SUPPORTIVE CARE IN PANCREATIC CAR TREATED WITH FERMENTED MISTLE

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SUMMARY

The treatment with fermented mistletoe extract Iscador® (ISC) was evaluated as part of the supportive care of pancreatic carcinoma patients in comparison with a parallel control group without ISC in a multicenter, epidemiological cohort study in Germany and Switzerland.

ISC was given in addition to conventional adjuvant chemotherapy (± radiotherapy) or passive aftercare, while the control group was treated with conventional therapy or passive aftercare alone. A total of 396 (201 ISC and 195 control) evaluable patients from 17 centers were treated and followed-up for a median duration of 15.2 vs. 10.1 months. The supportive ISC therapy was given for a median duration of 15 months.

The ISC group showed significantly fewer ADRs attributed to the conventional therapy (mainly Gemcitabin), fewer persistent disease- and therapy-related symptoms, better functional condition, shorter need for hospitalization, and significantly longer overall survival than the parallel control group without ISC therapy.

In the present study, the ISC treatment was well tolerated and showed a beneficial role in supportive care in pancreatic carcinoma patients.

AIM OF THE STUDY

Mistletoe therapy is a frequently used supportive treatment in cancer patients in Europe, mainly to reduce adverse drug reactions (ADRs) of conventional chemo- and/or radiotherapy and to improve quality of life. The present study was designed to evaluate the effectiveness and safety of the mistletoe *(Viscum album L.)* extract Iscador® (ISC), administered subcutaneously 2-3 times per week as part of supportive care in patients with any stage of pancreatic carcinoma, who received adjuvant chemo- and/or radiotherapy), or passive aftercare.

STUDY DESIGN AND METHODS

Design: In a multicenter, controlled, epidemiological cohort study in Germany and Switzerland, Iscador® (ISC) was applied in addition to conventional adjuvant chemo- and/or radiotherapy, or passive aftercare. The control group was treated with conventional therapy only. The study was performed according to Good Epidemiological Practice (GEP) rules. Unselected, chronologically ordered, standardized, anonymized data from medical records meeting the pre-specified eligibility criteria were documented until the last visit or death.

Outcome endpoints: The endpoints for effectiveness were number of adverse drug reactions (ADR) related to the conventional chemo- or radiotherapy, disease- and treatment-associated symptoms, general performance (Karnofsky-Index), duration of hospitalization, and disease-free survival (DFS) in the ISC-treated group as compared to the parallel control group without ISC. Safety of the ISC-therapy was assessed by the number of ISC-related ADRs.

Adjustment: All endpoint results were adjusted for baseline imbalances, therapy regimen, and confounder effects. The predefined confounders used for adjusting were: age, gender, center group, non-oncologic chronic diseases, tumor-multiplicity, UICC tumor stage, tumor surgery, post-surgical tumor staging (CR/NED vs. residual tumor), chemotherapy, radiotherapy, duration of chemotherapy, and additional supportive therapy with high-dose vitamins, minerals, and trace elements.

Test level: All statistical tests were performed on a significance level of $\alpha = 0.05$.

PATIENTS

A total of 396 evaluable patients (201 ISC and 195 control) from 17 centers was treated between 1993 and 2002 (median 1999) for pancreatic carcinoma of any UICC stage. They received conventional oncological treatment as well as supportive care. The median follow-up time was 15.2 (ISC) vs. 10.1 months (control), the median ISC-therapy duration was 15.0 months.

The baseline demographic characteristics and prognostic factors are summarized in **Table 1**, the treatment regimen is presented in **Table 2**.

There were some imbalances at baseline in age, tumor stage (pT and pN), UICC IIb, UICC IV, histopathologic tumor grade (pG 3-4), frequency of adjuvant chemotherapy, radiotherapy, and additional supportive therapy. Due to these differences, only multivariable-adjusted outcome results, confirmed in sensitivity analyses, were interpreted.

Pancreatic carcinoma Baseline criteria (Total sample - valid-N):		Mistletoe group (201)	Control Group (195)
Age, mean (SD) years		58.2 (10.7)	63.7 (9.8)
Body weight, mean (SD) kg		67.2 (11.5)	69.9 (13.5)
Gender, %	female	44.3	50.3
	male	55.7	49.7
Tumor localization, %	pancreas head	74.1	69.2
	pancreas body	13.9	10.8
	pancreas tail	7.5	10.8
	others	4.5	9.2
Tumor stage pT, %	early (1-2, is, x)	45.3	28.7
	advanced (3-4)	54.7	71.3
Tumor stage pN, %	lymph nodes – (N=0, x)	33.3	62.6
	lymph nodes + + (N>0)	66.7	37.4
Tumor stage pM, %	no metastases (M0, x)	71.1	65.6
	distant metastases (M1)	28.9	34.4
Tumor grade pG, %	less malignant (1-2, x)	83.5	73.8
	highly malignant (3-4)	16.5	26.2
Tumor stage UICC, %	UICC I	11.4	13.3
	UICC IIa	12.4	12.8
	UICC IIb	49.8	24.6
	UICC III	11.4	19.5
	UICC IV	15.0	29.8
Tumor multiplicity, %	solitary	87.6	93.3
	multiple	12.4	6.7
Tumor status post-surgery, %	CR	30.8	40.5
	residual tumor	69.2	59.5
Other chronic (non-oncologic) diseases, %		55.2	61.5

Table 1 (left): Baseline characteristics of demographic and prognostic criteria.

Table 2 (below): Therapy and observation.

Pancreatic carcinoma Therapy and observation measures (Total sample - valid-N):	Mistletoe group (201)	Control Group (195)
Tumor surgery, %	69.2	48.2
Chemotherapy (all), %	71.6	43.6
- Gemcitabine /combination, %	66.2	33.8
Chemotherapy duration, mean (SD), months	6.9 (7.3)	4.7 (6.3)
Radiotherapy, %	4.5	18.5
Other supportive therapy (overall), %	54.7	32.8
-analgesic therapy, %	80.6	71.8
-supportive high-dose vitamins, tmce elements, %	39.8	0.0
Mistletoe therapy duration, mean (SD), months	20.5 (18.6)	-
median (range), months	15.0 (1-87)	-
Follow-up duration, mean (SD), months	23.1 (24.3)	16.9 (21.5)
median (range), months	15.2 (0-159)	10.1 (0-123)

RESULTS

Figure 1: ADRs by adjuvant chemo- and/or radiotherapy

Among the patients treated with chemotherapy (± radiotherapy), the ISC group showed significantly fewer adjuvant therapy induced ADRs (13.7% vs. 48.9%, p<0.001) than the control group. The adjusted relative ADR risk (estimated as odds ratio, OR) was significantly lower in the ISC group compared to the control group: OR (95% CI) = 0.27 (0.12 - 0.61), p=0.001.

Figure 2: Disease- and therapy-related symptoms

Fewer patients in the ISC group showed persistence of confounder-adjusted disease- and therapy-related symptoms after the first therapy course (mean chemotherapy duration was 6.9 vs. 4.7 months). Particularly gastrointestinal and CNS symptoms and back pain achieved consistently better results in the ISC group.

Figure 3: Functional capacity assessment by Karnofsky-Index (KI)

At baseline, KI was worse in the ISC than in the control group (mean 74.1% vs. 80.3%, p<0.001). After the 1st therapy course, the adjusted KI improved in the ISC group but deteriorated in the control group (mean values 79.1% vs. 74.7%, mean difference: + 4.5%, p=0.003).

Figure 4: Duration of hospitalization during therapy and follow-up

The adjusted mean (95% CI) duration of hospitalization was 39.5 (32.8 - 46.3) days in the ISC group compared to 53.6 (48.6 - 58.7) days in the control group. Consequently, the ISC-treated patients needed shorter hospitalization (- 14.1 days on average) than the controls (p<0.001).

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INOMA UICC STAGES I-IV PATIENTS
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FIGURES

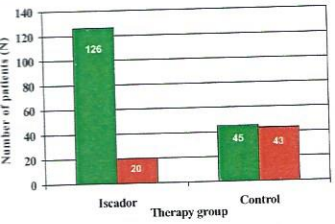

Figure 1: ADRs of conventional oncological therapy.

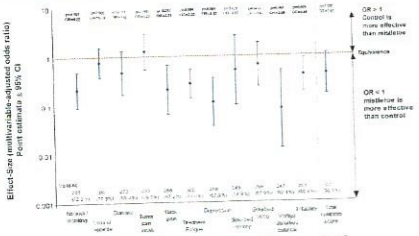

Figure 2: Symptom persistence at the end of the 1st oncological therapy course.

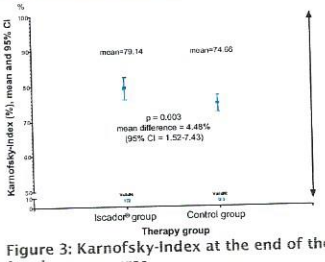

Figure 3: Karnofsky-Index at the end of the 1st therapy course.

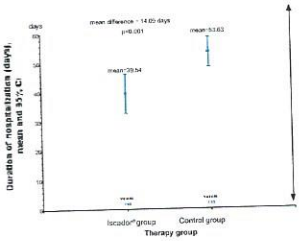

Figure 4: Duration of hospitalization during observation period.

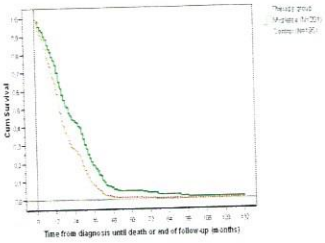

Figure 5: Overall survival (OS) in all patients (UICC stages I-IV).

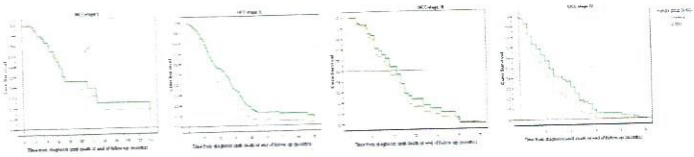

Figure 6: Overall survival (OS) stratified by subgroups UICC stage I, II, III, and IV

SAFETY OF ISCADOR® THERAPY

Systemic ADRs attributed to the ISC therapy were documented in three patients (1.5%). They were mild and unspecific such as dizziness, fatigue, depression, nausea, and low-grade fever. Local ADRs at the injection site of mild to medium severity occurred in 45 patients (22.4%), mainly as induration, edema, erythema, itching and local pain. Severe life-threatening or persisting ADRs did not occur. Tumor enhancement was not observed. In conclusion, the ISC therapy was well tolerated and can be regarded as safe.

Figure 5: Overall survival (OS)

The adjusted relative hazard to die from any cause during the therapy and follow-up period was significantly lower in the ISC group than in the controls. The adjusted mortality hazard ratio was HR (95% CI) = 0.58 (0.42 - 0.79), p=0.001.

Figure 6: OS in subgroups stratified for UICC stages I/IV

UICC I:
Valid-N = 49 (23/26), 27 events, HR (95% CI) (confounder-adjusted) = 0.80 (0.34-1.91), p (Wald) = 0.620, reduction of the estimated adjusted relative risk (hazard) for OS in the Iscador® group by approx. 20%.

UICC II:
Valid-N = 198 (125/73), 148 events, HR (95% CI) (confounder-adjusted) = 0.68 (0.45-1.03), p (Wald) = 0.071, reduction of the estimated adjusted relative risk (hazard) for OS in the Iscador® group by approx. 32%.

UICC III:
Valid-N = 61 (23/38), 55 events, HR (95% CI) (confounder-adjusted) = 0.79 (0.32-1.96), p (Wald) = 0.614, reduction of the estimated adjusted relative risk (hazard) for OS in the Iscador® group by approx. 21%.

UICC IV:
Valid-N = 88 (30/58), 85 events, HR (95% CI) (confounder-adjusted) = 0.65 (0.35-1.20), p (Wald) = 0.168, reduction of the estimated adjusted relative risk (hazard) for OS in the Iscador® group by approx. 35%.

DISCUSSION

The presented study is the largest systematic comparative clinical data evaluation concerning the supportive mistletoe treatment in pancreatic carcinoma ever performed. Despite the limitation of a non-randomized study design, the potential biases have been minimized by strict adherence to the GEP rules, unselected eligible patient data, parallel control group, systematic data quality monitoring, multivariable adjusting for baseline imbalances and confounders, and a re-confirmation of the results in sensitivity analyses.

The ISC-treated group reported significantly fewer ADRs of the conventional therapy, fewer disease- and therapy-related symptoms, and a longer overall survival (OS) as compared to the parallel group without ISC therapy.

The OS results suggest a possibly independent beneficial effect of the additional ISC therapy in all UICC stages (I-IV) of pancreatic carcinoma patients in the attempt to prolong survival.

Remarkable relative mortality hazard reduction in favor of the ISC treatment has been shown in UICC stages II and IV (metastatic disease). This might offer a new therapeutic chance for ISC as a supportive treatment, particularly along with the conventional adjuvant chemotherapy.

REFERENCES AND ACKNOWLEDGMENT

References
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