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New study: Mistletoe Extract in Patients with Advanced Pancreatic Cancer

The randomised, placebo-controlled, double-blind MISTRAL study on mistletoe therapy in pancreatic cancer has now been published internationally by the German Medical Journal/Deutsches Ärzteblatt (*Dtsch Arztebl Int 2024; 121: 347–54*). The MISTRAL trial was sponsored by the Center for Digestive Diseases, Karolinska University Hospital, a public, non-commercial, academic institution.

The MISTRAL study investigated whether mistletoe therapy can further improve the results of optimal, modern oncological palliative treatment. The study explored whether mistletoe extracts, given alongside comprehensive oncological treatment and palliative care, can further prolong overall survival and improve health-related quality of life in patients with pancreatic cancer. In addition to mistletoe therapy, participants in the MISTRAL study received optimal palliative medical care according to today's standards (including chemotherapy in 80% of cases).

In the MAPAC study from 2013/14, the main intervention was mistletoe therapy – with the result of a significant improvement in quality of life and overall survival. In the MISTRAL study, concomitant mistletoe therapy did not show any additional advantage in terms of survival time and quality of life. Frequent concerns about the safety and interaction profile of mistletoe therapy with chemotherapy could be ruled out. Further aspects of quality of life, the development of body weight as a measure of general health, biomarkers (laboratory values) and qualitative measures of subjective well-being are still being analysed.

How was the MISTRAL study designed?

Since patients with advanced pancreatic cancer have a short survival time and only limited treatment options available, the double-blind, randomised, placebo-controlled MISTRAL trial investigated whether mistletoe extracts (ME), given in addition to comprehensive oncological treatment and palliative care, can prolong overall survival (OS) and improve health-related quality of life (HRQoL) in 290 patients in 9 Swedish oncology centres. The main inclusion criteria were advanced, exocrine pancreatic cancer and an ECOG performance status between 0 and 2. Participants were randomly assigned to either the mistletoe therapy group (n = 143) or the placebo group (n = 147), stratified according to trial centre and recommendation of palliative chemotherapy. ME or placebo was injected subcutaneously three times a week for nine months and HRQoL was measured seven times during this period. Participants were also given medication for symptom control (analgesics, antiemetics, anxiolytics, glucocorticoids) and, if necessary, palliative medical care (multidisciplinary, delivered at home or as inpatient services).

What were the results?

There was no statistically significant advantage for mistletoe therapy either on the OS, or the HRQoL dimensions "global health" and "quality of life". The number, severity and outcome of adverse events were also comparable between the mistletoe and placebo groups, except for the more frequent local skin reactions under ME (66% vs. 1%). The adjusted hazard ratio for OS was 1.13 [0.89; 1.44], the median survival time was 7.8 months in the ME group and 8.3 months in the placebo group, and the first look at HRQoL (EORTC-QLQ C30 questionnaire, questions 29 and 30: 'How would you rate your overall state of health during the last week' and 'How would you rate your overall quality of life during the last week') was also comparable in both groups (p = 0.86).

Has the MAPAC study, which recorded significant improvements in quality of life and lifespan in patients with advanced pancreatic cancer due to mistletoe therapy, been refuted by the MISTRAL study?

No, because the two studies are not comparable. The conditions, the research question and the design differ significantly: The MAPAC study (1, 2), published in 2013/14, investigated the effect of mistletoe therapy as the main intervention in a group of patients with advanced pancreatic cancer. In these cases, palliative chemotherapy was no longer considered for these patients in the situation at the time.

The participants in the MISTRAL study received mistletoe therapy in addition to optimal palliative medical care by today's standards. As an expression of the difference between the two studies, the survival time of patients without mistletoe therapy was 2.7 months in the MAPAC study compared to 8.3 months in the MISTRAL study. In the MAPAC study, the survival time of patients with mistletoe therapy was increased to 4.8 months, while the survival time of 7.9 months for mistletoe patients in the MISTRAL study did not differ significantly from the group without mistletoe therapy.

The MISTRAL study also included patients with advanced stages of pancreatic cancer, 80% of whom received concomitant chemotherapy and comprehensive palliative oncological support in line with current standards (2019-2023). These measures have been proven to maintain the quality of life of pancreatic cancer patients and extend their lifespan (4). Only 20% of MISTRAL patients did not receive concomitant chemotherapy.

The MAPAC study was controlled and randomised, but not blinded and not placebo-controlled. Is the conclusion of the MISTRAL study therefore more credible?

Mistletoe therapy poses a particular challenge for blinding because it usually leads to a characteristic local reaction at the injection site. The authors of the MAPAC study decided against blinding for fear of having to discontinue the trial if patients' belonging to the treatment group became revealed.

The MISTRAL study publication states that 93 out of 140 patients who received mistletoe therapy reported a local reaction and therefore unblinding may have occurred in 65% of patients in the trial. However, the authors of the MISTRAL study assume that this had no influence on the results.

Do these findings conclude the research into mistletoe therapy for pancreatic cancer?

No, and the complete data from the MISTRAL trial has not yet been conclusively analysed. In addition to survival time and global quality of life, other aspects of quality of life, the development of body weight as a measure of general health, biomarkers (laboratory values) and a qualitative interview series with the patients were also documented. All this data has yet to be analysed and published.

Were there also positive results in the MISTRAL study?

Yes, in the past, there were some concerns about the safety and interaction profile of mistletoe therapy with chemotherapy due to a lack of data. The MISTRAL study has now answered both questions. According to the authors, there were no reasons for safety concerns: only two cases of severe side effects (1 urticaria and 1 pseudo-allergic reaction) occurred, which was in line with the known side effect profile of mistletoe therapy; the frequency of less than 1.5% occurrence was also in line with expectations based on the existing scientific literature.

Furthermore, the researchers found "no evidence of an influence of ME (mistletoe extracts) on the effect of chemotherapy in terms of prolonged or shortened survival or toxicity. However, this is only an assessment, as our study was not designed to investigate this question. However, this assessment is supported by a phase I study (3) which found no effect of ME on the metabolism of gemcitabine - the most commonly used chemotherapy for pancreatic cancer."

What does this mean?

Following the MAPAC study from 2013/14, in which the question on mistletoe's efficacy was answered positively, the Swedish researchers wanted to investigate whether mistletoe therapy could be used to further improve the results of optimal, modern oncological palliative treatment in a disease where modern medicine has reached its limits. Comprehensive palliative medical treatment can significantly increase the survival time of pancreatic cancer patients (4), but within this specific setting mistletoe therapy statistically is not likely to offer any additional benefits.

The patients in the MISTRAL study already had a much better survival time (8.3 months) due to the integrated palliative medical treatment provided in Sweden than the patients in the MAPAC study from 2013/14, who only received reduced symptomatic therapy to control pain and nausea (2.7 months). From the MISTRAL study, it may be concluded that mistletoe therapy does not provide any additional benefit when comprehensive modern palliative oncological care is provided for pancreatic cancer patients. This may differ in cases within different therapeutic settings. Therefore, as recommended in the German S3 guideline 'Complementary medicine in oncology', the decision as to whether to choose concomitant mistletoe therapy for any given pancreatic cancer situation should remain with the patients and their treating specialists, taking into account their individual situation and specific needs.

When is further data from the MISTRAL study expected to be published?

According to the authors, further publications are currently being prepared. However, they are obliged to maintain confidentiality about the exact timetable. Iscador AG, as the manufacturer of the study medication, will be informed with each subsequent publication by the authors in a conference. It remains our topmost priority to process the new results promptly and to make them available in summarised form on our homepage.

Original publication

- The publication is openly accessible in English and in German
  Wode K, Kienle GS, Björ O, et al. Mistletoe extract in patients with advanced pancreatic cancer: a double-blind, randomized, placebo-controlled trial (MISTRAL). Dtsch Arztebl Int 2024; 121: 347–54. DOI: 10.3238/arztebl.m2024.0080
- A short interview with the trial's main investigator, Dr Kathrin Wode (in German):
  https://www.aerzteblatt.de/archiv/239602/3-Fragen-an-Kathrin-Wode

Further Literature

(1) Tröger W, Galun D, Reif M, et al. *Viscum album* [L.] extract therapy in patients with locally advanced or metastatic pancreatic cancer: a randomised clinical trial on overall survival. Eur J Cancer 2013;49:3788-3797. DOI: 10.1016/j.ejca.2013.06.043

(2) Tröger W, Galun D, Reif M, et al. Quality of life of patients with advanced pancreatic cancer during treatment with mistletoe: a randomized controlled trial. Dtsch Arztebl Int 2014;111:493-502. DOI: 10.3238/arztebl.2014.0493

(3) Mansky PJ, Wallerstedt DB, Sannes TS, et al. NCCAM/NCI phase 1 study of mistletoe extract and gemcitabine in patients with advanced solid tumors. Evid Based Complement Alternat Med 201; ID964592. DOI: 10.1155/2013/964592

(4) Bayraktar S, Bayraktar UD, Rocha-Lima CM: Recent developments in palliative chemotherapy for locally advanced and metastatic pancreas cancer. World Journal of Gastroenterology 2010, 16:673-682.
"In the palliative setting, gemcitabine (Gem) has been a standard treatment for advanced pancreatic cancer since it was shown a decade ago to result in a superior clinical benefit response and survival compared with bolus 5-fluorouracil."

Koeppler H, Duru M, Grundheber M, Heymanns J, Jacobs G, Pandorf A, Rendenbach B, Schimke J, Weide R: Palliative treatment of advanced pancreatic carcinoma in community-based oncology group practices. J Support Oncol 2004, 2:159-163.
"The median survival of patients receiving cytotoxic treatment (mainly gemcitabine) was 42 weeks, and the median survival of patients receiving best supportive care was 21 weeks."

Kokoska ER, Stapleton DR, Virgo KS, Johnson FE, Wade TP: Quality of life measurements do not support palliative pancreatic cancer treatments. Int J Oncol 1998, 13:1323-1329.
"Patients receiving combined chemo- and radiation therapies, whether given as adjuvant or primary treatment, had significantly longer mean survival duration."

Seufferlein T, Porzner M, Heinemann V, Tannapfel A, Stuschke M, Uhl W: Duktales Pankreaskarzinom: Chirurgische Therapie, pathologische Aufarbeitung des Präparats, neoadjuvante, adjuvante und palliative Therapie. Dtsch Arztebl International 2014, 111(22):396-402.
„Beim metastasierten beziehungsweise lokal fortgeschrittenen Pankreaskarzinom soll bei einem ECOG Performance Status von 0 bis 2 eine palliative Chemotherapie durchgeführt werden (EG A, LOE 1a), da diese das Überleben der Patienten verlängert und die Lebensqualität verbessert.»

Sultana A, Smith CT, Cunningham D, Starling N, Neoptolemos JP, Ghaneh P. Meta-analyses of chemotherapy for locally advanced and metastatic pancreatic cancer. J Clin Oncol. 2007 Jun 20;25(18):2607-15. doi: 10.1200/JCO.2006.09.2551. PMID: 17577041
"There was a significant survival benefit for chemotherapy over best supportive care and gemcitabine combinations over gemcitabine alone. This supports the use of gemcitabine-based combination chemotherapy in the treatment of advanced pancreatic cancer."

Sullivan KM, Kozuch PS: Chemotherapy and other supportive modalities in the palliative setting for pancreatic cancer. Cancer J 2012, 18:633-641.
"The multi-agent cytotoxic chemotherapy regimen FOLFIRINOX (…) has significantly improved survival compared with gemcitabine alone (…)."