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Systematic Evaluation of the Clinical Effects of Supportive Mistletoe Treatment within Chemo- and/or Radiotherapy Protocols and Long-Term Mistletoe Application in Nonmetastatic Colorectal Carcinoma: Multicenter, Controlled, Observational Cohort Study

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In Europe, patients with colorectal carcinoma (CRC) frequently receive mistletoe extracts to improve quality of life and survival. This study was designed to evaluate supportive treatment with mistletoe extract Iscador (ISC) in nonmetastatic CRC patients under routine clinical conditions and to create well-founded hypotheses for future prospective clinical studies. The design of a multicenter, controlled, retrospective, observational cohort study with parallel groups met the Good Epidemiological Practice rules. Anonymous unselected standardized data from eligible patients with surgically treated stage I–III CRC and adjuvant therapy (AT) or conventional aftercare were included. End points were adjuvant therapy–related adverse reactions (AT-ADRs), symptoms, and disease-free survival (DFS). The results were adjusted for confounder effects. Eight hundred four (429 ISC vs 375 control) CRC patients from 26 centers were observed for a median of 58 versus 51 months; the median ISC therapy lasted 52 months. ISC patients showed fewer AT-ADRs (19% vs 48%, $p < .001$) and fewer persisting symptoms ($p < .001$). The DFS hazard ratio of 0.60 ($p = .013$) suggests a survival benefit in ISC patients versus controls. ISC was well tolerated without life-threatening ADRs, drug interactions, or tumor enhancement. These results suggest a beneficial effect of supportive care ISC therapy within AT protocols and long-term ISC treatment in stage I–III CRC patients, particularly improvement in AT-ADRs and symptoms and possible extension of DFS.

Key words: *colorectal carcinoma, mistletoe, observational cohort study, quality of life, supportive care therapy, survival*

Epidemiology

Colorectal cancer (CRC) has the second highest incidence and mortality of all cancers in both sexes in Europe (2006), with a yearly incidence and mortality of 412,900 cases and 207,400 CRC-related deaths, respectively (ie, 12.2% and 12.9% of all cancer cases), similar in males and females. In Germany (2004), the mean age at diagnosis was 69 (males) and 75 (females) years.[1] The cumulative 5-year survival rate for all CRC stages was about 60%. The International Union Against Cancer (UICC) stage-related estimated 5-year survival rate without adjuvant therapy (AT) is as follows: stage I, 10% relative incidence, 95% survival; stage II, 20% relative incidence, 62 to 76% survival; stage III, 38% relative incidence, 45 to 65% survival; and stage IV, 28% relative incidence, approximately 10% survival. The CRC incidence trend is presently not significantly changing, but the mortality fom CRC is continuously decreasing in both sexes. Data from the American Cancer Society on CRC epidemiology are similar to the results in Europe.[2]

Conventional Adjuvant Oncologic Therapy

In CRC, the first-line therapy with curative intention is a radical R0 resection of the tumor, including all positive regional lymph nodes (LNs). Although AT is not recommended in stage I, it is a well-established standard in stage III.[3] In stage II CRC with LN-negative patients, individually assessed high-risk patients should also receive AT.[4] In

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advanced and metastatic (stage IV) CRC, the treatment usually consists of chemotherapy-based on 5-fluorouracil (5-FU) or oral capecitabine combined with either leucovorin, folinic acid, levamisole, oxaliplatin, or irinotecan, as well as combined with new targeted therapy regimens. In rectal carcinoma stage II–III, neoadjuvant and/or adjuvant chemoradiotherapy is recommended depending on the precise diagnosis.[5]

Supportive Therapy

Cancer patients often suffer from severe disease-related symptoms and potentially life-threatening adjuvant therapy–related adverse drug reactions (AT-ADRs) that strongly depend on the therapy regimen[6] and might experience a substantial impairment in quality of life (QoL).[7]

Therefore, these two burdens (disease-related symptoms and AT-ADRs) are challenging to manage, and supportive therapy has hereby an important place in the treatment and aftercare of cancer patients. Prevention and effective supportive treatment of various conditions, such as pain, hematologic toxicity, gastrointestinal and central nervous system (CNS) symptoms, infections, mucositis, skin reactions, and psychological problems, are an essential part of the therapeutic management of cancer patients.[8,9]

In Germany and Switzerland, supportive therapy in patients with CRC and many other solid tumors is frequently accompanied by treatment with European mistletoe (*Viscum album L.*) extracts, with the intention to reduce the AT-ADRs, to improve the QoL, and to prolong survival. Unfortunately, published relevant clinical data are rather sparse, consisting mainly of case reports, small clinical studies, and only a few controlled clinical trials, which often show contradictory or inconclusive results and frequently suffer from methodological weaknesses.[10]

Aim of the Study

The present study was designed (1) to evaluate with standardized epidemiologic methods the safety and efficacy of the mistletoe product Iscador (ISC), a fermented extract from *Viscum album L.*, within chemo- and/or radiotherapy protocols and/or as part of a long-term supportive care in hospitals and practices in patients with surgically treated UICC stage I–III nonmetastatic CRC, followed by AT or conventional aftercare under routine clinical conditions, and (2) to create well-founded hypotheses for future prospective clinical studies.

Study Design and Methods

Design

A multicenter, controlled, retrospective, observational cohort study with parallel groups was carried out in agreement with the Good Epidemiological Practice (GEP) rules, according to Good Clinical Practice (GCP) adapted standard operating procedures, considering German and Swiss drug laws and European Union directive 2001/83/EC with all amendments.[11] A similar design was successfully used in pharmacologic-epidemiologic studies[12] and the results were compared with randomized clinical trials.[13,14]

This cohort study was characterized by sampling of anonymous data of eligible patients from original medical records in standardized case report forms (CRFs), irrespective of the outcome, and by a follow-up starting from the origin (ie, diagnosis or primary surgery), with prespecified end points. Treatments were usually finalized before study commencement.

Centers

The centers from a published list of tumor centers and practices in Germany and Switzerland, which were experienced in treating CRC patients in the course of oncology aftercare by AT either with or without additional supportive ISC, were contracted in random order and included in the study. The randomly selected centers, not the patients, accepted the study protocol, expecting enough patients eligible for the study, and signed an informed consent form for participation. From each center, the eligible patients were included in the study in chronological order, without any further selection until the predetermined maximum of cases was reached or, below the maximum, until eligible cases were available during the study acquisition period. The procedure was controlled by the study monitor. Owing to the retrospective, noninterventional study design, informed consent from patients was not required. The center investigators ensured that all patients' data were strictly anonymous before transferring them into standardized CRFs.

Patients

The eligible anonymous cohort patients' data were included according to the study protocol in chronological order without any further selection until a prespecified maximum number of 800 cases was achieved, and the data were extracted by study investigators from medical records into standardized CRFs under data quality and plausibility check by study monitors. All eligible data were from a cohort of surgically treated patients of both sexes and any age, with primary

nonmetastatic CRC in UICC/American Joint Committee on Cancer (AJCC) stages I–III, irrespective of the disease outcome and treatment compliance. The patients were treated in Germany or Switzerland between 1993 and 2002 after surgery with AT or conventional aftercare, either with or without supportive ISC therapy, and were followed for at least 3 years or until death. Data from patients with metastatic or recurrent disease at surgery or before the start of aftercare, other malignant tumors in the history, other mistletoe treatments, and missing essential data were excluded from the analysis.

End Point Criteria

The following predefined confounder-adjusted outcome end points were evaluated: (1) rate and adjusted risk of documented AT-ADRs, assessed by adapting the National Institutes of Health Common Toxicity Criteria (CTC) in oncology[15]; (2) predefined QoL surrogate criteria (adapted from the symptom scales of the EORTC QLQ-C30 questionnaire[7,8]), consisting of rate and adjusted risk of persistence of prespecified disease- and treatment-associated symptoms, particularly pain, skin, mucosal, gastrointestinal, and CNS symptoms; and (3) adjusted disease-free survival (DFS) calculated by the Cox proportional hazard regression method.

Given the planned median follow-up of about 5 years, DFS was also interpreted as an established surrogate criterion of overall survival.[16,17]

Safety

Safety was assessed by the number of patients with documented systemic and local ADRs attributed to the ISC therapy. The number and severity of ADRs were evaluated according to CTC. Any evidence of possible tumor enhancement in the ISC group was also documented.

Statistical Analysis

The analysis is based on established design and methods for observational cohort studies adapted to pharmacoepidemiologic research.[18–21] The analysis was performed according to the study protocol with the original data sets. Missing values were not replaced. In the present retrospective cohort study, the odds ratio (OR), not the relative risk (RR), was used owing to the necessity to adjust the end points to confounder effects by using the multivariable logistic regression, which delivers OR with 95% confidence intervals (CIs) and RR. In addition, OR has some biostatistical advantages over RR: it is a more robust estimate and has equal suitability for inverse question (ie, odds for getting the event versus odds for not getting an event in a group). The tests of hypotheses concerned the adjusted end point criteria difference between the therapy groups. Two-sided statistical tests were performed at $p \leq .05$, using the 95% CI method whenever possible. The test power has to be not less than 80%.

Bias Management

To minimize a possible bias inherent in any nonrandomized study owing to baseline imbalance, different therapy regimen, and other confounders (confounding bias), all QoL surrogate end point results were adjusted for confounder effects by multivariable logistic regression analysis using the adjusted OR with 95% CIs. In the survival analysis, after confirmation of the proportional hazard assumptions, multivariable Cox proportional hazard regression was used with an adjusted hazard ratio (HR) and its 95% CI. Only confounder-adjusted end point criteria results were considered for final interpretation. The predefined confounders used for adjusting were age, gender, center group (hospital vs practice), nononcologic comorbidity, tumor localization (colon, rectal), UICC tumor stage, histo-pathological tumor grading (pG), postsurgical staging (nonevident disease vs residual tumor), chemotherapy, radiotherapy, duration of chemotherapy, additional supportive therapy, and concurrent treatment with high-dose vitamins or trace elements.

The primary results were reconfirmed by sensitivity analyses using predefined multivariable models and adjusting procedures, such as stepwise elimination and forward selection procedures and the application of propensity scores for adjusting.[18,22]

Therapy

Commercially available batches of ISC were given to the patients according to the manufacturer's recommendations in two to three weekly subcutaneous injections of single ampoules per week. The choice of the treatment regimen in the particular patient was left at the discretion of the treating physician. About half of the patients (53%) started the ISC therapy with ISC Qu (quercus), 40% of the patients with ISC M (mali), and a marginal number of patients (7%) with ISC P (pini) or combinations of Qu, M, and P. The majority of the patients did not change the ISC host tree preparation during the supportive intervention. The ISC treatment was administered as supportive care therapy in addition to AT or conventional aftercare. AT consisted in both groups of adjuvant chemo- and/or radiotherapy with documented various

products and therapy regimens, applied at the discretion of the treating physician.

The groups considered as the control were those that had not taken ISC or any other mistletoe therapy. Treatment of comorbidity was left at the discretion of the treating physician and accepted for inclusion without restrictions.

Results

Eight hundred four consecutive eligible CRC patients (429 ISC patients and 375 controls) from 26 oncologic hospitals and private practices were included in the study without any further selection.

Baseline Characteristics and Treatment Regimen

The median follow-up duration was 58 (ISC group) and 51 (controls) months, and the median ISC therapy duration was 53 months. The baseline demography, prognostic factors, and treatment regimen are summarized in Table 1. Many baseline criteria did not considerably differ between the therapy groups; however, the ISC patients were, on average, younger and had more advanced disease with more symptoms, whereas the comorbidity was more frequent in the control group. About 54% of patients in both groups were treated with AT, mainly as 5-FU-based mono- or combination chemotherapy, and 17% also received radiotherapy for a similar duration. More ISC than control group patients (57% vs 34%) received various regimens of additional supportive therapy. The mean delay time from surgery to treatment initiation (1.0 month) did not differ between the treatment groups.

Outcome End Points

Among the 443 patients treated with AT, significantly fewer in the ISC group than in the control group experienced AT-ADRs (incidence rate 19.1% vs 48.3%, $p < .001$) (Figure 1). Particularly common AT-ADRs had a lower

Table 1. Summary of Baseline Demographic and Prognostic Criteria and Therapy Regimen

	Value		*p Value*
Baseline Demographic and Prognostic Criteria (initial sample size = 804; 429 vs 375)	*ISC Group % or Mean (± SD)*	*Control Group % or Mean (± SD)*	*(Fisher exact test or exact Mann-Whitney test)*
Age at onset of aftercare, mean (SD), yr	57.2 (11.2)	62.8 (11.7)	< .001
Body weight, mean (SD), kg	72.5 (11.1)	74.6 (13.7)	.023
Body height, mean (SD), cm	172.6 (9.3)	169.4 (9.0)	< .001
Gender			
Males	50.1	53.3	.396
Females	49.9	46.7	
Risk factors present (medical history), %			
Yes	72.7	62.9	.003
No	27.3	37.1	
Tumor stage, %			
Low risk (T1–T2, Tis)	43.1	32.3	
High risk (T3–T4)	56.9	67.7	.002
Tumor stage, %			
Node negative ($n = 0$)	48.5	68.5	
Node positive ($n > 0$)	51.5	31.5	< .001
Tumor grade, %			
Low (1–2)	80.2	85.0	
High (3–4)	19.8	15.0	.077
Tumor stage UICC, %			
I	32.4	27.8	
II	16.1	40.8	
III	51.5	31.4	< .001

Table 1. (*continued*)

Baseline Demographic and Prognostic Criteria (initial sample size = 804; 429 vs 375)	*Value*		*p Value*
	ISC Group % or Mean (± SD)	*Control Group % or Mean (± SD)*	*(Fisher exact test or exact Mann-Whitney test)*
Colon	59.8	67.4	.067
Rectal	36.2	30.2	
Multilocular	4.0	2.4	
Tumor multiplicity, %			
Solitary	95.2	90.3	.008
Multiple	4.8	9.7	
Tumor postsurgical status, %			
NED	97.9	96.4	.376
Residual tumor	2.1	3.6	
Comorbidity (concurrent diseases), %			
Yes	59.3	69.8	.002
No	40.7	30.2	
Surgery to aftercare/therapy begin time, mean (SD), mo	2.2 (4.2)	4.4 (6.0)	< .001
Aftercare/follow-up duration			
Mean (SD)	61.0 (31.1)	55.9 (28.3)	.014
Median (range), mo	57.8 (1–160)	50.7 (1–144)	

Treatment Regimen (initial sample size = 804; 429 vs 375)	*Value*		*p Value*
	ISC Group % or mean (± SD)	*Control Group % or mean (± SD)*	*(Fisher exact test or exact Mann-Whitney test)*
Radiation therapy received, %	17.8	16.5	.640
Chemotherapy received (5-FU based), %	53.3	53.6	.926
Other supportive therapy, %	56.5	34.1	< .001
Vitamins (high dose), trace elements, etc., %	32.9	0.8	< .001
Physical therapy, rehabilitation, %	10.5	22.9	< .001
ISC therapy duration			
Median (range), mo	52.0 (0.3–153.0)	NA	NA

5-FU = 5-fluorouracil; ISC = mistletoe extract Iscador; NA = not available; NED = no evidence of disease; UICC = International Union Against Cancer.

absolute incidence in the ISC group, such as diarrhea (20 vs 47), nausea (8 vs 42), loss of appetite (1 vs 22), dermatitis (1 vs 13), fatique (1 vs 9), and mucositis (2 vs 8). The adjusted OR estimating the risk (odds) of developing any AT-ADRs during the therapy was lower by 54% in the ISC group than in the control group (OR [95% CI] = 0.46 [0.28–0.77], $p = .003$). This difference is significant and clinically relevant.

Disease- and Therapy-Related Symptoms

Significantly fewer patients in the ISC than in the control group showed a persistence of individual symptoms at the end of AT (after a mean AT duration of 8 months in both groups) or conventional aftercare. The adjusted total symptom status (TSS), that is, status not free of any persisting symptom, revealed an OR of 0.30, $p < .001$. Particularly, the gastrointestinal and CNS symptoms, mucositis, and TSS showed consistently better results in the ISC group during and after the therapy course (Figure 2).

Disease-Free Survival

The adjusted relative hazard to experience a first tumor-related event (ie, recurrence, distant metastasis, or death) during the therapy and follow-up period was significantly lower in the ISC group than in the controls, despite the more

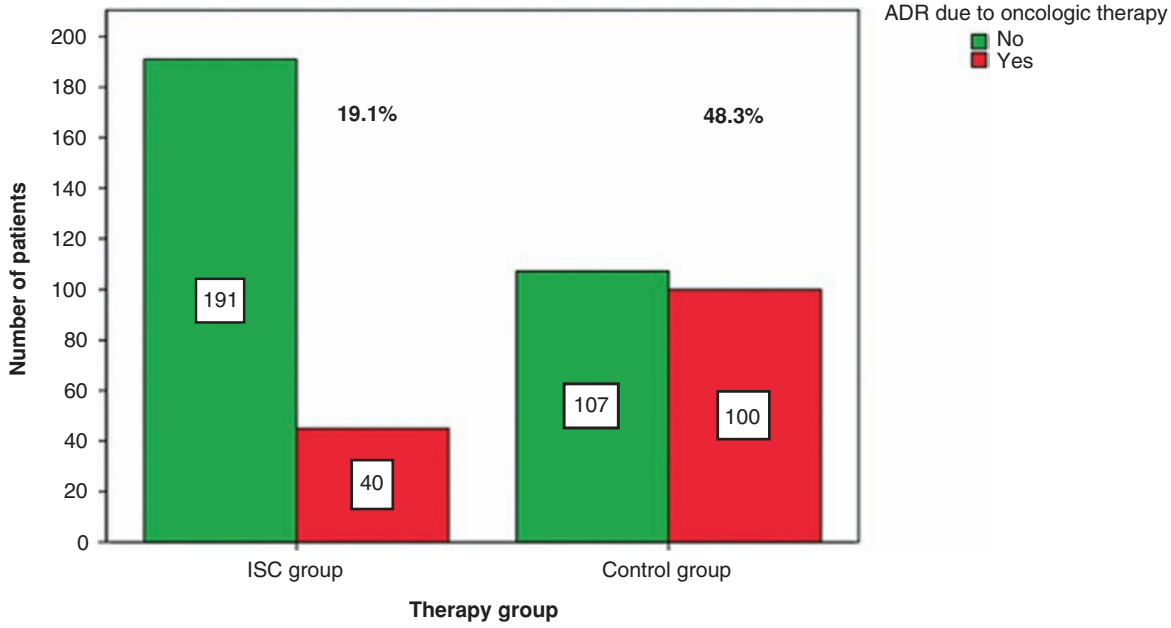

Figure 1. Adjuvant therapy adverse reaction (ADR) incidence and adjusted odds ratio (OR) in the mistletoe extract Iscador (ISC) versus the control group (incidence calculated in contingency tables using the Fisher exact test; adjusted OR calculated by logistic regression with the Wald test).

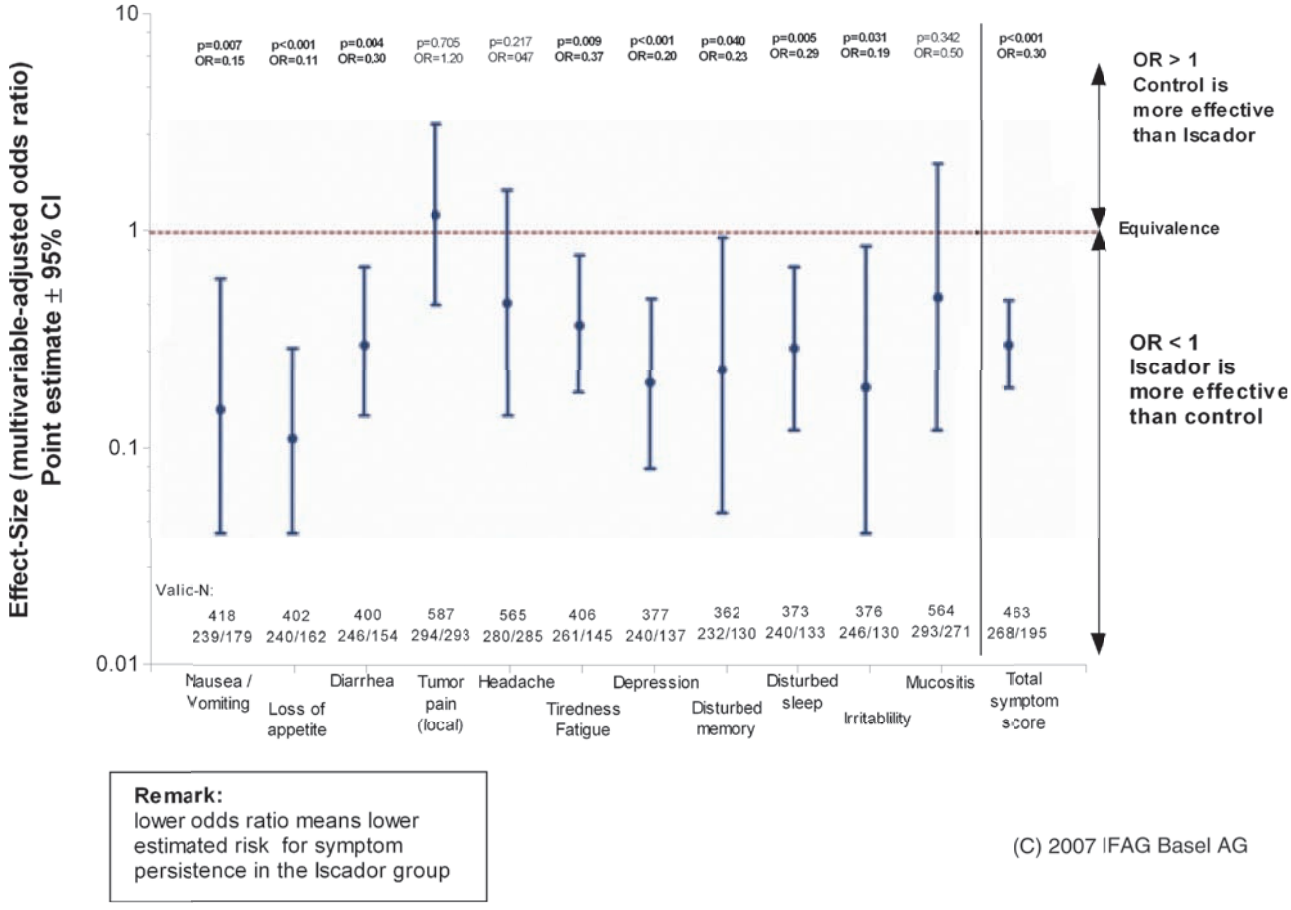

Figure 2. Symptom persistence odds ratio (OR) in the mistletoe extract Iscador group versus the control group; adjusted OR for single symptom persistence; and total symptom status, that is, persistence of any symptom, calculated by logistic regression and Wald test. Bars = 95% confidence interval (CI) of OR; points = OR point estimate.

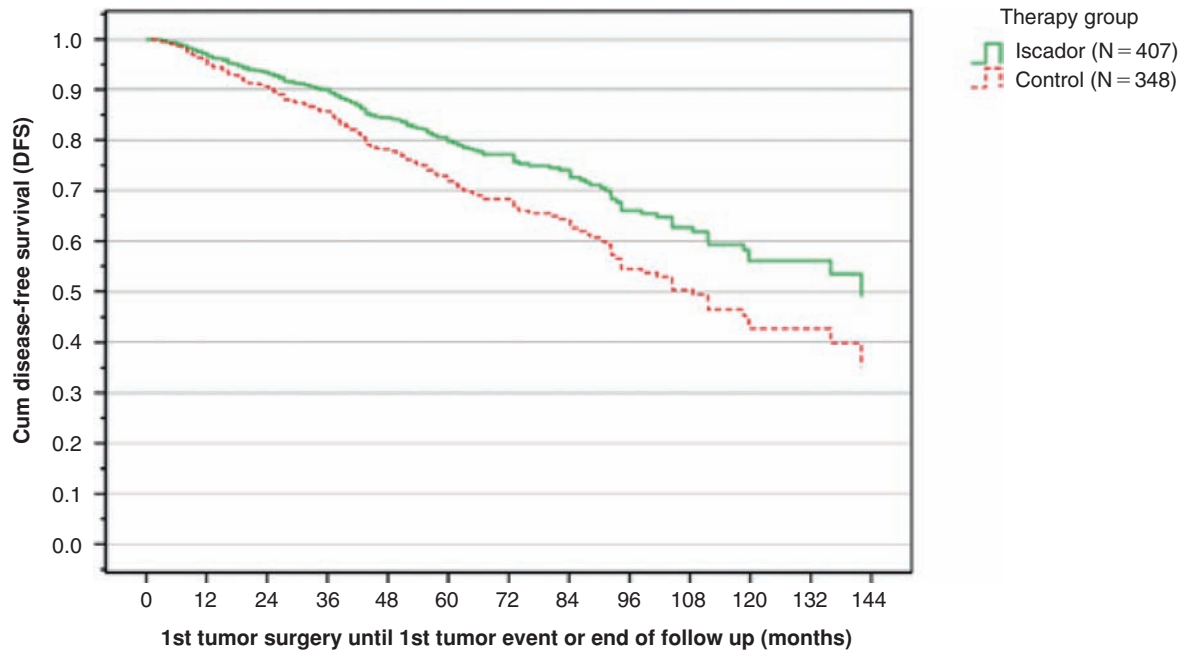

Figure 3. Disease-free survival hazard ratio (DFS-HR) estimated in the mistletoe extract Iscador group (*full line*) versus the control group (*dotted line*); adjusted DFS-HR calculated by Cox proportional hazard regression method (Wald test) and confirmed in sensitivity analyses.

advanced disease in the ISC group at baseline. The adjusted HR (95% CI) of 0.68 (0.51–0.92), $p = .013$, suggests a longer disease-free period and a survival benefit in ISC-treated patients (Figure 3).

Safety of the ISC Therapy

Systemic ADRs attributed to the ISC therapy were documented in 10 (2.3%) patients. All systemic ISC ADRs were mild to medium (grades 1–2) unspecific reactions such as dizziness, fatigue, depression, tinnitus, nausea, itching, pain, low-grade fever, and one case of acute allergic reaction. In five cases (1.2%), the ISC therapy was prematurely terminated owing to systemic ISC ADRs. Local ISC ADRs at the injection site of mild to medium severity, such as induration, edema, erythema, itching, and local pain, occurred in 100 (23.3%) patients, with two therapy discontinuations (0.5%).

Severe life-threatening or persisting ISC ADRs, interactions between ISC and other therapy, and ISC-related tumor enhancement (progression) were not observed.

Discussion

Cancer supportive care can be described as a system or complex network of medical, psychological, and sociologic interventions delivered at various times and places with different intentions. Whereas evaluating individual cancer treatments can be difficult, evaluating cancer supportive care is even more challenging and requires a research framework that relies on methodologies capable of addressing its individualized and complex nature. Access to supportive care is a central tenet of current cancer treatment policy and crucial to the philosophy of patient-centered care. During a long period of experimental and preclinical research, several hypotheses on the mode of action of mistletoe in cancer were elaborated.[23]

Recently, during an international symposium on new directions in cancer management at the Academia Nacional de Medicina de Buenos Aires, novel results on molecular mechanisms of mistletoe extracts, obtained from experimental settings and from translational clinical findings, were discussed within a forum of leading experts in oncology.[24]

It has been shown that ISC causes early cell-cycle inhibition followed by apoptosis in a dose-dependent manner within a broad panel of tumor cells.[25] Apoptotic cells are recognized by phagocytotic cells and removed from the body. Sufficiently cleared apoptotic and, in the case of successful chemotherapy, necrotic cells do not induce a chaotic chemokine or cytokine storm in the body; therefore, chemokine- and cytokine-related side effects are declining (see Figure 2), or, even more, immunologic ADRs or tumor-promoting inflammatory responses are

inhibited. It is rational to argue that supporting innate immune responses by ISC treatment and clearing tumor chemotherapy–associated cell debris are crucial to inhibiting promotion of tumor cell growth mediated by chronic inflammation. Also, therapeutic targeting of cancer-promoting (chronic) inflammatory reactions is still in its infancy; successful antiinflammatory therapeutic strategies might contribute to increase QoL and to prolong DFS.

The present study is the first and largest systematic standardized clinical data evaluation that highlights the challenge of supportive mistletoe treatment during AT and follow-up in CRC. Here we report the results of a comparative, clinical, observational cohort study with 804 evaluable primary, nonmetastatic CRC patients. The study shows a substantial statistically significant reduction in AT-ADRs, a significantly higher rate of symptom relief, and a significant prolongation of the DFS in the ISC group versus the control group. However, the effect on survival in particular needs to be interpreted with some caution because the applied study design shares some potential risk for bias with all nonrandomized observational studies. We attempted to effectively minimize these potential biases by systematic multivariable adjusting of end point criteria for baseline imbalance, treatment regimen, and other potential confounders, as well as by several other bias-reducing measures.[12]

The results from sensitivity analysis under various model conditions consistently and sufficiently reproduced the results of the main analysis and hence did not indicate the presence of any effective hidden confounder or selection bias. Sufficient quality of the standardized QoL data acquisition from the medical records in observational studies was reported.[26]

The study results also support earlier published evidence of a substantial clinical benefit on QoL surrogate criteria from a supportive mistletoe treatment in cancer patients.[23] Regarding toxicity in the present study, ISC treatment was well tolerated, without any life-threatening ADRs, particularly without severe allergic reactions. Tumor enhancement was not observed in the present study.

In the present study, significantly more test group patients received additional complementary therapies and high-dose vitamins and trace elements than in the control group. Such type of inhomogeneity is quite common in nonrandomized observational retrospective or retrospective cohort studies. As mentioned in the Study Design and Methods section, to minimize the possible confounding effect on the outcome measures, complementary and vitamin therapy, among others, was included as an adjusting factor (covariate) in the multivariate logistic regression (QoL criteria) and the Cox proportional hazard regression (survival analysis). Owing to this model, the possible confounding effect of such additional therapy was minimized, and the mistletoe therapy results became largely unbiased estimates. These results were confirmed in sensitivity analysis. Therefore, in this study, the adjusted outcomes could be interpreted as free of possible effects of the vitamin or trace element therapy or as adjusted results accounting for the possible confounding effect of the other therapies. This is also valid in case of larger significant baseline or therapy differences between the treatment groups provided that the relevant inhomogeneous criteria were included properly as covariates for adjusting.

To minimize the possible effects of unknown hidden confounders, several sensitivity analyses have been carried out, such as calculations by different sets of confounders and random subsamples from the whole study sample. All sensitivity analyses confirmed the results of the main analysis. Therefore, it seems unlikely that the reported results could be biased by hidden confounders.

Despite some possible methodological limitations inherent in any nonrandomized design, we must not miss the opportunity to evaluate novel aspects of supportive cancer care. The results of the present study suggest convincing evidence for a significant and clinically relevant benefit from supportive ISC therapy regarding (1) the decreased incidence of AT-ADRs; (2) the improvement in symptoms and, therefore, QoL; and (3) prolongation of DFS in long-term application.

Conclusion

These results suggest a beneficial effect of supportive care ISC therapy within AT protocols and long-term ISC treatment in stage I–III CRC patients, particularly improvement in AT-ADRs and symptoms and possible extension of DFS.

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References

1. Ferlay J, Autier P, Boniol M, et al. Estimates of the cancer incidence and mortality in Europe in 2006. Ann Oncol 2007;18:581–92.
2. American Cancer Society. Cancer facts & figures 2008. Atlanta (GA): American Cancer Society; 2008.
3. Chau I, Cunningham D. Adjuvant therapy in colon cancer—what, when and how? Ann Oncol 2006;17:1347–59.

4. Benson AB III, Schrag D, Somerfield MR, et al. American Society of Clinical Oncology recommendations on adjuvant chemotherapy for stage II colon cancer. J Clin Oncol 2004;22:3408–19.
5. Kahlenberg MS, Rousseau DL, Strasser J, et al. Rectal cancer: management of locoregional disease. In: Kelsen DP, Daly JM, Kern SE, et al, editors. Principles and practice of gastrointestinal oncology. 2nd ed. Philadelphia: Wolter Kluver - Lippincott Williams & Wilkins; 2008. p. 593–615.
6. Eder JP, Skarin AT. Systemic and mucocutaneous reactions to chemotherapy. In: Meyerhardt J, Saunders M, Skarin AT, editors. Colorectal cancer. 1st ed. Edinburgh: Mosby Elsevier; 2007. p. 57–104.
7. Kopec JA, Yothers G, Ganz PA, et al. Quality of life in operable colon cancer patients receiving oral compared with intravenous chemotherapy: results from National Surgical Adjuvant Breast and Bowel Project Trial C-06. J Clin Oncol 2007;25:424–30.
8. Arndt V, Merx H, Stegmaier C, et al. Quality of life in patients with colorectal cancer 1 year after diagnosis compared with the general population: a population-based study. J Clin Oncol 2004;22:4829–36.
9. Ludwig H, Zojer N. Supportive care. Ann Oncol 2007;18 Suppl 1:i37–44.
10. Horneber M, Bueschel G, Huber R, et al. Mistletoe therapy in oncology. Cochrane Database Syst Rev 2008;(2):CD003297.
11. European Union, European Parliament, European Council. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to human medicinal products. Official Journal of the European Communities 2001;L 311:67–128.
12. Schneider B. Analysis of therapeutic efficacy in observational cohort studies. Cancer Chemother Pharmacol 2001;47 Suppl:35–7.
13. Benson K, Hartz AJ. A comparison of observational studies and randomized clinical trials. N Engl J Med 2000;342:1878–86.
14. Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research design. N Engl J Med 2000;342:1887–92.
15. Heinrich M, Seegenschmied MH, Müller RP, et al. Common Toxicity Criteria (CTC). Dokumentation von Nebenwirkungen in der Onkologie. Dtsch Ärzteblatt 1999;96:355–60.
16. Buyse M, Burzykowski T, Carroll K, et al. Progression-free survival is a surrogate for survival in advanced colorectal cancer. J Clin Oncol 2007;25:5218–24.
17. Sargent DJ, Patiyil S, Yothers G, et al. End points for colon cancer adjuvant trials: observations and recommendations based on individual patient data from 20,898 patients enrolled onto 18 randomized trials from the ACCENT Group. J Clin Oncol 2007;25:4569–74.
18. Rosenbaum PR. Observational studies. 2nd ed. New York: Springer-Verlag; 2002.
19. Horwitz RI, Viscoli CM, Clemens JD, Sadock RT. Developing improved observational methods for evaluating therapeutic effectiveness. Am J Med 1990;89:630–8.
20. Breslow NE, Day NE. Statistical methods in cancer research. Vol II. The design and analysis of cohort studies. Lyon: World Health Organization; International Agency for Research On Cancer; 1987. IARC Scientific Publications No.: 82.
21. Feinstein AR. The role of observational studies in the evaluation of therapy. Stat Med 1984;3:341–5.
22. D'Agostino RB Jr. Propensity score methods for bias reduction in the comparison of a treatment to non-randomized control group. Stat Med 1998;17: 2265–81.
23. Kienle GS, Kiene H. [Mistletoe in the Oncology. Facts and conceptual basis]. Stuttgart: Schattauer; 2003.
24. Pasqualini CD, Mihich E, Zänker KS, editors. New directions in cancer management. Medicina (B Aires) 2007;67 Suppl II:1–118.
25. Ramaekers FC, Harsma M, Tusenius KJ, et al. Mistletoe extracts (Viscum album L.) Iscador® interact with the cell cycle machinery and target survival mechanisms in cancer cells. Medicina 2007;67 Suppl II:79–84.
26. Velikova G, Wright P, Smith AB, et al. Self-reported quality of life of individual cancer patients: concordance of results with disease course and medical records. J Clin Oncol 2001;19:2064–73.