Viscum album L. Therapy in Oncology: An Update on Current Evidence

Anja Thronicke\textsuperscript{a} Friedemann Schad\textsuperscript{a,b} Marion Debus\textsuperscript{c} Jan Grabowski\textsuperscript{d} Georg Soldner\textsuperscript{e}

\textsuperscript{a}Research Institute Havelhöhe at the Hospital Gemeinschaftskrankenhaus Havelhöhe, Berlin, Germany; \textsuperscript{b}Interdisciplinary Oncology and Palliative Care, Hospital Gemeinschaftskrankenhaus Havelhöhe, Berlin, Germany; \textsuperscript{c}Clinic Arlesheim, Arlesheim, Switzerland; \textsuperscript{d}Talpini, Webentwicklung, Waltrop, Germany; \textsuperscript{e}School of Spiritual Science, Medical Section at the Goetheanum, Dornach, Switzerland

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Abstract

\textbf{Background:} A majority of oncological patients apply add-on white-berry European mistletoe (Viscum album L., VA) extracts to reduce disease- and treatment-related symptoms and to improve health-related quality of life (HRQL). VA extracts exert various antitumor, pro-apoptotic, anti-proliferative, and immunomodulatory effects. Two current meta-analyses attribute life-prolonging and HRQL-improving properties to additive VA therapy. The aim of the present update was to review the current knowledge on VA extracts in clinical oncology. Hereby, we concentrated on studies with the highest clinical relevance in the field of lung, gastric, colorectal and pancreatic, gynaecological, as well as breast cancer applying the anthroposophical mistletoe preparations. 

\textbf{Summary:} The present update provides a brief overview regarding the use of VA preparations in clinical oncology reviewing current guidelines, systematic reviews, randomized controlled and real-world data studies. We have searched the pubmed.gov database of the National Library of Medicine with the search terms “mistletoe” and “cancer.” We found good evidence of add-on VA therapy to improve the HRQL of patients with breast cancer (American Society of Clinical Oncology – endorsed Society for Integrative Oncology guideline) and of HRQL-improving and survival-prolonging properties of VA therapy in pancreatic cancer. In the field of gastrointestinal, gynaecological, and lung cancer, new or updating integrative and/or oncological guidelines should consider clear recommendations on integrative therapies including VA therapy. Nevertheless, further clinical and real-world data trials need to be performed in this field. 

\textbf{Key Messages:} Evidence for add-on VA treatment for the improved management of cancer and cancer-related side effects is accumulating. Patients with breast cancer: good evidence for add-on VA therapy to improve the HRQL of oncological patients. Patients with pancreatic cancer: good evidence for add-on VA to improve HRQL and prolong survival. Patients with gastrointestinal, gynaecological, and lung cancer: update of guidelines is recommended with regards to integrative oncological therapies including add-on VA.

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Zusammenfassung
Hintergrund: Die Mehrheit onkologischer PatientInnen wendet zusätzlich zur standard-onkologischen Therapie Extrakten der Europäischen weißbeeren Mistel (Viscum album L., VA) an, um krankheits- und behandlungsbedingte Symptome zu reduzieren und die gesundheitsbezogene Lebensqualität (HRQL) zu verbessern. VA-Extrakte weisen diverse anti-tumorale, anti-apoptotische, anti proliferative und immun-modulatorische Wirkungen auf. Zwei aktuelle Meta-Analysen schreiben der Add-on-VA-Therapie lebensverlängernde und HRQL-ver bessерnde Eigenschaften zu. Das Ziel des vorliegenden Reviews war es, den aktuellen Wissensstand zu VA-Extrak ten in der klinischen Onkologie zu überprüfen. Hierbei konzentrierten wir uns auf Studien mit anthroposophischen Mistelpräparaten von höchster klinischer Relevanz bei Lungen-, Magen-, Darm- und Bauchspeichel drüsen krebs sowie gynäkologischem und Brustkrebs.

Zusammenfassung: Das vorliegende Update gibt einen kurzen Überblick über die Verwendung von VA-Präparaten in der klinischen Onkologie und berücksichtigt dabei aktuelle Leitlinien, systematische Übersichten, randomisierte kontrollierte Studien und Real-World-Data-Studien. Wir haben die Datenbank pubmed.gov der National Library of Medicine mit den Suchbegriffen „mistletoe“ und „cancer“ durchsucht. Wir fanden eine gute Evidenz der zusätzlichen VA-Therapie zur Verbesserung der HRQL von PatientInnen mit Brustkrebs (Leitlinie der Society for Integrative Oncology – unterstützt von der American Society of Clinical Oncology) und zur Verlängerung des Überlebens beim Pankreaskrebs. Auf dem Gebiet von Magen-, Darm- und gynäkologischen Tumoren sowie Lungenkrebs sollten neue oder aktualisierte integrative und/oder onkologische Leitlinien klare Empfehlungen zu integrierten Therapien einschließlich der VA-Therapie enthalten. Dennoch müssen in diesem Bereich weitere klinische Studien und Real-World-Data-Studien durchgeführt werden.

Kernaussagen: Es gibt immer mehr Belege, dass eine zusätzliche VA-Behandlung zur Verbesserung der Behandlung von Krebs und krebserkrankten Nebenwirkungen beiträgt. PatientInnen mit Brustkrebs: gute Evidenz, dass Add-on-VA-Therapie die HRQL von onkologischen PatientInnen verbessert. PatientInnen mit Bauchspeichel drüsenkrebs: gute Belege, dass eine zusätzliche VA-Behandlung zur Verbesserung der HRQL und zur Verlängerung des Überlebens beiträgt. PatientInnen mit gastrointestinalen, gynäkologischem und Lungenkrebs: Eine Aktualisierung der Leitlinien wird im Hinblick auf integrativ-onkologische Therapien einschließlich der Add-on-VA-Therapie empfohlen.

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Update on Add-On VA in Oncology

Introduction

To reduce tumour- and treatment-related fatigue, pain, nausea, and diarrhoea as well as to improve appetite and sleep, among other health-related quality of life (HRQL) aspects, up to 63% of oncological patients seek and utilize Viscum album L. (VA) preparations in German-speaking European countries [1–11]. VA preparations are complex multicomponent mixtures with numerous constituents and multiple anti-carcinogenic effects, and can be applied as subcutaneous and off-label intravenous, intratumoral, and intracavitary injections [12]. VA extracts mediate numerous antitumour, anti-apoptotic, anti-proliferative, and immunomodulatory effects and are involved in processes of DNA stabilization and repair as well as in the reduction of chromosomal damage [13–20]. Research into these mechanisms has been indicative for VA extracts being among the best-studied plant extracts [21].

The communication of scientific findings, developments, and standards in integrative oncology is becoming increasingly important for practitioners and patients. Thus, in spring 2019 an expert committee consisting of physicians, researchers, journalists, and information technology specialists was founded to review the current medical-scientific state of VA application in integrative oncology and to disseminate it via the website www.mistletoe-therapy.org. This website was launched in autumn 2019 and constantly reviews mechanisms, gives details on basic research, and gives a profound overview on clinical evidence of VA extracts in oncology [22]. In addition, more than 50 prospective, more than 30 prospective randomised, and more than 20 real-world data (RWD) studies have been published revealing growing evidence of advantages for add-on VA therapy in terms of HRQL, tolerability, clinical efficacy, and cost-effectiveness [22]. A guideline on complementary medicine for oncological patients has been published in 2021 [23] which recommends VA to be considered for improving HRQL.

The aim of the present update is to provide a brief overview regarding the use of VA preparations in main tumour entities reviewing current guidelines, reviews, and studies with the highest clinical relevance. The following five chapters summarize the up-to-date evidence-based knowledge of VA therapy on clinical outcomes including HRQL and overall survival. Accordingly, we have searched the pubmed.gov database of the National Library of Medicine. We applied the search terms “mistletoe” and “cancer” and the following filters: Clinical Study, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase III, Clinical Trial, Phase IV, Comparative Study, Controlled Clinical Trial, Guideline, Meta-Analysis, Practice Guideline, Pragmatic Clinical Trial, Randomized Controlled Trial, Review, Systematic Review, English. We found 171 studies and reviews (deadline: 14.02.2022): 74 reviews, 57 clinical studies, 51 clinical trials, 44 com-
Add-On VA Extracts for Patients with Lung Cancer

The evidence for add-on VA therapy in improving the HRQL of patients with lung cancer is good considering evidence-based published data. A recent meta-analysis by Loef and Wallach reviewing three lung cancer studies among 26 oncological studies indicates a significantly improved HRQL in patients in the VA group compared to control. A current guideline on complementary medicine for oncological patients recommends VA to be considered for improving HRQL [23, 24]. The Loef and Wallach meta-analysis was part of a systematic review searching studies with a control group including the terms “neoplasia,” “quality of life,” and “mistletoe” in the Medline, Embase, CENTRAL, CINAHL, PsycInfo, Science Citation Index, clinicaltrials.gov, and opengrey.org databases. The quality of the studies was assessed with the Cochrane Risk of Bias tool version 2 and a quantitative meta-analysis was performed.

Compared to the HRQL-ameliorating role of VA, however, its role in the improvement of clinical outcomes in lung cancer has not sufficiently been settled as guidelines are missing [25] or give no clear recommendations [26]. Nevertheless, a current systematic review on the clinical efficacy of VA therapy indicates a significant improvement of survival for patients with lung cancer receiving VA therapy [27]. This evidence is supported by results from a multicentre RWD study revealing that the combination of chemotherapy and VA therapy significantly prolonged overall survival of stage IV non-small cell lung cancer patients and even at similar costs compared to chemotherapy alone [28, 29]. It is considered by the authors of this review that these results should be considered in new editions of current guidelines or in new guidelines, especially in the palliative field.

Add-On VA Extracts for Patients with Gastric, Colorectal, and Pancreatic Cancer

In the field of gastrointestinal cancer, with gastric cancer being the exception, guidelines either do not mention VA therapies at all despite newer high-qualitative methodological evidence (pancreatic cancer) or do not give clear recommendations (colorectal cancer, CRC).

A current guideline from 2019 on gastric cancer provides an optional (“can”) recommendation (recommendation level 0, level of evidence 2b) for add-on VA therapy to improve the HRQL in these patients [30]. For the prolongation of life, this guideline currently does not recommend VA therapy as it debates that there are currently no data available. However, the results of two up-to-date systematic reviews from 2020 by Ostermann et al. and by Loef and Wallach, which were published after the update of the respective guideline, indicate a significant association of VA therapy with prolonged survival and improved HRQL of oncological patients including those with gastric cancer [24, 27].

A guideline for patients with CRC cites studies and systematic reviews that observed a weak evidence for VA therapy in improving HRQL in CRC, but the guideline itself does not give any VA recommendations [31]. Regarding the clinical efficacy of add-on VA therapy for CRC, data from prospective randomised studies are currently not available. However, a systematic review which among other evidence included data from RWD studies showed a significant risk reduction of mortality for patients with CRC when VA therapy was applied in addition to standard oncological care [32–34]. In addition, reduced hospital stays, significantly fewer side effects caused by chemotherapy and/or radiotherapy, and lower fatigue were observed in the VA group [33, 34]. Currently, a prospective RWD study is being conducted on the progression-free survival of patients with stage II–IV CRC under post-surgical oncological standard therapy with or without additional VA therapy [35]. In terms of a balanced evaluation strategy, further RCT and RWD studies on CRC VA treatment are advisable.

In 2013, a guideline for exocrine pancreatic cancer was published which does not contain any suggestions for complementary therapy with VA. Meanwhile, evidence for an additive effect of VA therapy in prolonging overall survival of patients with advanced or metastatic pancreatic cancer has been clearly shown and it is suggested by the authors of this review that it should be included in a new edition of the guideline. In the palliative therapy of advanced and metastasized pancreatic cancer VA therapy appears to be a clinically effective and well-tolerated therapy as shown by an RCT published by Tröger et al. [36–38] on overall survival and being confirmed by results of a multicentre RWD study [39]. The results of the RCT showed a highly significant risk reduction of mortality and a significant and clinically relevant improvement in HRQL in the VA group compared to the best supportive care group [38, 40]. In line, the results of the mentioned RWD indicate as well a significant survival advantage of additive VA therapy compared to che-
motherapy alone, VA therapy alone, or best supportive care [39]. In addition, another multicentre RWD study of patients with pancreatic cancer showed prolonged survival rates, an improved HRQL, and a reduction in side effects of standard oncological treatment in the VA group [41]. The results of a first-ever published RWD cost-effectiveness study for patients with stage IV pancreatic cancer revealed that chemotherapy plus VA therapy was equally cost-effective compared to chemotherapy alone [29].

**Add-On VA Extracts for Patients with Breast Cancer and Gynaecological Cancer**

For patients with breast cancer the evidence for the HRQL-improving properties of add-on VA extracts is good and based on various guidelines including the American Society of Clinical Oncology (ASCO) – endorsed Society of International Oncology (SIO) guideline [42–45]. This guideline lists VA therapy in the chapter “quality of life” and recommends it as an optional treatment for the improvement of the HRQL of breast cancer patients: “Acupuncture, mistletoe, qigong, reflexology, and stress management can be considered for improving quality of life (Grade C).” However, the discussion point of the ASCO is that subcutaneous VA therapy is currently not approved by the Food and Drug Association (FDA) [45]. Two prospective RCTs as well as a follow-up of one of both RCTs showed a significant improvement of HRQL, especially in the context of pain and nausea reduction, appetite, diarrhoea, and sleep [46–49]. These results have been confirmed by further RWD studies [50–54]. Regarding the clinical efficacy of VA therapy in terms of prolonged overall survival in breast cancer, the current meta-analysis of Ostermann and colleagues points to a significant risk reduction of mortality with additional VA therapy [27].

Even though a high proportion of female oncological patients seek complementary therapies, physicians will not find any or no clear guidance on complementary therapies in guidelines for gynaecological cancer. In a current guideline for ovarian cancer complementary therapies are not mentioned [55] even though RCT or controlled match-pair data reveal significant HRQL-improving and significant life-prolonging properties of add-on VA therapies for these patients. Further supporting data are expected in this field. As shown by a prospective controlled match-pair study, add-on VA therapy significantly improved survival in patients with metastatic ovarian cancer [56]. Further, a multicentre prospective RCT showed significantly improved fatigue, insomnia, and loss of appetite and significantly reduced nausea, pain, and chemotherapy-related side effects of VA therapy in addition to poly-chemotherapy compared to poly-chemotherapy alone in these patients [46].

Even though data from a prospective RCT showed a significant improvement of overall survival in patients with non-metastatic endometrial cancer being treated with add-on VA therapy compared to control [57], VA or any other complementary or integrative concept are not mentioned in the current guideline [58]. As to cervical cancer a guideline cites beneficial HRQL [10] and overall survival effects [56] of add-on VA therapy, however, without giving clear recommendations [59]. Results of a prospective, controlled match-pair study which was cited in this guideline revealed that add-on VA therapy significantly improved overall survival [56]. Further revisions of existing guidelines and further clinical evidence are needed for the role of add-on VA in the improvement of HRQL and other clinical outcomes of patients with ovarian, endometrial, and cervical cancer.

**International Integrative Oncology Guidelines by SIO and ASCO**

In the ASCO-endorsed SIO guideline “Clinical practice guidelines on the use of integrative therapies as supportive care in patients treated for breast cancer” from 2017, add-on VA therapy has already been recommended as an optional treatment for the improvement of HRQL in breast cancer patients [42–45].

In October 2020 both, the SIO and the ASCO agreed to jointly develop a further three evidence-based clinical practice guidelines for the safe and effective application of integrative therapies in the management of cancer-related pain, fatigue, and anxiety/depression [60]. These three guidelines are planned to be published by 2022.

It is assumed that add-on VA as an integrative therapy approach with an evident impact on cancer-related side effects in oncological patients may also find its way into these three guidelines. As the present update cannot replace a comprehensive systematic review, our findings should be interpreted with caution and in the light of existing and up-coming systematic reviews. However, the review presented here may be a necessary add-on to the current evaluation on the positive impact of mistletoe in oncology.

**Conclusion**

The quantity and quality of clinical studies for VA therapy have been constantly increasing in the last decade. For add-on VA therapy improvements of HRQL, reduction of standard-oncological side effects, and prolonging of sur-
vival in oncological patients have been shown. The good evidence of additive VA therapy to improve the HRQL of patients with breast cancer is represented by its recommendations in the ASCO-endorsed SIO guideline. In pancreatic cancer, evidence in terms of HRQL-improving and survival-prolonging properties of VA therapy is good and should be integrated in existing or newly developed oncological guidelines. Other guidelines, especially in the field of gastrointestinal, gynaecological, and lung cancer, should consider giving recommendations on integrative therapies including VA therapy.

Nevertheless, further clinical and RWD trials need to be performed in this field. As VA extracts are evidently involved in the improvement of cancer-related side effects, presumably their application will also find acceptance in the three new evidence-based clinical practice ASCO-SIO guidelines.

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Author Contributions

Anja Thronicke: conceptualization (conception and design of the study), data curation, formal analysis, investigation, methodology, validation, writing original draft, reviewing – review and editing, final approval of the version to be submitted. Friedemann Schad: conceptualization (conception and design of the study), data curation, formal analysis, funding acquisition, investigation, methodology, validation, writing original draft, reviewing – review and editing, final approval of the version to be submitted. Marion Debus: conceptualization (conception and design of the study), analysis and interpretation of data, funding acquisition, investigation, methodology, software, supervision, validation, writing – review and editing, final approval of the version to be submitted. Jan Grabowski: conceptualization (conception and design of the study), analysis and interpretation of data, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, writing – review and editing, final approval of the version to be submitted.

Data Availability Statement

All relevant data are within the manuscript and its supporting information files.

Preprint

A preprint version of this article is available on refubium (http://dx.doi.org/10.17169/refubium-30815), see also [61].
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