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Suppressing Effects of Sunitinib on Allergic Rhinitis: Previously Undefined Side Effects With Therapeutic Potential

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We observed 2 female patients (51 and 59 years old, respectively) who had had serious pollen allergy (hay fever) since childhood, expressed by rhinoconjunctivitis and asthma. For many years, these conditions were treated with antihistamines, β_2 agonists, and pulmonary corticosteroids. In 2007, both patients were diagnosed with metastatic renal cell cancer for which they had been treated with sunitinib monotherapy since October and November 2007, respectively. Since the start of anticancer treatment, allergic rhinitis–related comedication was not allowed, to prevent unwanted drug-drug interactions. To their surprise and despite this prohibition, during the pollen season of 2008, both patients experienced no allergic rhinitis complaints at all. In this study, we tried to elucidate the underlying mechanism for this remarkable observation.

Sunitinib malate is an anticancer drug currently used in the palliative treatment of metastatic renal cell carcinoma and gastrointestinal stromal cell

tumors.^{1,2} Treatment regimens exist of once-daily dosing of 50 mg for 4 consecutive weeks, followed by 2 weeks of rest.³ Sunitinib acts as a multitargeted tyrosine kinase inhibitor, known to inhibit the intrinsic tyrosine kinase activity of several specific proteins, including KIT, vascular endothelial growth factor receptor (VEGF-R), and the platelet-derived growth factor receptor (PDGF-R),⁴ resulting in reduced tumor vessel growth or carcinogenesis. Sunitinib-induced toxicities may be serious and quite diverse. They include hypertension, diarrhea, hand-foot syndrome, mucositis, vomiting, leukopenia, cardiotoxicity, and hypothyroidism.⁵

Of all these molecular targets inhibited by sunitinib, KIT is most likely to be involved in the pathogenesis of allergic rhinitis. KIT is encoded by the *c-kit* gene. It is a trans-membrane protein, expressed on a variety of cells, including mast cells, hematopoietic progenitor cells, melanocytes, germ cells, and gastrointestinal pacemaker cells. Heterozygous loss of function of KIT in mice results in macrocytic anemia, hair depigmentation, sterility, and reduced numbers of gastrointestinal pacemaker cells.⁶ Moreover, in mast cells, KIT acts as a receptor for the stem cell factor. Binding of stem cell factor on KIT is essential for the survival and differentiation, chemotaxis, and functional activity of mast cells.⁷ Mast cells on their part play a vital role in the symptomatology of allergic rhinitis.

Allergic reactions usually occur when an individual who has been sensitized to an allergen (eg, grass pollen) produces allergen-specific immunoglobulin isotype E antibodies (IgE) and subsequently encounters this particular allergen again.

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The allergen will then trigger the activation of IgE-binding mast cells in the exposed tissue. As a result, these mast cells degranulate, releasing a variety of mediators causing clinical symptoms. Therefore, inhibition of mast cell activity could reduce allergic symptoms.

METHODS

During all outpatient visits (usually at the beginning and at the end of a 4-weekly treatment cycle), we measured total serum IgE and specific IgE antibodies in our study patients. The resting period was occasionally prolonged with a couple of days due to common sunitinib-related toxicity. These serological tests are used routinely in the diagnosis and management of allergic disease. Skin tests and nasal challenge tests⁸ with birch and/or grass pollen extract were used to characterize the allergic status of the patients. Myelosuppression as a mechanism of impaired immune response in our study patients was also investigated by measuring total white blood cell counts before start of therapy and during all consecutive courses of sunitinib treatment.

Nasal provocation tests were performed at the beginning and end of 1 treatment cycle to evaluate the nasal response to birch pollen (patient 1) or grass pollen (patient 2). Nasal provocation tests were performed according to standard protocol with 3 consecutive doses of 100, 1000, and 10 000 biological units per milliliter (BU/mL) of the allergen. Symptoms of rhinoconjunctivitis were scored after each dose according to Lebel et al⁸ (maximum total score 33).

To assess the effects of sunitinib on the mast cell population, we measured serum tryptase levels. Total serum tryptase levels are used as indicators of mast cell number and activation.⁹

As sunitinib treatment was already given for several months to our 2 study patients, we could not measure tryptase concentrations from the start of therapy. As a result, we cannot exclude that tryptase levels in these patients were already extremely low prior to the start of anticancer treatment. Therefore, in a separate cohort of patients with renal cell carcinoma, we measured tryptase levels before the start of their first sunitinib courses and during the successive courses. The nonparametric Friedman test was used to assess fluctuations in this cohort. The Wilcoxon signed rank test was used for comparison between 2 time points (SPSS 15.0 for Windows; SPSS, Inc, an IBM Company, Chicago, Illinois).

RESULTS

Total serum IgE levels were moderately elevated but showed no significant changes during the 4 weeks of treatment with sunitinib compared to the values measured straight after the 2-week resting period (Table I). Specific serum IgE antibodies (Table I) and skin tests (data not shown) fluctuated but showed no significant alterations over the observed study period. White blood cell counts in our study patients were within the normal range before start of sunitinib treatment and during all the following treatment cycles. Table I depicts white blood cell counts during 2 treatment cycles.

Surprisingly, the 4 nasal provocation tests (2 per patient) were negative at 3 occasions and marginally positive (8 of 33 points maximally) at 1 occasion.

Also of interest: During the entire observation period of 3 months, total serum tryptase levels were extremely low (below threshold values) in both study patients. As shown in Table I, tryptase levels in the separate cohort of control patients with renal cell carcinoma changed significantly from normal pretreatment values to levels below the threshold, in most cases within the observation period of 2 treatment cycles ($\chi^2 = 20.24$; $P < .0001$). A drop was already seen after 1 treatment cycle ($P = .008$). Although these patients were not known for allergic rhinitis, we have no reason to suppose another mechanistic effect on mast cells in the control patients.

DISCUSSION

Up until now, the clinical benefit of mast cell inhibition through inhibition of KIT autophosphorylation has been investigated in patients with systemic mastocytosis, where it showed little effect.^{10,11} However, this lack of effect is caused by a specific mutation in the catalytic domain, which is typical for the majority of neoplastic mast cells in human mastocytosis, making these cells refractory to tyrosine kinase inhibitors. Cell growth of human mast cells carrying wild-type KIT is potently inhibited by inhibition of KIT.¹¹ Also, preclinical data in a murine model with allergen-induced airway inflammation showed that both induced airway hyperresponsiveness and chronic airway inflammation were significantly inhibited when these mice were treated with sunitinib.¹² These sunitinib-treated mice showed a lower expression of KIT in the airways (measured in bronchoalveolar lavage fluid) compared to non-treated mice. The clinical benefit of KIT inhibition

Table I Test Results in Study Patients and Control Patients

Study Patient 1	Cycles Studied				
	Start Cycle 9	End Cycle 9	Start Cycle 10	End Cycle 10	Start Cycle 11
Tryptase (<11.4 µg/L ^a)	<1.0 ^b	<1.0 ^b	<1.0 ^b	<1.0 ^b	<1.0 ^b
Total IgE (<100 µ/mL ^a)	258	307	139	306	341
Birch pollen IgE (<0.35 µ/mL ^a)	80.5	>100 ^c	87.0	>100 ^c	>100 ^c
Grass pollen IgE (<0.35 µ/mL ^a)	14.5	29.0	28.5	33.7	32.1
Nasal provocation total score ^d	NA	8	0	NA	NA
WBC (4.1-10.9 × 10 ⁹ /L)	5.4	8.4	4.8	5.8	3.9
Study Patient 2	Start Cycle 9	End Cycle 9	Start Cycle 10	End Cycle 10	Start Cycle 11
Tryptase (<11.4 µg/L ^a)	<1.0 ^b	<1.0 ^b	<1.0 ^b	<1.0 ^b	<1.0 ^b
Total IgE (<100 µ/mL ^a)	200	329	288	398	211
Birch pollen IgE (<0.35 µ/mL ^a)	21.0	50.8	41.3	52.1	28.7
Grass pollen IgE (<0.35 µ/mL ^a)	11.7	21.5	17.9	21.9	12.9
Nasal provocation total score ^d	NA	5	2	NA	NA
WBC (4.1-10.9 × 10 ⁹ /L)	4.3	NA	7.6	5.0	5.2
Tryptase in Control Patients (<11.4 µg/L ^a)	Start Cycle 1	End Cycle 1	Start Cycle 2	End Cycle 2	Start Cycle 3
Patient 1	4.4	<1.0 ^b	1.2	<1.0 ^b	<1.0 ^b
Patient 2	9.5	2.0	2.4	<1.0 ^b	NA ^e
Patient 3	3.6	<1.0 ^b	1.4	<1.0 ^b	NA ^e
Patient 4	7.5	<1.0 ^b	NA ^e	NA ^e	NA ^e
Patient 5	5.1	2.1	5.7	1.1	6.6
Patient 6	4.9	<1.0 ^b	<1.0 ^b	<1.0 ^b	2.7
Patient 7	2.9	<1.0 ^b	2.4	<1.0 ^b	1.9
Patient 8	6.4	<1.0 ^b	4.6	<1.0 ^b	NA
Patient 9	4.3	1.9	5.3	1.9	4.4

IgE, immunoglobulin type E; NA, not available; WBC, white blood cell count.

^aNormal values in microgram or units per (milli)liter.

^bBelow threshold values.

^cAbove detectable values.

^dAccording to standard protocol (total score may range between 0 and 33).

^eNot available due to cessation treatment because of worsened clinical performance.

in the treatment of asthma was confirmed in 33 severe corticoid-dependent asthmatic patients receiving masitinib, a KIT, and a PDGF-R tyrosine kinase inhibitor.¹³ These patients showed significant symptomatic relief as compared to 11 placebo-treated patients. In this report, the resolution of allergic symptoms in 2 cancer patients is correlated with decreased mast cell population and activity, most probably through inhibition of KIT. This mechanism of reduced mast cell population and activity is confirmed in our sunitinib-treated control patients.

However, as sunitinib is a myelotoxic compound,^{5,14} sunitinib-induced leukopenia may account for an impaired immune response in both our study patients, next to the above-mentioned mechanism. This is relevant because lymphocytic cell lines mediate the IgE response in allergic rhinitis. However, our study patients had normal white blood

cell counts during the entire observation period. Moreover, recent data show that sunitinib may act as an immunomodulator that enhances T-lymphocytic function.^{15,16} These results plead against sunitinib-induced myelosuppression as a possible mechanism of reduced symptoms of allergic rhinitis in our patients.

Although the costs and unfavourable safety profile do not justify treatment of allergic disorders with sunitinib, further elucidation of this sunitinib-related mechanism on allergic rhinitis may help researchers develop more effective medication for allergic disorders. For example, locally produced KIT ligand in the airways is responsible for the recruitment and adhesion of mast cells to the airway epithelium.^{17,18} Therefore, topical application of KIT inhibitors through inhalation or nasal spraying may be an efficient and safe treatment of local inflammation in

allergic disorders. Furthermore, little is known about the threshold dose of sunitinib, needed to effectively inhibit mast cell function. If lower dosages than those used in cancer treatment are sufficient to potently inhibit mast cell numbers, this could also improve the safety profile of sunitinib treatment in allergic disorders. In conclusion, along the known pathways responsible for allergic reactions, this observation suggests that sunitinib effectively inhibits mast cell proliferation and activity, resulting in a total absence of allergic rhinitis in our patients. This sunitinib-related mechanism may ultimately lead to the development of new therapeutic pathways in the treatment of (corticosteroid-resistant) allergic disorders.

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