Specific Immunotherapy in Hymenoptera Venom Allergy and concomitant Malignancies - A retrospective follow-up focusing on efficacy and safety

Hymenoptera Venom Immunotherapy & Cancer

Aeberhard J[1], Haeberli G[1], Müller UR[1], Helbling A[1,2]

[1]Allergy Unit Zieglerspital Clinic of Internal Medicine, Spital Netz Bern AG, Bern, Switzerland

[2]Division of Allergology, University Clinic of Rheumatology, Immunology & Allergology, Inselspital/University Hospital Bern, Switzerland[*]

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

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.18176/jiaci.0184

Correspondence:

Arthur Helbling, MD

Head of the Division of Allergology

University Clinic of Rheumatology, Immunology & Allergology

Inselspital/University Hospital

CH-3010 Bern, Switzerland

Tel.: ++ 41 31 632 22 69

FAX: ++ 41 31 632 42 08

Arthur.Helbling@insel.ch

3‘183/ max 3’ 500 words; Tables 1-4, supplementary material (appendix tables 1-3)

Presentation

The abstract of this article was presented at the 78th annual conference of the Swiss Society of Internal Medicine in Basel in May 2010.

Conflict of interest

The authors, as listed above, declare that there is no conflict of interest with any entity whatsoever, neither with a financial nor a non-financial interest in the subject discussed in this manuscript.

Abstract

Introduction: Malignancies are often considered as a contraindication for allergen specific immunotherapy. This aspect must be discussed in regards to the population with severe Hymenoptera venom allergy and cancer. The aim of this retrospective study was to conduct a further examination of patients with Hymenoptera venom allergy, venom immunotherapy (VIT) and a malignancy.

Methodology: All patients have been included who were referred for evaluation of a Hymenoptera venom allergy or for control during VIT from January 1, 2004 to December 31, 2008.

Results: 2% of patients (51 of 2594) with a documented Hymenoptera venom allergy (25 female, 26 male; mean age 58 years) had an additional diagnosis of malignancy. 42 patients had VIT (82 %): 25 patients with a known cancer, 16 with new malignancy during VIT and one was diagnosed cancer after completed VIT. The most frequent type of tumour was breast cancer in female patients (60%) and prostate cancer in male patients (39%). 7% of patients with VIT developed systemic allergic reactions during VIT. 19 patients experienced a field sting or underwent a sting challenge test during VIT - 95 % tolerated the sting well. VIT was definitively halted in 9 patients: Due to new cancer in seven, one had a reactivation of cancer and one had a progressive polyneuropathy.

Conclusion: Efficacy and side effects of VIT in patients with Hymenoptera venom allergy and cancer are comparable to those without malignancy if cancer is in remission. This study shows that these patients are also eligible for VIT.

Abstract 250/ max 250 words

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) in Hymenoptera venom allergy is an established treatment with an efficacy rate of 75-80 % in bee venom and over 90 % in Vespula venom allergic patients [1]. Systemic side effects of VIT are reported in 10-20 % of bee venom patients and in less than 10% of Vespula venom treated patients. In case of concomitant malignancies VIT has been considered contraindicated [2,3]. This practice was discussed in a position paper of the European Academy of Allergy and Clinical Immunology in 2015 [4]. It is thought that both VIT and carcinogenesis have a certain impact on the immune system: Immunotherapy is known to induce tolerance through IL-10 and TGF-α production from Fox-p3-positive T reg cells, whereas tumour cells with antigenic tumour structures may induce permissive tumour growth [5,6,7]. Though pathomechanisms of VIT with influence on malign tumours are only partially understood, concerns that VIT might stimulate their growth have been raised. Therefore, malignancies have been considered as a relative contraindication for allergen specific immunotherapy.

Recently, this assumption has been refuted for allergen specific immunotherapy of house-dust mite and pollen [8]. Hymenoptera stings are among the most frequent causes of anaphylaxis and responsible for an annual fatality rate in Europe of approximatively 200 individuals [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 (e.g. auto-injectors), antihistamines and corticosteroids are useful to treat acute symptoms, VIT is still the only causal therapy for Hymenoptera venom allergy [2]. Consequently, VIT needs to be discussed in exposed patients with malignant tumours and a severe Hymenoptera venom allergy. Therefore, the aim of this study was to further examine patients with Hymenoptera venom allergy and have been diagnosed with a malignancy before or during VIT, with a focus upon safety and efficacy of VIT.

doi: 10.18176/jiaci.0184

Methods

Patients

In this retrospective study carried out over five years, all patients who were referred to the Allergy Unit Zieglerspital with Hymenoptera venom allergy, documented by positive skin tests and/or venom specific IgE, were included (see table 1 and further details in appendix table $1_{a\text{-}c}$). In total, 2,594 subjects were observed either for evaluation or for controls during VIT from January 1, 2004 to December 31, 2008. The diagnosis of a Hymenoptera venom allergy was based on a standardised questionnaire, skin tests (insect venoms, common aero-allergens) and serologic tests (total IgE, specific IgE, baseline serum tryptase [bT]). The degree of severity was classified according to the criteria of H.L. Mueller [10]. All patients with a malignancy were included in the study, benign and histologically non-invasive tumours were excluded. The cohort subsumes patients with a malignancy diagnosed before VIT, after having completed VIT in one subject - and patients with a new malignant tumour during VIT. The design of this observational and retrospective study conforms to the requirements of our local ethical committee of the University of Bern: all patients were verbally informed, a written informed consent was not required.

Analyses

Skin testing was performed following the recommendations of the European Academy of Allergy and Clinical Immunology and was described earlier [11]. In addition, serologic analyses of bT, venom-specific and total IgE antibodies were measured by UniCAP (Thermo Fisher Scientific, Uppsala, Sweden) according to the manufacturer's instructions. bT levels ≥ 11.4 µg/l (95th percentile of the general population) were considered as elevated.

Venom immunotherapy

VIT was initiated by the ultrarush or a rush protocol as described in previous studies using Pharmalgen venoms [11,12]. VIT and was continued for a minimum of three years when not prematurely interrupted due to a malignancy [13]. For patients with an anaphylactic reaction

to the relevant insect after a successfully completed VIT and patients with elevated bT, VIT treatment was intended to be life-long.

Sting 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 challenge the patients in whom VIT had been stopped prematurely was made individually after consultation with the oncologist and in collaboration with the patient. The standardised procedure was performed according to the proposition of the European Academy of Allergy and Clinical Immunology [14].

Statistics

The statistics software R 3.0.2. was utilised for the following analyses. In order to estimate the incidence of malignancy in Hymenoptera venom allergic patients, the number of new diagnosed cancer in VIT treated patients during our study period was compared to the data provided by the Swiss Federal statistical Office 2009 [15]. The observed incidence rate $p = x/n$ was compared to the incidence rate of Swiss population π. As age is a known risk factor for malignancy, $p_i = x_i/n_i$ 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). For testing the null hypothesis, H_0^{age} against the alternative H_A^{age} a Monte-Carlo-version of a χ^2 was applied. A binomial test was performed to obtain 0.95-quantile and p-value, $\alpha = 0.05$ was considered significant (appendix table 2_a). Safety and efficacy were estimated by calculating the 95%-confidence region of side effects (there were no reaction, local reactions or non-specific reactions as opposed to systemic allergic reactions). Specifically, the reaction to re-exposure (no reaction as opposed to systemic reaction), therefore a standard logit-regression and the R-package „MultinomialCI“ was applied (appendix table 2_b). The geometric mean of bT levels for patients with cancer versus those without malignancy were calculated by the Mann Whitney U test (appendix table 2).

doi: 10.18176/jiaci.0184

Results

During the 5-year observational period 2,594 patients with Hymenoptera venom allergy were evaluated: 1,099 with a new diagnosed Hymenoptera venom allergy and 1,495 for control during VIT. 2 % of the subjects (51 of 2,594) – 26 males, 25 females, with a mean age of 58 years (range 17-86) - had a malignant tumour. 82 % of the patients (42 of 51) with Hymenoptera venom allergy and cancer received VIT – 21 males, 21 females, with a mean age of 59 years (table 1). 42 of a total of 1,495 patients with VIT were diagnosed with cancer either before VIT (25 subjects), during VIT (16 subjects) or after VIT (one subject). Four patients suffered from a second malignancy. 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 investigation.

Malignancy in Hymenoptera venom allergic patient with VIT

In this 5-year retrospective study comprising 2,594 patients with a well-documented Hymenoptera venom allergy, the overall incidence of cancer was 1.1 %. This number of affected patients is lower than in the general Swiss 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 the subjects (5 of 51) (table 2). Due to the fact that some malignancies (as e.g. lung cancer) are not represented in our study cohort, the cumulative incidences differ significantly from the general Swiss population. However, the incidences of the registered tumour sites in the present study did not differ from the correspondent incidences in the general Swiss population (appendix table 2_b).

Indication for venom immunotherapy

According to the EAACI guidelines 46 of 51 patients with malignancy and Hymenoptera venom allergy satisfied the indication for VIT [1,12]. Five of 51 patients had a mild or moderate allergic reaction (grade I or II) following insect stings, thus, VIT was not compelling.

Four of 46 patients declined to start VIT and 42 of 46 subjects had VIT: 38 by ultrarush, four by a rush protocol [1].

Baseline serum tryptase

BT was available from 49 of 51 (96 %) patients with a mean value of 5.27 µg/l [range <1.0 - 60.2 µg/l]). In 9 of 49 (18 %) patients bT was elevated (mean 23.18 µg/l). Three of 9 had suffered recurrent systemic reactions after Hymenoptera stings. An underlying systemic mastocytosis was suspected in five patients and confirmed in one by bone marrow biopsy while a cutaneous mastocytosis was found through the use of skin biopsy in four. In addition, in four of 9 patients with elevated bT breast cancer was diagnosed.

Follow-up

In the 24 out of 25 patients (96 %) who had a diagnosed malignancy before VIT was initiated, cancer remained in remission during VIT, which means that no tumour progression or relapse was documented. Only one patient of this group suffered a tumour expansion (bone metastasis in prostate carcinoma three years after initiation of VIT).

A total of 16 subjects were diagnosed with new cancer during VIT; one was affected two-fold (a bilateral low differentiated breast cancer) (table 3). VIT was stopped in case of the onset of an advanced disease, and respectively paused during cancer therapy (surgery, chemotherapy and/or radiation) - with the exception of the following patients: In one case an application of the maintenance dose (that was well tolerated) overlapped adjuvant chemotherapy due to breast cancer. Another patient had VIT (maintenance dose) during radiation of the prostate, and the prostate cancer remained in remission throughout five years of further observation. VIT was well tolerated in a patient without specific treatment for prostate carcinoma and the tumour did not progress during the one year of follow-up.

Another patient was analysed for an anaphylactic reaction six years after a regularly stopped and well tolerated VIT with honey bee venom. This patient had recently been diagnosed with bladder carcinoma and therefore was included in the study cohort.

doi: 10.18176/jiaci.0184

VIT was prematurely terminated in 9 of 42 patients: in one subject due to cancer progression (metastasis), in seven patients due to a newly diagnosed cancer and in one due to a possible side effect to VIT (polyneuropathy).

Safety - side effects of venom immunotherapy

11 of 42 patients with VIT (five with cancer in remission, six with new cancer during VIT) complained about having side effects (table 4). Four mentioned non-specific symptoms such as tiredness, headache or a prickling sensation in their fingers, two experienced large local reactions at the site of injection, and one complained about all of these symptoms. One patient with a new prostate carcinoma during VIT developed a progressive polyneuropathy [16,17]. Three had a systemic reaction: All were allergic to honey bee venom (grade III and IV according to H.L. Mueller), two of them had an elevated bT. The overall probability for a clinical relevant side effect (systemic allergic reaction) amounts to 1.7 % (95 % confidence interval 0.000 - 0.196) while there was a probability of 92.8 % (95 % confidence interval 0.310 - 0.196) for no reaction or a minor reaction (local or non-specific reaction).

Efficacy - Hymenoptera sting re-exposure

VIT failure 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 had a sting challenge or a field sting of the relevant insect: 19 of 42 patients on VIT experienced either a field sting or had been challenged with the relevant insect during VIT [14]. No sting challenge was performed in the patients that had to interrupt VIT or that were still on therapy at the end of the investigation. 11 of 13 patients with a field sting during VIT tolerated it well, while two of 11 developed a large local reaction, and one of 11 experienced palpitations and profuse sweating after a bee sting, symptoms resolved within 30 minutes after self-administered epinephrine. Six patients had a controlled insect sting challenge and all of them tolerated it well. Overall, 18 out of 19 had no signs of systemic symptoms after re-

exposure with the relevant insect during VIT (probability 0.738, 95 % confidence interval 0.619 - 0.863). The calculated risk for a systemic allergic reaction to re-exposure with the relevant insect amounts to 2.4 % (95 % confidence interval 0.000 - 0.184). Three patients suffered anaphylaxis after a field sting six to 14 years after having completed VIT successfully before (0.071, 95 % confidence interval 0.000 - 0.232). Two of them had a bee venom allergy, one a Vespula allergy, two of them had an elevated bT with a suspected cutaneous mastocytosis.

Discussion

In this 5-year retrospective single center study comprising 2,594 patients with a well-documented Hymenoptera venom allergy, the overall-incidence of cancer was 1.1 %. This finding might be explained by the specific population studied. The most frequent malignancy in the study cohort was breast cancer in women and prostate cancer in men. Both of these malignant tumours account for the highest incidence of neoplasms in the general Swiss population (crude ratio breast cancer 136.2; crude ratio prostate carcinoma 162.0). The seminoma was the fourth most frequent tumour in our cohort, whereas this tumour occurs in less frequent neoplasms in the Swiss population (crude ratio 11.0) [15]. While the frequency of seminoma in patients with Hymenoptera venom allergy was remarkably high, common tumours such as lung cancers were not present or rare, such as hematologic malignancies or lymphomas. The cancer sites that were not found in our study cohort account for the only statistically significant difference of the incidence of different neoplasms compared to the tumour data in general Swiss population. An explanation for the complete absence of patients with bronchus carcinoma (amongst others) in the study cohort might be that the morbidity and mortality in these patients are high and therefore Hymenoptera Venom may not have priority. Meanwhile, patients with seminoma were the fourth most frequent cancer site in our cohort, which 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 tumour sites emphasise an underlying selection bias.

The course of VIT in the study cohort is largely comparable with prior data in Hymenoptera venom allergic patients. Altogether, the present study, even though based upon a small sample size and without long term data, does not suggest neither a stimulation of tumour growth induced by VIT nor an increased risk for side effects of VIT in patients with a malignancy in remission. In conclusion, VIT is safe in Hymenoptera venom allergic patients with a stable tumour disease.

Cancer was newly diagnosed during the course of VIT in 16 patients and VIT was consequently discontinued. Nevertheless, VIT could be resumed in half of the patients after completion of the cancer treatment (table 3). The decision to continue VIT was always determined in accordance with the treating oncologist and the consent of the patient. In all of the eight patients who resumed VIT after an intermission for cancer treatment, VIT was well tolerated (in only two patients the preparation had to be changed to Alutard due to systemic reactions after the application of the maintenance dose, hereafter VIT was well tolerated). Overall, the incidence of systemic side effects to VIT in patients who had been diagnosed with cancer during therapy is in accord with the side effects of VIT in Hymenoptera venom allergic patients without cancer which has been described in numerous previous studies [1,2,11,17,18]. Therefore, it is safe to resume VIT after cancer treatment has been conducted.

Regarding the efficacy of VIT it was a concern that the impact of the cancer, or its treatment, might reduce the immunologic response to VIT. Nevertheless, data from this present study shows a comparable risk for a systemic reaction to a sting of the relevant insect to the data of prior studies in a population without neoplasms (cancer), where VIT failure is registered in 0-9% of Vespula venom allergic and in up to 20% of bee venom allergic patients [1,17]. Concerning long-term efficacy there were three patients suffering a systemic reaction six to 14 years after a completed VIT (course 3-5 years), and all of them had at least one risk factor for treatment failure (bee venom allergy and/or elevated bT). This finding, although achieved utilising a study design that is not compatible to investigate long-term effects, is in line 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 our cohort of Hymenoptera venom allergic patients with a malignant tumour (cancer) compared to studies investigating the prevalence of elevated bT in Hymenoptera venom allergic patients in different centers

doi: 10.18176/jiaci.0184

[17,18,20]. This co-occurrence is striking, although the mean age of the study patients is 58 years and bT levels are known to increase with age [20,21]. Nevertheless, as it has been shown in earlier studies, an elevated bT poses a risk factor for systemic allergic reactions but is not considered as a contraindication for VIT [11,17,22,23]. A disproportionately high occurrence of an elevated bT level was discovered in patients with breast cancer, in which almost one third was affected. Data from a previous study suggest a certain impact of mast cells on the tumour growth due to an increased mast cell load found at the periphery of malign tissue of various different neoplasms such as colon carcinoma, lymphoma, lung cancer, melanoma, and also breast cancer [24,25]. A recent study investigating molecular subtypes of breast cancer suggests a correlation of the concentration of mast cells close to the tumour tissue with different types of breast cancer [26]. Fundamentally, a higher number of tryptase-positive mast cells were associated with less aggressive breast cancer types, and as such indicated a positive prognostic factor. Whether the mast cells found in and around tumour tissue lead to a serologic detectable higher bT lever remains unknown. But it could be speculated that this might explain the finding of a high prevalence of elevated bT in patients with breast cancer. Regarding safety of VIT in these patients with elevated bT and breast cancer our results show no systemic side effects and thus, do imply safe therapy also in this cohort. Consequently, patients with breast cancer and with elevated bT are equally eligible for VIT.

The limitations of the present study are that the results represent the retrospective experience of a single center, and the recruiting of the cohort suggests a selection bias. Furthermore, it describes a small sample size with a largely heterogeneous entity of neoplasms, which prevents the statistical identification of effects related to specific cancers. Nevertheless, in the absence of larger and prospective studies, this data may help clinicians in their decision when treating patients with a Hymenoptera venom allergy and a history of cancer.

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

Acknowledgments

We thank Ottavia Maier-Stecher, Brigitte Salvisberg from the Allergy Unit Zieglerspital and Tobias Fissler, Gabriel Fischer and Luana Pozzi from the Institute of Mathematical Statistics of the University of Berne.

References

1 Bonifazi F, Jutel M, Biló BM, Birnbaum J, Mueller U; EAACI Interest Group on Insect Venom Hypersensitivity. Prevention and treatment of Hymenoptera venom allergy: guidelines for clinical practice. Allergy 2005 Dec;60(12):1459-70.

2 Bousquet J, Lockey R, Malling HJ. Allergen immunotherapy: therapeutic vaccines for allergic diseases. A WHO position paper. J Allergy Clin Immunol 1998 Oct;102(4Pt1):558-62

3 Wöhrl S, Kinaciyan T, Jalili A, Stingl G, Moritz KB. Malignancy and Specific Allergen Immunotherapy: The Results of a Case Series. Int Arch Allergy Immunol 2011;156:313–319.

4 Pitsios C, Demoly P, Bilò MB, Gerth van Wijk R, Pfaar O, Sturm GJ, et al. Clinical contraindications to allergen immunotherapy: an EAACI position paper. Allergy 2015 Aug;70(8):897-909.

5 Palomares O, Yaman G, Azkur AK, Akkoc T, Akdis M, Akdis CA. Role of T reg in immune regulation of allergic diseases. Eur J Immunol 2010 May;40(5):1232-40.

6 Wasiuk A, de Vries VC, Hartmann K, Roers A, Noelle RJ. Mast cells as regulators of adaptive immunity to tumours. Clin Exp Immunol 2009 Feb;155(2):140-6.

7 Fridman WH, Remark R, Goc J, Giraldo NA, Becht E, Hammond SA, et al. The immune microenvironment: a major player in human cancers. Int Arch Allergy Immunol 2014;164(1):13-26.

8 Bozek A, Kozłowska R, Jarzab J. The safety of specific immunotherapy for patients allergic to house-dust mites and pollen in relation to the development of neoplasia and autoimmune

disease: a long-term, observational case-control study. Int Arch Allergy Immunol 2014;163(4):307-12.

9 Helbling A, Hurni T, Mueller UR, Pichler WJ. Incidence of anaphylaxis with circulatory symptoms: a study over a 3-year period comprising 940,000 inhabitants of the Swiss Canton Bern. Clin Exp Allergy 2004 Feb;34(2):285-90.

10 Mueller HL. Diagnosis and treatment of insect sensitivity. J Asthma Res 1966;3:331-3.

11 Haeberli G, Brönnimann M, Hunziker T, Müller U. Elevated basal serum tryptase and Hymenoptera venom allergy: relation to severity of sting reactions and to safety and efficacy of venom immunotherapy. Clin Exp Allergy 2003;33:1216-1220.

12 Müller UR, Haeberli G. Use of beta-blockers during immunotherapy for Hymenoptera venom allergy. J Allergy Clin Immunol 2005 Mar;115(3):606-10.

13 Biló BM, Ruëff F, Mosbech H, Bonifazi F, Oude-Elberink JN; EAACI Interest Group on Insect Venom Hypersensitivity. Diagnosis of Hymenoptera venom allergy. Allergy 2005;60:1339-1349.

14 Ruëff F, Przybilla B, Müller U, Mosbech H. The sting challenge test in Hymenoptera venom allergy. Position paper of the Subcommittee on Insect Venom Allergy of the European Academy of Allergology and Clinical Immunology. Allergy 1996 Apr;51(4):216-25.

15 Available from: http://www.bfs.admin.ch/bfs/portal/de/index/infothek/lexikon/lex/2.topic.3.html

16 Reisman RE. Unusual reactions to insect stings. Curr Opin Allergy Clin Immunol 2005 Aug;5(4):355-8.

17 Ruëff F, Przybilla B, Biló MB, Müller U, Scheipl F, Seitz MJ, et al. Clinical effectiveness of Hymenoptera venom immunotherapy: a prospective observational multicenter study of the European academy of allergology and clinical immunology interest group on insect venom hypersensitivity. PLoS One 2013 May 20;8(5):e63233.

18 Müller UR, Helbling A, Berchtold E: Immunotherapy with honey bee and yellow jacket venom is different regarding efficacy and safety. J Allergy Clin Immunol 1992;89:529-535.

19 Lerch E, Müller UR. Long-term protection after stopping venom immunotherapy: results of re-stings in 200 patients. J Allergy Clin Immunol 1998 May;101(5):606-12.

20 Blum S, Gunzinger A, Müller UR, Helbling A. Influence of total and specific IgE, serum tryptase and age on severity of allergic reactions to Hymenoptera stings. Allergy 2011 Feb;66(2):222-8.

21 Guenova E, Volz T, Eichner M, Hoetzenecker W, Caroli U, Griesinger G, et al. Basal serum tryptase as risk assessment for severe Hymenoptera sting reactions in elderly. Allergy 2010 Jul;65(7):919-23.

22 Bonadonna P, Zanotti R, Pagani M, Caruso B, Perbellini O, Colarossi S, et al. How much specific is the association between Hymenoptera venom allergy and mastocytosis? Allergy 2009;64(9):1379-82.

23 Bonadonna P, Zanotti R, Müller U. Mastocytosis and insect venom allergy. Curr Opin Allergy Clin Immuno. 2010;10(4):347-53.

24 Amini RM, Aaltonen K, Nevanlinna H, Carvalho R, Salonen L, Heikkilä P, et al. Mast cells and eosinophils in invasive breast carcinoma. BMC Cancer 2007;7:165.

25 Kashiwase Y, Morioka J, Inamura H, Yoshizawa Y, Usui R, Kurosawa M. Quantitative analysis of mast cells in benign and malignant breast lesions. Immunohistochemical study on formalin-fixed, paraffin-embedded tissues. Int Arch Allergy Immunol 2004;134(3):199-205.

26 Glajcar A, Szpor J, Pacek A, Tyrak KE, Chan F, Streb J, et al. The relationship between breast cancer molecular subtypes and mast cell populations in tumor microenvironment. Virchows Arch 2017 Mar 18. [Epub ahead of print]

Tables

Table 1

Characteristics of the 51 patients with Hymenoptera venom allergy and malignancy

N patients total (with venom immunotherapy)	51 (42)
Mean age patients total (with venom immunotherapy) / range	58 (59) / 17-86 years
Male / female (N)	26 / 25
Allergic to (N)	
- 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 (N)	15 (29 %)
Baseline Serum Tryptase (N*)	
- < 11,4 µg/l	40
- ≥11,4 µg/l	9

N = number of patients

* not available in 2 patients

Table 2

Type of malignancy in 42 patients with Hymenoptera venom immunotherapy

Tumor Type	N of malignancy before VIT	N of malignancy during VIT	N of malignancy after VIT
breast cancer (*including one patient with two-sided breast cancer)	6	5*	0
prostate carcinoma (*including one patient with previously diagnosed colon carcinoma+)	4	5*	0
Seminoma	3	1	0
melanoma of skin	4	1	0
kidney carcinoma (*including one patient with previously diagnosed seminoma+)	2*	0	0
bladder carcinoma	0	1	1
ovarial carcinoma (*including one patient with previously diagnosed breast cancer+)	1	1*	0
thyroid carcinoma	0	1	0
M.Hodgkin	1	0	0
Non-Hodgkin-Lymphoma	0	1	0
spinalioma	1	0	0
angiosarcoma	1	0	0
cervix carcinoma	1	0	0
teratocarcinoma	1	0	0
Total	**25**	**16**	**1**

MA = malignancy

VIT = venom immunotherapy

NA = not available

+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 (N)	Definite Stop (8)	Temporary suspended (6)	Continued without interruption (2)
Malignancy (N)	**Breast cancer (3)** - stopped due to MA after 5 years of VIT, no indication for continuation (two patients) - stopped due to MA after 1.5 months of VIT, no continuation due to patients preference (one patient) **Two-sided breast cancer (1)** - stopped due to second MA 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 MA and no specific treatment planned - VIT continued during radiation of the prostate due to suspected systemic mastocytosis
	Prostate cancer (1) - stopped due to unexplained polyneuropathy after 5 years of VIT	**Prostate cancer (2)** - paused during prostatectomy, later resumed (both patients)	
	Non-Hodgkin lymphoma (1) - stopped due to MA after 3 years of VIT	**Bladder cancer (1)** - paused during surgery, later resumed	
	Thyroid cancer (1) - stopped due to MA after 5 years of VIT, no continuation due to patients preference though given indication for continuation because of elevated bT	**Seminoma (1)** - paused during orchiectomy and adjuvant chemotherapy, later resumed and paused again two years later due to MA relapse, continuation after axillar lymph node dissection and chemotherapy	
	Ovarial cancer with peritoneal carcinomatosis (1) - stopped due to MA after 3 years of VIT, no continuation due to metastatic MA	**Melanoma (1)** - paused during MA excision, later resumed	

MA = malignancy

bT = baseline serum Tryptase

VIT = venom immunotherapy

Table 4

Reported side effects of venom immunotherapy in patients with malignancy before respectively during venom immunotherapy

	Side effect	Allergy to insect venom	Allergy grade	Baseline serum tryptase (µg/l)	Tumor Type
known cancer before VIT	SR (feeling of faintness and dyspnoe with decreased peak-flow at maintenance dose)	BV	3	2.90	angiosarcoma
	Unspecific (tiredness at maintenance dose)	BV	4	3.42	melanoma
	Unspecific (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 retarded therapy solution)	BV/ VV	4 / 4	19.20	thyroid carcinoma
	SR (twice dizziness and confusion with collapse 30 minutes after maintenance dose, no objective circulatory symptoms; no reaction after change to a retarded therapy solution)	BV/ VV	4 / 4	33.70	prostate carcinoma; colon carcinoma
	Unspecific (Lymph node swelling, temporal dysesthesia)	BV	3	3.29	Non-Hodgkin-lymphoma
	unspecific (feeling of dizziness without blood pressure involvement during up-dosing, maintenance dose well tolerated)	VV	3-4	2.51	breast cancer
	unspecific (polyneuropathy, unexplained)	hornet	3	3.28	prostate carcinoma
	unspecific (tingling sensation in palms at maintenance dose)	VV	4	5.89	prostate carcinoma

Allergy grade according to H.L. Mueller

VV = Vespula venom

BV = bee venom

SR = systemic allergic reaction

LLR = large local reaction

doi: 10.18176/jiaci.0184