



Mistletoe as complementary treatment in patients with advanced non-small-cell lung cancer treated with carboplatin-based combinations: A randomised phase II study

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KEYWORDS

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Abstract *Introduction:* Mistletoe preparations, such as iscador, are common complementary medications. This randomised phase II study of iscador combined with carboplatin-containing regimens was conducted in chemotherapy-naïve advanced non-small-cell lung cancer (NSCLC) patients to assess its influence on chemotherapy-related side-effects and QoL.

Methods: Patients with advanced NSCLC were randomised to receive chemotherapy alone or chemotherapy plus iscador thrice weekly until tumour progression. Chemotherapy consisted of 21-day cycles of carboplatin combined with gemcitabine or pemetrexed.

Results: Seventy-two patients (control: 39; iscador: 33) were enrolled in the study. Most (65%) were in stage IV, and 62% had squamous histology. Median overall survival in both groups was 11 months. Median TTP was 4.8 months for the controls and 6 months in the iscador arm ($p = \text{NS}$). Differences in grade 3–4 haematological toxicity were not significant but more control patients had chemotherapy dose reductions (44% versus 13%, $p = 0.005$), grade 3–4 non-haematological toxicities (41% versus 16%, $p = 0.043$) and hospitalisations (54% versus 24%, $p = 0.016$).

Conclusion: No effect of iscador could be found on quality of life or total adverse events. Nevertheless, chemotherapy dose reductions, severe non-haematological side-effects and hospitalisations were less frequent in patients treated with iscador, warranting further investigation of iscador as a modifier of chemotherapy-related toxicity.

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1. Introduction

Approximately, 60% of non-small-cell lung cancer (NSCLC) patients present with advanced or metastatic disease and are not candidates for potentially curative

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treatments; therefore, management of these patients focuses on prolonging survival without compromising quality of life (QoL). Systemic therapy is the only treatment modality proven to increase survival, relieve symptoms and improve QoL in those patients.¹ Doublet chemotherapy combinations with a platinum compound and a third-generation cytotoxic agent have been accepted as the 'standard of care' for patients with advanced NSCLC, with response rates of 30–40% and a median survival of 8–11 months for patients with good performance status.²

Gemcitabine and carboplatin (GC) is one of the standard combinations³ and was the most used first-line chemotherapy treatment for patients with advanced NSCLC in Rambam Health Care Campus during the study period. Since 2009, a pemetrexed/carboplatin (PC) combination was also used for adenocarcinoma patients, following the study of Scagliotti et al. that showed superior overall survival (OS) with this combination compared to CG in this patient group.⁴

Mistletoe extracts (ME) are one of the most frequently prescribed unconventional cancer therapies in Central Europe.⁵ ME are complex multi-component mixtures, containing various biologically-active substances, such as glycoproteins, particularly the mistletoe lectuins I, II and III, polypeptides (e.g. viscotoxins), peptides, amino acids and oligo- and poly-saccharides.⁶ The conclusion of a review by the Cochrane Database group was that the evidence from controlled clinical trials (RCT) does not support the impact of ME on cancer survival. Nevertheless, there is some evidence that ME may offer benefits on measures of QoL during chemotherapy for breast cancer patients.⁷ In the only study published on ME in NSCLC, patients were randomised to three treatment arms: ME (Iscaidor, Weleda, Germany), Polyerga Neu (sheep spleen glycopeptides) and injections of vitamin B mixture as a placebo group. There was no significant difference in OS. The only difference favourable to ME was the subjective improvement in feelings of well-being reported by these patients compared to the other two groups.⁸

Recently, a novel phase I dose escalation study of ME and gemcitabine combination in patients with advanced solid tumours was published as an abstract form.⁹ According to the reported conclusions, the gemcitabine/mistletoe combination demonstrated limited toxicity with good tolerability and compliance of ME. The addition of the extract allowed the use of higher doses of gemcitabine without alterations of gemcitabine plasma concentrations.

The aim of this randomised phase II study of ME (iscaidor) in combination with carboplatin-containing regimens conducted in chemotherapy-naïve advanced NSCLC patients was to assess the possible influence on chemotherapy-related side-effects and QoL.

2. Patients and methods

This single-centre, randomised phase II study on patients with advanced NSCLC treated with gemcitabine/carboplatin (GC) or pemetrexed/carboplatin (PC) chemotherapy combination was approved by our Institutional Ethics Committee and was written in the National Institutes of Health (NIH), code number NCT00516022. The original study was planned to include only patients treated with the GC combination. Following the approval of the PC combination as first-line treatment for patients with NSCLC adenocarcinoma, an amendment to the protocol to include these patients was made and approved in July 2009.

Patients over the age of 18, with histologically proven NSCLC were eligible for the treatment if they fulfilled the following criteria: stage not-operable IIIA or IIIB or IV (tumour-node-metastasis (TNM) classification), performance status (PS) ≤ 2 (Eastern Cooperative Oncology Group (ECOG) classification), measurable disease with one or more disease sites measured by computed tomography (CT) according to RECIST criteria,¹⁰ life expectancy of more than 12 weeks, treatment combination of GC or PC, written informed consent. Exclusion criteria were: prior chemotherapy, central nervous system metastases, hypercalcaemia, other life-threatening medical conditions, inadequate patient compliance. Prior radiotherapy was allowed if given more than three weeks prior to entry to the trial and not targeted to the only evaluable lesion.

2.1. Randomisation

Eligible patients who had signed the informed consent were randomised either to chemotherapy alone or chemotherapy with mistletoe extract. Randomisation was stratified according to disease stage (unresectable IIIa and IIIB versus IV) and was independently performed by the Statistic and Quality of Treatment Unit at Rambam Health Care Campus.

2.2. Chemotherapy treatment

Carboplatin AUC 5 IV day 1 was combined with either gemcitabine 1000 mg/m² IV days 1 and 8 (GC combination) or with pemetrexed 500 mg/m² IV day 1 (PC combination). Cycles were repeated every 3 weeks for up to six cycles. All patients in the PC combination received oral folic acid daily, vitamin B12 injection every 9 weeks and dexamethasone prophylaxis. Antiemetic treatment was given according to the Multinational Association of Supportive Care in Cancer (MASCC) guidelines.¹¹ In general, 5HT3 antagonist IV was given on day 1 and dexamethasone IV was given on days 1 and 8 with GC

and PC on days 2–3 or 2–4. Modifications, as needed, were made for non-responding patients.

Dosage of chemotherapy was reduced for patients if World Health Organisation (WHO) grade 3 non-haematological toxicity, grade 4 anaemia, thrombocytopenia or neutropenic fever in the prior cycle were accrued. In the GC combination, the day 8 gemcitabine dose was omitted if, on that day, the absolute neutrophil count (ANC) was less than $1500/\text{mm}^3$ and/or the platelet count was less than $100,000/\text{mm}^3$. Chemotherapy treatment was discontinued in the presence of disease progression, intolerable toxicity, concurrent serious medical conditions or completion of six cycles of therapy.

2.3. Mistletoe treatment

Fermented mistletoe extract, iscador Q® (Weleda, Germany) was given to patients in the intervention arm. Treatment was started on day 1, with serial subcutaneous injections of iscador Q serial 0 (0.01–1 mg) given on seven consecutive days as a hypersensitivity test. Injections of iscador Q 10 mg were started on day 9 and given every other day until tumour progression, not related to the time of finishing chemotherapy treatment in responding patients. The dosage of iscador was planned to be reduced by 50% in any WHO grade III toxicity that could be related to mistletoe extract. Treatment with iscador was discontinued in the presence of hypersensitivity to iscador, concurrent serious medical conditions or disease progression. Patients with stage III disease who entered the study continued with radical radiation or surgery after completion of chemotherapy.

Safety was assessed before each cycle using the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0.¹² Evaluation of tumour response was done according to the Response Evaluation Criteria in Solid Tumours (RECIST) criteria.¹⁰

2.4. Patient evaluation and follow up

CT of the thorax, abdomen and pelvis done within four weeks prior to day 1 of the first cycle of chemotherapy was required. Thereafter, CT was performed after every three cycles of chemotherapy and repeated at least every three months after the end of chemotherapy or radiotherapy, unless disease progression became evident. CT scans of brain or bone scan were performed in patients with symptoms suggestive of metastatic disease involving the respective sites. Time to tumour progression (TTP) was defined as time from randomisation to the date of documentation of disease progression, and OS as the time from date of randomisation until the date of the last follow-up or death.

QoL was assessed using the European Organization of Research and treatment of Cancer core questions on the Quality of Life Questionnaire, version 2 (QLQ-C30)

and the lung cancer module (QLQ-LC13).^{13,14} This self-administered questionnaire was completed by patients after randomisation, on day 1 of every cycle until the end of the chemotherapy treatment.

2.5. Statistical methods

The primary end-point of toxicity was evaluated using non-parametric statistical methods. Toxicity was defined as all grade ≥ 3 CTCAE side-effects recorded up to 4 weeks from the last chemotherapy cycle. Significance testing for differences in toxicity rates was performed by the χ^2 method. Mann–Whitney non-parametric test was done on total number of severe side-effects, and on haematological and non-haematological severe side-effects. The working hypothesis assumed 50% grade ≥ 3 CTCAE in the control arm. For a reduction of 20% in these toxicities, the study was planned to include 84 patients in each arm. In the quality of life (QoL) assessment, the difference between baseline and all cycles was calculated for all single items of the questionnaire European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30/ LC13 as the delta between reported results after two cycles of chemotherapy and baseline. Positive differences represent deterioration in the QoL of the questioned item. Differences in deltas of the QoL items between the treatments arms were compared using the Wilcoxon rank sum test. Overall survival and time to tumour progression were estimated using the Kaplan–Meier method. The log-rank test was used for comparison of time-to-event end-points. Two-tailed *p* values of 0.05 or less were considered as statistically significant. Multivariate analysis (logistic regression model) for toxicity rate adjusted to stage was used to determine the relationship between iscador and severe toxicity. Statistical analyses were performed with SPSS (Statistics Products Solutions Services) 18.0 software for Windows.

3. Results

3.1. Patient characteristics

From February 2007 to December 2010, 79 patients entered the study. Seven patients (three control arm, four iscador arm) were excluded due to brain metastases seen in CT done before randomisation (three patients), different diagnosis (one patient), different stage (one patient), different chemotherapy regimen (one patient) and performance status-3 (one patient). The main characteristics of the 72 patients who entered the study are presented in Table 1. Median age of patients in the control arm was 62 years and in the iscador arm was 63 years. Thirty-six and 33 percent of the patients had stage IIIA unresectable at diagnosis or stage IIIB in control and iscador groups, respectively. There were no significant differences in the general characteristics of patients between groups except

Table 1
Baseline characteristics of patients.

	Control group (n = 39)	Iscador group (n = 33)
Male/female (%)	28/11 (72/28)	28/5 (85/15)
Median age (range)	62 years (42–80)	63 years (50–85)
<i>Disease stage</i>		
IIIA	5 (13%)	3 (9%)
IIIB	9 (23%)	8 (24%)
IV	25 (64%)	22 (67%)
<i>Histology</i>		
Squamous cell carcinoma	25 (64%)	19 (58%)
Adenocarcinoma	13 (34%)	11 (33%)
NSCLC – not specified	1 (2%)	3 (9%)
<i>Performance status</i>		
0	6 (15%)	1 (3%)
1	21 (54%)	22 (67%)
2	12 (31%)	10 (30%)

that the number of patients with PS 0 was 6 in the control arm and 1 in the iscador arm ($p = 0.04$). More patients with squamous cell carcinoma (61%) entered the study, compared to adenocarcinoma histology (33%). This difference happened due to nine months of recruiting only patients planned for the CG combination, although the PC combination was being given as standard therapy for adenocarcinoma patients before the amendment to the protocol was made.

3.2. Treatment characteristics

The median number of chemotherapy cycles was four in the control arm and five in the iscador arm. Main treatment characteristics are presented in Table 2. In the control group, 23 patients received the CG combination and 16 patients received CP compared to 25 patients and eight patients, respectively, in the iscador group. The chemotherapy doses on day 1 of cycle one of the treatments was similar in both groups. According to the treating physician's decisions, drug doses were

Table 2
Chemotherapy treatment characteristics.

	Control group	Iscador group
Number of cycles: median (range)	4 (1–6)	5 (1–8)
<i>Number of patients</i>		
Gemcitabine/carboplatin	23 (59%)	25 (76%)
Pemetrexed/carboplatin	16 (41%)	8 (24%)
<i>Number of patients</i>		
1–3 Chemotherapy cycles	18 (46%)	9 (28%)
4–6 Chemotherapy cycles	21 (54%)	20 (60%)
≥7 Chemotherapy cycles	0	4 (12%)
<i>Carboplatin</i>		
1st Cycle mean dose (range)	94% (60–100%)	95% (75–100%)
<i>Gemcitabine</i>		
1st Cycle mean dose (range)	95% (70–100%)	94% (75–100%)
<i>Pemetrexed</i>		
1st Cycle mean dose (range)	91% (60–100%)	100%

reduced in some patients in the first cycle. During the first cycle, the doses of carboplatin, gemcitabine and pemetrexed were reduced in the control arm in 10/39 (26%), 5/23 (22%) and 5/16 (31%) patients, respectively. The corresponding dose reductions in the iscador arm were made in 8/33 (24%), 5/25 (20%) and 2/8 (25%) patients, respectively. The differences in the rate of drug dose reductions during the first chemotherapy cycles were not significant.

The mean doses of carboplatin and gemcitabine in the first-cycle were 94–95% and 91% in the control group compared to 100% in the iscador group for pemetrexed. In the control arm, 18 (46%) patients received 1–3 chemotherapy cycles, compared to nine (27%) patients in the iscador arm.

3.3. Chemotherapy side-effects and QoL

Grade 3–4 toxicities in the two arms are shown in Fig. 1 and detailed in Table 3. The rate of patients with grade 3–4 toxicities in the control arm was higher than in the iscador arm (57% versus 48%). This difference was not statistically significant. However, the incidence of non-haematological toxicity was significantly lower in the iscador arm ($p = 0.04$). In the iscador arm, 82% of the patients did not have grade 3–4 toxicities and none of the patients had two or more events during the treatment period, compared to the control arm where only 59% of the patients did not have grade 3–4 toxicities and 15% had two or more events. The rate of grade 3–4 haematological toxicities was without statistical significance, 49% in the control arm compared to 42% in the iscador arm ($p = 0.07$). Using an alpha of 0.05 and a power of 80%, it can be concluded that the difference in the rate of total severe side-effects between the two groups is less than 20%. The number of patients who were hospitalised due to side-effects was significantly higher in the control arm (21/39, 54%) compared to the iscador arm (8/33, 24%) ($p = 0.02$). Most of the hospitalisations accrued in the first three cycles. In the control arm, there were 13 events ≤3 cycles and eight events ≥4 chemotherapy cycles, compared to a total of eight hospitalisation events in the iscador arm, four in the first three cycles and four in cycle 4. The duration of hospitalisation was similar between the groups, from 2–11 hospitalisation days.

Another point related to the difference in the number of side-effects was the need to reduce chemotherapy doses during the treatment period. In the control group, 17 (44%) patients had dose reductions during treatment compared to four (13%) patients in the iscador group ($p = 0.005$).

Among patients treated with CG combinations, gemcitabine was not given on day 8 in 7/23 (31%) in the control arm versus 1/25 (4%) in the iscador arm ($p = 0.013$).

Although, iscador treatment was not found to be an independent prognostic factor for reduced total grade 3–4 toxicities in the multivariate analysis, it was found

to be associated in this model with reduced non-haematological grade 3–4 toxicities ($p = 0.044$) (adjusted odds ratio 0.3, CI 0.11–0.97).

QoL forms could be analysed for 28 (72%) patients in the control group and 27 (82%) in the iscador group, for those who had completed questionnaires at baseline and after the second chemotherapy cycle (1st day of chemotherapy cycle 3). There was no statistically significant difference in the primary QoL questionnaires between the two groups in any item and no statistically significant difference between the two groups in any of the items in the EORTC QLQ-C30 questionnaire. Mean deltas of all QLQ-LC13 items are presented in Table 4. Only the difference in peripheral neuropathy was significant ($p = 0.03$) in favour of the iscador group.

3.4. Mistletoe toxicity

Mistletoe toxicity was mild. Five patients had a local reaction to the injections, only one of whom had grade 2 toxicity with severe local inflammation at the injection sites. Two patients stopped the iscador treatment during the chemotherapy period, one being the patient with grade 2 local toxicity. The other patient was helped to inject by a family member; this help was stopped after 4 weeks and the patient discontinued the iscador treatment.

3.5. Time-to-tumour progression (TTP) and overall survival (OS)

Median TTP was 4.8 and 6 months for the control and the iscador groups, respectively ($p =$ non-significant). Median OS for stage III patients was 13.3 months in the control group compared to 15.9 months in the iscador group. For stage IV patients, median OS was 8.9 months

compared to 8.3 months. There was no significant difference between the two groups. All three patients in stage IIIA in the iscador group had good partial response and underwent definitive surgery; two are free of disease more than 2 years from the surgery.

4. Discussion

In the current randomised phase II study, the primary end-points of significantly improving QoL and reducing total adverse effects were not reached. Nevertheless, the addition of iscador to standard chemotherapy was associated with a reduction in grade 3–4 non-haematological toxicities and decreased needs for hospitalisation and dose adjustment during chemotherapy. The study group is relatively small, mainly due to the fact that, after the initiation of the study, many patients were treated with drug regimens that excluded them from entering the study.

The two arms were well balanced and represented an unselected population of patients with NSCLC. The relatively high percentage of patients with ECOG performance status 2 may explain the relatively short median survival time of less than nine months in patients with metastatic disease, which is relatively low compared to 10.3 months in the study of Scagliotti et al.⁴

Viscum album L., also known as European mistletoe, is a semiparasitic shrub that grows on other trees and has been used in cancer treatment for decades. Mistletoe extracts are complex multi-component mixtures, containing various biologically active substances such as glycoproteins, in particular the mistletoe lectins I, II and III (ML I, ML II, ML III), polypeptides (e.g. viscotoxins), peptides, amino acids and oligo- and poly-saccharides. Furthermore, they contain innumerable enzymes, sulphurous compounds, fats, flavonoids, phenylpropanes, lignans, alkaloids and various other proteins.⁶ Mistletoe

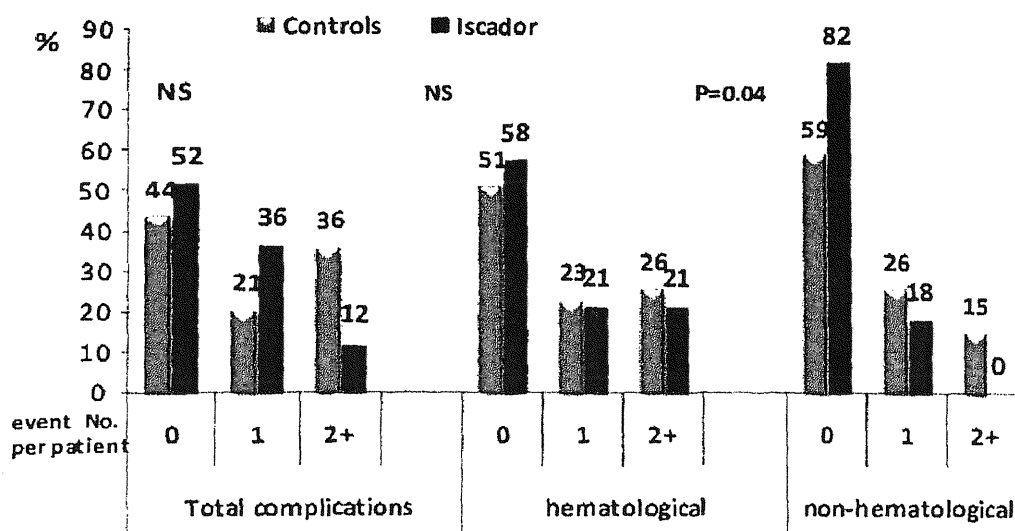


Fig. 1. Grade 3–4 toxicities: percentage of grade 3–4 toxicities in the two arms.

Table 3
Number of patients with various grade 3–4 toxicities during chemotherapy.

	Control group	Iscador group
Neutropenia	10 (25%)	9 (27%)
Neutropenic fever or infection	2 (6%)	2 (6%)
Anaemia	5 (13%)	2 (5%)
Thrombocytopenia	15 (39%)	6 (18%)
Haemorrhage	3 (8%)	0
Gastrointestinal: nausea, vomiting, stomatitis, diarrhoea	7 (18%)	0
Chemotherapy-related pain	4 (10%)	2 (6%)
Hypersensitivity	1 (3%)	0
Anorexia	0	1 (3%)
Neurotoxicity	2 (6%)	0
Musculoskeletal	1 (3%)	0
Dyspnoea	1 (3%)	0
Metabolic	2 (6%)	1 (3%)
Haematologic (sum)	19 (49%)	14 (42%)
Non-haematologic (sum)	16 (41%)	6 (18%)
All complications	24 (61%)	18 (54%)

Table 4
Mean deltas between reported results after two cycles of chemotherapy and baseline of QLQ-LC13 items.

	Control arm mean delta (SD)	Iscador arm mean delta (SD)	P value
Dyspnoea	3 (31.7)	0.8 (26.7)	0.8
Coughing	−6 (37.5)	−17.3 (29.8)	0.1
Haemoptysis	2.4 (33.9)	−3.7 (26.7)	0.7
Sore mouth	10.7 (37.5)	2.5 (20.5)	0.5
Dysphagia	11.9 (39.8)	1.2 (21.6)	0.2
Peripheral neuropathy	22.6 (37.5)	1.2 (23.5)	0.03
Alopecia	15.5 (29.4)	6.2 (18.6)	0.2
Pain in chest	3.6 (38.9)	−4.9 (40)	0.2
Pain in arm and shoulder	−3.6 (29.2)	2.5 (35.7)	0.4
Pain in other parts	−1.3 (43.5)	−5.6 (49.8)	0.7

lectins, the main studied components of mistletoe, have two effects, directly via abrupt damage to the tumour cells, predominantly due to inhibition of protein synthesis and apoptosis, and indirectly via stimulation of immunological processes. Activation of the immune system becomes apparent through, among other things, the increasing number and activity of natural killer cells and TH-cells. In addition, β -endorphin is released. Furthermore, elevated activation state of lymphatic cells, significant increase in serum cytokine level and increased phagocytic and respiratory burst activities are recorded during treatment with mistletoe lectins.^{15,16} Other than the lectins, viscotoxins are the most important typical mistletoe constituents. The effects of the viscotoxins are less well researched than those of the lectins but it is known that, like the mistletoe lectins, they have some immunogenic effects.^{17,18}

The possible mechanism of mistletoe extracts as reducers of chemotherapy toxicity level is not well known. In a phase I study from the National Center for Complementary and Alternative Medicine (NCCAM), published in abstract form, done with ME and gemcitabine in patients with advanced solid tumours, no effects on measured cytokines (IL-6, IL-12, INF γ , TNF- α) were observed,⁹ seemingly ruling out the cytokine inflammatory theory as the cause for chemotherapy toxicity modifier. In this phase I study, although the maximal tolerated dose of gemcitabine was elevated by 30% without significant side-effects, gemcitabine pharmacokinetics were unaffected, ruling out drug–drug interactions between the chemotherapy and the ME. Theoretically, MEs may alter the metabolism of cytotoxic drugs by modifying cytochrome P450 activity. However, no such interaction was found in a recent *in vitro* study.¹⁹

Reduction of chemotherapy-related toxicity was reported in another prospective randomised study involving 224 patients with breast carcinoma, ovarian carcinoma or NSCLC.²⁰ The randomisation was between treatment with ME or Lentinan (Chinas immunomodulating phytopharmakon). A reduction of 50% in the number of adverse events (AE) and severe AE was seen in the ME-treated group compared to the control group.

The reduction in severe side-effects in the current study was not translated to significant improvement in QoL. Although trends for improvement were seen in most of the questionnaire items, the standard deviations for each single item were large. The difficulty of showing significant differences in QoL questionnaires was also seen in other randomised trials with NSCLC patients. For instance, in the study comparing gemcitabine and navelbine to the same drugs with cisplatin, the haematologic and non-haematologic side-effects were lower in the doublet arm, but no statistically significant difference in QoL was seen.²¹ In a systematic review of controlled clinical trials on the influence of ME on QoL of cancer patients, 22/26 randomised controlled trials reported a QoL benefit.²² The main improvements according to this review were related to items such as coping, fatigue, sleep, appetite and emotional and functional well-being, less consistently in regard to side-effects of oncological treatment. Although ME seems to have impact on QoL, few of the studies were highly methodologically designed. One well-designed study with negative results included over 400 patients with squamous cell carcinoma of the head and neck. The patients were randomly assigned to surgery alone or to surgery with adjuvant radiotherapy and then randomly again to no additional treatment or to treatment with ME for one year. No difference was seen regarding QoL, but the study did not include patients on chemotherapy and a sub-set analysis of patients undergoing radiotherapy was not reported.²³

The possible effect of ME on survival and time-to-tumour progression was not addressed in the current study. According to the Cochrane Database, evidence from RCT supports the view that the application of ME having an impact on survival or leading to an improved ability to fight cancer or to withstand anticancer treatments is weak.⁷ Nevertheless, a systematic literature review of OS in studies on iscador showed better survival for the iscador treatment groups, with limitations of moderate heterogeneity and publication bias. Improvement was seen mainly in matched-pair studies and was not significant in randomised studies.²⁴ Theoretically, decreasing the need for dose reduction may improve survival in the iscador treated patients. However, a larger study is needed to see such a difference in survival.

5. Conclusion

No definite conclusion of a possible effect of iscador on quality of life and total adverse events could be drawn. Nevertheless, chemotherapy dose reductions, severe non-haematological side-effects and hospitalisations were less frequent in patients treated with iscador, warranting further investigation of iscador as a modifier of chemotherapy-related toxicity.

Conflict of interest statement

None declared.

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