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Quality of Life of Cancer Patients under Adjuvant Mistletoe Treatment

Results of a prospective, non-randomized, controlled, open study (post-marketing surveillance) with Iscador® M

Reprint from Schweiz. Zschr. GanzheitsMedizin 2005;17(5):???–???
Cancer is the second most frequent cause of death in Western industrial countries, after cardiovascular disease. For women in the European Union, breast cancer is the most frequent form of cancer and gynaecological cancers – excluding breast cancer – are in third place [1]. The frequencies of gynaecological cancers, expressed as new cases per 100,000 women per year are as follows: breast: 92.0, body of the uterus: 15.4, ovaries: 14.4, cervix: 10.3 [1]. There has been a considerable increase in knowledge of the risk factors for the development of cancer and in the efforts to prevent the disease. It is nevertheless essentially impossible to predict whether an individual will develop cancer or what the clinical course will be. For example, the great majority of breast cancer patients in the European Union exhibit none of the known risk factors [2].

In this context, accompanying therapy with a mistletoe extract, such as Iscador® M, can cause additional improvement in the various symptoms of gynaecological cancers, expressed as new cases per 100,000 women per year are as follows: breast: 92.0, body of the uterus: 15.4, ovaries: 14.4, cervix: 10.3 [1]. There has been a considerable increase in knowledge of the risk factors for the development of cancer and in the efforts to prevent the disease. It is nevertheless essentially impossible to predict whether an individual will develop cancer or what the clinical course will be. For example, the great majority of breast cancer patients in the European Union exhibit none of the known risk factors [2].

After a reliable diagnosis, the fundamental pillars of therapy are operations, chemotherapy and/or radiation. There is very intensive research into chemotherapy and the probability of survival and the period of survival have improved [3]. It is however impossible to overlook the considerable physical and psychological stress to which the patients are exposed during treatment. The side-effects of cytostatic therapy (e.g. nausea and vomiting, myelosuppression, immunosuppression and alopecia) can often not be adequately influenced, even with highly active drugs (such as 5-HT₃-antagonists for nausea and vomiting). This results in a considerable restriction to the patient’s quality of life.

Background: Mistletoe extracts (Viscum album L.) are applied in anthroposophic medicine in addition to conventional oncologic therapy, with the intention of reducing adverse events of chemotherapy and thereby improving the patients’ quality of life. Aim of the study: Documentation of the efficacy and tolerability of the anthroposophical mistletoe preparation Iscador® M in the treatment of patients with gynaecological cancer during chemotherapy, especially regarding the quality of life. Design: Prospective, controlled post-marketing surveillance. Methods: 36 female patients received a therapy with Iscador® in addition to the chemotherapeutical treatment, 37 female patients of the control group received exclusively a conventional therapy. The period of observation covered 6 months. Results: In comparison to the control patients, the Iscador® patients showed better blood parameters and less physical and psychical impairment usually associated with chemotherapy. Conclusion: In summary, more patients of the Iscador® group experienced an amelioration or a stabilisation of their general condition and good tolerance of the mistletoe preparation.

Key words: prospective study, gynaecological cancer, mistletoe, chemotherapy, adverse events, quality of life, Iscador

Lebensqualität von Tumorpatientinnen unter begleitender Misteltherapie
Ergebnisse einer prospektiven, nicht randomisierten, kontrollierten, offenen Studie (AWB) mit Iscador® M


Schlüsselwörter: prospektive Studie, gynäkologische Tumoren, Misteltherapie, Chemotherapie, Nebenwirkungen, Lebensqualität, Iscador

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In this context, accompanying therapy with a mistletoe extract, such as Iscador® M, can cause additional improvement in the various symptoms
and thus in the patient’s general condition. Mistletoe therapy has been used in anthroposophical medicine for cancer treatment for more than 80 years and its efficacy has also been demonstrated in various clinical studies [4]. It can improve quality of life during cytostatic therapy [5, 6] and prolong survival time [5, 6, 7].

Mistletoe (Viscum album L.) lives semiparasitically on trees and occurs in central Europe as deciduous, fir and pine mistletoe. Its main components include mistletoe lectins (glycoproteins) and viscotoxins (polypeptides), followed by flavonoids, polysaccharides and others [8]. Mistletoe lectins I-III (ML I-III) have been best studied. It has been shown that the crude extract produces non-specific immunostimulation, and is antimitugenic. It also stabilises the DNA of peripheral mononuclear cells and induces cytostasis and apoptosis in malignant cells [9]. As there are differences in the content of the individual components – thought to be linked to mistletoe’s high host specificity – different extracts are prepared, depending on the host plant.

The preparations used in this observational study were isolated from apple and oak mistletoe, as is evident in the designations of the medicine as Iscador® M (malus) or Iscador® Qu (quercus). These are recommended for the treatment of gynaecological cancers [10]. Mistletoe is harvested twice yearly. The content of viscotoxins is higher in summer and the content of mistletoe lectins is higher in winter. For the production of Iscador, the extracts are fermented, combined, sterile filtered and diluted to different extents. The finished product is available as a solution for subcutaneous injection in 1 ml ampoules and as Series 0, 1 and II, with 1 × 7 ampoules each. The concentration of the extract increases from Series 0 to II and therapy is started with Series 0. The patient can perform the injections herself and can switch to Series I or II if the tolerability is good or if the response is inadequate [10].

The present observational study is intended to illuminate the course of mistletoe therapy and its influence on the physical and psychological well-being of the patients under everyday clinical conditions, i.e. outside the conditions of a clinical study.

### Material

#### Observational Plan and Patients

The present observational study took place between 1 May 2000 and 31 December 2001, with patients in the Department of Gynaecology in Vienna General Hospital suffering from gynaecological tumours. All patients were given conventional treatment (operation followed by chemotherapy) and then could decide to be additionally treated with Iscador® M.

After the diagnosis had been established or after the operation (followed by histological and cytological findings), the possible use of mistletoe was discussed for the first time with the study manager. The data for the first documentation sheet were then collected. The criteria listed in Table 1 were used to assign the patients to the observational study. The patients in the mistletoe group were given the first prescription and the information brochure for themselves and for their general practitioner. Therapy adjustment and medical dose control were normally performed by the patient’s general practitioner.

Three identical questionnaires were completed anonymously during the therapy:

**Table 1. Criteria for participation in the observational study**

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria (Participation and Evaluation)</th>
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| Patients aged between 30 and 70 years | |}

**Documentation at time point I:** About 2 to 3 weeks, after the diagnosis had been made at the first discussion.

**Documentation at time point II:** At the end of the 4th to 5th months, at the interim investigation after the chemotherapy cycle

**Documentation at time point III:** At the end of the 6th month at the final investigation.

#### Documentation and Dosage

The personal data in the questionnaire included date of birth, gender, type of tumour and therapy. In addition, 21 questions had to be answered in 5 theme complexes (Table 2).

Changes in the patients’ blood parameters were recorded in 4 questions and answered by the study manager responsible for the observational study. 1 point was awarded for each value lying outside the normal range for leukocytes and B- and T-lymphocytes and 1 point for a lack of reduction in tumour marker. Thus, the maximal total score of 4 points would represent a rather unfavourable blood count.

7 questions provided information on the physical stress suffered by the patients as a result of chemotherapy: the number of postponements of chemotherapeutic treatment, an inadequate blood count as the cause of the postponement, the interval till the therapy was continued, the intensity of the stress on the patient, the number of
Original Articles

Table 2. Organisation of the Themes in the Questionnaire

<table>
<thead>
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<tbody>
<tr>
<td>Number of Questions</td>
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<tr>
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<tr>
<td>Blood values</td>
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<td>Physical stress (chemotherapy)</td>
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<td>Psychological stress (chemotherapy)</td>
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<td>General condition</td>
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<td>Acceptance of mistletoe therapy</td>
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Table 3. Comparison of Mistletoe and Control Groups

<table>
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<tr>
<td>Mistletoe Group</td>
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<tr>
<td>All patients</td>
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<tr>
<td>Died</td>
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<tr>
<td>Study discontinued</td>
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<tr>
<td>Evaluated patients</td>
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<tr>
<td>Average age (years)</td>
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<tr>
<td>Breast cancer</td>
</tr>
<tr>
<td>Cervical cancer</td>
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<tr>
<td>Ovarian cancer</td>
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<tr>
<td>Vulva or womb cancer</td>
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</table>

physical side-effects, the consequent stress on the patient and the change in her general condition a few days before chemotherapy. A high total point score (maximum 28) in this group of questions indicates that the patient has been exposed to intense physical stress by the chemotherapy.

The psychological effects of chemotherapy on the patients were mapped by 3 questions, covering the degree of fear of chemotherapy, sadness and restless sleep. Thus intense psychological stress can be awarded up to 10 points.

In addition, 2 questions related to the patient’s general condition can express quality of life which is felt to be negative and frequent pain, with a maximum score of 7 points.

It was also planned to record the patients’ attitudes to complementary medicine, in particular, mistletoe therapy, on the basis of 5 questions. A high total score of 23 points then represents weak acceptance and lack of conviction of the benefits of treatment with a mistletoe preparation.

If possible the therapy with Iscador® M and dose adjustments were performed by the patients’ general practitioners. Alternatively, this could be performed by a consultant in Vienna General Hospital or an independent examining doctor with experience in mistletoe therapy. If the patient has been admitted to hospital, the ward physician should administer the injection. Dosage, dose adjustment and the switch from Series 0 to Series 1 was performed on the basis of product information for Iscador® M and other official instructions from Weleda Austria. The mistletoe therapy was not performed on the day of the chemotherapy and on the following day.

Results

Findings on Admission and Demographic Data

The group of patients who fulfilled the inclusion criteria and who decided for the mistletoe therapy (mistletoe group) consisted of 43 women, of whom 36 were evaluated (Table 3). 4 patients died during the period of chemotherapy. 2 others discontinued their participation during the period of chemotherapy. The patients in the mistletoe group (average age 58 years) were on average 9 years younger than the patients in the control group (average age 67 years). As regards the disease, there were somewhat fewer vulva and womb carcinomas and mammary carcinomas in the mistletoe group than in the control group. Conversely, there were more patients with cervical and ovarian cancer in the mistletoe group.

In so far as was necessary, the patients in both groups were given Neupogen®, which is indicated for the treatment of neutropenia after chemotherapy.

The Iscador® patients generally spontaneously took enzymes, vitamins, trace elements and other supportive preparations.

Clinical Course

At the start of the study, the patients in the Iscador® group had on average somewhat poorer blood values than in the control group (2.7 and 2.2, respectively) (Fig. 1). This means that they more frequently exhibited deviations from the normal range for leukocytes, B- and T-lymphocytes and no reduction in tumour markers. Additional deterioration till the intermediate investigation was less intense (3.6) than in the control group (4.0). By the final investigation, the initial value had been recovered. The blood values of the control group had a total score of 3.0, which is poorer than the initial value.

The physical stress suffered by the patients from the side-effects and postponements of cytostatic therapy increased slightly but regularly in the Iscador® group (11:14:16) (Fig. 2). The stress increase in the control group was greater (from 9 to 19) and remained at about the same level at the end of the period of observation (18). Physical impairment, such as problems in defecation, loss of appetite and vomiting, occurred more rarely in the mistletoe therapy than in the control group. The overall group average for all three postponements in the mistletoe...
group and 24 in the control group. A poor blood count was given as the reason about as often in the two groups (9 or 10). On the other hand, poor general condition (including the consequences of other diseases) was a much rare reason in the mistletoe group than in the control group (5 versus 13).

The initial rating of the psychological stress (fear, sadness and restless sleep) was initially similar in the two groups (6.1 versus 6.3) (Fig. 3). After the first cycle of chemotherapy, there was less deterioration in the mistletoe group than in the control group (8.3 and 9.1, respectively). By the final investigation, the Iscador® patients had recovered more quickly (6.0) and, in particular, slept better than the patients without mistletoe therapy (7.6).

The general condition was initially rated better in the Iscador® group (4.1) than in the control group (5.9) (Fig. 4). Thus, at the start of the investigation, the Iscador® patients felt that their quality of life was more positive and they suffered less pain. The deterioration in this group (5.3; control 6.3) was somewhat more marked, but was followed by greater improvement (from 5.3 to 3.9) than in the control group (from 6.3 to 6.1) up to the time of the final investigation.

As expected, the acceptance of complementary therapies and of the mistletoe therapy was initially greater in the Iscador® group (5.9) than in the control group (8.8) (Fig. 5). At the interim investigation, both groups rated the mistletoe therapy less well (8.0 or 9.1). However, their opinions of the benefits of Iscador® therapy improved towards the end of the observational study (5.7 or 7.5).

It is possible to compare the changes in both groups in the different theme complexes by plotting the relative changes in percent of the initial values at the time of the first measurements (Table 4). Positive percentage values then correspond to deterioration and negative values to improvement relative to the first investigation.

The deterioration in the blood parameters and in physical and psychological stress from the chemotherapy at the second time point was much less marked than in the control group. In contrast, the initial deterioration in the general condition in the mistletoe group was greater than in the control group (29% versus 6%), as was the deterioration in the attitude towards mistletoe therapy (36% versus 4%). However, the relative changes in the results at the final documentation relative to the first investigation are, almost without exception, less than in the control group. In particular, the blood values and the psychological stress from chemotherapy in the mistletoe group returned to the level before treatment, while there was still marked deterioration in the control group (36% and 21%, respectively). However, the patients in the control group had modified their original opinions on the benefits of complementary therapies to a greater extent. They considered that Iscador® treatment was of much greater benefit than they initially did (−15%; mistletoe group −3%).

### Table 4. Change in the total number of points of the theme complexes as percent of the initial values at the first time point for the mistletoe group (n = 36) and control group (n = 37). A positive value corresponds to relative deterioration.

<table>
<thead>
<tr>
<th>Theme Complex</th>
<th>Timepoint II (months 4 to 5)</th>
<th>Timepoint III (month 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mistletoe Group [%]</td>
<td>Control Group [%]</td>
</tr>
<tr>
<td>Blood values</td>
<td>33</td>
<td>86</td>
</tr>
<tr>
<td>Physical stress (chemotherapy)</td>
<td>27</td>
<td>53</td>
</tr>
<tr>
<td>Physical stress (chemotherapy)</td>
<td>36</td>
<td>44</td>
</tr>
<tr>
<td>General condition</td>
<td>29</td>
<td>6</td>
</tr>
<tr>
<td>Acceptance of mistletoe therapy</td>
<td>36</td>
<td>4</td>
</tr>
</tbody>
</table>

**Discussion**

The present observational study demonstrates an advantage for those patients who decided for accompanying Iscador® therapy, with respect to both physical and psychological stress from the chemotherapeutic treatment. This effect of mistletoe therapy is in agreement with the results from other studies [4, 7].

The positive blood values and the reduction of the adverse physical effects from chemotherapy, including vomiting, loss of appetite and problems with defecation, are presumably...
Fig. 1. Blood values; Number of deviations from the normal range (leukocytes, B- and T-lymphocytes) and non-reduced tumour markers per patient: 4 questions, maximum total score is 4 points. A low value corresponds to low deviations from the normal range. Changes in the average total number of points at time points I to III for the mistletoe group (n=36) and the control group (n=37).

Fig. 2. Physical stress from side-effects and postponements of chemotherapy: 7 questions, maximum total score per patient is 28 points. A low value corresponds to low physical stress. Changes in the average total number of points at time points I to III for the mistletoe group (n=36) and the control group (n=37).

Fig. 3. Psychological stress from chemotherapy (fear, sadness, restless sleep): 3 questions, maximum total score per patient is 10 points. A low value corresponds to low psychological stress. Changes in the average total number of points at time points I to III for the mistletoe group (n=36) and the control group (n=37).

Fig. 4. General condition (quality of life and pain): 2 questions, maximum total score per patient is 7 points. A low value corresponds to good general condition. Changes in the average total number of points at time points I to III for the mistletoe group (n=36) and the control group (n=37).

Fig. 5. Acceptance of complementary therapies and of mistletoe therapy: 5 questions, maximum total score per patient is 23 points. A low value corresponds to good acceptance. Changes in the average total number of points at time points I to III for the mistletoe group (n=36) and the control group (n=37).

Fig. 6. Evaluation of the change in general condition at the end of the therapy by the patients in the mistletoe group (n=36) and in the control group (n=37).
directly connected with their more favourable psychological condition, characterised by less fear and sadness and more peaceful sleep. A total of less then half of the Iscador® patients had to postpone planned chemotherapy because of inadequate general condition, relative to the number in the control group who had to do this. Thus accompanying therapy with Iscador® M also contributed to optimisation of the implementation of the chemotherapy treatment regimen.

However, direct comparison between the groups is made more difficult by the fact that the patients themselves decided for or against mistletoe therapy – as is usual in therapeutic practice. As a consequence, there were non-random differences in the composition of the groups. Although there was good agreement between the groups with respect to group size, mortality and discontinuations for other reasons, there were slight differences in the frequencies of different types of tumour and a marked difference in average age. The patients in the Iscador® group were on average nine years younger, which may have had a favourable effect in principle on their general condition and also on their ability to perform the injections themselves. The latter can be more difficult for older patients with impairment of the locomotor system and vision and may thus be a factor for rejection of the mistletoe therapy.

The advantage for Iscador® therapy is nevertheless so clear, particularly at the final investigation at 6 months, that it may be assumed that this therapy has a favourable effect. At the interim investigation, these effects were not yet so marked and the patients in the mistletoe group also had a more critical attitude, probably because they had expected more rapid onset of activity. In comparison to their original attitudes, there was greater acceptance of Iscador® therapy in both groups, but particularly in the control group, as the success of the Iscador® therapy became more evident. Adverse effects from mistletoe therapy were only as expected, both in type and frequency [10].

Markedly more patients in all in the Iscador® group reported improvement or stabilisation of their general condition within the period of observation, according to their own evaluation, than was the case in the control group.

The results of the present study demonstrate the positive effect of accompanying Iscador® therapy during chemotherapy. This conclusion is also supported by many previous studies. The Iscador® patients suffered from less physical and psychological impairment from the typical side-effects of chemotherapy, corresponding to improvement or at least stabilisation of their general condition.

Literature


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