Reprint Antibiotika · Chemotherapeutika · Virustatika · Zytostatika ArzneimForschDrugRes

Antibiotics · Antiviral Drugs · Chemotherapeutics · Cytostatics

Efficacy and Safety of Long-term Complementary Treatment with Standardised European Mistletoe Extract *(Viscum album L.)* in Addition to the Conventional Adjuvant Oncological Therapy in Patients with Primary Non-metastatic Breast Cancer

Results of a multicentre, comparative, epidemiological cohort study in Germany and Switzerland

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Summary

Objectives: The purpose of the study was to evaluate the therapeutic efficacy and safety of long-term complementary therapy in primary, non-metastatic breast cancer patients in UICC stage I–III with a standardized European mistletoe extract (*Viscum album L.*, Iscador®, "mistletoe extract") given in addition to conventional adjuvant oncological therapy (i.e. chemo-, radio-, and hormonal therapy; "conventional therapy").

Methods: The multicentre, comparative, retrolective, pharmaco-epidemiological cohort study with parallel groups design and randomly selected centers was carried out according to Good Epidemiological Practice (GEP) rules. The study group patients received subcutaneous mistletoe extract injections for at least three months in addition to the conventional therapy, while the control group was treated with conventional therapy only. The patients were followed up for at least three years or until death. The primary endpoint for efficacy was the overall incidence of adverse drug reactions (ADRs) attributed to the conventional therapy. Secondary endpoints were symptoms associated with disease and treatment, as well as the survival. All endpoints were adjusted to baseline imbalance, therapy regimen and other confounders by the logistic regression or the Cox proportional hazard regression. Safety was assessed by the number of patients with ADRs attributed to the mistletoe extract treatment, the ADR severity and the evaluation of a possible tumor enhancement.

Results: 1442 patients (710 study and 732 controls) were eligible for the "per protocol" analysis of efficacy and safety.

Key words

- **Breast cancer**
- **Iscador®**
- **Mistletoe, adjuvant therapy, cohort study, efficacy, safety**
- ***Viscum album L.***

Arzneim.-Forsch./Drug Res. 54, No. 8, 456–466 (2004)

At baseline, the mistletoe extract group had a more advanced disease and worse prognostic factors profile. After a median follow up of 67 vs. 61 months, and a median mistletoe extract therapy duration of 52 months, significantly fewer study group patients (16.3 %) than control patients (54.1 %) developed one or more ADRs attributed to the conventional therapy (adjusted odds ratio (95 % confidence interval, CI): OR = 0.47 (0.32–0.67), p < 0.001). In the mistletoe extract group, several symptoms more frequently disappeared, and the overall estimated survival was significantly longer (adjusted mortality hazard ratio (95 % CI): HR = 0.46 (0.22–0.96), p = 0.038). Systemic ADRs attributed to the mistletoe extract treatment developed 0.8 %, and local ADRs 17.3 % of the patients. The ADR severity was mild to intermediate (WHO/CTC grade 1–2). Severe mistletoe extract therapy-related ADRs or tumor enhancement were not observed.

Conclusions: The results of the present study confirmed the safety of the complementary therapy of patients with primary, non-metastatic breast cancer with a standardized mistletoe extract and showed considerably fewer ADRs attributed to concurrent conventional therapy, as well as reduced disease and treatment-associated symptoms, and suggested a prolonged overall survival in the mistletoe extract group as compared with controls.

1. Introduction

Breast cancer has the highest incidence (25.9 %) and mortality (17.1 %) of all types of cancer in women in Germany. In the United States about 175,000 new cases occur each year and approximately 43,000 women die of breast cancer in the USA and about 1 million women world-wide [1, 2]. Treatment of breast cancer requires multimodal therapy with primary surgery followed by adjuvant radio-, chemo- and/or hormonal therapy depending on individual criteria relating to tumour status, lymph node disease, menopause and hormone receptor status (adjuvant therapy) [3–6]. In view of the frequent side effects of adjuvant therapy [7, 8] and the risk of a substantial impairment in quality of life [9–14], complementary treatment to limit or prevent the symptoms associated with the disease or treatment is becoming increasingly important. This is despite the fact that there is still no convincing evidence of its effectiveness in reducing the progression of the disease and prolonging survival [15–17]. Of the complementary treatments used by cancer patients, European mistletoe extracts *(Viscum album L.)* are the most common in Europe, especially in Germany [18, 19]. In recent studies the most important components of mistletoe (lectins, viscotoxins and other components) have been defined more accurately, their properties researched in pharmacological and toxicological studies and the extract standardised for its active components. In-vitro and in-vivo investigations have identified immunomodulatory and cytostatic effects (overview in [20–23]). However so far only individual case reports and results from smaller, non-randomised studies support prophylaxis of tumour recurrence and extended survival. Controlled clinical studies that have been published show conflicting results and have methodology weaknesses (overview in [24–26]). Discussion of the safety and possible toxicity of mistletoe extracts has also been controversial [27–29]. There are practical and ethical reservations concerning implementation of randomised, controlled trials (RCT) to prove extension of survival, as these trials would have to be carried out over a prolonged period (5 to 10 years) and in view of the relatively good prognosis for non-metastatic breast cancer they would have to include a large number of patients.

For this reason we decided to carry out a retrolective, controlled, epidemiological cohort study using the IFAG standard concept Retrospect™ [30]. This type of study is recognised in epidemiological research [31, 32] and according to EU guidelines permits valid statements to be made on the efficacy and safety of medicinal products that have been on the market for some time ("well established use") [33]. Controlled, epidemiological studies can also achieve EBM evidence level II and thus contribute to the clinical evidence of efficacy [34, 35]. Detailed literature comparisons of the results of randomised, controlled studies with those of controlled, epidemiological observational studies have shown that well designed, implemented and analysed epidemiological studies generally have similar results to randomised, controlled studies [36–40].

The aim of this study was to investigate under practice conditions the efficacy and safety of standardised European mistletoe extract *(Viscum album L.*, Iscador®[1]), "mistletoe extract") as complementary treatment in addition to conventional therapy in the long-term postoperative care of primary non-metastatic breast cancer. This mistletoe extract has been on the market for a long time and is often used as complementary cancer treatment, especially in Germany and Switzerland.

[1] Manufacturer: Weleda AG, Arlesheim (Switzerland).

Arzneim.-Forsch./Drug Res. 54, No. 8, 456–466 (2004)