean \pm SEM	Median	Range	Mean \pm SEM	
Physical measurement							
Area, cm ²	20	2-90	32.75 \pm 8.623	8	0-22	9.542 \pm 1.982	P < 0.001
Diameter	3.8	1-8	3.967 \pm 0.6059	2	0.1-4.8	2.508 \pm 0.4497	P < 0.001
Sonographic measurement							
Area, cm ²	8	0-56	19.03 \pm 5.614	3	0-44	13.61 \pm 4.805	P < 0.001
Diameter	3	0-8	3.775 \pm 0.727	1.5	0-4	1.942 \pm 0.365	P < 0.001

Table: 3 Nodal status and disease stage before and after mistletoe therapy

	Before (n = 12)		After (n = 12)	
	No. of patients	%	No. of patients	%
Nodal Status				
Negative	4	33.3	7	58.3
Positive	8	66.6	5	41.6
Disease Stage				
0	0	0	1	8.3
I	0	0	5	41.6
II	6	50	3	25
III A	4	33.3	2	16.6
III B	2	16.6	1	8.3

Table: 4 Response of breast tumor to mistletoe therapy

	Complete remission	Partial remission	No change	Overall response rate
Clinical assessment	3	7	2	10 (83.3 %)
Sonographic assessment	1	5	6	6 (50 %)

Discussion:

Mistletoe extract (*Viscum Album* Extract or European mistletoe) is the most frequently used plant extract to treat across an array of solid tumours especially in gynecological and breast-cancer treatment (Fasching, 2007; Molassiotis *et al.*, 2006; Molassiotis *et al.*, 2005). Mistletoe extract possesses potent cytotoxic and apoptosis-inducing effects, which are the key pathways in the treatment of cancer. (Eggenschwiler, 2007; Bussing, 1999; Elsässer-Beile, 1998). A significant morbidity and mortality was observed in women with breast cancer across world. A systematic literature review conducted by Osterman *et al.*, (2009) concluded that adjuvant treatment of cancer patients with the mistletoe extract allied with a better survival. Quality of life improvement in cancer patients with mistletoe extract was reported by glut of studies (Semiglazov *et al.*, 2006; Semiglazov *et al.*, 2004; Piao *et al.*, 2004; Steuer-Vogt *et al.*, 2001; Kim *et al.*, 2012). A comparative evaluation between quality of life, adverse events and survival analysis depicted clear pictorial manifestations of mistletoe extract (Sandeep roy, 2014). In the future, the manifestations of mistletoe extract must be evaluated in broad number of subjects with effective study designs.

Mistletoe extract contains most active group of constituents for the management of cancer. In this investigation, mistletoe extract treatment in the breast cancer patients causes an overall clinical response rate of 83.3 %, as determined by physical examination and 50 % by sonographic measurement. A similar study which was conducted by Moliterni *et al.*, (1997) found overall clinical response rate was 88 % in breast cancer patients treated with doxorubicin and paclitaxel. Clinically, doxorubicin combination with docetaxel in breast cancer patients significantly decreased the tumour size and overall response rate was observed as 93 % and 67 % by physical and sonographical assessment respectively (Mincwitz *et al.*, 1999). The overall response rate for the combination of doxorubicin and cyclophosphamide was 85 %, with a complete remission of 14 % (Dieras *et al.*, 1998).

Side effects were observed by mistletoe treatment which included reddening of skin, and allergic skin reaction, fever, pruritus at the injection and local inflammatory skin reaction at the injection site.

Physical measurement of tumour seems to be a vague method for determining tumour regression rate in cancer patients. The estimated overall response rate was higher in physical measurement than sonography. The complete remission was observed in

25 % of patients with physical measurement while it was found 8.33 % with sonography.

The correlation between sonography and physical measurement was poor, however the use of techniques like mammography, magnetic resonance imaging must be evaluated in cancer patients treated with mistletoe extract for comparative efficacy of same. Emerging technologies, flawless study designs and effective outcomes will be needed in imminent studies.

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