**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 treatment in cancer patients in Europe, mainly to reduce adverse drug reactions (ADRs) of conventional chemotherapeutic agents/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 chemotherapy/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 chemotherapy/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 chemotherapy/ or radiotherapy, disease and treatment-related 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 α = 0.05.

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**RESULTS**

**Figure 1:** ADRs by adjuvant chemotherapeutic and/or radiotherapy

Among the patients treated with chemotherapy (± radiotherapy), the ISC group showed significantly fewer adjuvant therapy-induced ADRs (13.7% vs. 18.9%, 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) = 0.70 (0.60 - 0.81), p < 0.001.

**Figure 2:** Disease- and therapy-related symptoms

Fewer patients in the ISC group showed persistent of confounder-adjusted disease- and therapy-related symptoms after the first therapy course (mean chemotherapeutic 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 (K)

At baseline, KI was worse in the ISC than in the control group (mean 74.1% vs. 80.3%, p < 0.001). After the first 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).
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.

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 CEP rules, unselected eligible patient data, parallel control group, systematic data quality monitoring, and 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 (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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