

FROM THE DEPARTMENT OF ONCOLOGY II, FINSEN INSTITUTE, RIGSHOSPITALET, DK-2100 COPENHAGEN, DENMARK.

MISTELTOE (ISCADOR) THERAPY IN STAGE IV RENAL ADENOCARCINOMA

A phase II study in patients with measurable lung metastases

M. KJAER

Abstract

The public interest in alternative cancer therapy is considerable. Since the 1920s advocates of anthroposophical medicine have postulated a highly significant effect of mistletoe plant extracts on life quality and survival of patients with most solid tumours. Fourteen patients, 8 men and 6 women, median age 65, range 47–74 years, with earlier untreated histologically verified renal adenocarcinoma stage IV and clearly measurable lung metastases were treated with subcutaneous injections of Iscador every second day in escalating doses over 3 weeks followed by maintenance therapy, 20, 30, and 50 mg/ml on respective days. Patients were evaluated monthly and disease status classified according to WHO criteria. No response was demonstrated. 2/14 patients died without change of the disease (NC) after 30 and 60 days respectively. The median time to progressive disease (PD) was 108 days, range 33–348 days. First site of PD was lungs in 10/12, outside lungs in 2/12 patients. All patients have died. The median survival was 330 days, range 44–694, which in a retrospective comparison was quite similar to earlier phase 2 studies in the same type of patients. Apart from local reactions around the injection sites and moderate fever on the day of injection the treatment was well tolerated with no major toxicities. It is concluded that Iscador under the conditions chosen for the study had no objective or life prolonging effects postulated for most solid tumour types by advocates of anthroposophy.

Key words: Mistletoe extract, Iscador, renal adenocarcinoma, lung metastases, phase II study.

Over the last decade there has been an increasing tendency among cancer patients in many countries to seek 'alternative' medical treatment as supplement to or substitute for traditional oncological therapy. It has been estimated that as many as 50–60% of cancer patients use alternative medical procedures in the broad sense (1, 2), but precise data concerning the enormous personal and

economical resources invested by the patients in this area are lacking.

One of the most popular and debated alternative treatments in Denmark is mistletoe therapy. A fermented whole-plant extract of the saprophyte plant, *Viscum album*, mistletoe, has been used for the treatment and prophylaxis of malignant disease by advocates of anthroposophical medicine since the 1920s (3) mainly in Switzerland, Austria and West Germany. The basic hypothesis in this treatment is that cancer is the expression of an unbalance between the immune surveillance mechanisms of the individual and the proliferating tumour cells. The designing principle, a concept developed by Rudolf Steiner (4), is weakened, resulting in a malignant disease. Thus the therapy must be directed towards the strengthening of this principle. Mistletoe is regarded as such a strengthening procedure with effects mediated through cytotoxic and immunological mechanisms (5–7). The treatment has no serious side effects and has a pronounced impact on the quality of life of the patients according its advocates (8) who have also stated that the effect of mistletoe is on survival. Tumour regression in the traditional sense is not a prerequisite for effect of the treatment and it is not the main goal of the treatment. What matters is life quality and survival. These basic assumptions differ very much from those of classical oncology where therapeutically induced tumour regression as a rule is a prerequisite for response, prolonged survival, and eventual cure.

The literature concerning the effect of mistletoe on

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patients with cancer is very large and heterogeneous and consists mainly of 3 types of documentation:

1) Innumerable published case stories describing the clinical effect in different clinical settings (9, 10).

2) A large number of patient series with different tumour types treated with misteltoe preferentially in adjuvant setting and compared with regard to survival with untreated or traditionally treated historical control materials. The results of these studies are quite uniform and describe a highly significant positive effect on survival in the misteltoe treated groups. Activity has been described in patients with breast cancer (10, 11), gastrointestinal cancer (11), lung cancer (12), cancer in the female genital organs (11), renal cancer (13), bladder cancer (11, 13) and malignant melanoma (11).

The positive effect on survival is present irrespective of tumour type, stage, sex, and other prognostic factors.

3) A few attempts have been made to document the effect of misteltoe in prospective randomized clinical trials in patients with gastric carcinoma (14), breast cancer (15), and lung cancer (16). However, all these studies can be severely criticized concerning trial methodology and must be considered with scepticism. Prospective, randomized double-blind studies have not been reported.

In conclusion we are faced with a treatment modality founded on hypotheses which are basically different from what is usually accepted in classical oncology. The retrospective nature of most published data makes it difficult to evaluate the effect of misteltoe on malignant disease.

Legislation concerning alternative medications in Denmark. Alternative medications in Denmark can be used and prescribed according to 3 exceptions from the law on medical drugs issues by the Ministry of the Interior in 1978 (17–19). Most of the preparations can therefore be bought freely and used by anyone. Misteltoe, however, must be prescribed by a physician presumably due to the fact that it is administered by subcutaneous or intramuscular injections, but it is not a registered medical drug in Denmark. These legislative procedures have the consequences that a central control of the market is impossible and that patients have to pay for their treatment without any reduction in price.

Thus, misteltoe is considered a drug in the medical sense by the National Health Service but excepted from some of the rules concerning distribution and control. This attitude from the Danish Health Authorities poses specific administrative and ethic problems for the use of misteltoe in the official oncology setting.

The choice of misteltoe preparations, doses and dose schedules for specific tumour types. The misteltoe preparation Iscador has been produced since the 1920s by the Society for Cancer Research, Arlesheim, Switzerland and marketed by Weleda AG, Arlesheim, Switzerland (3).

Only limited pharmacokinetic and pharmacodynamic studies exist in humans and it must be underlined that Iscador is a whole plant extract of misteltoe and cannot be

described completely in all its chemical complexity as it contains several proteins, glycoproteins, lipids and other molecular structures which to some extent are unidentified (5, 7).

As no active single chemical/molecular component of Iscador has been identified traditional data from phase I trials do not exist. However, there exists a pronounced clinical tradition obtained in Switzerland, Germany and Austria since 1920 where doses, dose schedules, etc. have been determined. In a clinical trial these data must be accepted.

According to the Rudolf Steiner hypotheses the choice of treatment for the individual patient depends on a number of factors relating to the misteltoe preparation, to the malignant disease and to the condition of the patient. The most important of these can be summarized as follows:

- time of plant picking
- sun, moon, planets
- host trees
- sex of the patient
- tumour type and site
- metal.

It is essential in this context to stress that the misteltoe plant is a genuine saprophyte—it can only live on a host tree—and misteltoe preparations therefore differ depending on which host tree it has grown on. In the Iscador series the following types are available:

Iscador A (*Viscum abietis*) fir trees
 Iscador M (*Viscum mali*) apple trees
 Iscador P (*Viscum pini*) pine trees
 Iscador Qu (*Viscum querci*) oak trees
 Iscador U (*Viscum ulmi*) elm trees.

It is possible to strengthen the biological effect of the preparation through the binding of different metals to the extracts. The following are available:

argentum—silver
 cuprum—copper
 hydrargyrum—mercury.

Different misteltoe preparations are used for men and women and for different tumour types in a rather complex scheme (20). The choice of preparation for the individual patient is based on these hypotheses and on tradition.

Purpose of the study. We decided to perform an open phase 2 study of the effect of Iscador in good performing patients with stage IV renal adenocarcinoma and clearly measurable lung metastases, generally designed as earlier phase 2 studies in this disease performed by our group (21).

Disseminated renal adenocarcinoma was chosen because it is almost totally unaffected by presently known systemic therapies (22–24) and therefore does not repre-

Table 1

Renal adenocarcinoma. Misteltoe treatment. Patient characteristics and summary of results

Characteristic	Male	Female
Total	8	6
Median age years (range)	61 (47–74)	65 (47–73)
Earlier nephrectomy	2	3
Median time from nephrectomy to misteltoe (range)	44 months–8 years	40 months (27 months–4 years)
Median performance status at treatment start (range)	1 (1–2)	2 (1–3)
Metastatic disease outside lungs	4	3
Median time with known metastatic disease before misteltoe (range)	6 months (0 days–12 months)	6 months (1 month–3.5 years)
Median duration of treatment (range)	330 days (60–694 days)	134 days (30–445 days)
Response	0	0
Median time to PD (range)	180 days (33–348 days)	62 days (50–180 days)

sent ethical problems when treated with misteltoe as first-line treatment.

Material and Methods

Fourteen patients with histologically proven renal adenocarcinoma and clearly measurable lung metastases on plain chest radiogram and/or computerized tomographic scan who had not earlier been treated with chemotherapy or hormone therapy were included in the study after given informed consent. Patient characteristics are shown in Table 1.

In case of earlier nephrectomy for renal adenocarcinoma no attempt was made to obtain material for histological examination from the lung metastases. If nephrectomy had not been performed material for histological examination was obtained either by ultrasound-guided biopsy from the primary or by x-ray TV-guided fine-needle aspiration from the lung metastases.

The following examinations were performed before start of therapy in all patients: physical examination, hematology, liver biochemistry, creatinine, chest radiogram, computerized tomographic scan if indicated, bone scan, and ultrasound scan of the kidney bed in nephrectomized patients. A visual analogue scale (VAS) (25)—a 100 mm long horizontally placed, unmarked but end-barred line—was used to assess well-being and quality of life during treatment. The two extremes of the scale were marked: 'I feel as bad as I possibly could' ... 'I feel very good'.

Treatment schedule with misteltoe. The treatment schedule for Iscador was agreed between the responsible investigator and the anthroposophical hospital Lukas Klinik in Arlesheim, Switzerland which is the main proponent for misteltoe treatment of malignant disease in Western Europe.

For male patients was used Iscador Qu c. Cu (*viscum quercii*)—misteltoe from oak trees strengthened with copper ions. For female patients Iscador M. c. Cu (*viscum mali*)—misteltoe from apple trees also strengthened with copper ions.

The treatment of both sexes was given in a cyclic fashion with subcutaneous injections of 1 ml extract every 2 days preferably around 8 o'clock in the morning according to the schedule shown in Table 2. The schedule consisted of an induction phase with escalating doses over a 3-week period followed by a maintenance phase. Injections were given at alternating sites in the shoulders or the epigastric region by the patients themselves, their relatives, a home nurse or in our out-patient clinic. Treatment was greatly individualized in the sense that local reactions in the injection regions were kept within 5×5 cm and body temperature below 38.5°C, before escalation to the following dose.

Patients were followed weekly in the induction phase with physical examination and blood tests, thereafter every second week and monthly after additional 2 months. Reevaluation of disease status was performed monthly and response classified according to World Health Organization criteria (26). Side effects were followed closely at

Table 2
Iscador. Treatment schedule

Strength mg/ml*	Monday	Tuesday	Wednesday	Thursday	Friday
Week 1	0.1	—	1	—	10
Week 2	1	—	10	—	20
Week 3	10	—	20	—	30
Week 4	20	—	30	—	50
Subsequent weeks	20	—	30	—	50

Men, Iscador Qu c. Cu (*Viscum querci*). Women, Iscador M c. Cu (*Viscum mali*).

*mg fresh plant extract per ml.

Table 3
Additional treatment

Treatment	No. of patients
Treatment of primary	
Embolization	3
Radiotherapy	2
Treatment of metastases	
Radiotherapy of lung/mediastinal metastases	3
Radiotherapy of bone metastases	3
Radiotherapy of other metastases	6
Experimental chemotherapy	
Phase 1, after off-study	3
Other procedures	
Pleuradesis, talc	1

each visit. Treatment was continued not only until disease progression but until terminal deterioration or death of the patients. No dietary regulations or alterations in normal every day life style was imposed on the patients while on Iscador therapy.

All patients were seen by the responsible investigator. The protocol was approved by the Danish Health Authorities and by the Central Ethics Committee for Copenhagen.

Results

Response (Table 1). No response was registered during Iscador treatment. Twelve of 14 patients showed progressive disease (PD) after a median duration of 108 days (range 33–348 days). Two out of 14 patients went into terminal phase without response (NC) after 30 and 60 days of treatment respectively. First site of PD was lungs in 10/12 patients, brain and bone in 2/12 patients. According to established response criteria this result with 95% probability excludes antineoplastic activity $\geq 20\%$ (27).

Side effects. Side effects of treatment were minimal. Induration at the injection sites developed gradually in all

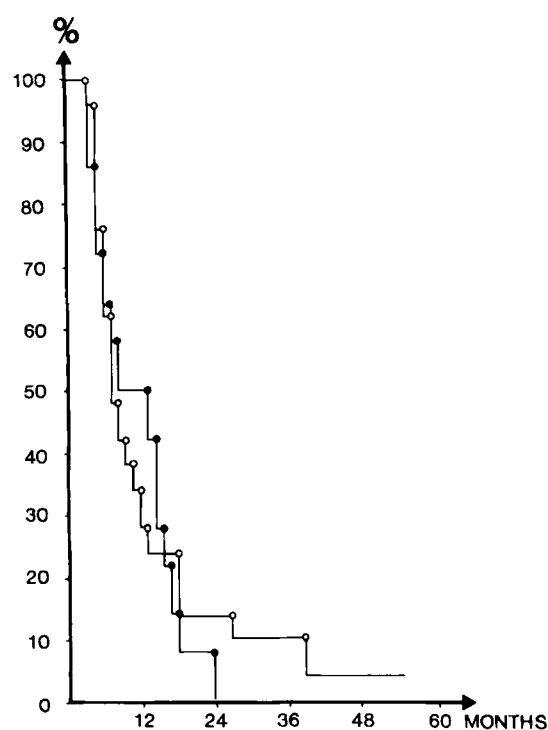


Figure. Survival of 14 misteltoe treated patients compared with the survival of 21 patients treated with high-dose MPA in our institution 1982–1984 (21). ○---○, high-dose medroxyprogesterone acetate (MPA); ●---●, misteltoe.

patients as small nodules in the subcutaneous tissue. In one patient a rather severe local reaction with ulceration of the skin developed but it subsided spontaneously with changing injection sites. In 2 patients it was impossible increase the dose beyond 20 and 30 mg/ml respectively per injection due to severe acute local reactions and temperature rise above 39°C.

Survival. All patients in the study have died with progressive renal adenocarcinoma. Autopsy was performed in 6/14 patients. The median survival was 330 days, range 44–694 days. The Figure shows the survival rates calculat-

ed according to Kaplan & Meier (28). Survival was calculated from the first day of treatment. Compared with the survival of 21 patients with similar tumour manifestations participating in a phase 2 trial with high-dose MPA in our institution 1982–1984 (21) no differences could be demonstrated. Thus, a life prolonging effect of misteltoe could not be demonstrated under the conditions chosen for the comparison.

Additional treatment. During the course of misteltoe therapy 11/14 patients received additional treatment for palliative purposes. Data are summarized in Table 3. The most common treatment was external beam radiotherapy for symptomatic distant metastases outside the lungs. Three patients had progressive oesophageal and bronchial compression from mediastinal metastases and received mediastinal radiotherapy. Significant bleeding from the primary tumour was managed by arterial embolization and/or external beam radiotherapy usually 20 fractions of 2.0 Gy to a total dose of 40 Gy given from opposing fields. After PD on misteltoe 3 patients received experimental chemotherapy.

No significant changes in laboratory parameters, WBC, thrombocytes, ESR could be demonstrated during the Iscador therapy.

Quality of life. Along with the progression of the disease a progressive increase in VAS score could be demonstrated. The median (+ range) score at treatment start was 17 (1–52) mm, and at the time of documented PD 64 (11–99) mm, which was significantly different ($p < 0.05$). The latest values obtained before death were 62 (range 12–81) mm which was not significantly different from the PD-values.

Discussion

Rudolph Steiner's concept of strengthening the positive forces in the organism through diet, eurythmie, artistic performances, and misteltoe appeals to most people as a pure and much more natural way of dealing with disease than toxic and cell-destroying drugs or irradiation in our polluted and overcrowded societies. As oncologists working in a traditional setting I think we have a profound obligation to look at the tendencies which effect our patients in their daily lives and contact with other people. One such tendency is 'the escape' of our patients to alternative medicine, among others misteltoe therapy.

The primary purpose of the present study was to get experience from this therapy in a group of well-defined and closely followed patients. From the massive literature it is evident that misteltoe is assumed to have its principal effects on survival and quality of life. Tumour response is not regarded as a prerequisite for survival although case stories about partial or complete response have been reported (9). The adequate way to test the effect of misteltoe would therefore be through a randomized clinical trial. However, such a trial in good performing stage IV renal

adenocarcinoma patients with measurable disease in the lungs would in our department have taken 8–10 years. Therefore we decided to perform a phase 2 study. It is the first study published of its kind concerning misteltoe treatment. No response or effect on survival was found.

This might not be surprising in a material of patients with stage IV renal adenocarcinoma which is virtually refractory to all types of systemic treatment (22–24). However, a highly significant effect of misteltoe as adjuvant treatment on the survival compared with historical controls has been reported in patients with gastric cancer, colonic cancer, non small cell lung cancer, cancer of the female genital organs, bladder cancer and malignant melanoma irrespective of tumour type, stage, sex or other prognostic factors (11–16). The majority of these tumour types range among the least sensitive to conventional systemic treatment (29, 30). Most, if not all, of the alternative procedures in use today are without any documented effect upon the clinical behaviour of malignant disease (31–33). Nevertheless many of our patients use alternative treatments. The question is why? It is of course impossible to give a complete answer to this question. However, I think at least part of the explanation depends on the fact that traditional oncology has developed into a highly technological, rational, and unhuman discipline, prescribing drugs or irradiation therapy which are very toxic and which may spoil the quality of life for months with, for many patients, a very marginal benefit. This was possible to do without much discussion 10 years ago when the public interest in oncology was less pronounced than it is today. Now, in many European countries anti-pollution, anti-smoking, etc. is intensively discussed, i.e. measures which may seem to be more 'pure' and natural ways of combating cancer. Anthroposophy with its ideas about strengthening of the natural forces of the organism very much lies in this line of thinking and hence its popularity. I do not think that this development can be debated or converted within a short time span. Of importance is, however, that classical oncology realizes this development in our society and generates attitudes to deal with the problem. These attitudes should imply a greater understanding for alternative thinking and most important efforts to develop anticancer drugs which are less toxic and more acceptable to the general public than those we know of today.

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Request for reprints: Dr Mogens Kjaer, Dept Oncology II, Finsen Institute, Rigshospitalet, 49 Strandboulevarden, DK-2100 Copenhagen Ø, Denmark.

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