Viscum album L. therapy in oncology – an update on current evidence

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Abstract

Aim: 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 (HRQL) of life. 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 study was to review the current knowledge on VA extracts in clinical oncology.

Methods: 290 clinical research articles including systematic reviews and guidelines were screened and analysed for their association with add-on VA therapy in patients with gynaecological, lung or gastrointestinal cancer.

Results: We found a good evidence of add-on VA therapy to improve the HRQL of patients with breast cancer (ASCO-endorsed SIO 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.

Conclusion: The present update provides a brief overview regarding the use of VA preparations in clinical oncology reviewing current systematic reviews, randomized controlled and real-world data studies. In addition, current guidelines as to their suggestions in the context of VA therapy are highlighted as evidence in the improved management of cancer and cancer-related side effects for this treatment is accumulating.

Keywords: VA extracts, VA therapy, oncology, integrative oncology, guidelines

Introduction

To reduce tumour- and treatment-related fatigue, pain, nausea and diarrhoea as well as to improve appetite and sleep, among other HRQL aspects, up to 63% of oncological patients seek and utilize VA preparations [1-11]. In oncology, the complementary therapy with VA extracts is among the most common integrative therapies used in German-speaking European countries and the daily dose prescription of VA preparations rank ahead of several oncological drugs such as carboplatin, nivolumab, pembrolizumab and pemetrexed [12]. VA extracts mediate numerous antitumor, 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 reviews mechanisms, gives details on basic research and gives a profound overview on clinical evidence of VA extracts in oncology [22]. Several up-to-date clinical guidelines, systematic reviews, a previously published HTA report, and a Cochrane analysis confirm the improvement of HRQL in oncological patients treated with add-on VA therapy [11, 23-34]. In addition, more than 50 prospective, more than 30 prospective randomised and more than 20 RWD studies have been published revealing a growing evidence of advantages for add-on VA therapy in terms of HRQL, tolerability, clinical efficacy and cost-effectiveness [22, 35]. Currently, a guideline (consultation version) on complementary medicine for oncological patients is expected to be published in 2021 [36] which recommends VA to be considered for improving HRQL. The following three chapters summarize the up-to-date evidence-based knowledge of VA therapy in the management of cancer-related side effects and clinical outcomes including overall survival of lung, gastrointestinal, gynaecological and breast cancer patients.

Materials and Methods

Data source

In spring 2019 an expert panel consisting of German and Swiss physicians, researchers and information technology specialists was founded to review the current medical-scientific state of VA application in integrative oncology. 290 articles including preclinical, RWD and clinical research, systematic reviews and national or international guidelines in association with VA extracts and/or therapy were collated by the expert team until December 2020. To establish a systematic access for medical practitioners, researchers, administrations and patients in the future the results were published on the website www.mistletoe-therapy.org initiating a solid base and resource for scientific development in this field [22]. An alphabetically sorted literature compendium was as well published on the website. For the current update the most relevant literature on mechanisms and clinical effects of VA extracts in gynaecological, lung or gastrointestinal cancer were reviewed.

Ethics statement

The study complies with the principles laid down in the Declaration of Helsinki as revised in 2013. Ethical approvals or informed consent were not needed as this manuscript only reviews published manuscripts and does not involve participation of humans.

Results

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. 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 and a current guideline (consultation version finished, final version is under review) on complementary medicine for oncological patients, which is expected to be published in 2021, recommends VA to be considered for improving HRQL [23, 36].

Compared to VA's HRQL-ameliorating role, however, it's role in the improvement of clinical outcomes in lung cancer has not sufficiently been settled as guidelines are missing [37] or give no clear recommendations [38]. 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 [39]. 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 [40,

41]. 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 [42]. 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 [23, 39].

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 [43]. 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 [39, 44-46]. In addition, reduced hospital stays, significantly fewer side effects caused by chemotherapy and/or radiotherapy and lower fatigue were observed in the VA group [45, 46]. 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 [47]. 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, the 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 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 a RCT published by Tröger et al. [48-50] on overall survival and being confirmed by results of a multicentre RWD study [51]. 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 [25, 52]. In line, the results of the mentioned RWD indicate as well a significant survival advantage of additive VA therapy compared to chemotherapy alone, VA therapy alone or best supportive care [51]. 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 [53]. 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 [41].

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 [32, 33, 54, 55]. This guideline lists VA therapy in the chapter ”quality of life“ and gives it a ”can“ recommendation 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 [55]. 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 [26-28, 56]. These results have been confirmed by further RWD studies [57-61]. 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 [39].

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 [62]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 [63]. Further, a multicentre prospective RCT showed significantly improved fatigue, insomnia, 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 [26].

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 [64], VA or any other complementary or integrative concept are not mentioned in the current guideline [65]. As to cervical cancer a guideline cites beneficial HRQL [10] and overall survival effects [63] of add-on VA therapy, however, without giving clear recommendations [66]. Results of a prospective, controlled match-pair study which was cited in this guideline revealed that add-on VA therapy significantly improved overall survival [63]. 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.

The present work is limited as it does not represent a comprehensive systematic review.

International integrative oncology guidelines by SIO and ASCO

In the ASCO-endorsed SIO "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 given a ,can, recommendation for the improvement of HRQL in breast cancer patients [32, 33, 54, 55].

In October 2020 both, the SIO and the ASCO agreed to jointly develop 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 [67]. 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.

Conclusions

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 survival 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 to give 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.

Ethics statement

The study complies with the principles laid down in the Declaration of Helsinki as revised in 2013. Ethical approvals or informed consent were not needed as this manuscript only reviews published manuscripts and does not involve participation of humans.

Availability of data and material

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

Competing interests

The authors declared the following conflicts of interest with respect to the research, authorship, and/or publication of this opinion article: FS reports grants from Astrazeneca (travel costs and honoraria for speaking), Helixor Heilmittel GmbH (travel costs and honoraria for speaking), grants from Abnoba GmbH, and grants from Iscador AG, outside the submitted work. The other authors have declared that no competing interests exist. No payment was received for any other aspects of the submitted work. There are no patents, products in development, or marketed products to declare. There are no other relationships/conditions/circumstances that present a potential conflict of interest.

Funding

The creation of the website www.mistletoe-therapy.org was financed with funds from the Medical Section, Goetheanum Switzerland and the Goetheanum Swiss Fund 2019. The funders had no role in data collection and analysis, decision to publish, or preparation of the manuscript.

Acknowledgement

We would like to thank all members of the mistletoe-therapy.org expert committee for their dedicated, reliable and outstanding research work.

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