



Original article

Immune-related and adverse drug reactions to low versus high initial doses of *Viscum album* L. in cancer patients



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ARTICLE INFO

Keywords:

Adverse drug reaction
High dose
Integrative oncology
Mistletoe
Viscum album L.
Safety

ABSTRACT

Background: Immune-related adverse drug reactions (ADRs) to immunotherapy agents have been associated with beneficial clinical outcomes in oncology. *Viscum album* L. (VA, European mistletoe) is frequently used as an immunomodulatory agent alongside conventional cancer treatment in Europe. VA has been associated with improved quality of life and a reduction in chemotherapy-related ADRs. Beneficial effects of VA are believed to be related to its immunomodulatory properties. Current guidelines recommend commencing with a low dose and increasing slowly overtime, however, off-label prescribing of high initial doses is common.

Purpose: We investigated ADR profiles related to subcutaneous VA therapy commencing with low, recommended doses versus higher than recommended doses.

Study Design: Retrospective cohort study.

Methods: Medical records of 1361 cancer patients treated between 2003 and 2013 were assessed. Patients were divided into two groups based on whether the dose of their first VA injection adhered to current guidelines. Patient characteristics and suspected VA-related ADRs were compared between dose groups.

Results: Of 1361 cancer patients, 516 (38%) started with a recommended, low dose of VA (≤ 0.02 mg) and 845 (62%) started with a higher dose (> 0.02 mg). Groups did not differ by age or gender, but significant differences were observed for type ($p < 0.001$) and stage of cancer ($p = 0.05$). Starting with a high dose of VA was significantly associated with a higher incidence of VA-related ADRs compared to starting with a low dose (20.7% versus 0.8%, $p < 0.001$). Adjusting for age, gender, tumour type and stage of disease, produced an odds ratio of 37.5 (95% CI = 15.7–122.8, $p < .001$). Almost all ADRs, irrespective of the initial VA dose, were of mild or moderate intensity. Most ADRs were immune-related, general disorders and administration site conditions, many of which are desired reactions, such as pyrexia and local reactions. Overall, no serious ADRs occurred.

Conclusions: Starting VA therapy with a higher than recommended dose was associated with a high frequency of ADRs, however, nearly all ADRs were expected, of mild to moderate intensity and most were desired reactions. Future research is necessary to investigate whether higher incidences of immune-related events are indicators of beneficial immunomodulation and better clinical outcomes.

Introduction

Viscum album L. (VA, European mistletoe) is a semi-parasitic shrub that has been used as a traditional medicine in Europe for centuries to treat cardiovascular disorders, epilepsy, infertility, hypertension and arthritis (Singh et al., 2016). More recently, aqueous extracts of VA have been used as immunomodulators alongside first-line therapies in

cancer patients. VA therapy has been associated with improvement in health-related quality of life (HRQL) and a reduction in chemotherapy-related adverse drug reactions (ADRs) (Büssing et al., 2012; Kienle and Kiene, 2010). Mixed findings have been published regarding a beneficial effect on overall survival (Axtner et al., 2016; Horneber et al., 2008; Tröger et al., 2013). The main active components of VA extracts are thought to be mistletoe lectins (ML-I, ML-II and ML-III) and

Abbreviations: ADR, adverse drug reaction; CI, confidence interval; CTCAE, Common Terminology Criteria for Adverse Events; HRQL, health-related quality of life; ICD, International Classification of Diseases; ICH, International Conference on Harmonization; IL, interleukin; IQR, interquartile range; MedDRA, Medical Dictionary for Regulatory Activities; ML, mistletoe lectin; NA, not applicable; NK, natural killer; NO, Network Oncology; No., number; OR, odds ratio; VA, *Viscum album* L.; QuaDoSta, Quality assurance; Documentation and Statistics, US, United States of America; SmPC, Summary of Product Characteristics; SOC, System Organ Class; SD, standard deviation; TNF- α , tumour necrosis factor alpha

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<http://dx.doi.org/10.1016/j.phymed.2017.09.004>

Received 22 March 2017; Received in revised form 18 July 2017; Accepted 19 September 2017

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viscotoxins. Lectins are the most studied components of VA and have been shown to stimulate the secretion of IL-1, IL-6, IL-12 and TNF- α (Hajto et al., 1998; Ribereau-Gayon et al., 1996). They are also thought to enhance cytotoxic NK-cell activity (Beuth et al., 1992), induce apoptosis (Büssing and Schietzel, 1999) and to have anti-angiogenic properties (Elluru et al., 2009). The concentrations of lectins and other compounds in VA extracts vary depending on the stage of growth of the plant, the location and species of the host tree, harvesting season, and on the technique of extract preparation which can differ considerably between producers (Urech and Baumgartner, 2015). Abnoba GmbH is one of the major producers of VA extracts used in Germany (Abnoba GmbH, 2014). In Europe, all medicinal or biological products require a Summary of Product Characteristics (SmPC or SPC) document to be authorised for marketing (European Commission, 2009). SmPCs provide information to healthcare professionals on how to use a medicinal product safely and effectively. Importantly, they should be updated throughout the lifecycle of a product as new efficacy or safety data emerge. Many physicians experienced in the use of VA therapy believe that beginning with a higher than SmPC-recommended dose produces better clinical outcomes including improved HRQL. To date, this belief is largely based on clinical case studies and physicians' experiences (von Schoen-Angerer et al., 2015), as well as on the hypothesis that beneficial effects of VA therapy are mediated by robust stimulation of the immune system (Kienle et al., 2016; Orange et al., 2016). Furthermore, it has been suggested that the induction of pyrexia (fever) or injection-site reactions (e.g. redness around the site of subcutaneous injection) through the use of higher doses of VA, particularly at the beginning of treatment, may correlate with better clinical outcomes (Büssing et al., 2008; Schläppi et al., 2016; Werthmann et al., 2013). For example, Büssing et al. (2008) showed that the induction of moderate local reactions in response to VA injections was associated with better T cell function and significantly higher quality of life. Werthmann et al. (2013) described a cutaneous squamous cell carcinoma case in which the patient received low followed by high peri-lesional VA. The tumour disappeared clinically after 10 months of treatment and the patient was recurrence-free 4 years later. The authors stated that “dose dependency may be presumed because of lack of response under lower dosages, and stronger local skin reactions (reddening and swelling) and tumour remission under high dosage.” In light of such observations, the following questions have arisen: Are the beneficial effects of VA therapy based on optimal immunomodulation indicated by the presence of immune-related reactions (i.e. local reactions and pyrexia)? Apart from the palliative setting, should higher initial doses of VA be recommended as standard practice? As a first step towards answering these questions we investigated the different ADR profiles related to VA therapy commencing with the SmPC recommended dose (described as “low dose group” hereafter) or doses that were higher than SmPC recommended (described as “high dose group” hereafter). Using the comprehensive Network Oncology clinical database, patients were retrospectively divided into two groups based on whether their first ever VA injection was a recommended or higher than recommended dose. We present here a comparison between the two groups in terms of demographic and disease characteristics at the time of first VA treatment and suspected VA-related ADRs.

Methods

Subjects

Network Oncology (NO) is a conjoint clinical registry of European hospitals and out-patient practitioners specialised in integrative medicine (Schad et al., 2013). Documentation officers extract patient information, cancer diagnoses, therapies, adverse events and disease progress from patient files and record data using the QuaDoSta software that was developed at Havelhohe Research Institute (Schad et al., 2004). The NO project was approved by the ethical committee of the

Medical Association Berlin (Eth-27/10). The present study involved the analysis of data from consenting patients treated between 2003 and 2013, with a focus on patients' first exposure to VA therapy. All patients with an identification number, birth date, gender, cancer diagnosis date, ICD-10 code (ICD-9 codes were converted to ICD-10 codes), a start date for VA therapy and a corresponding dose, type of preparation and injection documented were assessed. Only patients who had a subcutaneous injection of Abnobaviscum VA (Abnoba GmbH, Pforzheim, Germany) were included in the final analyses.

Study design

Patients were retrospectively divided into two groups based on whether their first ever injection of VA was a recommended (≤ 0.02 mg) or higher than recommended dose (> 0.02 mg) according to SmPC. Suspected ADRs to patients' initial VA injection were assessed for both groups. Local reactions > 5 cm and increased body temperatures > 38 °C, along with all other documented adverse events, were considered as suspected VA-related ADRs if a causal relationship between VA and an event was described by physicians as at least a reasonable possibility. ADRs were classified as MedDRA version 15.0 preferred terms (the Medical Dictionary for Regulatory Activities developed under the auspices of the International Conference on Harmonization: ICH) and grouped by System Organ Class (SOC) (Steering Committee, 1994). ADRs were evaluated in terms of severity (mild, moderate, severe, life-threatening or death-related ADR) according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (US Department of Health and Human Services, 2009) and designated as serious or non-serious according to ICH guidelines (ICH Steering Committee, 1994).

Statistical analysis

Continuous variables were described as mean and standard deviation (SD) or medians with interquartile range (IQR) and categorical variables were summarised as frequencies and percentages. An independent *t*-test and Pearson's Chi-squared tests were used to investigate differences in continuous (age) and categorical (gender, cancer diagnosis, stage of disease, VA preparation type) independent variables between dose groups. A multivariable logistic regression was performed to estimate odds ratios (OR) and 95% confidence intervals (CI) for experiencing an ADR following a high versus low initial dose of VA. The model was adjusted for gender, age, tumour type and stage. For all analyses, a two-sided *p*-value of less than 0.05 was considered statistically significant. Analyses were conducted and figures created with R version 3.2.3 and R Studio version 0.99.891.

Results

Classification of low and high dose groups

A total of 1361 cancer patients who commenced treatment with Abnobaviscum VA preparations between January 2003 and July 2013 were divided into two groups based on the dose of their first VA injection. According to the SmPC for Abnobaviscum VA, 516 patients (37.9%) received a recommended initial dose (low dose group) and 845 patients (62.1%) received a higher than recommended dose (high dose group). While all injections in the low dose group were of 0.02 mg, the high dose group ranged from 0.1 mg to 40 mg, with a median of 0.2 mg (IQR = 0.2–10 mg).

Characteristics of patients

The distributions of low and high initial doses of VA over time were similar, although high initial doses occurred more frequently in recent years (Fig. 1). Patient age at the time of first VA injection did not differ

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