Mistletoe Therapy in Cancer

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European White-Berry Mistletoe (*Viscum album*)

Chronological specialties of European mistletoe

	Mistletoe	**Higher organized plants**
Photosynthetic activity	Throughout the year	Rest in winter
Development of vegetative and generatative organs	Simultaneous	In succession
Flowering time	Late winter	Warm half of year
Ripe fruits	Early winter	Summer or autumn
All steps of development	Highly delayed	Normal
Germination rest	Non-existent	Existent

Morphological specialties of European mistletoe

	Mistletoe	**Higher Organized Plants**
Growth of roots	Sinker growth in direction of host tree, independent of gravity	Geotropic - according to gravity
Growth of shoots	In all directions (globular bush) independent of gravity and light	Heliotropic - in the direction of the sun
Germination	With light	Frequently in the dark
Photosynthesis	Upper surface and underside of leaves; all parts of the plant are green	Upper surface only
Formation of Organs	Delayed, juvenile, reduced (no roots, primitive flowers, no real seeds, primitive uniform leaves)	Normal

The Founders of Mistletoe Therapy in Oncology

He pointed out the idea:

Rudolf Steiner, PhD (1861-1925)
Philosopher, Founder of Anthroposophy

She developed and administered the first mistletoe injection products:

Ita Wegman, MD (1876-1943)
Physician, Head of the Clinical-Therapeutic Institute (Switzerland)

History of Mistletoe Therapy

A) External and oral application

Hippocrates (460 – 377 b.C.)
- recommendations for spleen diseases.

Arabian physicians (10. – 12. century)
- epilepsy, dizziness, cardiac insufficiency, dropsy, infertility.

Hildegard von Bingen (1098 – 1179)
- hepatopathic conditions.

Herbal books of medieval times (15. century)
- beneficial for wound-healing, softening, analgesic, birth easing.

History of Mistletoe Therapy

A) External and oral application

Paracelsus (1494 – 1541), John Colbatch (1670 – 1728)
- specific against epilepsy.

Albrecht von Haller (1708 – 1777)
- spasmolytic, gynecology.

Homeopathy (19. century)
- congestive headache, dizziness, angina pectoris, asthma, rheumatism, uterine haemorrhage, depression.

Popular medicine in Central Europe (19. century)
- hypertension, prophylactic against arteriosclerosis.

History of Mistletoe Therapy

B) Parenteral application

Gaulthier (1907)
- distinct reduction in blood pressure after i.v. application.

R. Steiner, I. Wegman (1917)
- injection therapy with mistletoe products against cancer.

Madaus (1938)
- intracutaneous segmental therapy of degenerative and inflammatory joint diseases.

Dinkelaker/Kass (1982)
- Viscum album D3 – D14 i.v.:
  vegetative balancing, mind relieving, spasmolytic (blood vessel, bronchial tubes), analgesic (migraine, neuralgia).

HELIXOR® History

1971	Development of new mistletoe preparations named HELIXOR by the Association for Leukemia and Cancer Therapy in Stuttgart
1972	The first batch was successfully tested in cancer patients
1973-77	13 reports on clinical trials
1979-81	2 clinical trials published
1975	HELIXOR company founded in Marburg
1976	First registration of HELIXOR in Germany
1979	HELIXOR FOUNDATION for public welfare founded
1980	Relocation of HELIXOR company to Rosenfeld
1982	New registration of HELIXOR A/M/P according to the new German Drug Law

HELIXOR—Three Different Types

Fir mistletoe

- Viscum **a**bietis → HELIXOR® A

Apple tree mistletoe

- Viscum **m**ali → HELIXOR® M

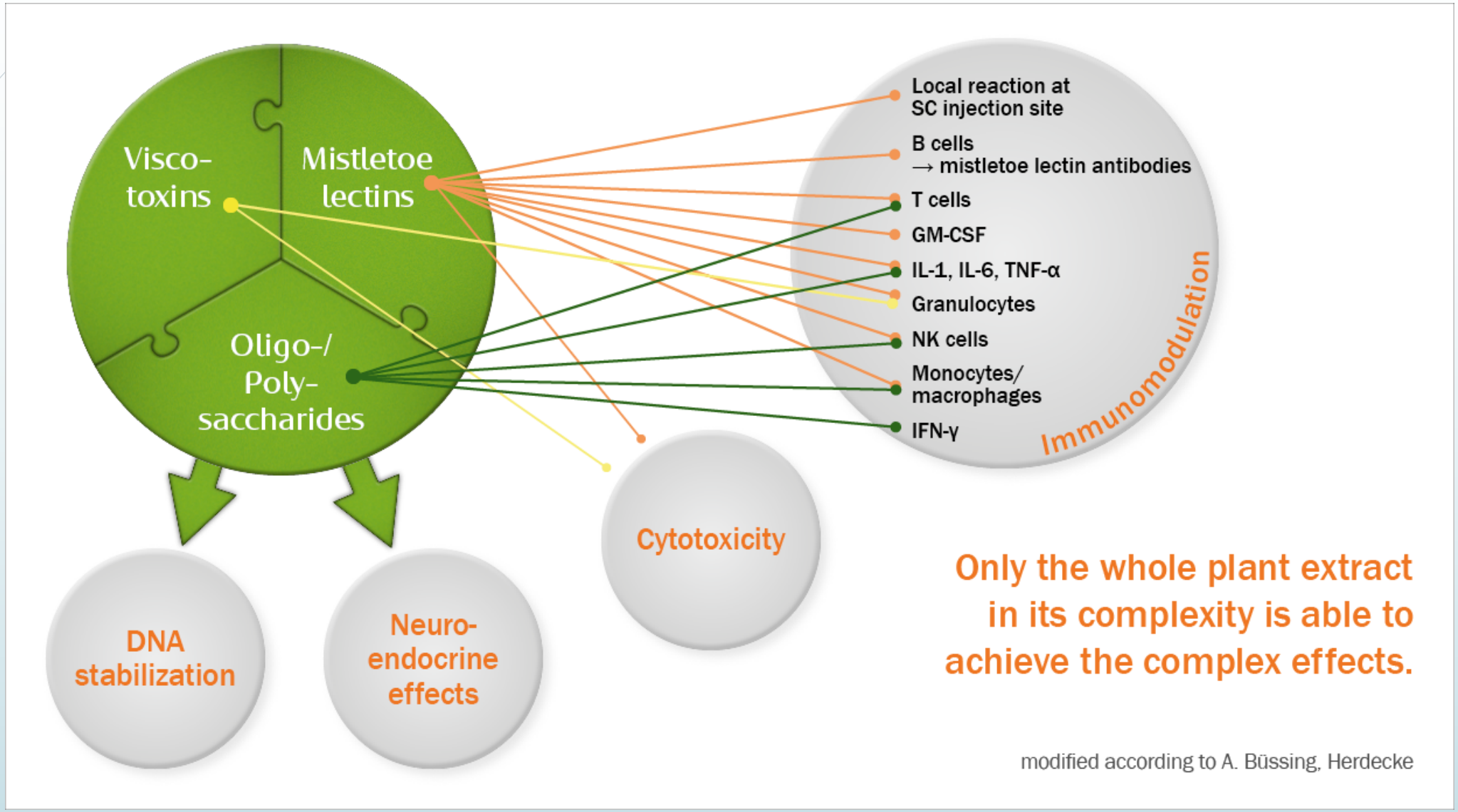
Pine mistletoe

- Viscum **p**ini → HELIXOR® P

Constituents of *Mistletoe Extracts*

Structural types	Constituents	Effects on cancer cells	Effects on immunocompetent cells
Glycoproteins	Mistletoe lectins ML I, II, III (RIP II)	Cytotoxicity by inhibition of the ribosomal protein synthesis + induction of apoptosis (intrinsic pathway)	Activation of macrophages Increase in eosinophils Release of TNF-α, IL-1, IL-2, IL-6
	Visalb CBA = cbML	Weak cytotoxicity	Adjuvant stimulation of immune response
Polypeptides	Viscotoxins $A_{1\text{-}3}$, B, 1-PS, U-PS	Cytotoxicity by lysis of cell membrane	Activation of macrophages Enhanced phagocytosis activity of granulocytes
Oligo- and Polysaccharides	Arabinogalactane Rhamno-galacturonane	Indirect immune-mediated tumor inhibition	Stimulation of T-helper-cells ($TH_1 \uparrow$, IFN$\gamma \uparrow$) Enhanced NK-cell activity
Flavonoids	Derivates of quercetine	Induction of apoptosis	Antioxidative, anti-inflammatory + antinociceptive effects
Phenylpropane glycosides	Syringin	-	Immune protection Protection against stress (adaptogen) Antioxidative effects
Triterpenoids	Oleanic, ursolic and betulinic acid	Induction of apoptosis and cell differentiation, Anti-angiogenesis	Anti-inflammatory + antioxidative effects Immune protection

Whole Extract = Active Ingredient of Mistletoe



Clinical Benefits of Mistletoe Therapy

- Inhibition of malignant growth **without harm to healthy tissue**
- Increase of **endogenous resistance and regulation**
- Stimulation of **thermoregulation**
- Improvement of **general condition and performance**, irrespective of the local tumor situation
- Decrease of tumor associated pain

Excerpt from „Monography Viscum album“, Commission C, Federal Health Administration in Germany, Bundesanzeiger 38 (Nr. 99 a) 55 (04.06.86)

Use of Helixor® in Oncology

	Main Indications	Therapeutic Aim
Palliative Therapy	• inoperable or metastasizing cancer	• improvement of quality of life • increase of survival
Adjuvant Therapy	• prevention of relapse after surgery or chemotherapy/ radiotherapy	
Supportive Therapy	• during chemotherapy or radiotherapy	• immunoprotection • improved tolerance of oncologic therapies
Prophylactic Therapy	• defined precancerous lesions	• involution of precancerous lesions

Indications for Helixor®

- All kinds of cancer (all sites and histological types)
- All cancer stages
- At any point in the course of cancer
- After cancer cure – for prophylaxis of relapse
  in secondary or other prevention

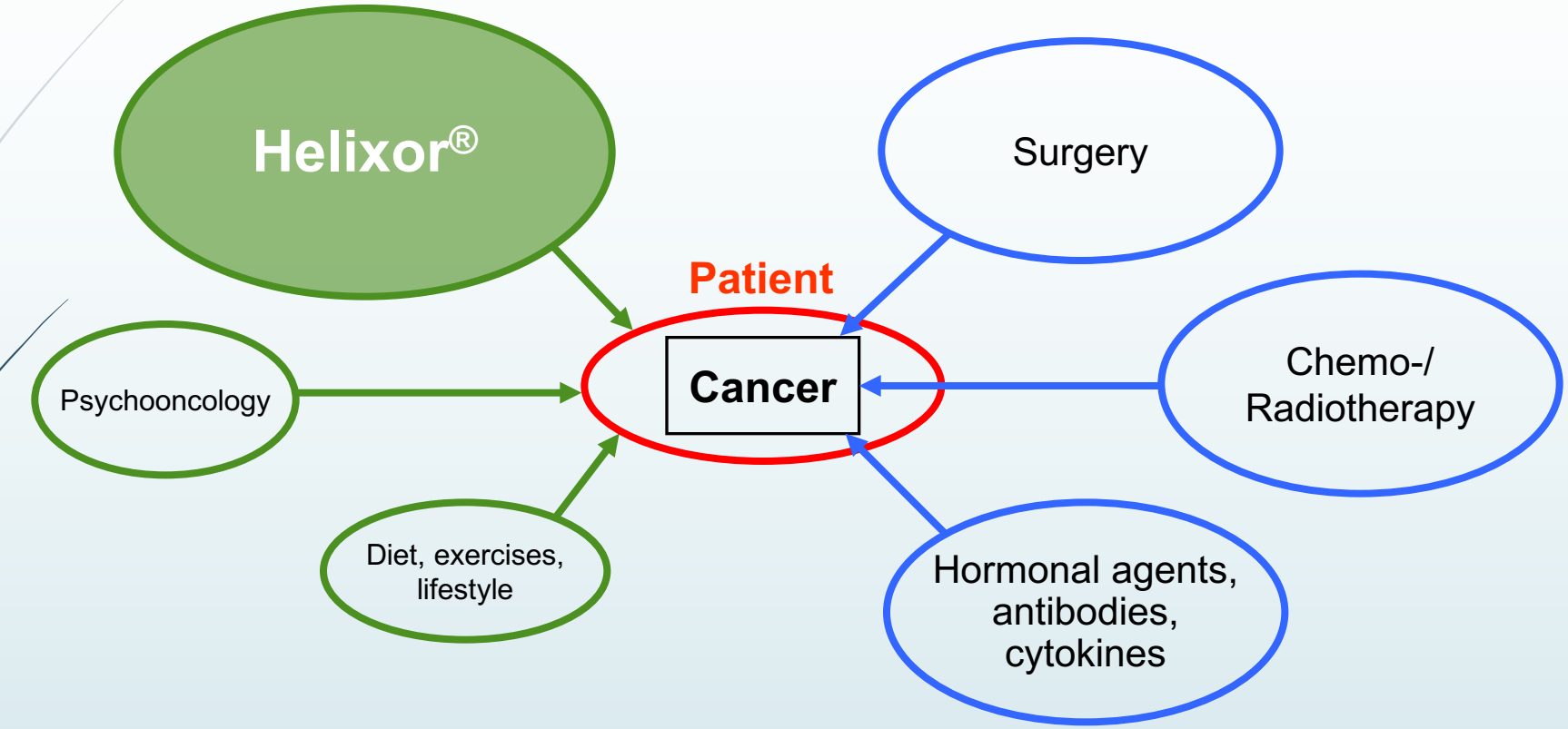
Helixor® is not aimed at the tumor directly but at the host organism by

- Activating the potencies of resistance, self-healing and regulation
- Protecting the organism from adverse effects of standard therapies
- Significantly enhancing the quality of life

Contraindications to Helixor®

Contraindications	*Measures*
Allergy to mistletoe products	As a precaution: no further mistletoe therapy
Acute inflammatory disease, high fever	Continuation of mistletoe therapy after regression of symptoms
Acute hyperthyroidism with tachycardia	
Chronic granulomatous and autoimmune diseases (if florid or treated with immunosuppressants)	Mistletoe therapy only in inactive disease if immunosuppressants are no longer required

Integrative Oncology



Stimulation of salutogenesis ← **Therapeutic Aim** → Intervention in pathogenesis

Relevant Oncological Effects of Mistletoe Therapy

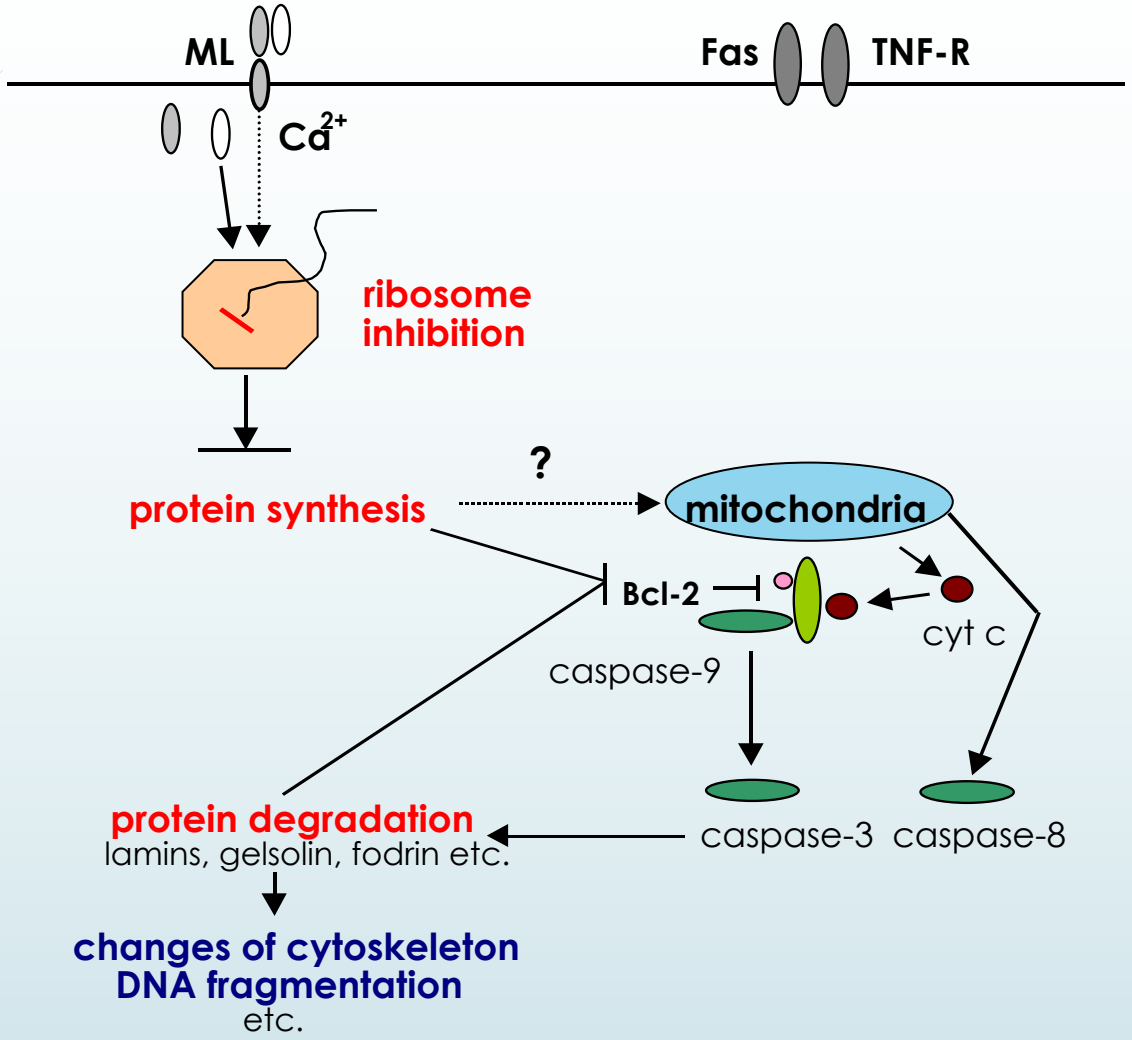
Effects	Mode of Action
tumor inhibition	• direct: dose-dependent cytotoxicy (protein synthesis ↓, induction of apoptosis ↑) • indirect: inhibition of tumor angiogenesis • indirect: immunologic effector cells ↑
Immunomodulation (infections ↓)	• number of immunologic effector cells ↑ • activity of immunologic effector cells ↑ • release of cytokines ↑
DNA- and cytoprotection	• lymphocytes: DNA-stability ↑, DNA-repair ↑ • immunosuppressive effect of chemotherapy ↓
Improvement of quality of life (psychotropic effects)	• β-endorphin↑ and other neuroendocrine effects • restoration of circadian rhythms

Cytotoxic Effects of Helixor®

- Dose-dependent inhibition of cell growth as well as induction of cell death
- Malignant cells significantly stronger inhibited than normal cells
- Cytostatic drug-resistant cells stronger inhibited than sensitive cells
- Mechanism: inhibition of ribosomal protein synthesis and induction of apoptosis (intrinsic pathway) mediated by mistletoe lectins
- Proof of efficacy in > 40 different malignant cell lines
- Highest efficacy in breast cancer, leukaemia, myeloma, lymphoma, and prostate cancer
- Strongest *in vitro* effects by Helixor® P (M), weakest by Helixor® A
- Cytotoxicity is counteracted by anti-mistletoe lectin antibodies which are produced after 2 – 4 weeks mistletoe therapy

Helixor® Literature Synopsis 2008 (24 publications)

Mechanisms of ML-Mediated Cytotoxicity



Protein synthesis inhibition may induce mitochondrial triggers such as RIP and cytochrome C which activate the caspases. Bcl-2 regulates apoptosis by binding of Apaf-1 and by regulating the induction of mitochondrial permeability transition.

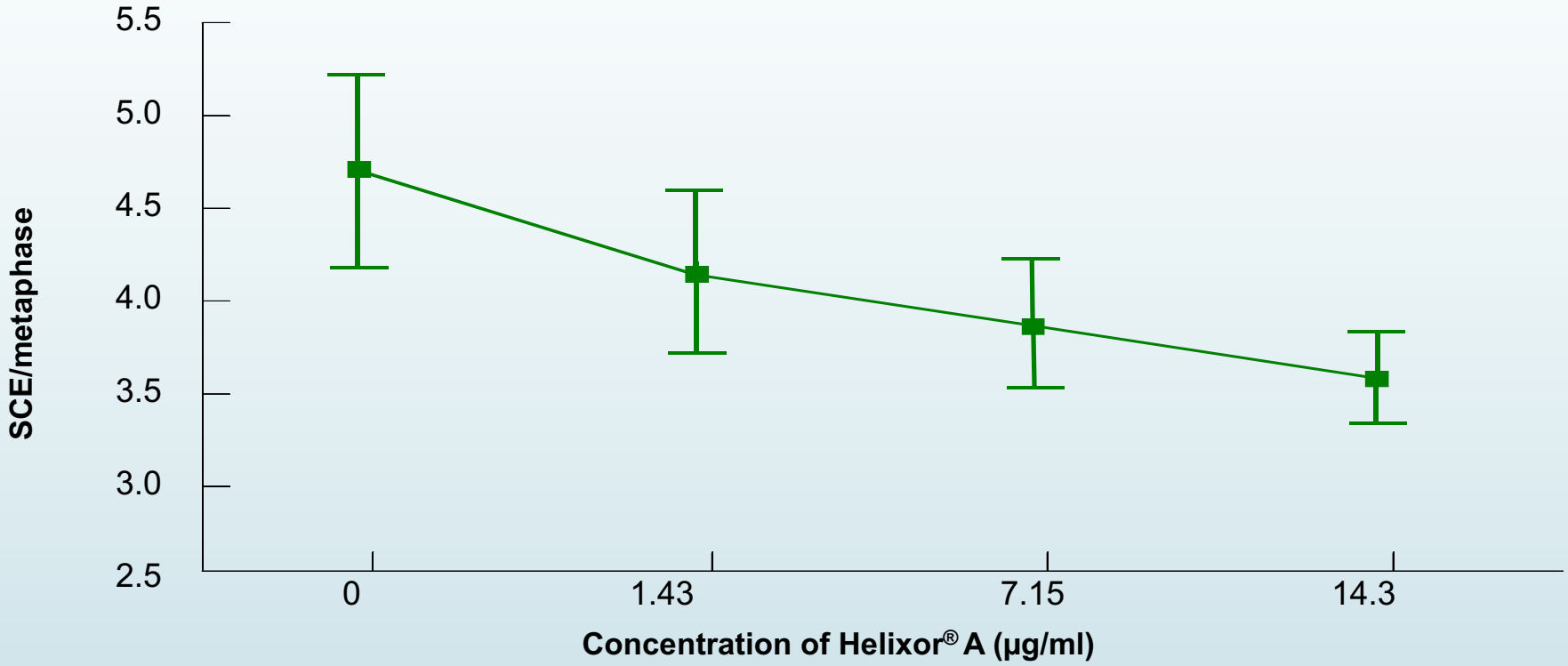
Büssing, A. et al.: Zeitschrift für Onkologie 31, 2, 1999

DNA-Stabilization by Helixor® A

Publications of Büssing et al.	*Journal/Year*
Significant reduction of sister chromatid exchange frequency (= cytogenetic damage, mutagenicity) in PBMC	Eur. J. Cancer 1994
DNA-protection of PBMC from mutagenic and immunosuppressive effects of cytostatic drugs	Cancer Letters 1995
DNA-protection only in normal PBMC, whereas in malignant cell-lines the cytotoxic effect of chemotherapy is additionally increased	J. Exp. Clin. Cancer Research 1996
Also in animal experiments: stronger cytotoxic effect on lung metastases by combination of cyclophosphamide + mistletoe	Forsch. Komplementärmedizin 1996

DNA-Stabilization and Antimutagenic Effect of *Viscum album* L. Extracts

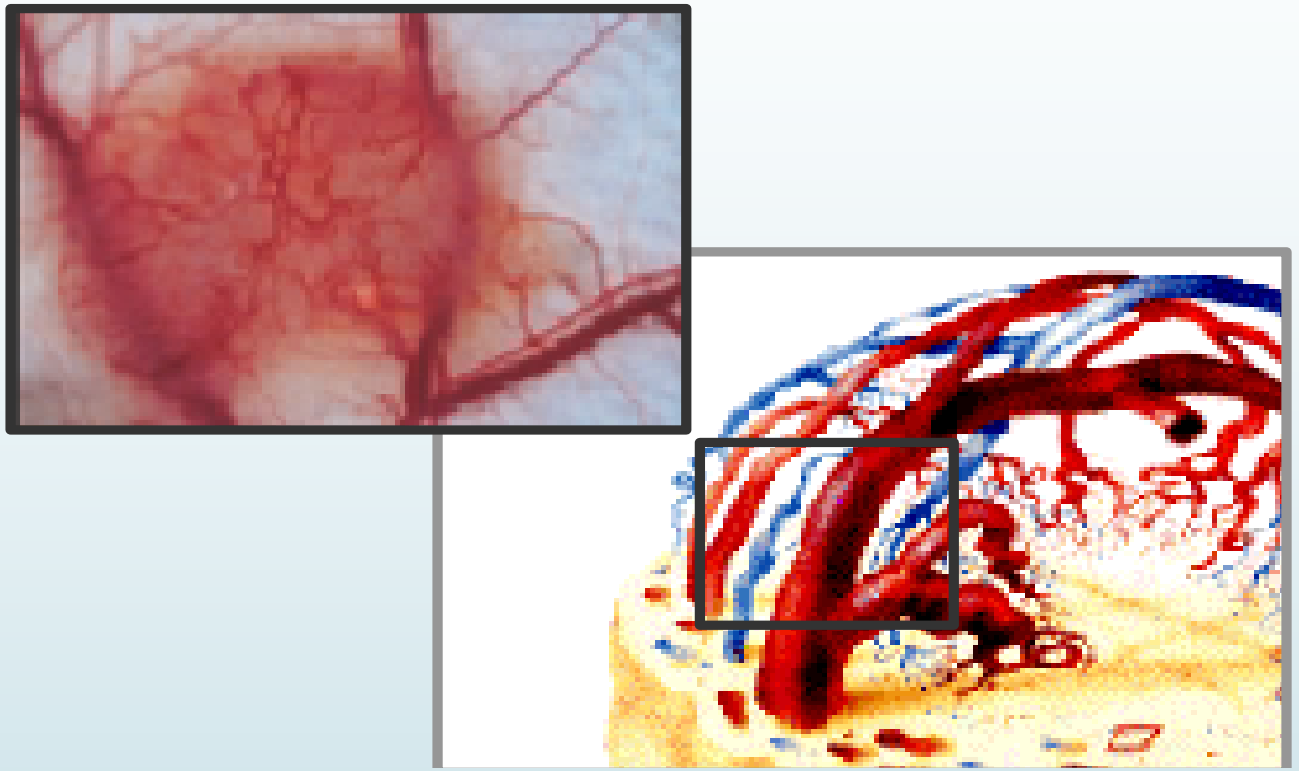
Significant decrease in sister chromatid exchanges (SCE) of phytohaemagglutinin-stimulated peripheral blood mononuclear cells after treatment with Helixor® A ($p < 0.0001$).



Büssing, A. et al.: European Journal of Cancer 1994, 30A (12), 1836-1841

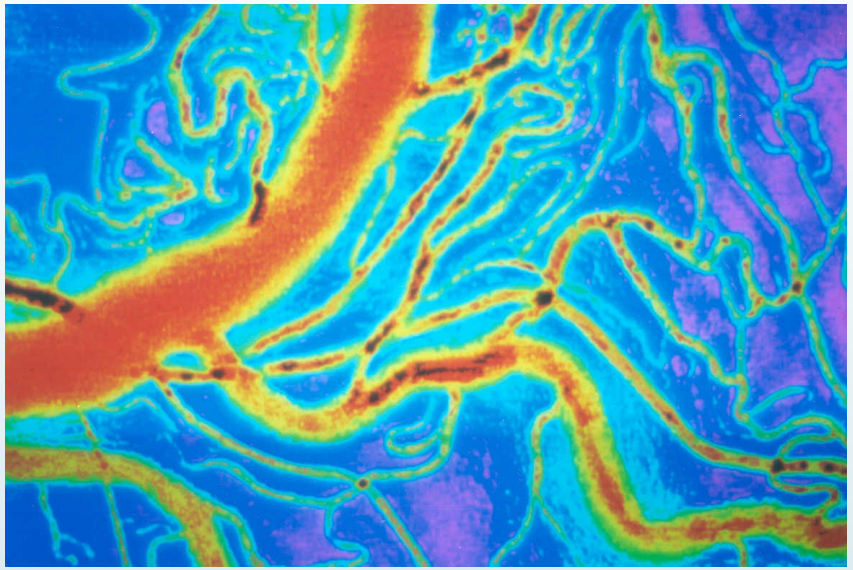
Anti-Angiogenesis

A further mechanism of mistletoe anti-tumour-activity?

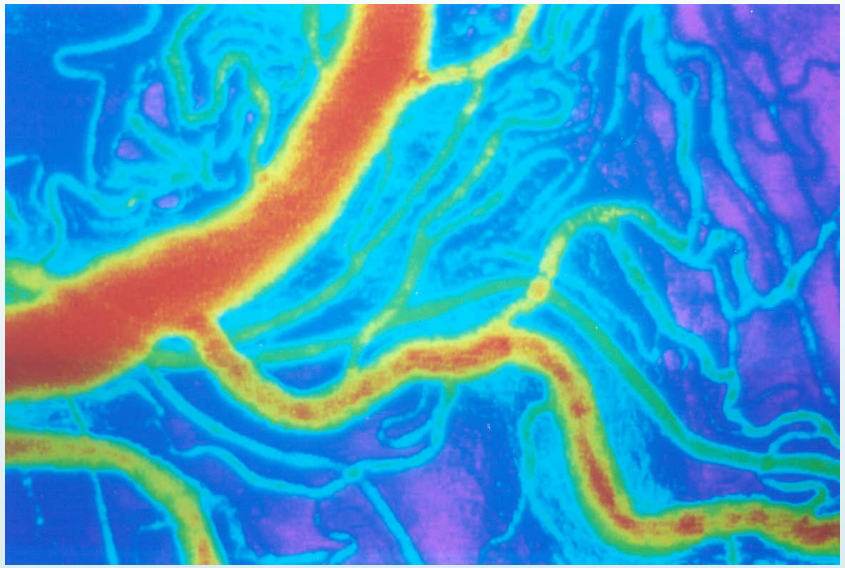


Klopp, R. et al.: Changes of Microcirculation in the Tumour and in the Peritumoural Tissue after Application of Standardized Mistletoe Extract – DZO 35, 2003, 5 - 14

Changes in the condition of blood microcirculation of the tumour tissue in animals allocated to verum group at various time points of observation (1/1000s, vital microscopic example of finding, detailled picture, EDP processed primary picture in pseudo coloured transformation).



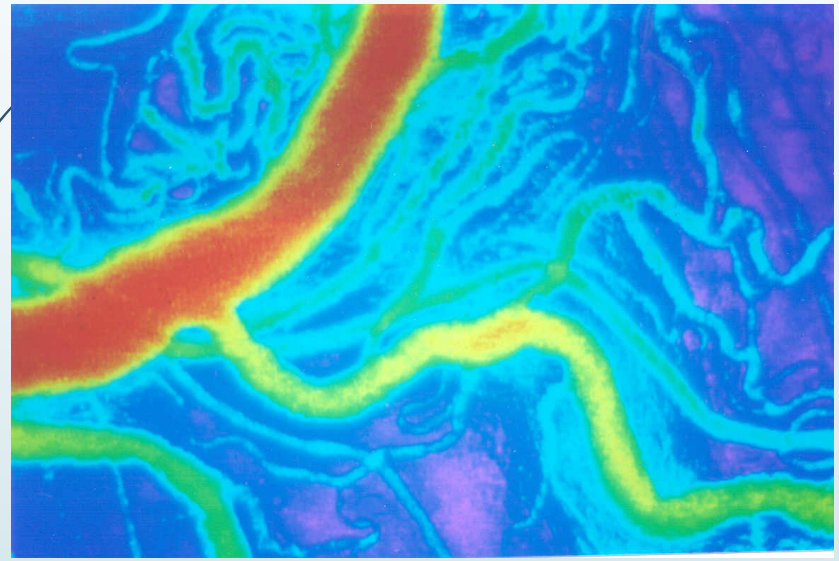
Condition of blood distribution in the micro-vascular net (capillary vessels, arteriolas, venules) at day 0, prior to application of mistletoe extract.



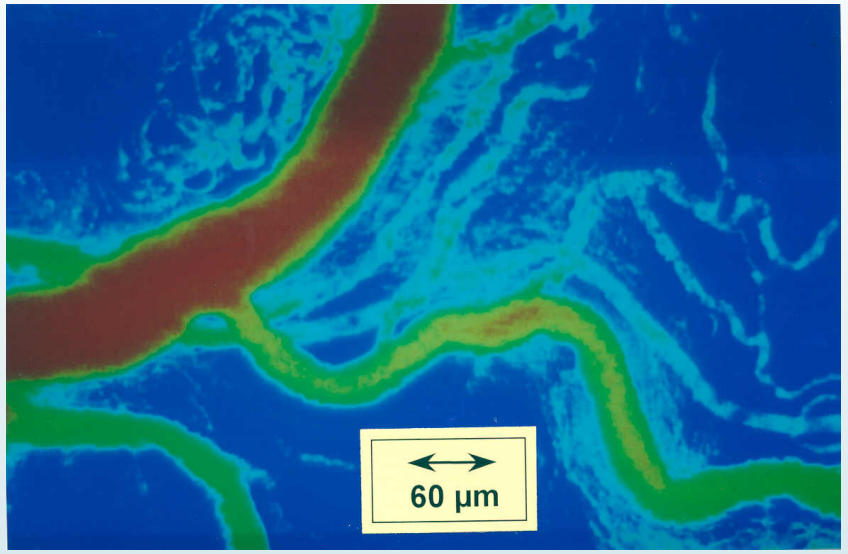
Condition of blood distribution after treatment by mistletoe extract at day 14.

Klopp, R. et al.: Changes of Microcirculation in the Tumour and in the Peritumoural Tissue after Application of Standardized Mistletoe Extract – DZO 35, 2003, 5 - 14

Changes in the condition of blood microcirculation of the tumour tissue in animals allocated to verum group at various time points of observation (1/1000s, vital microscopic example of finding, detailled picture, EDP processed primary picture in pseudo coloured transformation).



Condition of blood distribution at day 28.

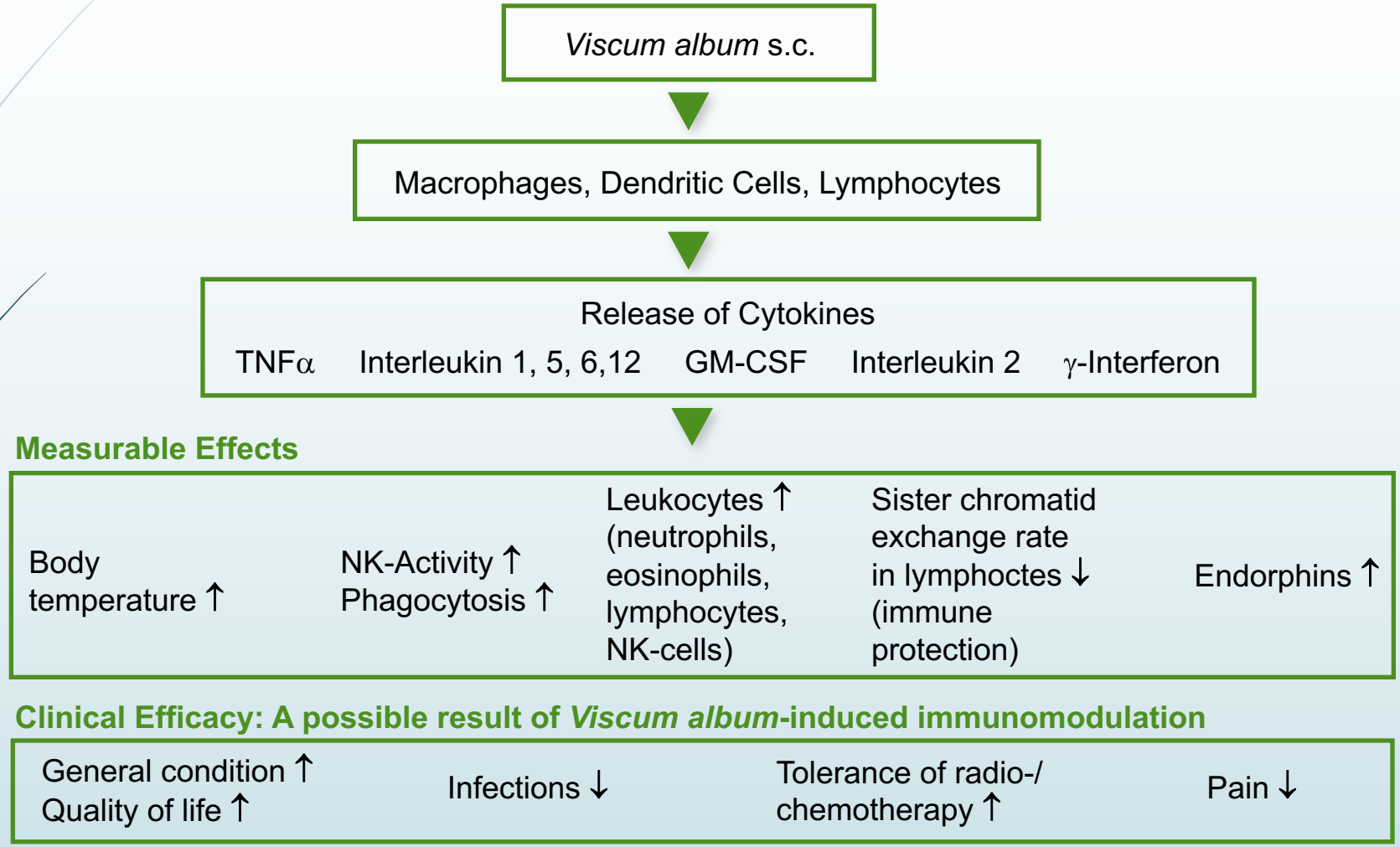


Condition of blood distribution at day 35.

Inhibition of Angiogenesis by *Viscum album*

Author	Year	Journal	Model	Test Substance	Result
in vitro					
Park, W.-B. et al.	2001	Cancer Biother. Radiopharm.	chorioallantois-membrane assay	*Viscum album* coloratum lectin	dose-dependent increase of avascular eggs
Hong, S. et al.	2007	Anti-Cancer Drugs	ECV 304 endothelial cells	Helixor® A	70 – 80 % inhibition of neoangiogenesis via induction of thrombospondin-1
Moon, J.M.	2010	Doctoral thesis Seoul Nation. Univ.	eutopic/ectopic endometrial stromal cells	Helixor® A	significant decrease of VEGF expression
in vivo					
Yoon, T.J. et al.	1995	Cancer Letters	B16-BL6 melanoma	*Viscum album* L. coloratum extract	size of primary tumours ↓, neoangiogenesis ↓
Klopp, R. et al.	2003	DZO	NMRI nude mice, human adeno-ca HP29	Helixor® P	tumour volume ↓, microcirculation in tumour tissue ↓↓, in surrounding healthy tissue ↑

Immunological Effects of *Viscum album* Products

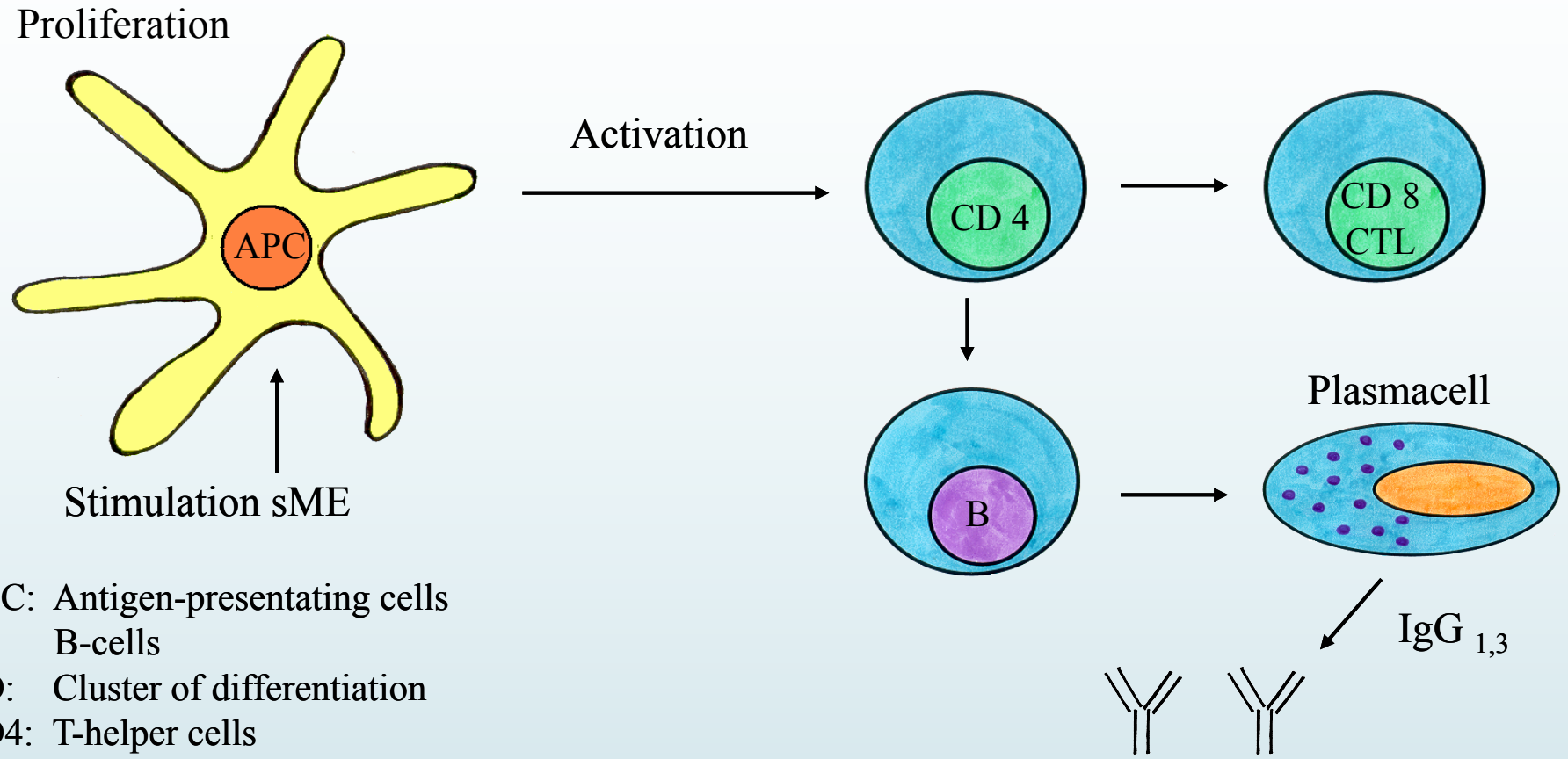


Immunological Effects of Mistletoe Extracts

- Activation of antigen-presenting cells
  (monocytes, macrophages, dendritic cells)
- Increase of granulocytes: neutrophils, eosinophils after 1 month
- Increase of phagocytosis activity
- Increase and activation of lymphocytes (CD4+ ↑, CD25+ ↑)
- Increase of FasL on lymphocytes
- Increase of Natural Killer (NK) cells and of NK activity
- Modulation of cytokine release: TNF-α, IL-1, IL-6, IL-2, IL12, IFN-γ, IL-4, IL-5, IL-10, GM-CSF
- Induction of antibodies to mistletoe antigens
  (esp. anti-ML antibodies)

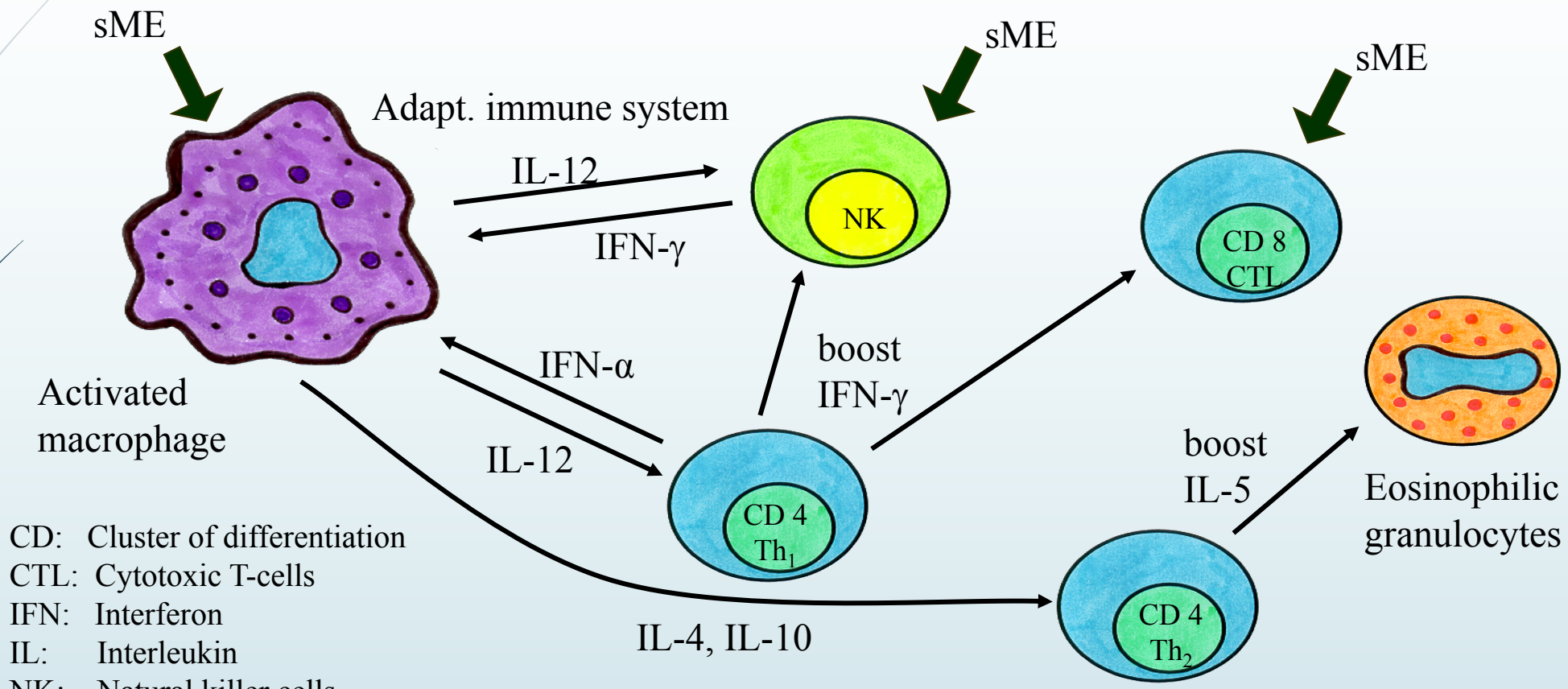
Berg, P.A., Stein, G.M.: DMW 126, 2001, 339-345 (modified and updated 4/2002)

Activation of Dendritic Cells by Standardized Mistletoe Extract (sME)



APC: Antigen-presentating cells
B: B-cells
CD: Cluster of differentiation
CD4: T-helper cells
CTL: Cytotoxic T-cells
IgG: Immunoglobulin G
sME: Standardized mistletoe extract

Activation of Cellular Immune System by Standardized Mistletoe Extract (sME)



CD: Cluster of differentiation
CTL: Cytotoxic T-cells
IFN: Interferon
IL: Interleukin
NK: Natural killer cells
sME: Standardized mistletoe extract
Th: T-helper cells

The Scientific Basis of Mistletoe Therapy

- Mistletoe belongs to the best investigated herbal medicines
- More than 2,000 scientific publications
- More than 130 clinical studies
- More than 40 prospective-randomized clinical studies

Literature:

- Kienle/Kiene: Die Mistel in der Onkologie, Schattauer 2003
- Kienle/Kiene: Eur J Med Res 2007
- Horneber et al.: Cochrane Review 2008
- Kienle et al.: J Exp Clin Cancer Res 2009
- Kienle/Kiene: Integr Cancer Ther 2010
- Kienle et al.: Forsch Komplementmed 2011

Cochrane Review on Mistletoe Therapy

21 randomised clinical trials (out of a total of 80 clinical studies):
n = 3484 randomised patients

Primary Endpoints	**n =**	**benefit of mistletoe therapy found**
Quality of life + prevalence of chemotherapy-related adverse events	16	14 of 16
Survival	13	6 of 13
Tumor response	7	2 of 7

Horneber, M.A. et al.: Mistletoe therapy in oncology (review). The Cochrane Collaboration, Wiley 2008

Cochrane-Review on Mistletoe Therapy

Analysis of studies on quality of life: n = 14/16 beneficial

Assessment during chemotherapy (QoL or treatment-related side effects):

Positive result: all 9 trials

Assessment during radiotherapy, rehabilitation or sole mistletoe treatment:

Positive result: n = 5 (2 studies on psychosomatic self regulation)

No difference to control group: n = 2 (both studies on sole mistletoe treatment effect)

Analysis of studies on survival: n = 6/13 beneficial

Positive result: n = 6 (among them 1 of 5 studies with an ML-related standard dose
5 of 8 studies with a dose escalation schedule)

No positive result: n = 7 (positive trend: n = 4)

Negative result: n = 0

Antitumoral effects: only in studies with higher dosage and long-term therapy > 1 year

Horneber, M.A. et al.: Mistletoe therapy in oncology (review). The Cochrane Collaboration, Wiley 2008

Cochrane-Review on Mistletoe Therapy

Statement on drug safety of mistletoe products:

12 prospective randomized studies (total 2,978 patients) with data on drug safety:

- local inflammatory reactions at the s.c. injection site in up to 1/3 of the patients
- systemic reactions (fever, flu-like symptoms) in approx. 10 %
- serious adverse reactions are seldom
- no evidence of negative influences on survival of cancer patients

Horneber, M.A. et al.: Mistletoe therapy in oncology (review). The Cochrane Collaboration, Wiley 2008

Analysis of Clinical Studies with Helixor®

Total

- studies: **30**
- patients: **5,962** (without control groups)

Methodology

- prospective-randomized: **10**
- prospective non-randomized: **6**
- retrospective: **14**

Tumor type

- breast: **9**
- colorectal: **6**
- others: **4**
- several entities: **11**

Indication*

- palliative therapy in inoperable/metastasizing tumors: **20**
- prevention of relapse: **18**

Parameters*

- survival: **16**
- response rate: **5**
- quality of life: **14**
- relapse rate: **1**
- reduced side effects of oncological therapies: **8**
- immune parameters: **4**

Results

- advantage with Helixor® compared to controls: **21**
- significant advantage: **15**
- trend: **6**
- no advantage: **4**
- single-arm cohort studies with significant improvement: **2**

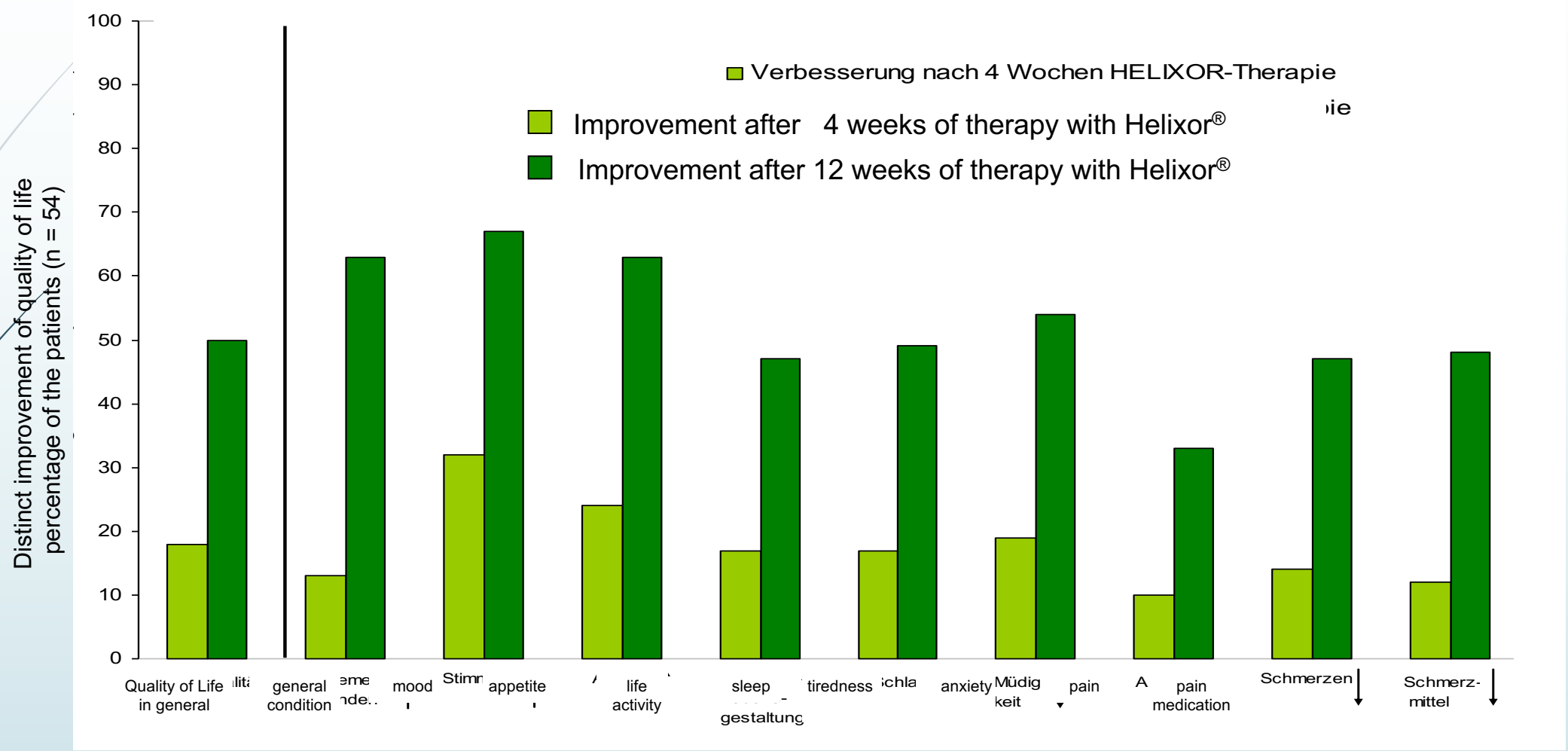
* Multiple references possible

RCTs on Mistletoe Therapy of Cancer
Assessment of Methodological Study Quality

Acc. to Kienle et. al.: Anthroposophic Medicine – Effectiveness, utility, costs, safety; Schattauer Stuttgart 2006

Autor, Jahr	Results	Methodological Criteria											n	Loss
		A)	B)	C)	D)	E)	F)	G)	H)	I)	J)	K)		
Piao 2004	s	+	+	–	(–)	+	+	+	(+)	+	+	+	233	4%
Auerbach 2005	s, t, 0	+	–	(+)	(+)	+	–	+	(+)	+	(+)	+	23	17-30%
Grossarth 2001	s	+	+	–	(–)	+	+	+	(–)	+	+	–	34	0%
Dold 1991	t, t, s	+	+	–	–	+	(–)	+	(+)	+	+	(–)	337	17%
Lange 1985	s	+	+	–	(–)	+	(–)	+	(+)	+	+	–	68	35%
Borrelli 2001	s	+	–	(+)	(+)	+	+	(+)	+	(–)	(+)	–	30	0%
Grossarth 2001	s	+	+	–	(–)	+	(–)	+	(–)	+	+	–	78	20%
Kleeberg 2004	-t	+	+	–	(–)	(–)	(–)	(+)	+	(+)	(+)	(+)	204	24%
Salzer 1991	t	+	(+)	–	(–)	(+)	(–)	+	(+)	(+)	+	–	210	16%
Douwes 1986	t	+	–	–	(–)	+	+	+	+	–	(+)	–	60	0%
Gutsch 1988	s	+	–	–	(–)	+	(–)	+	+	(+)	+	–	677	20%
Salzer 1979, 1983	s	+	–	–	(–)	+	–	+	+	(+)	(+)	–	137	57%
Cazacu 2003	s	(+)	–	–	(–)	+	+	(+)	(+)	(–)	–	–	64	n.s.[IV]
Salzer 1987	t	+	(+)	–	(–)	+	–	+	–	–	–	–	50	48%

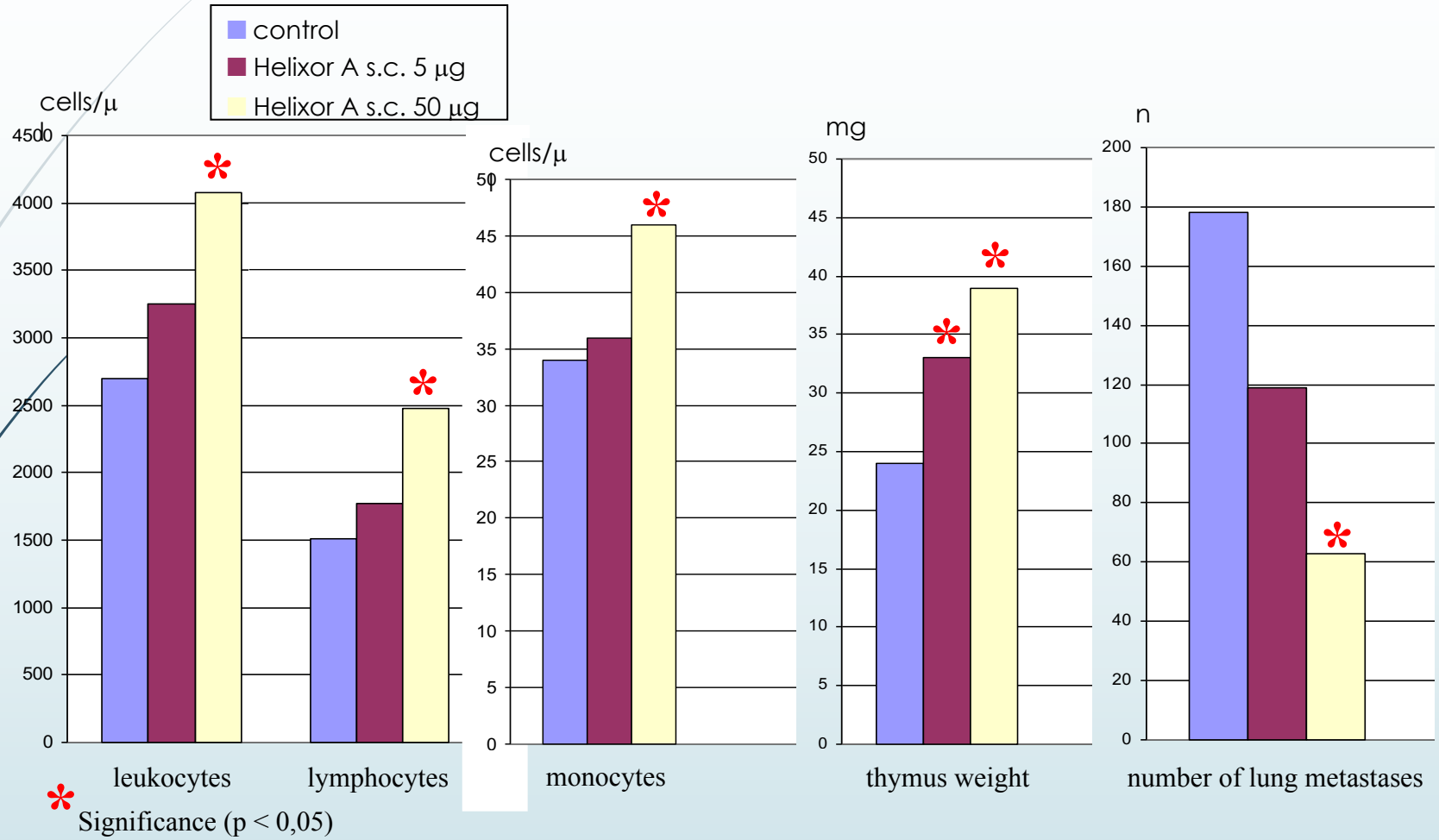
Benefit for Patients with Advanced Tumors Receiving Mistletoe Therapy



Quality of life during palliative therapy with Helixor®, survey of 54 tumor patients

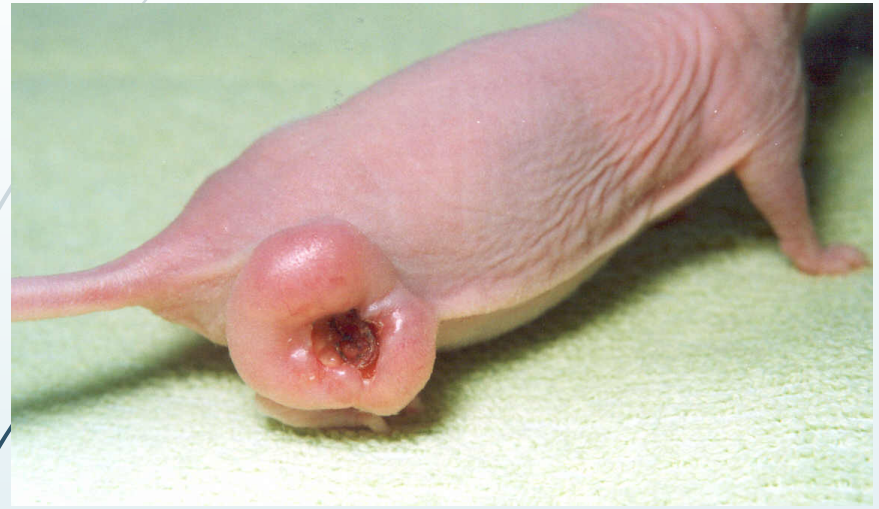
Liedtke. S.: Ärztezeitschrift für Naturheilverfahren 12/2002, 806

In Vivo Efficacy of HELIXOR (BALB/c-Mice with L-1-Sarcoma)

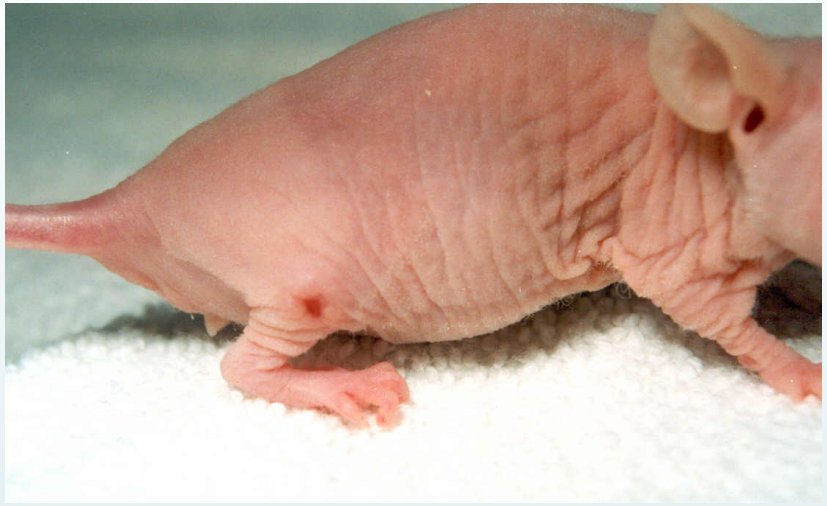


Source: Braun, J.M. et al.: Cancer letters 170, 2001, 25-31

Single 50 ug injection over 8 weeks



before



after

Influence of Complementary Mistletoe Therapy on Quality of Life in Breast, Ovarian and Lung Cancer

- prospective-randomized multicenter study -

Objectives:

- Influence of Helixor® on quality of life of cancer patients and on side effects of chemotherapy compared with Lentinan® (immunostimulating injection product made of shiitake mushroom)
  QoL: Karnofsky Performance Index = KPI
  Functional Living Index Cancer = FLIC
  Traditional Chinese Medicine (= TCM) Index
- Safety of Helixor®

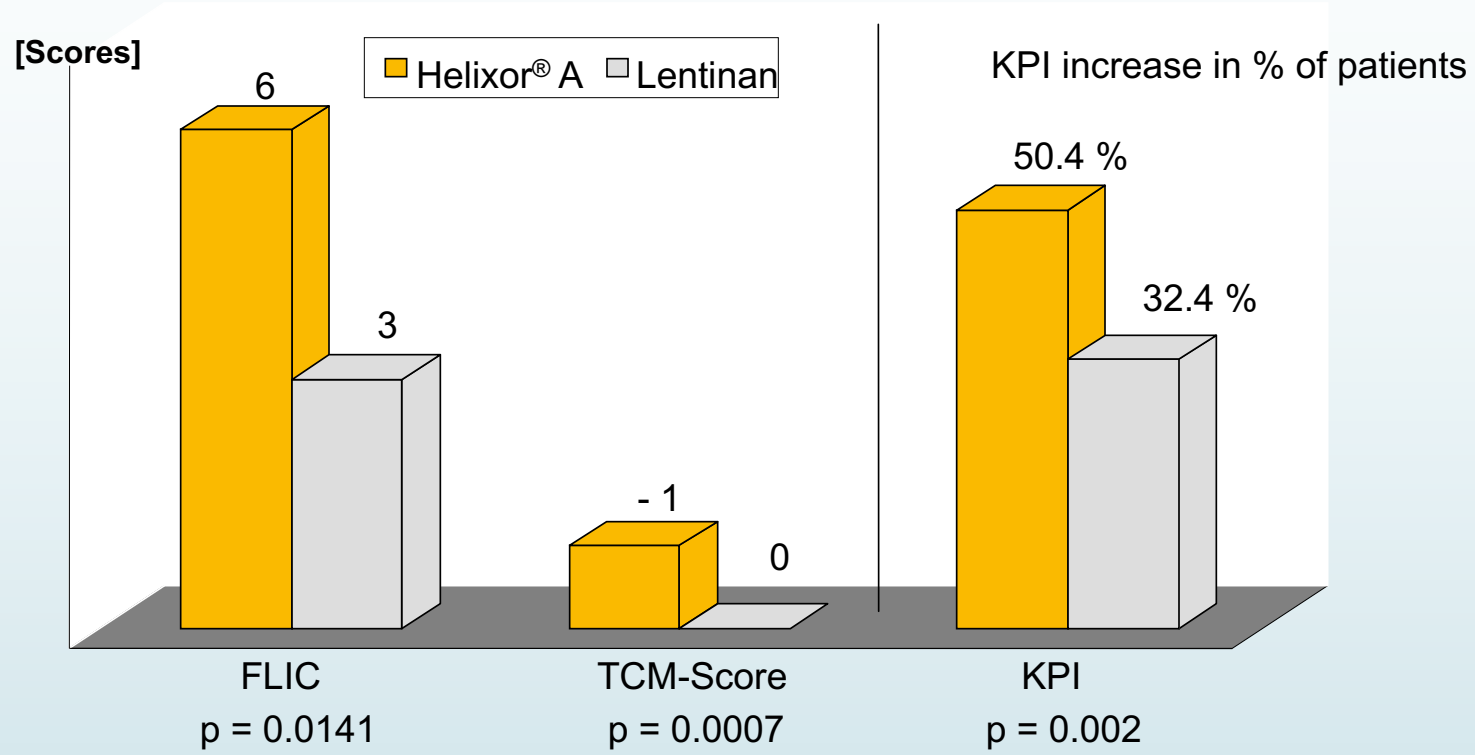
Study: Multicentric, prospective, randomized, open

Indication: Non-small cell lung (n = 94), breast (n = 68), ovarian (n = 71) cancer

Piao, B.K. et al.: Anticancer Research 24, 2004, 303-310

Influence of Complementary Mistletoe Therapy on Quality of Life in Breast, Ovarian and Lung Cancer

General Results / Quality of Life

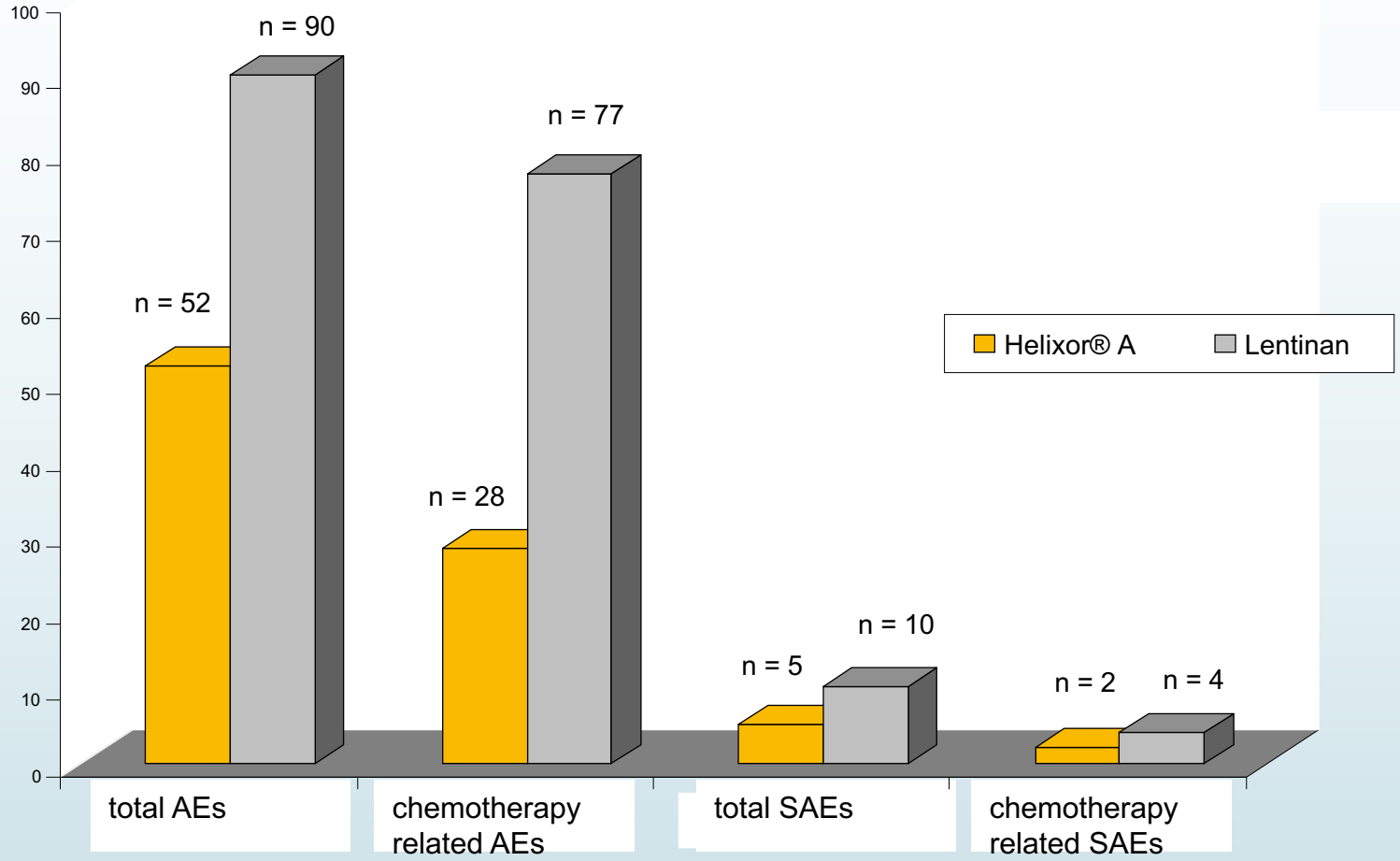


FLIC = Functional Living Index Cancer, *TCM-Score* = Traditional Chinese Medicine Score, *KPI* = Karnofsky Performance Index

Piao, B.K. et al.: Anticancer Research 24, 2004, 303-310

Influence of Complementary Mistletoe Therapy on Quality of Life in Breast, Ovarian and Lung Cancer

Adverse and Serious Adverse Events



Piao, B.K. et al.: Anticancer Research 24, 2004, 303-310

Influence of Complementary Mistletoe Therapy on Quality of Life in Breast, Ovarian and Lung Cancer

Results:

- *Significant increase of quality of life* through complementary Helixor® therapy compared to the control group (large compliance of the results within the 3 different indices for recording quality of life)

- *Significantly less side effects of chemotherapy*
(i. a. nausea, vomiting, bone marrow depression, infections)

- *Good tolerance and low rate of side effects with Helixor® A*
  7 x local reaction > 5 cm ∅ at s.c. injection site
  4 x fever
  1 x angioedema and nettle rash

Piao, B.K. et al.: Anticancer Research 24, 2004, 303-310

Influence of Complementary Mistletoe Therapy on Quality of Life in Breast, Ovarian and Lung Cancer

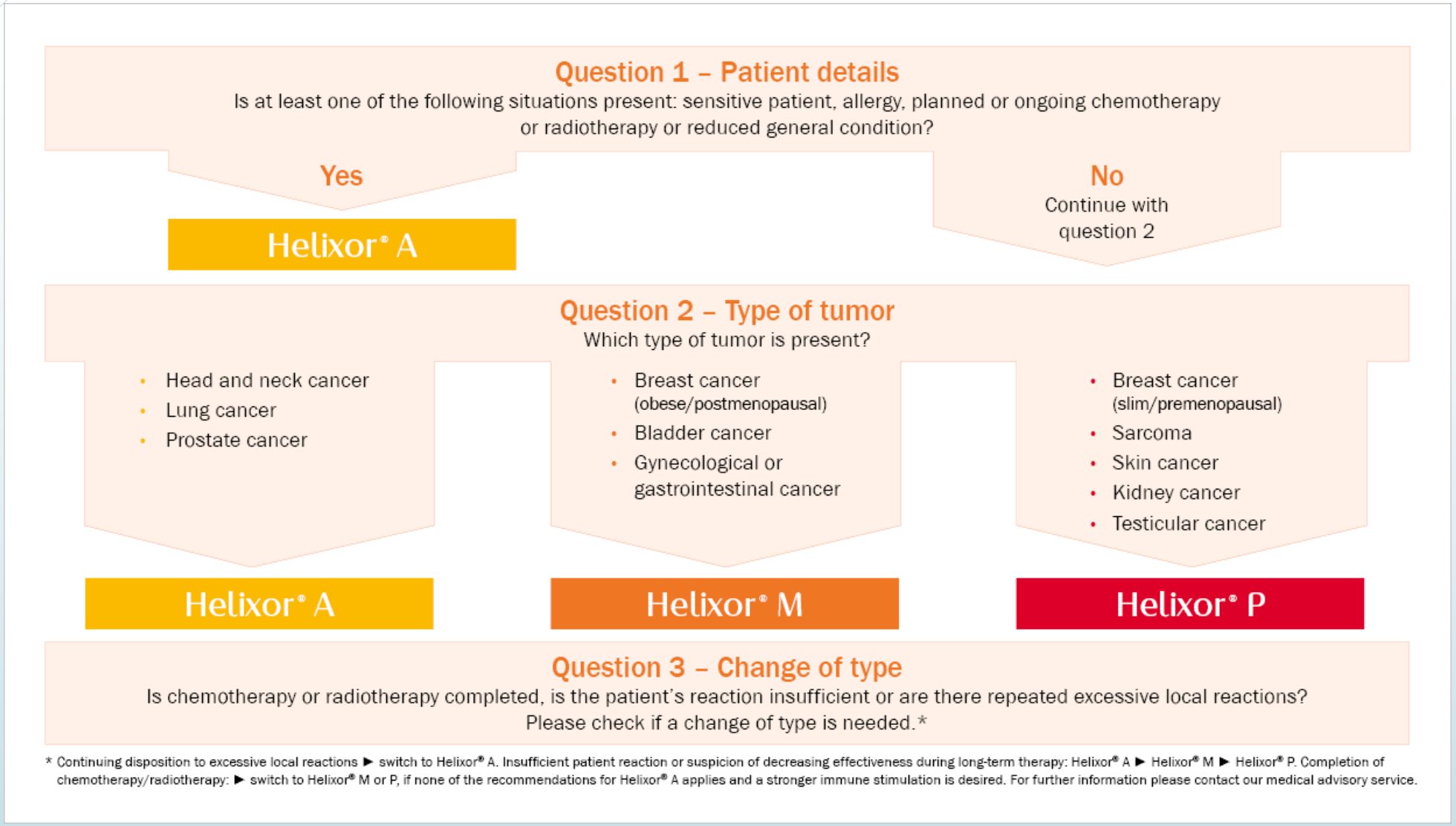
Which QoL-variables are significantly improved with Helixor® therapy?

- Fatigue
- Insomnia
- Anorexia
- Nausea
- Pain
- Physical activity

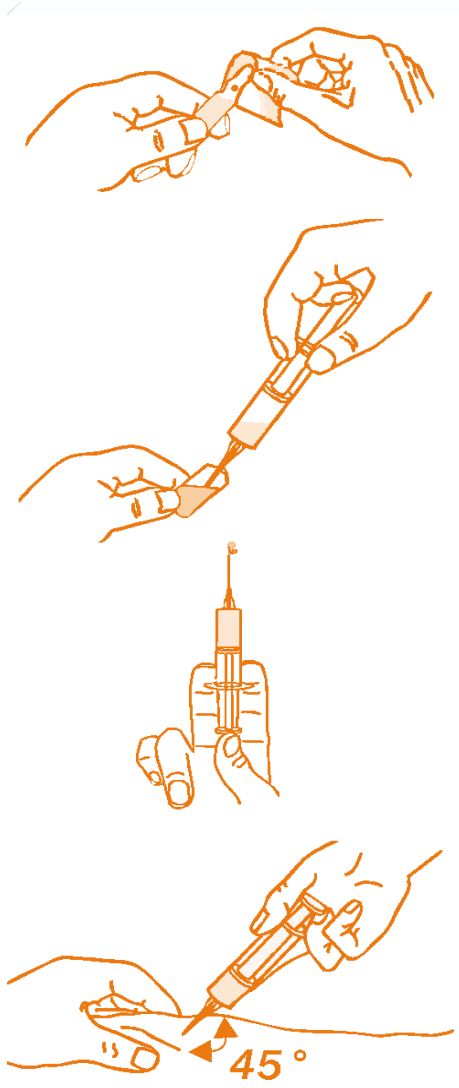
Piao, B.K. et al.: Anticancer Research 24, 2004, 303-310

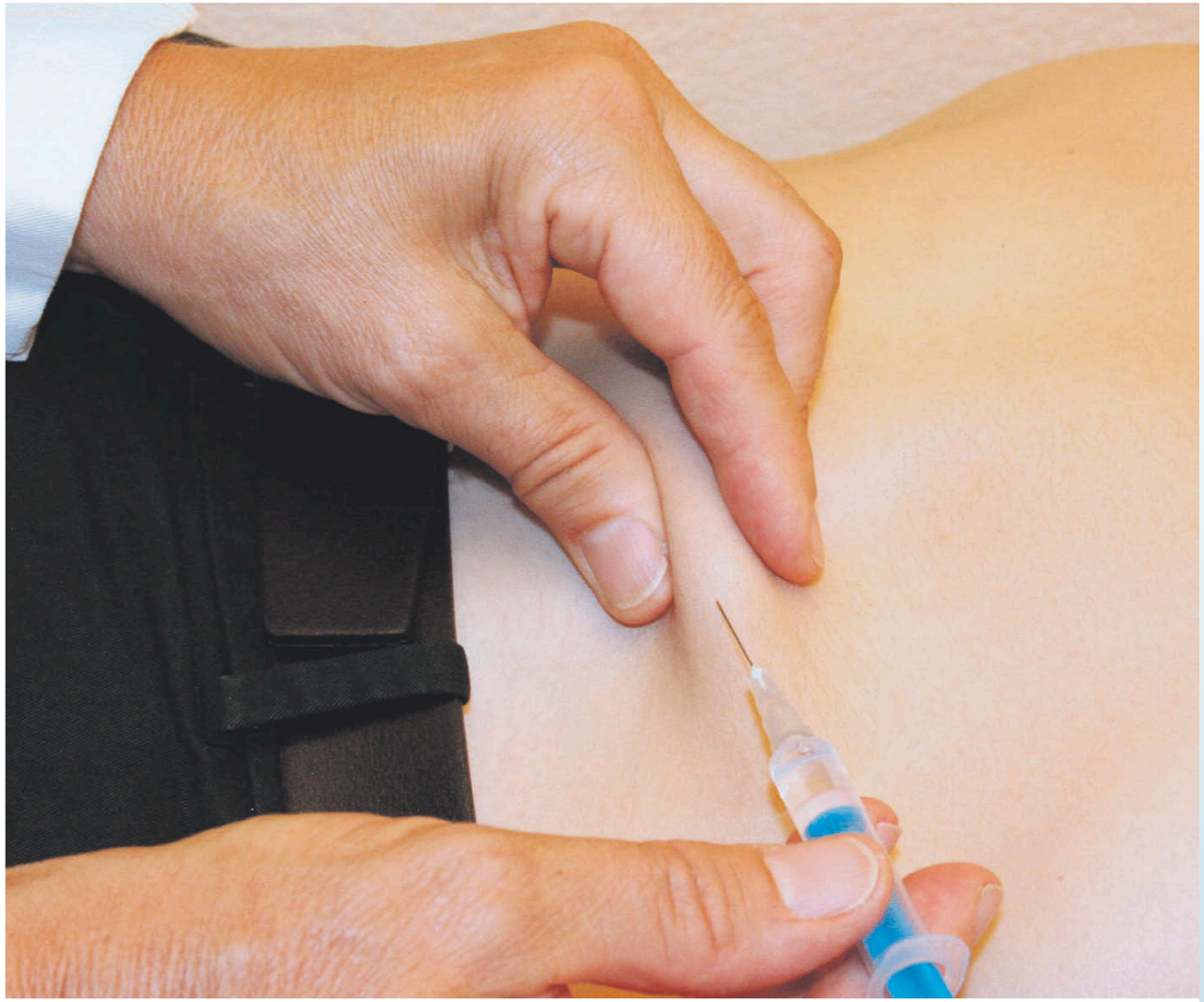
Therapy Guidelines

Helixor®-Selecting and Changing Types



Subcutaneous Injection of Helixor®

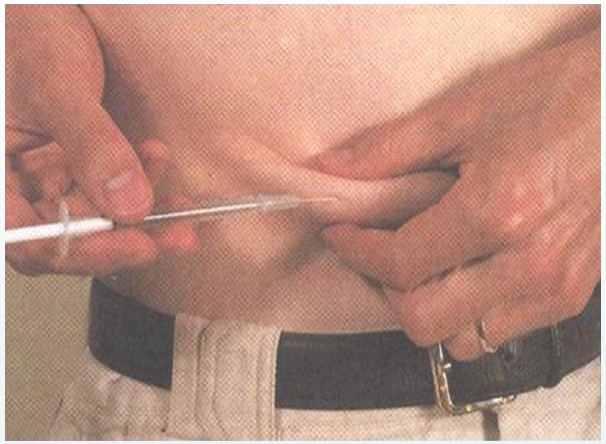




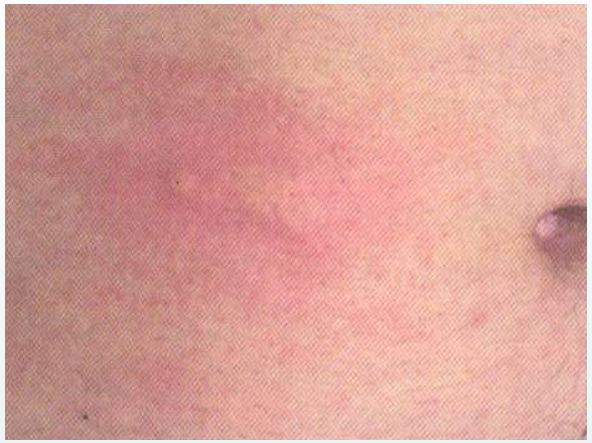
Local Skin Reaction at Subcutaneous Injection Site

- Redness, swelling, subcutaneous induration (infiltration by activated T-helper cells)
- Maximum size 48 – 72 hours after injection (delayed-type immune reaction), strictly dose-dependent
- Important indicator during induction therapy showing an immunologically effective dosage
- Mediated by mistletoe lectins (MLs)
  → will disappear when anti-ML-antibodies are increasing

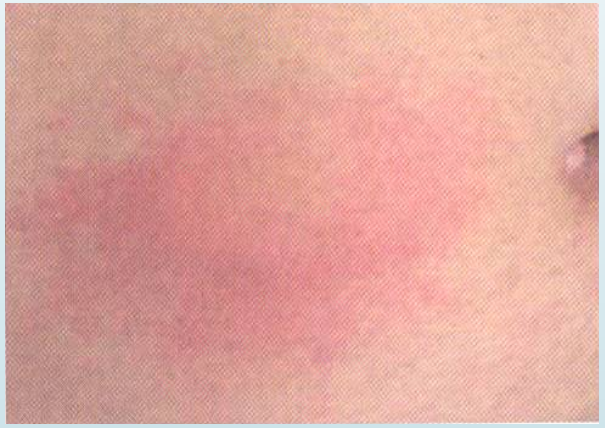
Local Skin Reaction to Subcutaneous Helixor®



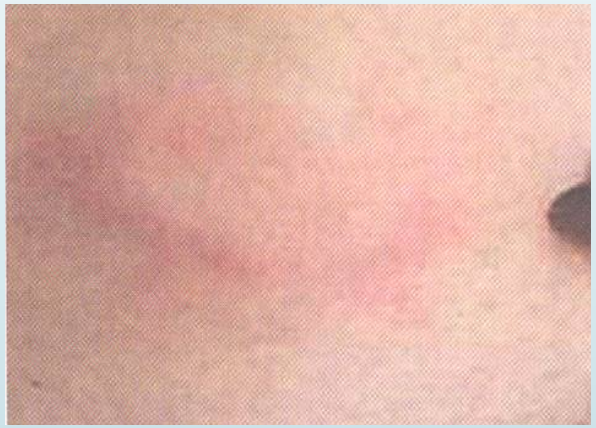
Typical site of injection



Local erythema, appr. 3 x 5 cm, 6 h p.i.

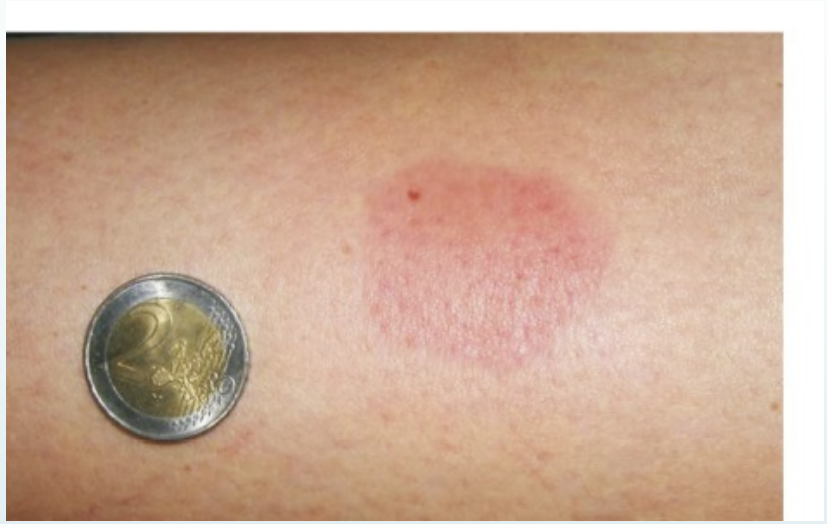


Local erythema, appr. 12 h p.i.

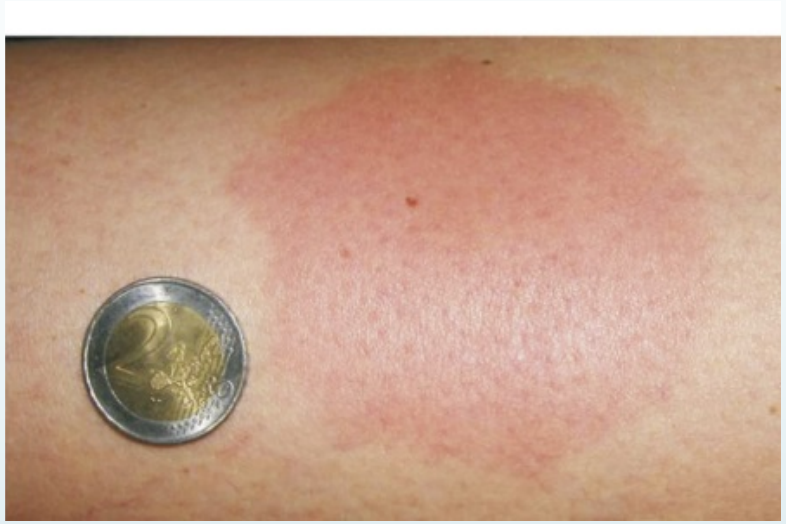


Slight induration, appr. 24 h p.i.

Local Skin Reaction to Helixor®



Desired local reaction



Excessive local reaction

Measures in Case of a Local Skin Reaction

1) Local inflammation ≤ 5 cm diameter

- Next injection - not before local skin reaction of the last injection has disappeared
- Maintenance of the last dose - as long as each injection is followed by a reaction
- Further stepwise dose increase according to the schedule - as soon as no reaction occurs any longer

Measures in Case of a Local Skin Reaction

2) Local inflammation > 5 cm diameter

Therapy pause until redness and swelling have disappeared

▼

Dose reduction

▼

Maintenance of this reduced dose,
as long as there is redness and swelling < 5 cm after injection

▼

Further stepwise dose escalation,
as soon as no reaction occurs any longer

Subcutaneous Injection of Helixor®

The following injection sites should be avoided:

- Focus of inflammation and its surrounding
- Operation scar
- Radiation field
- Breast cancer: breast and arm of the operated side

Basic Rules of Mistletoe Dosage

1) Slow dose escalation **(induction therapy)**
   → To avoid side effects
   → To find out optimal dosage

2) Individual **maintenance dosage** according to
   a) Cancer stage
   b) The patient‘s reaction

3) Rhythmic dose variation and interpolation of pauses
   → To avoid tolerance

4) Sufficient continuance of maintenance therapy

Choice of Injection Intervals

	Injections	Pauses
Adjuvant Therapy	3 x 1 amp. s.c./week	After 4 weeks 14 days pause
Palliative Therapy	*Good general state of health:* 3 x 1 amp. s.c./week *Reduced general state of health, rapid progression:* daily injection	No!

Duration of Helixor® Therapy

I. In case of adjuvant therapy (prevention of relapse after curative surgery):
   - Intensive treatment in the first two years, followed by phasing out:

     ⇒ *From the third year: only 2 injections per week*

     ⇒ *Third year: 3 weeks pause after every 4 cycles*

     ⇒ *Fourth year: 4 weeks pause after every 4 cycles*

     ⇒ *Fifth year: 8 weeks pause after every 4 cycles*

II. In case of palliative treatment after palliative surgery, in metastasizing cancer:
   - No breaks
   - Helixor® as a permanent, palliative treatment

Dosage schedule for heme CA's (leukemia, lymphoma, myeloma)

HELIXOR A daily injection: Initial Therapy

Week 1	1-1-1-1-1-1-1 mg
Week 2	5-5-5-5-5-5-5 mg
Week 3	10-10-10-10-10-10-10mg
Week 4	10-10-20-20-30-30-30mg
Week 5	20-20-30-30-50-50-50mg
Week 6	70-70-80-80-100-100-100mg

Dosage schedule for heme CA's (leukemia, lymphoma, myeloma)

Maintenance Therapy

Chronic lymphocytic leukemia, low-grade non-Hodgkin's lymphoma, Hodgkin's lymphoma stage Ia - IIIa, multiple myeloma

→ 150mg daily

Chronic myeloid leukemia, acute leukemia, high-grade non-Hodgkin's lymphoma, Hodgkin's lymphoma stage Ib – IIIb, IV

→ 200mg daily

Response Criteria

A) *Adjuvant Therapy* (prevention of relapse)

1. Local reaction at subcutaneous injection site
2. Increase in body temperature
3. Improvement of general condition
4. Increase in WBC count: WBC, eosinophils, lymphocytes

B) *Palliative Therapy* (metastasizing tumors) additionally

5. Inhibition of tumor growth

Adverse Drug Reactions (ADR) to Mistletoe Products

- most often: harmless and self-limiting
- very rare: serious ADRs
- as a rule: most ADRs are nothing else than desired pharmacological effects exceeding the desirable level

  - in very sensitive patients

  - after overdosing or

  - after a too rapid dose increase

Prof. Dr. P.A. Berg, University of Tübingen, 2001

Adverse Drug Reactions to Mistletoe Products

Adverse drug reactions	Measures
Inflammatory local reaction at sc injection site > 5 cm	➔ Therapy pause until the symptoms subside ➔ Dose reduction ➔ No anti-inflammatory or antipyretic drugs
Fever > 38 °C, flu-like symptoms	
Swelling of regional lymph nodes	
Allergic reaction (urticaria/nettle rash > exanthema > angioneurotic edema > dyspnea > anaphylaxis)	➔ Usual anti-allergic therapy ➔ Discontinue mistletoe product
Activation of inflammation (and other rare events)	➔ Therapy pause until the symptoms subside ➔ Removal of the focus of inflammation

Different modes of application of HELIXOR

	Therapeutic aims	Importance
Subcutaneous injection	immunomodulation	usual application
Intravenous infusion	easing the pain, inhibition of cancer growth when other therapies are ineffective	experimental therapy (not yet proven in clinical trials)
Intrapleural instillation	killing cancer cells in the pleural cavity, pleurodesis	proven in longstanding clinical experience and two clinical trials
Intraperitoneal instillation	killing cancer cells in abdominal cavity, inhibition of ascites production	few clinical experiences
Intratumoral injection	tumor necrosis, followed by strong immunological reaction	experimental therapy (only animal studies performed)

Other Modes of Helixor® Administration Besides SC Injection

Mode of Administration	Indication
Intravenous infusion	Progressive metastasizing cancer
Intrapleural instillation	Malignant pleural effusion
Intraperitoneal instillation	Malignant ascites
Intralesional infiltration	Inoperable cancer
Intravesical instillation	Superficial bladder cancer

Helixor® Intravenous Infusion

Not yet registered but supported by the German monograph “Viscum album” (Commission C)

Indication:

- progressive metastasizing cancer
  - in which an effective standard treatment is not available/feasible
  - refractory tumor pain
  - rapid deterioration of general condition
  - as an adjunctive to chemotherapy for reduction of toxicity

Contraindication:

- acute inflammatory disease, high fever
- allergy to mistletoe preparations
- floride autoimmune disease
- symptomatic hyperthyroidism
- gravity (precaution)

Helixor® Intravenous Infusion

Not yet registered but supported by the German monograph “Viscum album” (Commission C)

Precautions:

- pretesting with 0.1 ml out of Helixor® M 1 mg for exclusion of allergy
- very strict indication
- close monitoring of signs of an allergic reaction (esp. in patients with former SC mistletoe therapy)
- drugs for emergency treatment must be available

Frequency	• 1-3x/week with or without additional SC administration at days without infusion. • Daily infusion over 2 weeks in case of rapid deterioration of general condition. • immediately before and during administration of chemotherapy for reduction of toxicity.
Drip speed	• 26 drops/minute = 3 hours of infusion

Helixor® M Intravenous Infusion

Dosage	• 250 ml 0.9 % sodium chloride solution (at body temperature) with 50 mg Helixor® 100 mg dose increase from week to week 200 mg 400 mg 600 mg Further dose increase up to a maximum dose of 2.000 mg, if required
Stop of dose increase	• in case of - sufficient clinical response - fever - flu-like symptoms - eosinophilia
Duration	• long-term treatment over months if required • in case of a cancer response and clear improvement of complaints with SC administration only

Intravenous Infusion Protocols

Frequency:

1. 1-2x/week plus s.c. application on days without infusion
2. 3x/week if there is no s.c. application

Other:

- 40 drops/minute ~ 2 hours of infusion
- i.v. dosage 250ml isotonic sodium chloride solution with 50mg HELIXOR
- s.c. dosage 100-200mg 2-3x/week
- long-term application is possible; in case of remission continue only with s.c. application

Thank you for your attention!