ANTICANCER RESEARCH *24*: 303-310 (2004)

Impact of Complementary Mistletoe Extract Treatment on Quality of Life in Breast, Ovarian and Non-small Cell Lung Cancer Patients. A Prospective Randomized Controlled Clinical Trial

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Abstract. *Standardized aqueous mistletoe extracts have been applied to cancer patients for several decades as complementary medicine. A multicentric, randomized, open, prospective clinical trial was conducted in three oncological centers in the People's Republic of China in Bejing, Shenyang and Tianjin. Following the guidelines of "Good Clinical Practice" (GCP) this study was performed to get information on efficacy, safety and side-effects of the standardized mistletoe extract (sME). Two hundred and thirty-three patients with breast (n=68), ovarian (n=71) and non-small cell lung cancer (NSCLC; n=94) were enrolled into this study. Two hundred and twenty-four patients fulfilled the requirements for final analysis (n=115 treated with sME HELIXOR® A; n=109 comprising the control group being treated with the approved immunomodulating phytopharmacon Lentinan). All patients were provided with standard tumor-destructive treatment schedules and complementarily treated with sME or Lentinan during chemotherapy according to treatment protocol. Biometrically, the patients of the control and sME treatment group were comparable regarding distribution, clinical classification (WHO) and treatment protocols. Analysis was performed according to the "Intention to treat principle". Quality of life (QoL) was significantly ($p<0.05$) improved for patients who were complementarily treated with sME, as determined by the questionnaires FLIC (Functional Living Index-Cancer), TCM (Traditional Chinese Medicine Index) and the KPI (Karnofsky Performance Index) in comparison to the control group. Additionally, the occurrence of adverse events (AEs) was less frequent in the sME than in the control group (total number of AEs 52 versus 90 and number of serious AEs 5 versus 10 in study and control group, most of them due to chemotherapy). Only one serious AE was allocated to complementary treatment in each group (1 angioedema in sME group). All other side-effects of the sME (7 harmless local inflammtory reactions at subcutaneous injection site, 4 cases with fever) were self-limiting and did not demand therapeutic intervention. This study showed that complementary treatment with sME can beneficially reduce the side-effects of chemotherapy in cancer patients and thus improve quality of life.*

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Key Words: Mistletoe extract, cancer patients, quality of life, randomized controlled trial.

Aqueous extracts from mistletoe are widely used in complementary cancer treatment as immunomodulating agents (1). They were introduced into oncological treatment by Rudolf Steiner around 1920 and there are many reports on clinical efficacy (2). However, the evidence of these results is controversial because of the problem of adequate methodology in evaluating the efficacy of complementary medicine (3).

The production of market-authorized mistletoe extracts is standardized. The biochemical analysis of these drugs shows that they contain different pharmacologically relevant substances (4). There is a great body of data on the biochemical and physiological effects of defined substances, for example mistletoe lectins 1-3, viscotoxins, membrane vesicles, polysaccharides (1,5).

Mistletoe extracts with defined amounts of mistletoe lectin-1 (ML-1) yielded promising experimental and clinical results (6-8). Recent research showed that the same can be found with sME with a predominant content of ML-3 (9,10). However, randomized controlled trials of adequate methodology to evaluate the clinical benefit of sME are still missing though urgently needed (2).

Table I. *Patient flow chart: Number of patients with corresponding treatment and evaluation scheme.*

Patients randomized 233											
No measurable tumor and/or metastases 117						Measurable tumor and/or metastases 116					
NSCLC 31		breast 45		ovarian 41		NSCLC 63		breast 23		ovarian 30	
Helixor 17	Lentinan 14	Helixor 23	Lentinan 22	Helixor 21	Lentinan 20	Helixor 31	Lentinan 32	Helixor 12	Lentinan 11	Helixor 14	Lentinan 16
w : n	w : n	w : n	w : n	w : n	w : n	w : n	w : n	w : n	w : n	w : n	w : n
5: 1	6: 9	5: 1	3: 1*	3: 1*	6: 13	1: 1*	4: 1*	6: 10	6: 6	6: 9	2: 2*
6: 14	7: 2	6: 20	6: 13	6: 11	7: 4	4: 1*	6: 19	7: 1	7: 4	8: 5	3: 2*
7: 1	8: 3	7: 1	7: 7	7: 1	8: 1	5: 1	7: 9	8: 1	8: 1		6: 5
8: 1		8: 1	12: 1	8: 8	9: 2	6: 25	8: 2				7: 4
						7: 1	9: 1				8: 2
						8: 2					9: 1
			n.e. 1	n.e. 1		n.e. 2	n.e. 1				n.e. 4
K: 17	K: 14	K: 23	K: 21	K: 20	K: 20	K: 29	K: 31	K: 12	K: 11	K: 14	K: 11
T: 17	T: 14	T: 23	T: 20	T: 20	T: 20	T: 27	T: 31	T: 12	T: 11	T: 14	T: 11
F: 17	F: 14	F: 23	F: 21	F: 20	F: 19	F: 29	F: 31	F: 12	F: 11	F: 14	F: 11
E: 16	E: 14	E: 18	E: 14	E: 20	E: 20	E: 29	E: 31	E: 12	E: 11	E: 14	E: 11

Treatment scheme described in weeks (w:n): w = duration of medication in weeks : n = number of patients treated
* patients with ≤ 4 weeks of treatment
n.e.: number of not evaluated patients
Number of patients, evaluated by: K: Karnofsky Index; T: TCM; F: FLIC; E: tumor evaluation.

Table II. *Total study population. Comparison of sex and tumor characteristics in treatment groups.*

ALL		Helixor N=118		Lentinan N=115		total N=233		*p*-value
		N	%	N	%	N	%	
center	Beijing	22	18.6	24	20.9	46	19.7	0.709
	Shenyang	64	54.2	65	56.5	129	55.4	
	Tianjin	32	27.1	26	22.6	58	24.9	
sex	male	27	22.9	24	20.9	51	21.9	0.753
	female	91	77.1	91	79.1	182	78.1	
pT	1	10	8.5	16	13.9	26	11.2	0.121
	2	46	39.0	31	27.0	77	33.0	
	3	36	30.5	31	27.0	67	28.8	
	4	19	16.1	23	20.0	42	18.0	
	X	7	5.9	14	12.2	21	9.0	
pN	0	51	43.2	43	37.4	94	40.3	0.325
	1	19	16.1	18	15.7	37	15.9	
	2	33	28.0	27	23.5	60	25.8	
	3	9	7.6	16	13.9	25	10.7	
	X	6	5.1	11	9.6	17	7.3	
M	0	73	61.9	75	65.2	148	63.5	0.683
	1	45	38.1	40	34.8	85	36.5	

Table III. *Total study population. Demographic characteristics and general anamnesis.*

ALL	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	*P*-VALUE
age	Helixor	118	0	52.6	9.4	31.0	46.0	50.0	61.0	70.0	0.618
	Lentinan	115	0	51.7	10.1	25.0	45.0	51.0	59.0	70.0	
	total	233	0	52.2	9.7	25.0	45.0	51.0	60.0	70.0	
weight	Helixor	118	0	63.0	10.6	39.0	56.0	62.0	70.0	92.0	0.030
	Lentinan	115	0	60.8	10.3	42.0	54.0	59.0	65.0	100.0	
	total	233	0	61.9	10.5	39.0	55.0	60.0	67.0	100.0	
body mass	Helixor	118	0	23.7	3.4	15.8	21.0	23.4	26.4	33.0	0.457
index	Lentinan	115	0	23.3	3.3	16.5	20.8	22.9	25.5	32.0	
	total	233	0	23.5	3.4	15.8	20.8	23.4	25.8	33.0	

Table IV. *Functional Living Index-Cancer (FLIC).*

Key Words		Abbreviated questions of FLIC
1)	Depression	Do you feel depressed and how often?
2)	Stress	Are you able to handle daily stress?
3)	Thoughts about the disease	How often do you think about your disease?
4)	Leisure-time activity	Are you able to enjoy leisure-time activity?
5)	Nausea	Does nausea influence your daily activity?
6)	General condition	How do you feel today?
7)	Activity	Do you feel well enough to perform activities in the house?
8)	Dismay of relatives	Indicate how your tumor disease influences your social surrounding
9)	Despair	How often do you feel discouraged?
10)	Job satisfaction	How often were you satisfied with your job?
11)	Comfort	How comfortable/uncomfortable do you feel today?
12)	Derealization	Have relatives been derealized recently?
13)	Influence of pain	How does pain influence your daily life?
14)	Worry about tumor disease	How often has your tumor disease imposed a hardship on you?
15)	Daily activity	How much housework are you able to do?
16)	Social connections	How often did you meet with those closest to you?
17)	Nausea frequency	How often do you suffer from nausea?
18)	Fear for the future	How strong is the intensity of your fear for the future?
19)	Social connections	How often did you meet with friends?
20)	Pain	How much of the pain was based on your tumor disease?
21)	Trust in treatment	Do you trust in your treatment?
22)	Appearance	How is your appearance today?

Here we report on a prospectively randomized clinical multicenter study to evaluate the impact of sME administered complementarily to the standard treatment of patients with breast, ovarian and non-small cell lung cancer (NSCLC).

Patients and Methods

The informed consent was signed during the screening procedure. From July 2000 until October 2001, a total of 233 patients suffering from breast (n=68), ovarian (n=71) and non-small cell lung cancer (NSCLC; n=94) were enrolled into this randomized controlled trial (RCT) (Table I). Out of these, 224 patients were evaluated in the final analysis (115 in the study group, 109 in the control group).

The vote of the ethics commission was received from the Hospital Guan An Men, Research Institute of TCM, China. Randomization was carried out by this study centre. A computer-generated random list with varying block size was generated for each participating center and cancer entity. Treatment centers comprised: Guang An Men Hospital, Bejing; Liaoning Tumor Hospital, Shenyang; Tianjin Tumor Hospital, Tianjin, China. All are specialized in consensus-based tumor-destructive treatment modalities (Table II).

The RCT was performed following the "Guidelines on Clinical Trials for New Phytopharmaca" and "Good Clinical Practice" (GCP). The study was not blinded. After histological diagnosis (in accordance with the Medical Administration Authority, Ministry of Health, People's Republic of China) all patients underwent conventional chemotherapy including cyclophosphamide (C), adriamycin (A), cisplatin (P), 5-fluorouracil (F), vinorelbine (V),

Table V. *Total study population. Karnofsky Performance Index evaluated as reduced, stable and increased.*

ALL		Helixor N=115		Lentinan N=108		Total N=223		strat. p-value
		N	%	N	%	N	%	
KPI	Reduced	4	3.5	12	11.1	16	7.2	0.002
	Stable	53	46.1	61	56.5	114	51.1	
	Increased	58	50.4	35	32.4	93	41.7	

Table VI. *Total study population. Comparison of scores for each Traditional Chinese Medicine Index (TCM) symptom.*

TCM Criteria	Missing value		Remarkable Improvement		Improvement		Deterioration		Stable	
N	HELIXOR N	Lentinan N / %	HELIXOR N / %	Lentinan N / %	HELIXOR N / %	Lentinan N / %	HELIXOR N / %	Lentinan N / %	HELIXOR N / %	Lentinan
General fatigue	0	1	7 (6.1 %)	2 (1.8 %)	37 (32.5 %)	30 (27.5 %)	6 (5.3 %)	17 (15.6 %)	65 (56.1 %)	61 (55.0 %)
Insomnia	0	2	11 (9.6 %)	2 (1.9 %)	21 (18.4 %)	18 (16.7 %)	4 (2.6 %)	9 (9.3 %)	79 (69.3 %)	78 (72.2 %)
Anorexia	1	1	10 (8.8 %)	4 (3.7 %)	31 (27.4 %)	19 (17.4 %)	12 (10.6 %)	27 (24.8 %)	61 (53.1 %)	58 (54.1 %)
Nausea	0	1	2 (1.8 %)	0 (0 %)	18 (15.8 %)	6 (5.5 %)	(11.4 %)	14 (26.6 %)	28 (71.1 %)	8174 (67.9 %)
Pain	1	1	5 (4.4 %)	19 (17.4 %)	18 (15.9 %)	5 (4.6 %)	3 (2.7 %)	8 (7.3 %)	88 (77.0 %)	76 (70.6 %)

Remarkable improvement means improvement in at least two steps: from “middle” to “none”, from “serious” to “slight” or “none”. Improvement means improvement in one step: from “slight” to none, from “middle” to “slight”, from “serious” to “middle”.

mitomycine (M), ifosfamide (I), vindesine (Vi), or carboplatin (cP); breast cancer: CAP, CAF; ovarian cancer: CP, IcP; NSCLC: VP, MViP. After randomization, patients of the study group were complementarily treated with the standardized mistletoe extract HELIXOR® A (sME; Helixor Heilmittel GmbH & Co. KG, Rosenfeld, FRG), subcutaneously, 3 times per week, with escalating dosages starting with 1 mg up to a maximum dose of 200 mg independently from the chemotherapy schedule. Patients of the control group were treated with the authority approved phytopharmacon Lentinan, intramuscularly, 4 mg per injection, daily. Lentinan, a phytotherapeutic agent, belongs to the national second class of new phytopharmaca (Authorization No. 92 Z-61 for Drugs; Ministry of Health) and is a protected preparation. Lentinan, a purified polysaccharide, is a biological response modifier and its antitumor activity is mediated by the augmentation of the activity of NK-cells, macrophages and cytotoxic T-lymphocytes. Lentinan is regularly used with Tegafur (a prodrug of 5-FU) and is considered to prolong survival and improve quality of life (QoL) in combination with other chemotherapeutic agents (12).

Study and control groups of patients were demographically comparable, especially concerning tumor entity, stage and conventional treatment (Tables II and III). Inclusion (exclusion) criteria were fixed, followed international standards and mainly comprised: histologically verified breast, ovarian and NSCL cancers; indication for chemotherapy, however, no tumor-destructive treatments applied during the previous month; age 18-70 years; KPI >50%; survival expectancy > 3 months; hospital bound patients; no additional immunomodulating therapy.

There were 9 patients in whom it was not possible to take measurements of the endpoints of interest (Table I, Patients with ≤4 weeks of treatment were not evaluated for QoL because of the short observation period). These 9 patients were excluded from the analysis, because there is no methodologically acceptable way to impute the missing observations for an analysis of the total set of patients enrolled in the study.

Quality of life (QoL) measurement. QoL was evaluated regularly by the internationally approved questionnaires FLIC (Functional Living Index-Cancer) (Table IV), TCM (Traditional Chinese Medicine Index) comprising nausea, vomiting, fatigue, insomnia, anorexia and the KPI (Karnofsky Performance Index). QoL evaluation was performed "at screening" as well as at the end of the treatment.

Table VII. *Total study population. Difference of Traditional Chinese Medicine Index (TCM) total score between screening and final investigation.*

ALL	GROUP	N	NMISS	MEAN	SDEV	MIN	MEDIAN	MAX	strat. *p*-value
TCM score	Helixor	113	2	-1.3	2.4	-8.0	-1.0	5.0	0.0007
	Lentinan	107	2	-0.2	2.3	-6.0	0.0	6.0	
	total	220	4	-0.8	2.5	-8.0	0.0	6.0	

Table VIII. *Total study population. Difference of Functional Living Index-Cancer (FLIC) between screening and final investigation.*

ALL	GROUP	N	NMISS	MEAN	SDEV	MIN	MEDIAN	MAX	strat.*p*-value
FLIC score	Helixor	115	0	9.0	16.6	-32.0	6.0	56.0	0.0141
	Lentinan	107	2	4.7	17.5	-32.0	3.0	89.0	
	Total	222	2	6.9	17.1	-32.0	4.5	89.0	

Safety. Evaluation of safety of the treatment with the sME consisted of analysis of the number and severity of adverse events (AEs), the duration, treatment, outcome and the causes of AEs (chemotherapy, sME, Lentinan, basic disease or others).

Statistics. Statistical analysis was performed using SAS Version 8.02 and StatExact Version 5. Analysing the trial population and describing the efficacy criteria, safety criteria and quality of life questionnaires at baseline and at final end of treatment, binary and categorical data were evaluated with Fisher's exact test, while continuous data were compared by means of Wilcoxon-Mann-Whitney test (University of Heidelberg, Germany, Institute of Medical Biometry and Informatics).

Results

The influence of standardized mistletoe extract (sME) HELIXOR® A treatment on side-effects and toxicity of chemotherapy correlating to QoL can be reproducibly evaluated by standardized questionnaires, for example FLIC and TCM Index as well as the KPI Index. Thus, these questionnaires were determined before and after chemotherapeutic treatment of breast, ovarian and NSCL cancer patients.

The Karnofsky Performance Index (KPI) evaluates the physical conditions of patients and classifies them as reduced, stable or increased. In total 223 patients could be evaluated (sME group n=115; control group n=108) (Tables I and V). As shown in Table V, patients complementarily treated with sME presented an increased KPI in 50.4 % (32.4 % in the control group) and a reduced KPI in 3.5 % (11.1 % in the control group; Table V). The KPI improvement of the study group was statistically significant as compared to the control group ($p=0.002$) (Figure 1).

According to TCM, various symptoms were evaluated by scoring. As shown in Tables I and VII a total of 220 patients could be evaluated (sME group n=113; control group n=107). Concerning nausea, fatigue, insomnia and anorexia, more patients improved and fewer patients deteriorated in the study group as compared to the control group (Table VI, Figure 1). However, the difference in the overall TCM score between the beginning and termination of the tumor-destructive chemotherapy demonstrates a statistically significant improvement of the quality of life in the sME study group ($p=0.0007$) as compared to the control group (Table VII). The TCM score consists of the sum of five symptoms; each symptom is quantified with four levels reaching from 0 to 3 and a higher level expresses higher severity in the symptom. Therefore, an improvement in TCM comparing baseline and final examination results in a negative number. A change of –1 describes an improvement by one level in the total TCM score and may be interpreted as the improvement in one single symptom of one level while no change in severity happens in the three remaining symptoms.

The Functional Living Index-Cancer (FLIC) consists of 22 questions on physical, psychological and social well being, nausea and pain (Table IV). As shown in Table I and VIII a total of 222 patients could be evaluated (sME group n=115; control group n=107). The global FLIC score demonstrated a significant improvement ($p=0.0141$) of QoL for patients of the sME study group as compared to those of the control group (TableVIII). Especially the symptoms of nausea and pain presented significant improvements for patients of the study group (results not shown).

The total number of adverse events (AEs) was 52 in the sME study group and 90 in the Lentinan control group (serious AEs: 5 *versus* 10) (Figure 2). Chemotherapy-related AEs were 28 for the sME and 77 for the Lentinan group.

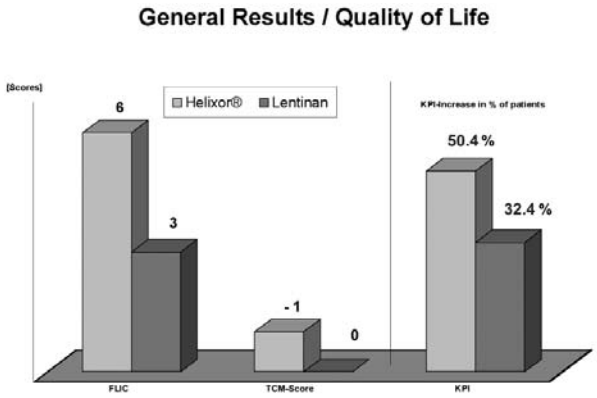

Figure 1. *Improvement of quality of life evaluated by KPI-, FLIC-and TCM-indices.*

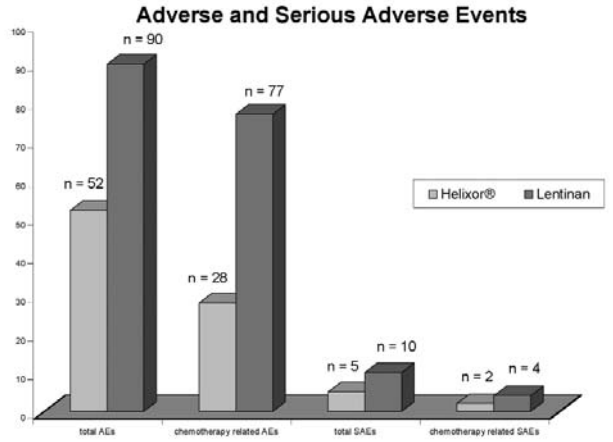

Figure 2. *Adverse events (AEs)and serious adverse events of the sME and Lentinan group. The majority of AEs in both groups was due to chemotherapy, and the HELIXOR® group significantly gained by reduction of chemotherapy-related events.*

Each symptom of an adverse event was classified as one AE, for example nausea and vomiting following standard chemotherapy were registered as two AEs, despite being pathogenetically closely related. If all simultaneously occurring and closely related symptoms were registered as one patient-related AE, the total number of AEs and SAEs would drop from 52 to 32 for the study group and from 90 to 59 for the control group, respectively. However, the relationship of AEs and SAEs between the study and control group would be unchanged.

In the therapy as well as in the control group only one serious AE was allocated to complementary treatment on account of hospitalization. In the study group one patient responded to the sME application with angioedema and urticaria. After discontinuation of the sME administration and anti-allergic treatment, the patient recovered from angioedema within 2 days, however, skin reactions remained for about 7 days. All other side-effects of sME (fever in 4 patients, rubor/pruritus at the injection site in 7 patients) were harmless, self-limiting and did not warrant therapeutical intervention. Also, in the control group, one serious AE occurred which was allocated to the phytopharmacon Lentinan. All other cases of serious AEs were allocated to chemotherapy or to the basic disease. Thus, sME appears to be a safe and well tolerated drug.

Discussion

Previous clinical investigations have shown that complementary application of aqueous standardized mistletoe extracts (sME) can relevantly reduce the side-effects of standard tumor-destructive chemo-/radiotherapies (6-8,11). On the basis of pharmacological, pharmacokinetical and pharmatoxicological investigations, an approval for the conduction of a clinical trial for imported drugs (sME; HELIXOR® A) was officially given by the Authority for Drug Surveillance and Administration, People's Republic of China (Application No. A960162; Authorization No. ZL 2000001). This randomized controlled trial (RCT) was carried out following the "Guidelines on Clinical Trials for New Phytopharmaca" and "Good Clinical Practice" (GCP) to evaluate efficacy, safety and side-effects of sME. In three oncological centers (Bejing, Shenyang, Tianjin) breast, ovarian and NSCL cancer patients were randomized into a study group (standard chemotherapy and complementary sME application) and control group (standard chemotherapy and Lentinan injection).

Biometrically, patients of the study and control groups were comparable with respect to age, clinical classification (WHO) and treatment protocols. Accordingly, a valid conclusion concerning primary study goals (safety of sME administration, influence on side-effects of tumor-destructive therapies, quality of life) can be drawn. Evaluation of recurrence-free, metastasis-free and overall survival is not useful because of the limited follow-up time as well as the short treatment period with sME.

Usually most of the patients receiving sME develop a distinct local inflammatory skin reaction at the subcutaneous injection site. This kind of reaction usually does not occur after intramuscular Lentinan application. In case of subcutaneous injection of placebo (such as physiological saline), this reaction does not occur, either. Thus, blinding was not possible in this clinical trial because

most of the patients as well as clinicians would have recognized whether sME, Lentinan or placebo was applied after a short treatment period.

For many drugs, except most anticancer chemotherapeutical substances, placebos make blinding possible by helping to control measurement bias when accessing the outcome of a trial. It may be hypothesized that differences in the information provided to patients may be responsible for differences in the outcome (for example QoL) of this trial. However, patients allocated to the control group received Lentinan, which is a well known immunmodulating drug in China and Japan; therefore the risk of getting an information bias as well as seeking treatment (HELIXOR®) outside the trial is very low.

Far fewer AEs were recorded in the sME study group than in the control group (Figure 2). Altogether 5 serious AEs in the sME study group and 10 serious AEs in the Lentinan control group were registered; only one serious AE in each group was allocated either to sME or to Lentinan. All other side-effects of sME (fever, rubor and pruritus at the injection site) were harmless, self-limiting and did not afford therapeutical intervention. Thus, sME treatment was regarded as safe.

Twenty-eight AEs in the HELIXOR® group were related to chemotherapy in comparison to 77 AEs in the Lentinan group. Since most of the AEs were related to chemotherapy, the definitely lower number and severity of AEs within the study group points to a more beneficial effect of sME on tolerance of chemotherapy, as compared to the control group. This is in accordance with a significant improvement of QoL which was demonstrated concurrently by the standard questionnaires (FLIC, TCM) as well as the KPI Index for the patients of the sME study group as compared to those of the control group (Figure 1).

This RCT demonstrated a biometrically significant benefit for the patients of the study group (complementarily treated with sME) as compared to the control group (treated with the China-approved phytopharmacon Lentinan) under tumor-destructive chemotherapy. The significant results of the HELIXOR® group may be much better interpreted in the light of the proven beneficial effects of Lentinan (control group) in previous studies (12). However, further studies on defined tumor entities and stages (after precise stratification) and appropriate numbers of patients are needed to prove the clinical efficacy of sME in cancer parients.The actual RCT was an approval study for the People's Republic of China and obviously demonstrates the beneficial effect of complementary sME application during tumor-destructive chemotherapy.

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Received May 27, 2003
Revised September 12, 2003
Accepted December 19, 2003