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Cancer: Still a contraindication for allergen immunotherapy? Specific immunotherapy and cancer

David El-Qutob[a]*, Antonio Letrán[b], Victor Matheu[c] and Enrique Fernandez-Caldas[d,e]

ABSTRACT

Allergen immunotherapy (AIT) is currently more than 100 years old. It is considered an evidence-based efficacious immune therapeutical treatment. It is at this time the only causative treatment for allergic respiratory and venom allergic diseases. Though clinical indications for AIT are well established, clinical contraindications to AIT differ among several guidelines. Regarding malignant neoplasia, traditionally, it has been considered as a relative or absolute contraindication with the concern that AIT might stimulate tumour growth even though pathogenic impact of AIT in cancer is not well understood. Furthermore, this contraindication is often based on observational case series, or case reports, with little real evidence-based data. Therefore, should cancer still be contemplated as an absolute contraindication for AIT?

Keywords: Cancer, Neoplasm, Specific immunotherapy, Allergen, Contraindication

INTRODUCTION

Allergen immunotherapy (AIT) is an evidence-based efficacious and causative treatment option for respiratory and venom allergy.[1] It is considered a disease-modifying intervention in IgE-mediated allergic disease with both a therapeutic, even beyond ending of AIT, and potential preventive effect (short- and long-term prevention) by immunologic changes that result in immune modification.[2] Clinical indications for AIT are widely accepted in IgE mediated diseases in which sensitization is relevant for the symptoms, and the symptoms are of sufficient severity and duration. The availability of standardized high quality allergen extracts is also warranted.[3] Several controversies exist concerning contraindications differing between various guidelines.[4] A clinical contraindication to AIT is a condition where the allergen must not be administered to the patient due to safety reasons. In this direction autoimmune disorders, beta-blockers or angiotensin-converting-enzyme inhibitors, malignant neoplasia, or children below 5 years of age, have been classically considered "absolute" or "relative" contraindications to start/continue AIT.[5] However, most of the studies regarding these issues are observational case series, or case reports, and only little evidence-based data concerning contraindications to AIT exists.[6]

In this paper, we discuss which should be the better clinical decision in patients with malignant diseases and a hypothetical AIT prescription.

CANCER AS A CONTRAINDICATION IN AIT

AIT has been considered a contraindication in patients with concomitant malignancy in some

[a]Allergy Unit, University Hospital of La Plana, Vila-real, Spain
*Corresponding author: elqutob@comv.es
Full list of author information is available at the end of the article

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position papers,[1,6] and usually as a relative contraindication.

However, some associations and guidelines consider this condition an absolute contraindication for AIT.[7–9] Although the pathogenic impact of AIT in cancer is not well understood, concerns that AIT might stimulate tumour growth have been raised. In fact, the possible risk of disease progression due to AIT in patients with malignancy is speculative, and this contraindication has been established for safety and ethical reasons, since immunological effect of AIT in cancer cannot be established. However, AIT is considered safe in absence of a significant prevalence of new cases of neoplastic diseases.[10] Furthermore, venom immunotherapy (VIT) is commonly used in cancer patients in remission.[11] In 2011, a case series study where patients suffered, or had suffered, from stage 1 cancer (4 melanomas, 1 lung cancer, 1 breast cancer) and concomitant IgE-mediated allergy who received AIT safely was reported.[12] Aeberhard et al studied 42 subjects with severe Hymenoptera venom allergy and cancer, previously diagnosed (25 patients of malignancy, 16 diagnosed with malignancy during VIT, and 1 patient was diagnosed with cancer after end of VIT).[13] The most frequent type of tumour was breast cancer in females (60%) and prostate cancer in males (39%). In this study, 7% of individuals presented a systemic allergic reaction during VIT, indicating that the risk for systemic allergic reactions to a sting of the relevant insect is comparable to that reported in a population without neoplasms.[14] VIT was discontinued in 9 subjects (new diagnosis of cancer in 7 patients, recurrence of cancer in 1, and progressive polyneuropathy in 1). The authors concluded that adverse effects of VIT in patients with Hymenoptera venom allergy and in cancer remission are similar to those observed in venom allergy subjects without cancer. These reports may have important limitations which may be present in all case series studies, such as uncontrolled studies and selection bias.

IMMUNOLOGIC INTERACTION BETWEEN CANCER AND AIT

Although robust evidence is missing, acting on Th2 immunity might alter malignancy. It has been shown that low dose (1 and 3 μg/mL) of recombinant Der p 2 could enhance *in vitro* cell motility and invasiveness of non-small cell lung cancer cells, promoting metastatic ability of carcinoma cells.[15]

Elevated IgG4 levels in colorectal cancer actively collaborate with macrophages to model an immunosuppressive microenvironment; this may also impair the functions of the anticancer effector cells.[16] The shift of serum IgG4/IgE indicates a role for high IgG4 in disease progression and could have a poor prognostic outcome in metastatic disease, as it could enhance tolerance induction.[16] IgG4 could have a protective role similar to a blocking antibody as well as the stimulation of the secretion of CCL1 and IL-10 to support a regulatory cell recruitment and help to modulate a tolerogenic environment.[17–19] This could be achieved due to the chronic antigenic stimulus that directs the change of the B cells to IgG4 as well as the subsequent change of state of the macrophage subtype M2a towards the M2b that would secrete CCL1 and IL-10.

In parallel, local increases in natural regulatory T cells (nTreg cells) which express the transcription factor forkhead box P3 (FOXP3) and IL-2 receptor (CD25),[20] has been associated with subcutaneous immunotherapy, because patients after immunotherapy have increased numbers of $CD4^{+}CD25^{+}$ cells.[21–23] It has been shown that $FoxP3{+}CD25^{+}$ regulatory T-cell infiltration is high in persistent and precancerous lesions, and longitudinal data show improved outcomes with lower regulatory T-cell levels,[24] which could exert a suppressive capability.[25] Some evidence also shows that mast cells may be important mediators of Treg-dependent tolerance of allograft[26] Several tumor models have documented the accumulation of mast cells, as well as Treg cells at the tumor location.

Allergen specific immunotherapy has been identified as a clear promoter of local inducible regulatory T (iTreg) cell responses in the nasal mucosa. iTreg cells produce regulatory cytokines, such as interleukin (IL)-10, IL-35, and tumoral growth factor beta (TGF-beta).[27] Tolerance induction could be enhanced by increases in serum IgG4 levels. These increases must be related to elevated IL-10 production and suppression of the late response.[16] Patients' sera after

allergen immunotherapy have IgG-associated IgE-blocking activity for both basophil activation (increased allergen stimulated basophil CD63) and IgE-FAB inhibition that paralleled increases in IgG4 levels.[21] High-dose allergen exposure, including allergen specific immunotherapy, restores dendritic cell activity, which produces IL-12, IL-27, and IL-10 and promotes immune deviation from a Th2 to Th1 response and induction of Treg and Breg cells that produce IgA, IgG, and IgG4 blocking antibodies.

CONCLUSIONS

Currently, an active cancer will be a relative contraindication for the use of SIT, and the use of AIT in patients with past cancer, or in remission, would not be contraindicated. Like some authors suggest, low grade tumours, or in remission, should be removed from the guidelines as contraindication for AIT because, otherwise, many prescriptors of AIT would not choose this treatment as an option to subjects concomitantly suffering from cancer and an allergy susceptible of receiving AIT. Establishing contraindications in the guidelines should not be exclusively based in the opinion and consensus of experts in the field.[4,28] In fact, the recommendation of some guidelines of considering malignant neoplasms an absolute contraindication could be contradictory with the suggestion of considering VIT like a highly advised option in high-risk venom-allergic patients.[6]

Abbreviations

AIT = allergen immunotherapy, VIT = venom immunotherapy, FOXP3 = factor forkhead box P3, TGF = tumoral growth factor.

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Author details

[a]Allergy Unit, University Hospital of La Plana, Vila-real, Spain. [b]Allergy Unit, Hospital HLA Jerez Puerta del Sur, Jerez de la Frontera, Cádiz, Spain. [c]Service of Allergology, University Hospital of Canarias, Spain. [d]Inmunotek SL, Alcalá de Henares, Madrid, Spain. [e]University of South Florida College of Medicine, Tampa, Florida, USA.

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