

Original article

Immune-related and adverse drug reactions to low versus high initial doses of *Viscum album* L. in cancer patientsFriedemann Schad^{a,b}, Anja Thronicke^a, Antje Merkle^a, Harald Matthes^{a,b}, Megan L. Steele^{a,c,*}^a Research Institute Havelhoehe, Berlin, Germany^b Department of Oncology, Hospital Havelhoehe, Berlin, Germany^c Institute of Health and Biomedical Innovation, School of Public Health and Social Work, Queensland University of Technology, Brisbane, Australia

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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

* Corresponding author.

E-mail addresses: megan.steele@qut.edu.au, msteele@havelhoehe.de, meganleighsteele@outlook.com (M.L. Steele).

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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 Havelhoehe 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

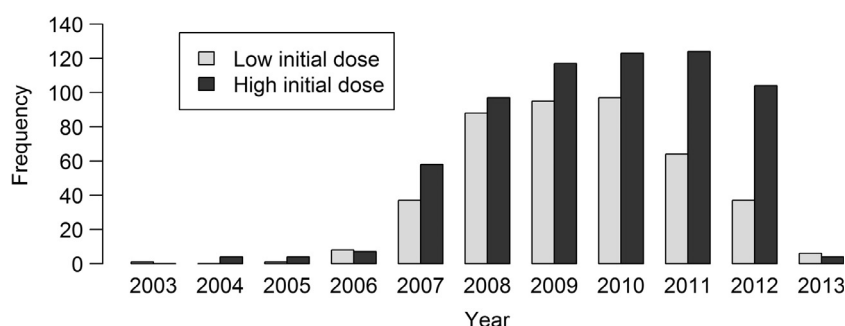


Fig. 1. Distribution of low and high initial doses of *Viscum album* L. over time. Data close was July 2013. The low frequency of injections shown for 2013 are due to a lag between data collection and entry into the database.

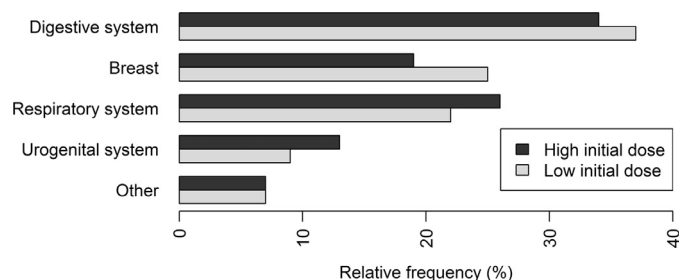


Fig. 2. Distribution of cancer diagnoses with respect to whether a low or high initial *Viscum album* L. dose was received.

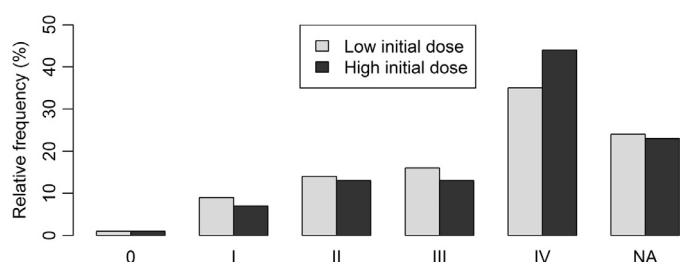


Fig. 3. Distribution of patients at different stages of disease (Union for International Cancer Control staging) with respect to whether a low or high initial *Viscum album* L. dose was received. NA = not applicable and represents patients whose disease stage was unknown at the commencement of *Viscum album* L. therapy.

significantly between dose groups (low VA = 63.6 ± 11.7 years, high VA = 63.3 ± 12.2 years; $t = 0.4$, $p = 0.7$). The proportion of females (low VA = 334, high VA = 528) to males (low VA = 182, high VA = 317) was also similar between groups ($\chi^2 = 0.6$, $p = 0.4$). Dose groups differed significantly by cancer diagnosis (Fig. 2, $\chi^2 = 27.9$, $p < 0.001$), with breast or digestive cancer patients more likely to receive a low dose and respiratory or urogenital patients more likely to receive a high dose. Patients with stage I to III cancer were slightly more likely to receive a low dose, while stage IV cancer patients were more likely to receive a high dose (Fig. 3, $\chi^2 = 11.0$, $p = 0.05$). Significant differences were also observed with regard to VA preparation type ($\chi^2 = 119.3$, $p < .001$). In the low dose group, 44.0% of patients received the preparation Abnobaviscum Fraxini, 22.3% received Abnobaviscum Mali, 22.1% received Abnobaviscum Quercus, with all other Abnobaviscum preparations (Abietis, Aceris, Amygdali, Betulae, Crataegi and Pini) making up the remaining 11.6% of patients. The high dose group consisted of a higher proportion of patients who received Abnobaviscum Fraxini (70.4%), with 11.7% receiving Abnobaviscum Quercus, 7.2% Abnobaviscum Mali and all other preparations making up 10.7% of patients.

Adverse drug reactions

Four out of 516 patients (0.8%) in the low dose group experienced an ADR upon initial injection compared to 175 out of 845 patients

Table 1

Frequency of adverse drug reactions according to patient, disease and treatment characteristics.

Variable	No ADR (n = 1182)	ADR (n = 179)	OR (95% CI)	p-value*
Initial VA dose (%)				
Low (≤ 0.02 mg)	512 (99.2)	4 (0.8)	Referent	
High (> 0.02 mg)	670 (79.3)	175 (20.7)	37.51 (15.66–122.8)	< 0.001
Gender (%)				
Male	433 (86.8)	66 (13.2)	Referent	
Female	749 (86.9)	113 (13.1)	1.33 (0.90–1.97)	0.1
Age (mean \pm SD)	63.9 \pm 12.2	60.2 \pm 10.1	0.98 (0.96–0.99)	0.001
Tumour type (%)				
Breast	239 (83.6)	47 (16.4)	Referent	
Digestive system	418 (86.9)	63 (13.1)	0.74 (0.45–1.24)	0.3
Respiratory system	310 (91.7)	28 (8.3)	0.38 (0.21–0.68)	0.001
Urogenital system	131 (82.9)	27 (17.1)	0.82 (0.45–1.48)	0.5
Other	84 (85.7)	14 (14.3)	0.90 (0.38–2.09)	0.8
UICC (%)				
IV	487 (88.4)	64 (11.6)	Referent	
III	159 (83.7)	31 (16.3)	1.82 (1.09–3.00)	0.02
II	152 (82.6)	32 (17.4)	1.42 (0.84–2.36)	0.2
I	93 (85.3)	16 (14.7)	1.19 (0.60–2.27)	0.6
0	7 (87.5)	1 (12.5)	–	–
NA	284 (89.0)	35 (11.0)	–	–

* Odds ratios (OR), 95% confidence intervals (CI) and p-values for associations between independent variables and adverse drug reactions (ADR) were calculated by multivariable logistic regression.

(20.7%) in the high dose group. Multivariable logistic regression, adjusting for age, gender, tumour type and stage of disease revealed a strong association between ADRs and starting VA therapy with a higher dose (OR = 37.5, 95% CI = 15.7–122.8, $p < 0.001$; Table 1). In addition, having stage III cancer compared to stage IV was positively associated with ADRs (OR = 1.82), while increasing age (OR = 0.98) and tumours of the respiratory system (OR = 0.38) were associated with less ADRs (Table 1). The model was not adjusted for preparation type since ADRs were only observed for three of the nine applied preparations. Although Abnobaviscum Fraxini made up only 60.4% of VA treatments, 94.4% of all ADRs were to this preparation. The remaining ADRs were to Abnobaviscum Quercus (3.9%) or Abnobaviscum Mali (1.7%).

Four patients in the low dose group each experienced only one ADR. In the high dose group, there were up to five ADRs per patient (median = 1, IQR = 1–2), with a total of 273 ADRs (Table 2). “General disorders and administration site conditions” were among the most frequent class of ADRs for both groups. Specific ADRs in the low dose

Table 2

Total number of adverse drug reactions to low and high initial doses of *Viscum album* L. preparations.

System organ class	Low dose group		High dose group	
	No. of patients	No. of ADRs (%)	No. of patients	No. of ADRs (%)
Blood and lymphatic system disorders	–	–	1	1 (0.4)
Cardiac disorders	–	–	1	1 (0.4)
Gastrointestinal disorders	–	–	5	7 (2.6)
General disorders and administration site conditions	2	2 (50.0)	174	253 (92.7)
Investigations	–	–	2	2 (0.7)
Nervous system disorders	–	–	3	3 (1.1)
Respiratory, thoracic and mediastinal disorders	–	–	1	1 (0.4)
Skin and subcutaneous tissue disorders	2	2 (50.0)	3	5 (1.8)
TOTAL	4	4 (100.0)	175*	273* (100.0)

No. = number; % = percentage of total adverse drug reactions (ADRs) per dose group;

*Some patients experienced multiple ADRs.

group were fatigue, swelling, erythema and urticaria. In the high dose group, pyrexia made up 61.9% of ADRs with local reactions making up 29.3%. The next most frequent class of ADRs in the high dose group were gastrointestinal disorders (diarrhoea, nausea and vomiting), followed by nervous system disorders (headache and syncope), and skin and subcutaneous tissue disorders (generalised erythema, pruritus, rash and urticaria).

In terms of severity, all four patients (0.8%) in the low dose group had mild ADRs. In the high dose group, 62 patients (7.3%) had mild ADRs, 103 patients (12.2%) had moderate ADRs (98 cases of pyrexia 39–40 °C, four cases of strong local reactions and a combined case of swelling, pruritus and erythema) and 10 patients (1.2%) had severe ADRs (eight cases of pyrexia > 40 °C, single cases of syncope and of combined pruritus and urticaria). Moderate ADRs occurred in response to doses ranging from 0.2 to 40 mg, with a median of 20 mg (IQR = 20–20). All except for one of the severe ADRs was a response to starting VA therapy with 20 mg of Abnobaviscum Fraxini. The exception was a patient who experienced a combined case of swelling, pruritus and erythema following 0.2 mg of Abnobaviscum Mali.

The only unexpected reaction was syncope (fainting): A 47-year old female fainted several hours after receiving a subcutaneous injection of 20 mg of Abnobaviscum Fraxini. The patient's medical record of the event notes VA causality as “likely”, but reports it was not a severe or serious event and hospitalisation was not required. According to CTCAE, however, any occurrence of syncope is classified as a moderate (grade III) event (US Department of Health and Human Services, 2009). The patient received the same type and dose of VA one week later and did not experience an ADR. Overall, no serious ADRs occurred (i.e. no ADRs resulted in death, were life-threatening, required inpatient hospitalisation or prolongation of existing hospitalisation or resulted in persistent or significant incapacity or congenital anomaly) and all patients in both groups recovered completely from all ADRs.

Discussion

Commencing VA therapy with a higher than recommended dose (i.e. > 0.02 mg) increased the relative risk of experiencing an ADR (20.7%) compared to commencing therapy at the recommended, low dose (0.8%). After adjusting for age, gender, tumour type and stage of disease, the odds of experiencing an ADR following a high dose were calculated as almost 38 times higher than following a low dose. Of key importance is the observation that almost all ADRs, irrespective of dose,

were of mild to moderate intensity. Furthermore, nine out of the ten cases in which severe ADRs occurred were in response to 20 mg of Abnobaviscum Fraxini, a dose which is 1000 times higher than the recommended starting dose. Interestingly, 95% of all ADRs were to Abnobaviscum Fraxini. This is most likely due to Fraxini possessing the highest concentration of lectins (up to 14,000 ng/mL) and viscotoxins (up to 95 µg/mL) compared to other preparations (Abnoba GmbH, 2014).

The majority of ADRs were “general disorders and administration site conditions” (low dose = 50%, high dose = 93%), many of which were immune-related, desired reactions, such as pyrexia and local reactions (Abnoba GmbH, 2014). With the exception of syncope, the only severe ADRs that occurred were intensified versions of desired reactions (pyrexia > 40 °C) and one case of hypersensitivity (combined pruritus and urticaria). Importantly, there were no serious ADRs and all patients fully recovered from all ADRs.

This study also revealed a number of differences between the patients who were treated with recommended or higher than recommended initial doses. Breast cancer patients were more likely to receive a recommended dose, while patients with tumours of the respiratory system or patients with late stage disease were more likely to receive a higher than recommended dose. We hypothesise that this difference may be due to healthier, early-stage cancer patients (mostly breast cancer patients) being less likely to undergo chemotherapy and be less affected by immunosuppression and treatment-related ADRs, and therefore have a reduced need for immunomodulatory therapy (Senkus et al., 2015). On the other hand, late stage cancer patients (mostly lung cancer patients) are in greater need of therapies that can help to overcome tumour and treatment-induced immunosuppression, symptoms of advanced stage disease, treatment-related ADRs and reduced HRQL (Kienle et al., 2016; Ohki et al., 2012; Whiteside, 2010). Interestingly, while being more likely to receive higher doses of VA, patients with late stage cancer and/or lung cancer were associated with experiencing less ADRs. Again, this observation is most likely explained by greater immunosuppression found in late stage cancer patients (Ohki et al., 2012).

While low initial doses were applied regularly in earlier years (2003–2006), the frequency of commencing VA with a higher than recommended dose has been increasing over the last decade (2007–2013). Likewise, the number of published studies assessing the safety and efficacy of high-dose VA therapy has increased in recent years (Kienle et al., 2011; Schläppli et al., 2016; von Schoen-Angerer et al., 2015; Werthmann et al., 2013; Wiebelitz and Beer, 2011). This trend reflects the feeling of many physicians practising integrative medicine, who believe that effectiveness of VA therapy is related to initiating a robust immune response, particularly at the commencement of VA therapy (Büssing et al., 2008; Orange et al., 2012; von Schoen-Angerer et al., 2015). Furthermore, an appreciation of the impact of the immune system during conventional anticancer therapy has been steadily growing in the field of oncology as a whole. Recent advances indicate that immune cells can shape the outcome of various anticancer therapies and breakthroughs in specific and non-specific immunotherapies have initiated a new era in the treatment of cancer (Coffelt and de Visser, 2015). While the use of VA seems to be evolving, current SmPCs still recommend the traditional approach of starting VA therapy at a low dose and gradually increasing the dose over time until an optimal dose is achieved. For example, it is recommended that treatment with Abnobaviscum should start with 1 mL of 0.02 mg, injected 3 times per week. If no reaction or a very minor reaction is observed after 8 injections of 0.02 mg, dose should be increased to 0.2 mg. After a further 8 injections, if no reaction or a very minor reaction is observed, the dose should be increased to 2 mg (Abnoba GmbH, 2014). Clearly, many physicians do not follow these guidelines, since 62% of the patients in our study received an initial dose of higher than 0.02 mg. In fact, initial doses ranged from 0.02 mg up to 40 mg, with a median of 0.2 mg. Research is therefore warranted to determine whether initiating

VA therapy at higher than recommended doses leads to better clinical outcomes and whether treatment recommendations should be updated. To answer this question, the two treatment modalities should be compared in a prospective trial assessing clinical outcomes (e.g. HRQL, chemotherapy-related ADRs, tumour response, progression-free and overall survival) as well as biomarkers for immunomodulation. Our study has shown a clear difference in the frequency of immune-related and overall ADRs. We have also shown that both low and high doses of VA are safe, thereby clearing the way for future research.

A limitation of this study is the possibility of under reporting of ADRs, especially mild or expected ADRs such as local reactions and pyrexia. The low number of ADRs documented in the low dose group resulted in a large 95% CI and prevented an in-depth comparison of the types of ADRs associated with a low compared to high VA starting dose.

In conclusion, although commencing VA therapy with a higher than recommended dose was strongly associated with experiencing ADRs compared to commencing with a recommended dose, nearly all ADRs were expected ADRs of mild to moderate intensity and most were desired reactions, such as local reactions and pyrexia. In this respect, initiating VA therapy with higher than SmPC recommended doses is safe when performed with diligence. Future research is required to investigate whether higher incidences of VA-induced immune-related events are good indicators of beneficial immunomodulation and can be causally associated with better clinical outcomes.

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Conflict of interest

The authors have no conflicts of interest to declare.

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