ORIGINAL ARTICLE

Specific Immunotherapy in Hymenoptera Venom Allergy and Concomitant Malignancy: A Retrospective Follow-up Focusing on Effectiveness and Safety

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Note: Due to the decision of the cantonal government of Bern, the Zieglerspital was closed at the end of September 2015. The Allergy Unit was merged with the Division of Allergology, University Clinic of Rheumatology, Immunology & Allergology, Inselspital. The present study is the last publication of the Allergy Unit Zieglerspital.

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Abstract

Introduction: Malignancies are often considered a contraindication for allergen-specific immunotherapy. Consequently, patients with severe Hymenoptera venom allergy and cancer require specific care. The aim of this retrospective study was to assess patients with Hymenoptera venom allergy and cancer undergoing venom immunotherapy (VIT).
Methodology: The study population comprised all patients referred for evaluation of Hymenoptera venom allergy or for a routine check-up during VIT from January 1, 2004 to December 31, 2008.
Results: Of the patients assessed, 2% (51 of 2594) had a documented Hymenoptera venom allergy and cancer (25 female, 26 male; mean age 58 years). Of these, 42 patients received VIT (82%): 25 patients had a previously diagnosed malignancy, 16 were diagnosed with malignancy during VIT, and 1 patient was diagnosed with cancer after completion of VIT. The most frequent type of tumor was breast cancer in female patients (60%) and prostate cancer in male patients (39%). Systemic allergic reactions during VIT were recorded in 7% of patients. A total of 19 patients experienced a field sting or underwent a sting challenge test during VIT: 95% tolerated the sting well. VIT was halted definitively in 9 patients (new diagnosis of cancer in 7 patients, reactivation of cancer in 1, and progressive polyneuropathy in 1).
Conclusion: The effectiveness and adverse effects of VIT in patients with Hymenoptera venom allergy and cancer in remission are comparable to those of patients without malignancy. Our findings show that patients with Hymenoptera venom allergy and cancer are eligible for VIT.

Key words: Allergy. Cancer. Hymenoptera venom allergy. Malignancy. Venom immunotherapy.

Resumen

Introducción: Las neoplasias malignas se consideran a menudo una contraindicación para la administración de inmunoterapia con alérgenos. Este aspecto es especialmente importante en los pacientes con alergia grave al veneno de himenópteros y cáncer. El objetivo de este estudio retrospectivo fue el revisar todos los pacientes diagnosticados de alergia al veneno de himenópteros, inmunoterapia con venenos (VIT) y malignidades.
Metodología: Se han incluido todos los pacientes que fueron remitidos para el estudio de alergia al veneno de himenópteros o para el control durante la VIT, desde el 1 de enero de 2004 al 31 de diciembre de 2008.
Resultados: El 2% de los pacientes (51 de 2594) con alergia al veneno de himenópteros (25 mujeres, 26 hombres, edad media 58 años) tuvieron un diagnóstico adicional de malignidad. Se administró VIT a 42 pacientes (82%): 25 pacientes con cáncer conocido, 16 con aparición de una neoplasia maligna durante la VIT y uno diagnosticado de cáncer tras haber finalizado la VIT. El tipo de tumor más frecuente fue el cáncer de mama en mujeres (60%) y el cáncer de próstata en varones (39%). El 7% de los pacientes con VIT presentó reacciones alérgicas sistémicas durante la administración de la VIT. Un subgrupo de 19 pacientes sufrió una picadura espontánea o fueron sometidos a la prueba de re-picadura durante la VIT, con buena tolerancia de la misma en el 95% de los casos. La VIT se suspendió definitivamente en

9 pacientes debido a: un nuevo cáncer (7 pacientes), reactivación de cáncer conocido (1 paciente) y polineuropatía progresiva (1 paciente). *Conclusión:* En pacientes con alergia al veneno de himenópteros y cáncer, la eficacia y los efectos secundarios de la VIT son comparables a aquellos pacientes sin malignidad si el cáncer se encuentra en remisión. Este estudio muestra que estos pacientes también son candidatos para la administración de VIT.

Palabras clave: Alergia. Cáncer. Alergia al veneno de himenópteros. Malignidad. Inmunoterapia con veneno.

Introduction

Venom immunotherapy (VIT) is effective for the treatment of Hymenoptera venom allergy in 75%-80% of cases of bee venom allergy and in over 90% of cases of *Vespula* venom allergy [1]. Systemic adverse effects of VIT are reported in 10%-20% of patients treated with bee venom and in fewer than 10% of patients treated with *Vespula* venom. VIT has been considered contraindicated in patients with concomitant malignancy [2,3]. This issue was discussed in a position paper of the European Academy of Allergy and Clinical Immunology (EAACI) in 2015 [4]. Both VIT and carcinogenesis have a specific impact on the immune system: immunotherapy induces tolerance through IL-10 and TGF-α production from Fox-p3–positive Treg cells, whereas tumor cells with antigenic tumor structures may enable tumor growth [5-7]. Although the pathogenic mechanisms of VIT in malignant tumors are only partially understood, concerns that VIT might stimulate tumor growth have been raised. Therefore, malignancies have been considered a relative contraindication for allergen-specific immunotherapy.

This assumption was recently refuted for allergen-specific immunotherapy in patients with allergy to house dust mite and pollen [8]. Hymenoptera stings are among the most frequent causes of anaphylaxis and are responsible for approximately 200 deaths annually in Europe [9]. Severe Hymenoptera venom allergy poses a considerable risk for many patients, particularly in high-exposure rural areas, and may have a debilitating impact on quality of life. Even though emergency medications such as epinephrine (eg, autoinjectors), antihistamines, and corticosteroids are useful for treatment of acute symptoms, VIT is still the only approach that addresses the underlying mechanisms of Hymenoptera venom allergy [2]. Consequently, VIT needs to be discussed in patients with malignant tumors and severe Hymenoptera venom allergy who are at risk of exposure. The aim of this study was to further examine patients with Hymenoptera venom allergy who were diagnosed with cancer before or during VIT, with emphasis on the safety and effectiveness of VIT.

Methods

Patients

We performed a 5-year retrospective study of all patients who were referred to the Allergy Unit Zieglerspital, Bern, Switzerland with Hymenoptera venom allergy, documented by positive skin test results and/or venom specific IgE (see Table 1 and further details in Supplementary Table 1a-c). From January 1, 2004 to December 31, 2008, a total of 2594 patients were assessed at their first visit or at a routine check-up during VIT. The diagnosis of Hymenoptera venom allergy was based on a standardized questionnaire, skin tests (insect venoms, common aeroallergens), and serologic tests (total IgE, specific IgE, baseline serum tryptase [bT]). The degree of severity was classified according to the criteria of Mueller [10]. The study population comprised only patients with a malignant tumor; those with benign and histologically noninvasive tumors were excluded. The cohort subsumed patients with a malignancy diagnosed before VIT, patients who developed a new malignant tumor during VIT, and patients who developed a tumor after VIT (1 case). The design of this observational and retrospective study conforms to the requirements of the Ethics Committee of the University of Bern: all patients were informed verbally that their data were to be used in the study. Written informed consent was not required.

Analyses

Skin testing was performed following the recommendations of the EAACI [11]. In addition, serologic analyses of bT and venom-specific and total IgE were performed using UniCAP (Thermo Fisher Scientific) according to the manufacturer's instructions. bT levels ≥11.4 µg/L (95th percentile of the general population) were considered elevated.

Venom Immunotherapy

VIT was initiated based on an ultrarush or rush protocol as described in previous studies using Pharmalgen venoms [11,12]. VIT was continued for a minimum of 3 years when not prematurely interrupted owing to a malignancy [13]. VIT was intended to be life-long for patients with an anaphylactic reaction to the relevant insect after successful completion of VIT and for patients with elevated bT.

Re-exposure

Patients who had not experienced a field sting during the course of VIT were challenged by the relevant insect before regular cessation of therapy. The decision to perform challenge testing in patients in whom VIT had been stopped prematurely was made individually after consultation with the oncologist and in collaboration with the patient. The standardized procedure was performed according to EAACI guidelines [14].

Statistical Analysis

R 3.0.2. was used for the statistical analyses. In order to estimate the incidence of malignancy in Hymenoptera venom–

Table 1. Characteristics of the 51 Patients With Hymenoptera Venom Allergy and Malignancy

Total no. of patients (with venom immunotherapy)	51 (42)
Mean age patients total (with venom immunotherapy) / range	58 (59)/17-86 years
Male/female, No. (%)	26/25
Allergic to, No.	
Vespula	21 (41%)
Honey bee	23 (45%)
Hornet	3 (6%)
Honey bee and *Vespula*	4 (8%)
Mean total IgE (kU/L)/range	172/7-966
Atopy, No.	15 (29%)
Baseline serum tryptase, No.[a]	
<11.4 µg/L	40
≥11.4 µg/L	9

[a]Not available in 2 patients.

allergic patients, the number of newly diagnosed cases of cancer in patients receiving VIT during the study period was compared with data provided by the Swiss Federal Statistical Office for 2009 [15]. The incidence rate p=x/n was compared with the incidence rate for the Swiss population π. As age is a known risk factor for malignancy, pi=xi/ni was tested for every subgroup according to age (0-14, 15-39, 40-44, 50-54, 55-59, 60-64, 65-69, 70-74, and 75+ years). A Monte-Carlo version of the χ^2 test was applied to test the null hypothesis, H_0^{age} against the alternative H_A^{age}. A binomial test was performed to obtain the 0.95 quantile and *P* value; α=0.05 was considered significant (Supplementary Table 2a). Safety was estimated by calculating the 95% confidence interval (CI) for adverse effects (there were no local reactions or nonspecific reactions as opposed to systemic allergic reactions), whereas effectiveness was estimated by calculating the 95% CI for reactions to re-exposure (no reaction, as opposed to systemic reaction); therefore, a standard logit-regression and the R-package "MultinomialCI" were applied (Supplementary Table 2b). The geometric mean of bT levels for patients with cancer compared with that of patients without cancer was calculated using the Mann-Whitney test (Supplementary Table 2).

Results

During the 5-year observational period, we evaluated 2594 patients with Hymenoptera venom allergy: 1099 with a newly diagnosed Hymenoptera venom allergy and 1495 who were attending routine check-ups during VIT. A malignant tumor was detected in 51 patients (2%, 26 males, 25 females, mean age of 58 years [range 17-86]). VIT was administered in 42 patients (82%, 21 males, 21 females, mean age of 59 years) (Table 1). Cancer was diagnosed in 42 of 1495 patients either before VIT (25 patients), during VIT (16 patients), or after VIT (1 patient). A second malignancy was detected in 4 cases. The 42 patients on VIT were treated for an average of 4.6 years (range 1.5 months to 25 years), and 22 were still on therapy at the end of this study.

Table 2. Type of Malignancy in 42 Patients With Hymenoptera Venom Immunotherapy

Tumor Type	No. of Malignancies Before VIT	No. of Malignancies During VIT	No. of Malignancies After VIT
Breast cancer (*including 1 patient with 2-sided breast cancer)	6	5*	0
Prostate carcinoma (*including 1 patient with previously diagnosed colon carcinoma[a])	4	5*	0
Seminoma	3	1	0
Melanoma of skin	4	1	0
Kidney carcinoma (*including one patient with previously diagnosed seminoma[a])	2*	0	0
Bladder carcinoma	0	1	1
Ovarian carcinoma (*including one patient with previously diagnosed breast cancer[a])	1	1*	0
Thyroid carcinoma	0	1	0
Hodgkin lymphoma	1	0	0
Non-Hodgkin lymphoma	0	1	0
Spinocellular carcinoma	1	0	0
Angiosarcoma	1	0	0
Cervical carcinoma	1	0	0
Teratocarcinoma	1	0	0
Total	25	16	1

[a]Previous carcinoma, not relevant for VIT.

Table 3. Influence of New Malignancy to Management of Venom Immunotherapy in 16 Patients With Hymenoptera Venom Allergy

Management of VIT (No.)	Definite Stop (8)	Temporarily Suspended (6)	Continued Without Interruption (2)
Malignancy (No.)	Breast cancer (3) - stopped owing to malignancy after 5 years of VIT, no indication for continuation (2 patients) - stopped owing to malignancy after 1.5 months of VIT, no continuation due to patient preference (1 patient) Two-sided breast cancer (1) - stopped owing to second malignancy after 5 years of VIT, no indication for continuation	Breast cancer (1) - paused during surgery and adjuvant chemotherapy, later resumed	Prostate cancer (2) - VIT continued because of locally limited malignancy and no specific treatment planned - VIT continued during radiation of the prostate owing to suspected systemic mastocytosis
	Prostate cancer (1) - stopped owing to unexplained polyneuropathy after 5 years of VIT	Prostate cancer (2) - paused during prostatectomy, later resumed (both patients)	
	Non-Hodgkin lymphoma (1) - stopped owing to malignancy after 3 years of VIT	Bladder cancer (1) - paused during surgery, later resumed	
	Thyroid cancer (1) - stopped owing to malignancy after 5 years of VIT, no continuation due to patient preference, although continued because of elevated bT	Seminoma (1) - paused during orchiectomy and adjuvant chemotherapy, later resumed and paused again 2 years later due to relapse of malignancy, continuation after axillary lymph node dissection and chemotherapy	
	Ovarian cancer with peritoneal carcinomatosis (1) - stopped owing to malignancy after 3 years of VIT, no continuation due to metastatic malignancy	Melanoma (1) - paused during excision of malignancy, later resumed	

Abbreviations: bT, baseline serum tryptase; VIT, venom immunotherapy.

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Malignancy in Hymenoptera Venom–Allergic Patients Undergoing VIT

The overall incidence of cancer was 1.1%, which is lower than in the Swiss general population (2.2%).

The most prevalent malignancy was breast cancer in 60% of women (15 of 25) and prostate carcinoma in 39% of men (10 of 26), followed by seminoma in 27% of men (7 of 26) and melanoma in 10% of patients (5 of 51) (Table 2). Given that some malignancies (eg, lung cancer) are not represented in our study cohort, the cumulative incidences differ significantly from those of the Swiss general population. However, the incidence for the tumor sites represented in this study did not differ from the corresponding incidence in the Swiss general population (Supplementary Table 2b).

Indication for Venom Immunotherapy

According to EAACI guidelines, 46 of 51 patients with malignancy and Hymenoptera venom allergy satisfied the criteria for VIT [1,12]. Since 5 of 51 patients had a mild or moderate allergic reaction (grade I or II) following insect stings, VIT was not considered indicated. Four of 46 patients declined to start VIT, and 42 of 46 patients underwent VIT: 38 by an ultrarush protocol, 4 by a rush protocol [1].

Baseline Serum Tryptase

bT was available for 49 of 51 patients (96%, mean 5.27 µg/L [range <1.0-60.2 µg/L]). In 9 of 49 patients (18%), bT was elevated (mean 23.18 µg/L). Three of the 9 patients had experienced recurrent systemic reactions after Hymenoptera stings. Underlying systemic mastocytosis was suspected in 5 patients and confirmed in 1 by bone marrow biopsy, while cutaneous mastocytosis was detected in skin biopsy in 4 patients. In addition, breast cancer was diagnosed in 4 of 9 patients with elevated bT.

Follow-up

In 24 of the 25 patients (96%) with a malignancy diagnosed before VIT was initiated, cancer remained in remission during VIT, ie, no tumor progression or relapse was documented. Metastasis was detected in only 1 patient in this group (bone metastasis in a patient with prostate carcinoma 3 years after initiation of VIT).

A total of 16 patients were diagnosed with a new malignancy during VIT; 1 was affected twice (bilateral, low-grade differentiated breast cancer) (Table 3). VIT was stopped in the case of advanced disease and paused during cancer therapy (surgery, chemotherapy, and/or radiation), with the exception of the following patients: 1 case involving application of the maintenance dose (well tolerated) overlapping with adjuvant chemotherapy for breast cancer; 1 case of VIT (maintenance dose) during radiation of the prostate (prostate cancer remained in remission throughout the following 5 years of follow-up); 1 patient with no specific treatment for prostate carcinoma who tolerated VIT well (the tumor did not progress during 1 year of follow-up).

Another patient experienced an anaphylactic reaction 6 years after successful completion of a well-tolerated VIT with honey bee venom. This patient had recently been diagnosed with bladder carcinoma and was therefore included in the study cohort.

VIT was terminated prematurely in 9 of 42 patients: in 1 case owing to cancer progression (metastasis), in 7 patients owing to a newly diagnosed cancer, and in 1 patient owing to a possible adverse effect of VIT (polyneuropathy).

Safety: Adverse Effects of Venom Immunotherapy

Eleven of 42 patients with VIT (5 with cancer in remission, 6 with new cancer during VIT) reported adverse effects (Table 4). Four mentioned nonspecific symptoms such as tiredness, headache, or a prickling sensation in their fingers, 2 experienced large local reactions at the injection site, and 1 reported all of these symptoms. One patient diagnosed with prostate carcinoma during VIT developed progressive polyneuropathy [16,17]. Three patients experienced a systemic reaction: all 3 were allergic to honey bee venom (grade III and IV according to Mueller [10]), and 2 had elevated bT. The overall probability of a clinically relevant adverse effect (systemic allergic reaction) was 1.7% (95%CI, 0.000-0.196), while the probability of no reaction or a minor reaction (local or nonspecific reaction) was 92.8% (95%CI, 0.310-0.196).

Effectiveness: Hymenoptera Sting Re-exposure

Failure of VIT was defined either as systemic allergic symptoms during an in-hospital sting challenge or as a self-reported systemic reaction after a field sting. Almost half the patients with VIT underwent a sting challenge or experienced a field sting by the relevant insect: 19 of 42 patients on VIT experienced either a field sting or had been challenged with the relevant insect venom during VIT [14]. No sting challenge was performed in patients who had to interrupt VIT or were still on therapy at the end of the investigation. Eleven of 13 patients who experienced a field sting during VIT tolerated the sting well, while 2 of 11 developed a large local reaction. One of the 11 patients experienced palpitations and profuse sweating after a bee sting, although symptoms resolved within 30 minutes after self-administration of epinephrine. Six patients had a controlled insect sting challenge, and all of them tolerated it well. Overall, 18 out of 19 patients had no signs of systemic symptoms after re-exposure to the relevant insect during VIT (probability, 0.738; 95%CI, 0.619-0.863). The calculated risk for a systemic allergic reaction on re-exposure to the relevant insect was 2.4% (95%CI, 0.000-0.184). Three patients experienced anaphylaxis after a field sting 6 to 14 years after having completed VIT successfully (probability, 0.071; 95%CI, 0.000-0.232). Two of them had bee venom allergy, 1 *Vespula* venom allergy, and 2 elevated bT with suspected cutaneous mastocytosis.

Discussion

In this 5-year retrospective single center study comprising 2594 patients with well-documented Hymenoptera venom allergy, the overall incidence of cancer was 1.1%. This low percentage might be explained by the specific population studied. The most frequent malignancies in the study cohort

Table 4. Reported Side Effects of Venom Immunotherapy in Patients With Malignancy Before Respectively During Venom Immunotherapy

	Adverse effect	Allergy to Insect Venom	Allergy Grade	Baseline Serum Tryptase, µg/L	Tumor Type
Known cancer before VIT	SR (feeling of faintness and dyspnea with decreased peak-flow at maintenance dose)	BV	3	2.90	Angiosarcoma
	Nonspecific (tiredness at maintenance dose)	BV	4	3.42	Melanoma
	Nonspecific (tiredness), LLR (both during maintenance dose)	VV	4	13.10	Breast cancer
	LLR (at maintenance dose)	BV	3	4.42	Breast cancer
	LLR (at maintenance dose)	BV	4	19.80	Seminoma
New cancer during VIT	SR (collapse with hypotension at maintenance dose; no reaction after change to a delayed therapy solution)	BV/VV	4 / 4	19.20	Thyroid carcinoma
	SR (dizziness and confusion with collapse 30 minutes after maintenance dose on 2 occasions, no objective circulatory symptoms; no reaction after change to a delayed therapy solution)	BV/VV	4 / 4	33.70	Prostate carcinoma; colon carcinoma
	Nonspecific (lymph node swelling, temporal dysesthesia)	BV	3	3.29	Non-Hodgkin-lymphoma
	Nonspecific (feeling of dizziness with no changes in blood pressure during up-dosing, maintenance dose well tolerated)	VV	3-4	2.51	Breast cancer
	Nonspecific (polyneuropathy, unexplained)	Hornet	3	3.28	Prostate carcinoma
	Nonspecific (tingling sensation in palms at maintenance dose)	VV	4	5.89	Prostate carcinoma

Abbreviations: BV, bee venom; LLR, large local reaction; SR, systemic allergic reaction; VV, *Vespula* venom
[a]Allergy grade according to Mueller [10].

were breast cancer in women and prostate cancer in men. Both of these malignant tumors account for the highest incidence of neoplasms in the Swiss general population (crude ratio for breast cancer 136.2; crude ratio for prostate carcinoma 162.0). Seminoma was the fourth most frequent tumor in our cohort, although it is less frequent in the Swiss population (crude ratio 11.0) [15]. While the frequency of seminoma in patients with Hymenoptera venom allergy was remarkably high, common tumors were either not present (eg, lung cancer) or rare (eg, hematologic malignancies and lymphomas). The cancer sites that were not found in our study cohort account for the only statistically significant difference in incidence compared with data for the Swiss general population. The complete absence of patients with bronchial carcinoma in the study cohort, for example, might be due to the high morbidity and mortality associated with the disease; consequently, Hymenoptera venom allergy may not be a priority. The finding that seminoma was the fourth most frequent cancer in our cohort is likely due to better outcomes in these patients and because they are generally younger and more active. The lower incidence of malignancy and the otherwise comparable distribution of age and tumor sites emphasize an underlying selection bias.

The course of VIT in the study cohort is largely comparable with prior data for Hymenoptera venom–allergic patients. Even though the present study is based on a small sample and lacks long-term data, it does not suggest stimulation of tumor growth induced by VIT or an increased risk for adverse effects of VIT in patients with a malignancy in remission. In conclusion, VIT is safe in Hymenoptera venom–allergic patients with stable cancer.

Cancer was newly diagnosed during the course of VIT in 16 patients, leading to discontinuation of VIT. Nevertheless, VIT was restarted in half of the patients after completion of cancer treatment (Table 3). The decision to continue VIT was always determined in accordance with the treating oncologist and the consent of the patient. VIT was well tolerated in all 8 patients who resumed VIT after an intermission for cancer treatment. The preparation had to be changed to Alutard in only 2 patients owing to systemic reactions after the application of the maintenance dose; thereafter, it was well tolerated. Overall, the incidence of systemic adverse effects to VIT in patients who had been diagnosed with cancer during therapy is consistent with the adverse effects of VIT in Hymenoptera venom–allergic patients without cancer, as described elsewhere [1,2,11,17,18]. Therefore, it is safe to resume VIT after completion of cancer treatment.

There was some concern over whether the impact of cancer, or its treatment, might reduce the immunologic response to VIT. Nevertheless, data from the present study show that the risk for systemic reaction to a sting of the relevant insect is comparable to that reported in a population without neoplasms (cancer), where VIT failure was registered in 0%-9% of *Vespula* venom–allergic patients and in up to 20% of bee venom–allergic

patients [1,17]. As for long-term efficacy, 3 patients experienced a systemic reaction 6 to 14 years after completing VIT (course lasting 3-5 years), and all of them had at least 1 risk factor for treatment failure (bee venom allergy and/or elevated bT). This finding, while achieved using a study design that is not suitable for the investigation of long-term effects, is consistent with data assessed earlier at the same center in Hymenoptera venom–allergic patients without cancer [19].

The prevalence of elevated bT (18%) was higher in the present cohort than in other studies investigating the prevalence of elevated bT in Hymenoptera venom–allergic patients [17,18,20]. This finding is striking, although the mean age of the study population was 58 years, and bT levels are known to increase with age [20,21]. Nevertheless, as shown in earlier studies, elevated bT is a risk factor for systemic allergic reactions but is not considered as a contraindication for VIT [11,17,22,23]. A disproportionately high frequency of elevated bT was found in patients with breast cancer, of whom almost one third were affected. Data from a previous study suggest a certain impact of mast cells on tumor growth due to an increased mast cell load at the periphery of malignant tissue in various neoplasms such as colon carcinoma, lymphoma, lung cancer, melanoma, and breast cancer [24,25]. A recent study investigating molecular subtypes of breast cancer suggests a correlation between the concentration of mast cells close to the tumor tissue and different types of breast cancer [26]. Essentially, a higher number of tryptase-positive mast cells was associated with less aggressive breast cancer and, as such, indicated a positive prognosis. Whether the mast cells found in and around tumor tissue lead to serologically detectable higher bT levels remains unknown. However, this possibility could explain the finding of a high prevalence of elevated bT in patients with breast cancer. As for the safety of VIT in patients with elevated bT and breast cancer, our results show no systemic adverse effects and, therefore, imply that therapy is also safe in this group. Consequently, patients with breast cancer and elevated bT levels are equally eligible for VIT.

The main limitations of the present study are that the results represent the retrospective experience of a single center and the recruitment process is subject to selection bias. Furthermore, our sample is small, with a largely heterogeneous selection of neoplasms, thus preventing the statistical identification of effects related to specific cancers. Nevertheless, in the absence of larger and prospective studies, our data may facilitate decision making for clinicians treating patients with Hymenoptera venom allergy and a history of cancer.

In conclusion, VIT is as effective and safe for Hymenoptera venom–allergic patients with cancer as for patients without cancer. Consequently, cancer should not be considered an absolute contraindication for VIT, and patients with Hymenoptera venom allergy and cancer are equally eligible for VIT if their cancer is in remission and other therapies do not have priority.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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