

Case Reports

Successful Desensitization Protocol for Hypersensitivity Reaction Caused by Sunitinib in a Patient with a Gastrointestinal Stromal Tumor

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Sunitinib is an orally bioavailable small molecule that inhibits multiple receptor tyrosine kinases. Generalized hypersensitivity reactions (HSR) to sunitinib have not been described. A patient with a gastrointestinal stromal tumor (GIST) who developed a type I HSR to sunitinib and who was successfully treated by drug desensitization is reported. A 51-year-old man with metastatic GIST developed a type I HSR during sunitinib treatment. Four days after treatment initiation, the patient presented to the Emergency Department with acute generalized urticaria and facial and throat swelling. Sunitinib was restarted 1 week later, using a desensitization protocol in which 10 escalating reduced doses, beginning with 0.05 mg, were given following pre-medication with prednisone and promethazine. This protocol was well tolerated and allowed us to continue the treatment, obtaining partial remission of the liver metastasis that was followed by complete resection. Sunitinib was temporarily discontinued before the operation and renewed after surgery by repeating the same desensitization procedure. At the time of this report, sunitinib has been continued for 1 year without evidence of recurrent disease. Oral desensitization appears to be an option for patients with hypersensitivity type I to sunitinib and may permit its safe administration to patients who experience HSR to this life-prolonging medication.

Key words: sunitinib – GIST – hypersensitivity reaction – desensitization

INTRODUCTION

Sunitinib (Sutent[®], Pfizer, New York, NY, USA) is an orally bioavailable small molecule that inhibits multiple receptor tyrosine kinases, including vascular endothelial growth factor receptors (VEGFR1, 2 and 3), platelet-derived growth factor receptors (PDGFR α and β), stem cell factor receptor (KIT), Fms-like tyrosine kinase-3 (FLT3), colony-stimulating factor receptor type 1 (CSF-1R) and the glial cell-line-derived neutrophilic factor receptor (RET) (1). Sunitinib was approved as monotherapy for treatment of patients with advanced gastrointestinal stromal tumors (GISTs) with disease progression or in patients with intolerance to

imatinib mesylate, based on a Phase III study proving advantage in survival compared with placebo (2). It was also approved as first-line treatment of metastatic renal cell carcinoma (RCC), after showing longer progression-free survival and better response rates than interferon α in these patients (3).

To the best of our knowledge, generalized hypersensitivity reactions (HSR) to sunitinib have not been described, although case reports of allergic interstitial nephritis, possibly related to the drug in patients with RCC, have been published (4). Continuing sunitinib therapy despite HSR is especially important in GIST, where sunitinib remains the

only approved second-line treatment. Desensitization protocols to overcome HSR by gradual re-introduction of small amounts of the offending drug up to full therapeutic doses are available to many anti-cancer agents, including taxanes, platinum analogs, doxorubicin and monoclonal antibodies (5) but, to the best of our knowledge, have not been reported for sunitinib.

We now describe a patient with GIST who developed a type I HSR to sunitinib and who was successfully treated by drug desensitization which allowed safe prolonged continuation of this drug.

CASE REPORT

A 51-year-old man with metastatic GIST developed a type I HSR during sunitinib treatment in April 2008. Eight years earlier, he underwent partial resection of the jejunum due to GIST of the small intestine. Two years later, he was re-operated due to recurrent GIST in the tumor bed. Treatment with imatinib 400 mg/day was initiated 1 year later for persistent abdominal pain without evidence of recurrent tumor on imaging studies. Three years later, he was again operated on due to a recurrent pelvic mass. Two months after the last surgery, treatment with imatinib was stopped due to a cerebral vascular event suspected to be induced by imatinib. Nine months later, he was operated again due to recurrent GIST in the small intestine. Following this operation, imatinib was re-initiated at a dose of 800 mg/day and stopped after 6 months due to the appearance of a single liver metastasis.

Treatment with sunitinib 50 mg daily was started and planned for 4 weeks followed by a 2-week interruption. Four days after treatment initiation, the patient presented to our Emergency Department with acute generalized urticaria and facial and throat swelling. His blood tests were unremarkable—normal complete blood count (WBC 9800, 60% neutrophils and 34% lymphocytes)—and renal and liver functions were normal. He did not have an atopic background or other known hypersensitivity. Chronic medications included metformin, glibenclamide, omeprazole and fentanyl patch. Other possibilities for HSR were ruled out, and no other new drugs or cosmetic products were started.

The symptoms resolved following dexamethasone 20 mg IV and diphenhydramine 25 mg orally every 6 h for 24 h, and sunitinib was stopped. A desensitization protocol was designed, using 10 escalating reduced doses of sunitinib, ranging from 0.05 to 25 mg, prepared by the Pharmacy Department as detailed in Table 1. The two highest doses, 25 and 16 mg, were prepared by weighing the portion of powder from the contents of a 50 mg sunitinib capsule. For the other doses, suspensions were prepared by dispensing the contents of a 50 mg capsule in syrup simplex as a vehicle to a final concentration of 1 and 0.2 mg/cc from which proper volumes were used (Table 1).

Table 1. Sunitinib doses used in the desensitization protocol and the method of their preparation

Dose no. ^a	Sunitinib dose (mg)	Concentration (mg/cc) ^a	Volume (cc)
1	0.05	0.2	0.25
2	0.1	0.2	0.5
3	0.2	0.2	1
4	0.5	0.2	2.5
5	1	1	1
6	2	1	2
7	4	1	4
8	8	1	8
9	16	Not relevant ^b	
10	25	Not relevant ^b	

^aDoses 1–8 were prepared from suspensions by dispensing the contents of a 50 mg capsule in syrup simplex as a vehicle, to a final concentrations of 0.2 and 1 mg/cc; the proper volume of each dose was dispensed by suitable oral dispenser syringes.

^bDoses 9 and 10 were prepared by weighing the proper portion of powder from the contents of a 50 mg sunitinib capsule, and two empty gelatin capsules size No. 3 were filled with the powder to produce suitable dosage forms.

One week after the HSR event and after informed consent was given, the patient was hospitalized for the desensitization procedure. Complete blood count and routine serum chemistry studies including all liver and kidney function were normal.

One hour before treatment initiation, prednisone 20 mg and promethazine 25 mg were given orally. The 10 escalating doses were given hourly under close observation, including continuous cardiac and blood pressure monitoring. Physical examination for signs of adverse reactions was taken before each increasing dosage. The patient was discharged from hospital 24 h after the last dose. Treatment with this protocol was well tolerated except for a mild pruritic rash that developed 6 h after the last dose and resolved on oral prednisone 40 mg and promethazine 25 mg.

Due to the mild HSR that developed after the last dose, sunitinib was continued with reduced daily doses on days 2–4 (12.5, 25 and 37.5 mg, respectively) that were prepared by weighing the proper portion of powder from the contents of a 50 mg sunitinib capsule. In addition, prednisone and promethazine pre-medications for days 2–12 were given. Full daily doses (50 mg) were given from day 5. Sunitinib was then continued without any signs or symptoms of HSR.

Three months later, an abdominal computed tomography showed partial remission of the liver metastasis and right liver lobe lobectomy was performed. Sunitinib was stopped before the operation and restarted 2 weeks later, repeating the same desensitization protocol before giving the full daily dose. No HSR were observed and, at the time of this report, the patient has been on sunitinib treatment for 1 year since the last operation without evidence of recurrent disease.

DISCUSSION

IgE-dependent drug reactions may present with dermatologic, gastrointestinal, respiratory and/or cardiovascular manifestations. Our patient presented with a typical IgE-mediated reaction, with an urticarial eruption, gradually worsening and the start of laryngeal edema that appeared only on the 5th day of treatment, and less than an hour after the last sunitinib dose was administered. Frequently occurring side effects reported for sunitinib are mainly constitutional, i.e. fatigue and asthenia, and gastrointestinal (diarrhea, nausea, vomiting and mucositis). Other common adverse events include hypertension, hand-foot syndrome and hematological side effects. Cardiac toxicity and thyroid dysfunction have also been reported (3).

In data collected from clinical trials and from Pfizer Medical Information, there were several dermatological reactions, including hand-foot skin reaction, skin discoloration, dry skin, dermatitis, rash, hair color changes and alopecia (6). The generalized skin rashes (erythema, maculopapular or seborrheic dermatitis) were mainly Grade 1 or 2, tended to decrease over time, and rarely required dose reduction (7). The package insert states that administration of sunitinib is contraindicated in patients with known hypersensitivity to sunitinib or to any other component in the product.

Although dermatological reactions occur frequently with sunitinib, the occurrence of urticarial eruptions and other IgE-mediated drug reactions is not mentioned in the product information, nor reported in the literature.

The diagnosis of hypersensitivity reactions is made by clinical presentation. Unfortunately, other tests that may be performed are not standardized and have low sensitivity and specificity. Skin testing and/or RAST may be valuable in the evaluation of IgE-mediated chemotherapy reactions. However, skin testing is somewhat limited because of the lack of drug metabolites available for testing, unclear mechanisms responsible for reactions to certain drugs and possible toxicity of testing reagents (8). The drug-induced lymphocyte stimulation test has a very low sensitivity and usually the results do not correlate with the clinical presentation (9).

Treatment of advanced RCC may include several new drugs, such as sorafenib, temsirolimus and bevacizumab administered with interferon α , that can replace sunitinib in a hypersensitivity reaction situation. In imatinib-resistant GIST, the only approved treatment is sunitinib, allowing prolonged progression-free survival from 1.5 month to over 6 months (2). Metastatic GIST is a fatal disease when untreated, thus making the alternative of desensitization a reasonable approach. Desensitization by administration of

small doses of the drug with a gradual increase in doses has been shown to be effective for overcoming hypersensitivity of many medications, including anti-cancer agents. This approach was established for patients with trimethoprim-sulfamethoxazole sensitivity by Hughes et al. (10) 20 years ago. The same approach was reported as successfully used in patients with hypersensitivity to imatinib (11). This strategy was the base for using desensitization in the current case.

CONCLUSION

Oral desensitization appears to be an option for patients with hypersensitivity type I to sunitinib. This approach may permit clinicians to safely administer sunitinib to patients who experience HSR to this life-prolonging medication.

Conflict of interest statement

None declared.

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