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TREATMENT RESPONSES TO VISCUM ALBUM PINI (ISCADOR® P) IN NON-HODGKIN'S LYMPHOMA

EXPLORING A NEW THERAPEUTIC ROUTE

JUERGEN J. KUEHN

Lukas Clinic, Arlesheim, Switzerland

Abstract Beginning on May 1st 1999, 191 patients with non-Hodgkin's Lymphoma were accepted into a plan of treatment with *Viscum album Pini* (Iscador® P) and kept under observation for as much as over 8 years. There were 61 patients with follicular and 130 with non-follicular non-Hodgkin's lymphoma. The treatment groups were: monotherapy without chemotherapeutic pretreatment (group A); monotherapy after completing chemotherapeutic pretreatment (group B); and combined treatment together with chemotherapy (group C). Both partial and complete remissions could be observed in group A. The patient group B had progression-free periods of varying lengths (up to 95 months), and a few experienced transitions from partial to complete remission under treatment with mistletoe. Local and systemic tolerance was good without exception; the quality of life was influenced favorably. There was no shortening of survival times due to mistletoe therapy among the patients treated with *Viscum album* when compared with those who were not treated, both among those with follicular and with non-follicular non-Hodgkin's lymphoma. An analysis of greater patient numbers is in preparation. The effect of monotherapy with *Viscum album Pini* (Iscador® P) is demonstrated by means of the 3 best cases who had both partial and complete remissions. The clinical results presented here supported preclinical *in vitro* and *ex vivo* investigations into the significance of Interleukin-6 as a growth factor in B cells: a potential risk to patients with Non-Hodgkin's Lymphomas is unverifiable either experimentally at the preclinical stage or clinically. The positive clinical effects observed here call for a prospective randomized study.

Key words: Non-Hodgkin's Lymphoma, *Viscum album Pini* (Iscador® P), risk and efficacy, interleukin-6, case series

Resumen ***Respuestas al tratamiento de linfomas no-Hodgkin con* Viscum album Pini *(Iscador® P). Explorando una nueva vía terapéutica.*** Desde mayo 1999, un total de 191 pacientes con linfoma no-Hodgkin fueron tratamiento con *Viscum album Pini* (Iscador P), con un seguimiento que alcanza los 8 años. Fueron 61 pacientes con linfoma folicular y 130 con linfoma no-folicular. Se dividieron en 3 grupos: monoterapia sin pre-quimioterapia (Grupo A); monoterapia después de haber completado la quimioterapia (Grupo B); tratamiento combinado con quimioterapia (Grupo C). En el Grupo A se observaron remisiones completas y parciales. En el Grupo B se observaron intervalos libres de enfermedad (de hasta 95 meses) y algunas transiciones de remisión parcial a completa con el extracto de muérdago. La tolerancia al extracto, tanto local como sistémica, fue buena mientras que la calidad de vida mejoró favorablemente. No hubo disminución de la sobrevida relacionada con la administración de los extractos. Se prepara un análisis de un mayor número de pacientes tratados con los extractos. El efecto de la monoterapia con *Viscum album Pini* (Iscador® P) puede ser ilustrado con los 3 casos más llamativos que obtuvieron remisiones parciales y completas. No hubo evidencia de daño relacionado con la interleuquina 6 (IL-6) como factor de crecimiento de los linfocitos B. Los buenos resultados clínicos merecen confirmación en un estudio prospectivo randomizado.

Palabras clave: *Viscum album,* linfomas no-Hodgkin, IL-6

The Lukas Clinic in the Swiss village of Arlesheim near Basel is traditionally a tumour clinic specializing, besides standard therapies for tumours, in subcutaneous mistletoe therapy with *Viscum album* (Iscador®). It has 46 beds, 10 of which at most are used for the day clinic. About 12,000 consultations are held each year in the tumour outpatient unit.

In the majority of cases *Viscum album* (Iscador®) is indicated in patients experiencing conventional therapy with chemo- and radiotherapy. After conventional treatment non-conventional therapy with *Viscum album* is continued to sustain remission or, in the case of a progression, to sustain a sufficient quality of life for as long as possible. In each case indication for a *Viscum album* monotherapy is examined individually by an independent external second opinion review. If within the course of the disease a recurrence emerges, chemotherapeutic regimens are started in another clinic or via the Lukas Klinik which continues the *Viscum album* therapy.

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e-mail: j.j.kuehn@lukasklinik.ch

Patient's motive

The patients visit the clinic either because they were referred by an external oncologist for consultation about mistletoe therapy or because they come to the clinic on their own initiative in consultation with their own oncologists. The latter group constitutes the majority of patients. The reason for this is the high level of acceptance and esteem that mistletoe therapy enjoys in Switzerland and Germany. A significant motive is also the hope of making chemotherapy more bearable so that they experience fewer side-effects with an accompanying mistletoe therapy and at the very end the wish to omit chemotherapy. This hope is particularly expressed by patients with comorbidities that limit their quality of life, elderly patients and patients who have had poor experience with chemotherapeutic pre-treatment. Again and again, such expectations need to be disappointed, even at the Lukas Clinic. But there is still a clientele among the patients from whom the refusal of therapy must be accepted on ethical grounds and who can be offered an alternative treatment with mistletoe. Referral of lymphoma patients to the Lukas Clinic by external oncologists in hospitals and private practices is nowadays an increasing trend that is specific to Switzerland. In Germany the medical community still has major reservations to lymphoma treatment with mistletoe.

History

In the 1990s the question came up whether *Viscum album* could lead to increased Interleukin-6 (IL-6) levels. Interleukin-6 is a well-known growth factor for B-cells[1-3] and so the risk of triggering a progression in B-cell lymphoma is incurred[4, 5] by *Viscum album Pini* (Iscador® P). In 1998 a case was published in which histologic lymphoma cell infiltrates were described in a patient exposing a centrocytic non-Hodgkin's lymphoma at the injection sites of *Viscum album* (Iscador®) together with peripheral leaching and subcutaneous infiltration[6]. This case was considered to be a sign that mistletoe therapy might trigger a progression.

In 1999 another publication was released containing the case of a patient with a stage IV follicular lymphoma who received a *Viscum album* (Iscador®) mono-therapy. During treatment this patient achieved a partial remission which –after a pause in therapy– gave way to a progression but returned when treatment was renewed[7]. This case seemed to provide an indication that mistletoe therapy has a remission-inducing and not a progression-inducing effect.

A clinical research project began on May 1st 1999 at the Lukas Klinik in Arlesheim, Switzerland, by which all lymphoma patients attending the clinic were treated by a specialized doctor with standardized subcutaneous *Viscum album* therapy, which fulfilled the criteria of a unilateral prospective surveillance study; the documentation was done by means of regular clinical examinations, radio-imaging and laboratory testing[8, 9].

What is *Viscum album*?

The *Viscum album* extract (Iscador®) constitutes a standar-dized aqueous extract from all parts of the hemiparasite plant *Viscum album*. After extraction it is subjected to controlled fermentation with *Lactobacillus plantarum* followed by mixing of the saps from the winter and summer harvests by means of a high-speed centrifuge. The concentrate is diluted with physiological saline so that the 1 ml ampoules for subcutaneous injection contain 0,01 to 20 mg extract.

Analysis of the extract yields several substance classes: proteins of which the glycoproteins mistletoe lectin I, II and III and the thionins in the form of viscotoxins have been studied best. The *Viscum* compounds from various host trees on which the hemiparasite lives differ considerably with respect to their content substances[10]. The mode of action of the lectins has been well elaborated: it consists of an A- and B- chain of which the B-chain binds to specific membrane receptors. After endocytosis of the lectins hydrolysis is induced at the ribosomal site leading to a block of protein synthesis, the result of which is apoptosis[11, 12]. Another mode of action is immune modulation by the lectins: NK cells and dendritic cells as well as macrophages are activated which can attack tumour cells[13].

Retrospective analysis of clinical records

In 1999 the archives of the Lukas Clinic contained records of 15 patients treated with *Viscum* monotherapy for 5 to 37 years. It was evident from analysis that both patients with follicular B-cell lymphoma and patients with diffuse large B-cell lymphoma experienced sustained remission or even complete remission with monotherapy over the treatment period of 5 to 37 years; some patients were in late stages of the disease or they had been denied chemotherapy (Fig 1).

In patients with NHL, 15 of whom had been treated for short periods (1 to 15 months) and 12 for long periods (2 to 14 years) with *Viscum album* (Iscador®), the Interleukin-6 level was determined in the serum before and after *Viscum album* treatment and compared with the readings of 28 controls. No patient showed a statistically significant increase of IL-6 during treatment with *Viscum*. The level of IL-6 in serum decreased significantly in 37 patients with other malignancies[14] (Table 1). These results were confirmed with non-Hodgkin's cell lines by Hugo et al.[15, 16].

Retrospective study protocol

A total of 302 patients to be treated with *Viscum album* were enrolled into the study over a period of 8 years, starting on May 1st 1999 and ending on April 30th 2007. Morbus Hodgkin, myeloma and chronic lymphatic leukemia including the hairy cell leukemia were excluded so that 61 follicular B-cell lymphomas and 130 other B- and T-cell lymphomas could be analysed. Therapy with *Viscum album* commenced and continued for varying periods of time. 47 of the 61 follicular B-lymphomas and 108 of the 130 non follicular B- and T-cell lymphomas were treated with *Viscum album*. 16 patients with follicular lymphoma and 22 patients with other B- and T-cell lymphomas dropped out because they ceased the therapy or they did not reach the full dose of 42 ampoules regarded as the minimum treatment dose. 47 treated patients with follicular B-cell lymphoma and 108 treated patients with non follicular B- and T-cell lymphoma could be included and were compared to 14 and 22 non treated patients, respectively.

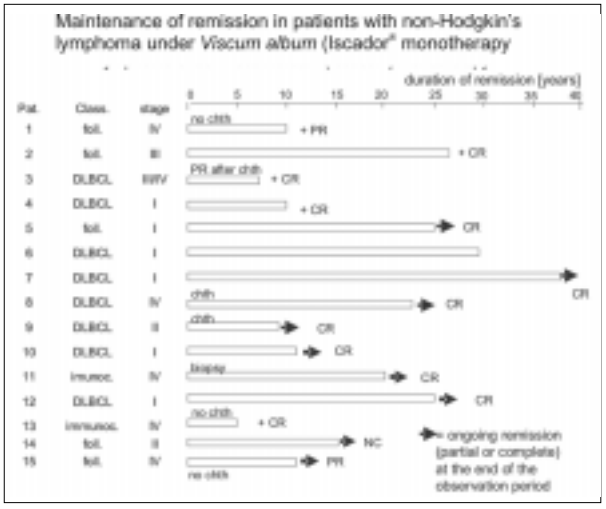

Fig.1.– Maintenance of remission in patients with non-Hodgkin's lymphoma under Viscum album (Iscador®) monotherapy.

Abbreviations: Class.:WHO classification of tumours 2001; foll.: follicular B cell lymphoma; DLBCL: diffuse large B cell lymphoma; immunoc.: immunocytoma (M.Waldenstroem); chth: chemotherapy; PR: partial remission; CR: complete remission; +: patient died

The patients of both lymphoma classifications were allocated into 3 groups upon commencing Viscum treatment according to their pre-treatment: patients without pre-treatment (chemotherapy/antibody therapy/radiotherapy) were accepted into group A; patients for whom pre-treatment was complete into group B; patients for whom pre-treatment was not complete into group C. The patients in groups A and B were in a position of watchful waiting that had been discussed with each patient's oncologist. The patients in group B commenced treatment with *Viscum* after reaching a complete (CR) or partial (PR) remission. A further subgroup of the patients in group B commenced treatment with *Viscum* after pre-treatment was completed unsuccessfully. The allocation to groups showed, among the patients with follicular B-cell lymphomas that 28% (n = 17) commenced *Viscum* therapy without pre-treatment, 54 % (n = 33) had completed pre-treatment and 18% (n = 11) began *Viscum* treatment before completing pre-treatment. Of the 33 patients of group B 5 had achieved a CR, 7 a PR and 21 patients had had no success in pre-treatment.

The percentage of patients without pre-treatment was significantly higher among patients with non follicular B- and T-cell lymphomas. The explanation for this is that most of these patients had been waiting for the beginning of chemotherapy for a very short time and had asked for a second opinion in hope of avoiding chemotherapy.

TABLE 1.– *Behavior of Interleukin-6 serum levels in patients with non-Hodgkin's lymphoma and other malignancies treated with s.c. injections of Viscum album (Iscador®)*

	Before first injection	24 h after last injection	72 h after last injection
Control (no treatment) (healthy volunteers) n=28	2.8 ± 0.3 pg/ml		
NHL patients n=15 short term (1-15 months)	1.6 ± 0.3 pg/ml n.s. vs control	2.4 ± 0.5 pg/ml n.s. vs control	1.8 ± 0.4 pg/ml n.s. vs control
NHL patients n=12 long term (2-4 years)		1.3 ± 0.4 pg/ml decrease vs control p<0.05	2.1 ± 0.3 pg/ml decrease vs control p<0.02
Cancer patients n=37 long term (2-4 years)	8.0 ± 1.0 pg/ml	2.7 ± 0.3 pg/ml p<0.05	

Abbreviations: NHL: non-Hodgkin's lymphoma; n.s.: non significant; vs: versus

Unfortunately most patients had to be disappointed because it is ethically unjustifiable to treat aggressive lymphomas without chemotherapy. Therefore these patients switched from group A to group C.

Examinations

Physical: every 3 months
Laboratory: CRP blood picture, LDH, β_2-microglobulin, immunoelectrophoresis; biochemistry (SGOT/PT, γ-GT, alkaline Phosphatase, creatinin); cytokine panel (IL-6, TNF-α, IL-10, soluble interleukin-2 receptor, LBP) every 3 months
Imaging: CT, PET-CT, PET, MRI, ultrasound. Frequency according to medical indication.

Treatment schedule

Excluding 6 follicular B-cell lymphomas and 18 non follicular B- and T-cell lymphomas who were treated temporarily with other Iscador preparations, all patients were treated with *Viscum album* Pini (Iscador® P) throughout the entire treatment period. The patients carried out the subcutaneous injections in the abdominal skin region by themselves three times weekly. A typical escalation scheme was implemented for the dosage: 0,01-1 mg three times weekly; after using 14 ampoules (4 x 0,01, 4 x 0,1 and 6 x 1 mg) there followed a further dosage increase to 1-20 mg, in some cases up to 10-30 mg three times weekly. Long-term treatment was established with 20 or 30 mg, using the dosage escalation as described before (1/1/10/10/20/20/20 mg or 10/10/20/20/30/30/30 mg).

Ethics

Many patients want to be active by themselves during watchful waiting:

i) one third experienced failure of pre-treatment

ii) some of these refused further conventional treatment

iii) most of these wanted to avoid side-effects of conventional treatment[17].

Some patients refused traditional oncological treatment for various reasons, mostly preferring “soft” treatment and “natural” remedies.

Apart from conventional treatment, the Lukas Clinic also specializes in anthroposophic medicine and combines evidence-based medicine with personalized treatment options (homeopathy, phytotherapy, psychotherapy, art therapies).

Treatment options are always discussed with a forum of oncologists to get a second opinion and to ensure informed consent from the patients.

Every oncologist dealing with the treatment of his patient is informed about all events and consultations with a detailed report after every appointment.

Collective analysis

The distribution pattern of B- and T-cell NHL treated in the Lukas Klinik shows no difference compared to the worldwide distribution. The study type is a retrospective controlled evaluation of 191 patients (61 with a follicular B-cell lymphoma and 130 with a non follicular B- or T-cell lymphoma). All patients were treated and documented by the author in the period between May 1st 1999 and April 4th 2007 (8 years). 47 of the follicular NHL and 108 of the other B and T cell NHL completed *Viscum* treatment, 14 of the follicular NHL and 22 of the other B and T cell NHL were not *Viscum* treated.

Results

The demographic and baseline data showed the following distribution among the follicular lymphomas: 63% of the patients are female (n = 39) and 46% (n = 22) are male. This distribution does not correspond to the distribution of the sexes in this type of lymphoma, a fact which can best be explained by women throughout Europe wishing complementary medicine more often than men. The comparison of patients with follicular NHL treated with *Viscum* and those not treated showed greater age in the *Viscum* group and a higher FLIPI score. Thus the two prognosis factors age and FLIPI were unevenly distributed within the Viscum group.

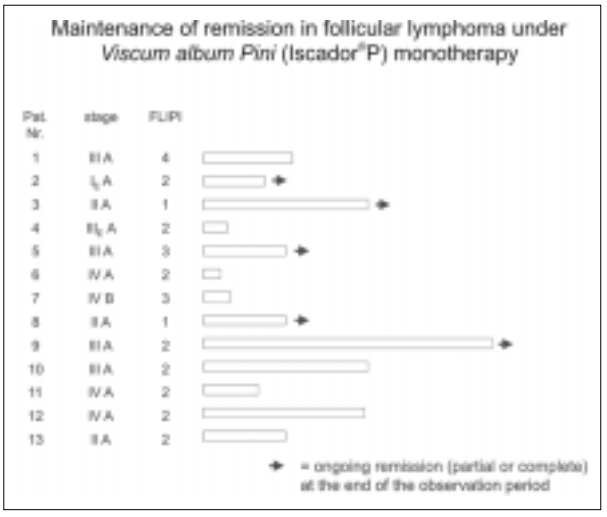

Fig. 2.– Maintanance of remission in non-Hodgkin‘s lymphoma under *Viscum album Pini* (Iscador®P) monotherapy

TABLE 2.– *Triggering and maintenance of remissions (partial and complete) by* Viscum album Pini *(Iscador® P) monotherapy*

Name	Classification (WHO) FLIPI, IPI	Triggering of remission yes/no	Maintenance PR (months)	Maintenance CR (months)	Status at the end of observation
RR	follicular IIA FLIPI 2	yes		40	CR 3/2007
MR	follicular IIIA FLIPI 2 + DLBCL	yes		36	PD 2/2006 NC 3/2007
PI	follicular IVB FLIPI 1	PR by chth CR by Viscum		27.5	CR
HE	follicular IVB FLIPI 3	yes		43	CR 1/2004
NC	follicular IVA FLIPI 1	yes	11		PD
PR	follicular IIIA FLIPI 1	yes	47		PD
WS	DLBCL IVA IPI 3	no		82, CR by chth	CR 1/2007
SH	DLBCL IIA IPI 3	PR by radioth. CR by Viscum	PR after radiotherapy	95	CR in 1/2007

Abbreviations: FLIPI: Follicular Lymphoma International Prognostic Index; IPI: International Prognostic Index; DLBCL: diffuse large B cell lymphoma; PR: partial remission; CR: complete remission; chth: chemotherapy; radioth.: radiotherapy; PD: progressive disease

The distribution of the prognosis factors age and Ann Arbor stage in the non follicular B- and T-cell lymphomas is also unequally distributed in respect to the *Viscum* group. In the assessment of a progression among the follicular and non-follicular lymphomas, the marker sIL-2R favours an increase better than the parameters LDH and β_2-microglobulin (p = 0,001 and 0,002 respectively). Thus, these results seem to confirm those of a multi-center trial held in Japan[18, 19]. This means that the markers sIL-2R and β_2-microglobulin are better discriminators in respect to progression and regression than LDH. This statement has to be further validated within a prospective trial.

Remissions in follicular lymphoma treated exclusively with *Viscum album Pini* (Iscador®P) last between 3 and more than 80 months (Fig. 2) The induction of long-lasting CR with *Viscum album* (Iscador®) monotherapy could be achieved in 5 patients with follicular lymphoma, induction of PR with *Viscum album* (Iscador®) monotherapy was seen in 3 patients, 2 with follicular B cell and 1 with diffuse large B cell lymphoma (DLBCL). The duration of remissions was between 11 months and 95 months, regardless of high Ann Arbor stage and prognostic score in some cases (Table 2) by *Viscum album Pini* (Iscador® P).

Presentation of best cases

All cases presented here are non-Hodgkin's lympho-mas who received Iscador® P exclusively, but were treated by the author over long periods of time and had a good outcome.

Patient N° 503492 (7) with a follicular B-cell lymphoma stage IV with infiltration of bone-marrow was treated for more than 12 years with *Viscum album* P exclusively. He experienced a complete remission in the mediastinum and, after interrupting *Viscum* therapy, relapsed with new mediastinal lymphomas. The abdominal lymphomas also showed partial remission during treatment. and a progression after interruption of treatment Thus, this case may represent a single case study, showing remission by *Viscum album* treatment and progression after interruption of treatment and again remission after renewing the *Viscum album* treatment. After 13 years a progression started again and two different chemotherapies did not show a response, but after a third chemotherapy remission could be achieved. The patient continued with *Viscum album* throughout the period of chemotherapy. Further treatment was necessary because of relapse but he achieved no response to Lutetium/Rituximab. The disease has remained stable up to now despite a chronic hydronephrosis of the right kidney caused by the lymphoma. Bone-marrow infiltration is not seen any longer. The patient has survived now for almost 21 years and continues the Iscador treatment. He is in excellent condition without any symptoms.

Patient N° 525298: This is a patient aged 73 who was diagnosed with a diffuse large B-cell lymphoma in the pit of the stomach 5 years ago. The patient refused chemotherapy and therefore there was an ethical indication for a *Viscum album* therapy with Iscador® P together with a successful eradication of helicobacter infiltration. There is no evidence for the effectiveness of helicobacter eradication in diffuse large B-cell lymphoma in the stomach except for some rare case reports[20, 21]. There was some discussion, therefore, that in this case a transformation of the diffuse large B-cell lymphoma to MALT lymphoma

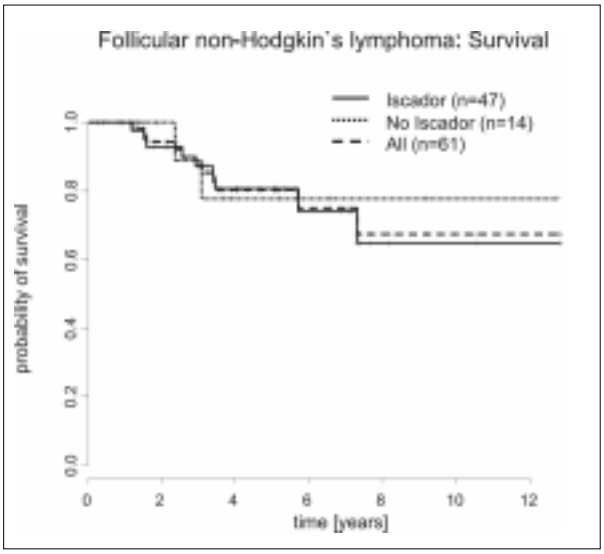

Fig. 3.– Follicular non-Hodgkin's lymphoma: Survival curve

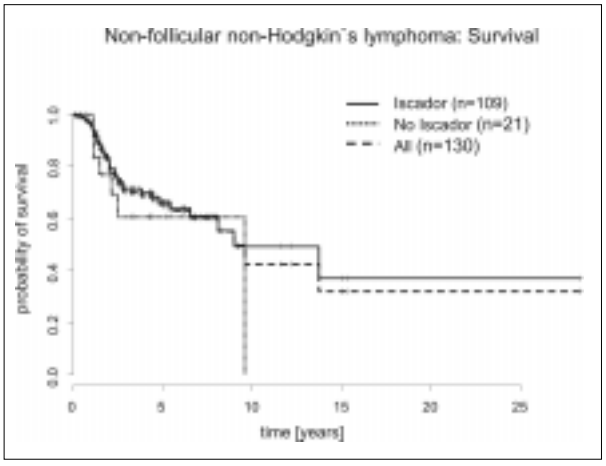

Fig. 4.– Non-follicular non-Hodgkin's lymphoma: Survival curve

had taken place, but this could not be confirmed by the pathologist. At a recent gastroscopic check-up no lymphoma infiltration could be seen. A final gastroscopic check-up took place on February 2nd 2006 without a pathological result. The latest information came from May 23rd 2007 and the patient remains free from relapse now for almost 5 years while continuing to take *Viscum album* therapy.

Patient no. 525851: This is a female patient, now 78 years old with an aggressive angioimmunoblastic T-cell lymphoma stage III B, diagnosed 4 years ago. Lymph nodes were seen in the cervix, the mediastinum and the abdomen where lymph node excision was done by laparoscopy. She refused chemotherapy and achieved a partial remission less than 2 years after first diagnosis with Iscador® P monotherapy. Elevated LDH and sIL-2R were normalized under the Iscador® treatment. The patient is still alive and in best condition without any symptoms deriving from the lymphoma.

Survival curves

The survival curves (Fig. 3, 4) were established for patients treated with and without *Viscum album* in the follicular and non-follicular group. The distribution of the prognostic factors age, FLIPI and Ann Arbor stage, respectively, was unfavourable for the treatment group. Nevertheless, no significant differences were seen between both groups. The number of patients in the untreated groups was very small, so the result may show only a trend. If the sample sizes in the two treatment groups (treated and not treated) were larger it might be easier to answer the question of how *Viscum* treatment affects survival.

Discussion

Mistletoe therapy for malignancies is widespread in Europe, particularly in Switzerland and Germany[22]. Copious pre-clinical results describing the effectiveness of mistletoe therapy are available[23]. There is some evidence for clinical effectiveness deriving from prospective randomized studies[24] that show a positive influence on the quality of life[25]. Increase in survival seems likely as suggested by retrospective studies conducted in recent years[26, 27].

The surveillance study carried out retrospectively in the Lukas Clinic and presented here was initiated following references by a single author[4, 5], above all in Germany, to determine the risk of interleukin-6 stimulation by mistletoe therapy.

No increases among lymphoma patients taking *Viscum album* could be seen in the many measurements of serum IL-6 (there are more than 1000 of them, data not shown). This was confirmed by a prospective investigation into this question[14]. In experimental investigations of lymphoma cell lines, IL-6 stimulation could be excluded. It could be shown that proliferation induced by interleukin-6 was counteracted by *Viscum album Pini* (Iscador® P)[15, 16]. Apart from a case report[7], clinical indicators of mistletoe therapy's effectiveness with lymphomas were missing, and thus there was a need to carry out clinical studies. The work presented here refers to a retrospective surveillance study performed at the Lukas Clinic in the period May 1st 1999 – April 30th 2007 (8 years). The clinic's specialization in mistletoe therapy did not permit the inclusion of patients into a control group, but there is evidence from this data that the risk of *Viscum album* inducing tumour progression by stimulation of IL-6 is to be excluded. The induction of partial and complete remissions

in follicular and non-follicular lymphomas after monotherapy with *Viscum album* (Iscador®) taken as primary signs of efficacy also point in this direction. This is underlined by cases in which remission was of very long duration.

The results presented here are derived from a preliminary interim analysis. An analysis with extended numbers of patients is underway. The preliminary results particularly indicating sustaining of remissions must be confirmed further in a prospective randomized clinical study design, including chemo-, radio- and antibody therapy. Besides treatment during watchful waiting and after completion of pre-treatment, quality of life should be a special target of examination in patients who undergo chemo-, antibody and radiotherapy to confirm the reduction of side-effects of basic oncological treatment by *Viscum album*, as was shown in some trials[17]. Patients in whom chemotherapy cannot be carried out because of various reasons (e.g. age, co-morbidity) could be offered a *Viscum* treatment as a feasible alternative treatment option and should be included in an observational study. In follicular lymphoma the lymphocyte count seems to be an independent prognostic factor[28]. Therefore, the behavior of the lymphocyte count under combined treatment with chemo- and *Viscum album* therapy should not be overlooked, since there are reports that *Viscum album* may increase lymphocyte count[29]. Examination of specificity and sensitivity of the marker sIL-2R in diagnosis and follow-up of NHL should be included.

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Over the past decade, a great change has occurred in how we think about cancer. Where once we viewed cancer as an unfathomed black box, now we have pried open the box and cast in the first dim light. Where once we thought of cancer as a bewildering variety of diseases with causes too numerous to count, now we are on the track of a single unifying explanation for how most of all cancers might arise. The track is paved with cells.

Durante la última década, se produjo un gran cambio en nuestra manera de enfocar al cáncer. Hubo un tiempo en que considerábamos al cáncer como una impenetrable caja negra pero ahora hemos entreabierta esta caja y proyectado el primer haz de luz. Antes, se le atribuía al cáncer una impresionante variedad de enfermedades con causas de las más numerosas, mientras que hoy estamos en vías de encontrar una sola explicación unificando la forma en que la mayoría de los cánceres surgen. El camino está pavimentado de células.

J. Michael Bishop

How to Win the Nobel Prize: An unexpected Life in Science.
Cambridge MA: Harvard University Press, 2003, p 135