Metastatic paraganglioma and treatment with sunitinib: a case report

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ABSTRACT

Sunitinib malate is a small kinase inhibitor with activity against a number of tyrosine kinase receptors. We treated a young man suffering from a metastatic paraganglioma with sunitinib. In this report we discuss a number of related questions including the correct dosage, schedules and timing of administration of the molecule, the main side effects and their treatment, and evaluation of the treatment response by CT scan.

Treatment with sunitinib started at a dose of 50 mg daily for 4 weeks followed by 2 weeks off (4/2). Because of the side effects, the dose was reduced to 25 mg daily (4/2) and then to 25 mg daily (2/1). This resulted in a significant decrease in the plasma chromogranin A value and the radiological size of the metastases, as well as important clinical improvement. After 6 cycles the treatment was stopped because of a rise in plasma NSE values and disease progression. Sunitinib malate can induce marked toxicity, in which case the daily dose should be reduced and a different schedule of administration adopted. Response evaluation by CT scan should take into account tumor necrosis caused by sunitinib. Sunitinib malate is a interesting molecule for targeted therapy also for advanced neuroendocrine tumors. There has been evidence of significant clinical improvement, as in the case reported here. Free full text available at www.tumorionline.it

Introduction

Sunitinib malate (Sutent, Pfizer) is a small kinase inhibitor with activity against a number of tyrosine kinase receptors and FMS-like tyrosine kinase-3[1-4]. The antitumor activity of sunitinib in patients with renal cell carcinoma and gastrointestinal stromal tumors (GISTs) is well known[5]. A multicenter phase II study was performed to assess the safety and efficacy of sunitinib in patients with advanced neuroendocrine tumors[6]. One hundred and seven patients with advanced neuroendocrine tumors (66 pancreatic endocrine tumors and 41 carcinoids) were treated with sunitinib, and the overall stable disease (SD) rate was 68% in patients with pancreatic endocrine tumors and and 83% in patients with carcinoids. The 1-year survival rates were 81.1% and 83.4%, respectively.

On the basis of these results and to verify the antitumor effect of the molecule, we have treated with sunitinib off-label a young man with advanced paraganglioma considered in the past for every kind of therapy but with scarce responses, and a very poor quality of life.

Patient and methods

Our patient, a man who was 37 years old at the time of writing, at age 13 underwent surgery for the removal of a large left retroperitoneal mass. The tumor, measuring 17 × 14 × 9 cm and weighing 1300 g, was histologically diagnosed as an extra-adrenal

paraganglioma. Three years later bone metastases were detected at L2, L3, and L4, which were treated with chemotherapy [doxorubicin, cyclophosphamide, vincristine and dacarbazine (modified CYVADIC)] for 6 cycles, followed by radiotherapy for a total dose of 46 Gy. This resulted in radiologically complete disease control. Nine years later new metastatic bone lesions appeared (L1, D3, D4, cranial and sacral bones) along with recurrence of the lesions in L2, L3, and L4. The patient was treated with radiotherapy (total dose 46 Gy) followed by 5 cycles of radiometabolic therapy with ^{131}I-MIBG, resulting in stable disease. Seven years later the patient again underwent surgery consisting of L1-L2 lumbar laminectomy with stabilization of D9-S1, and resection of the right humerus with infibulation and cementation. Bone marrow biopsy revealed extra-adrenal paraganglioma positive for synaptophysin, chromogranin A and NSE, and negative for S100 protein, cytokeratin, CD 31, CD 34 and EMA.

In December 2006 the patient came to our observation. He was paraplegic and under prolonged therapy with cyclophosphamide 50 mg daily plus oral vinorelbine 100 mg every 14 days. The last documented plasma value of chromogranin A was 1998 ng/mL (normal range, 19.4-98.1 ng/mL). The disease was restaged. Chromogranin A was now 8476 ng/mL and CT scan showed a large, solid, vascularized metastatic lesion of the occipital skull with osteolysis. The mass measured 5.5 × 7.5 cm and infiltrated the subcutaneous soft tissue. There were other solid vascularized lesions with osteolysis of D3, D4, D5, L1, and L2, and involvement of the sacral and iliac bones with destruction of the left acetabulum. OctreoScan showed high receptor density in the lesions of the skull, dorsal and lumbar spine, as well as the left sacral region (Figure 1). Histological revision confirmed the histological type.

After a short treatment based on octreotide LAR (30 mg i.m. every 15 days) in association with thalidomide (100 mg daily), which was stopped almost immediately because of neurotoxic complications, in April 2008 the patient started treatment with sunitinib at a dose of 50 mg daily for 4 weeks followed by a 2-week off period (4/2). At the start of therapy, serum VEGF was 261.13 pg/mL (normal range, 13-182 pg/mL, standard deviation 45 pg/mL), chromogranin A 2012 ng/mL, and NSE 13 ng/mL (normal range, 0-12 ng/mL). Treatment was interrupted after 19 days because of a serious episode of hematuria with fever and abdominal cutaneous herpes. The chromogranin A value was 1551 ng/mL. The second cycle started in July 2008. Because of the previous signs of toxicity, we decided to change the sunitinib dose from 50 to 25 mg daily, 4/2. This schedule was continued during the third cycle, which, however, was interrupted after 3 weeks because of severe oral candidosis along with depressive syndrome [TSH 18.8 μIU/mL (0.4-4.0), NSE 8.9 ng/mL, chromogranin A 1620 ng/mL]. Thyroid ultrasonography was normal. CT scan showed a slight reduction of the metastatic osteolytic lesion of the skull, which was now 7 × 8 cm. The expansive lesion of L3 was unchanged but showed a favorable colliquative evolution. Regression of the paravertebral lesions of D6 and D12, the left iliac bone, left acetabulum (7.8 cm), and sacrum (5.6 cm) was observed. The patient reported subjective improvement, and objectively he was able to make small steps with crutches. The herpes infection showed a partial improvement. We integrated the therapy with levothyroxine and restarted treatment with octreotide LAR at a dose of 30 mg every 28 days. After a long recovery period, the patient started the fourth cycle in November 2008 with a new schedule of sunitinib (25 mg daily for 2 weeks followed by a 1-week off period, 2/1), which was continued through the fifth and sixth cycles. At the next checkup, plasma chromogranin A was 1451 ng/mL and NSE 20.40 ng/mL. CT scan showed significant enlargement of the metastatic lesion of the skull along with a new metastatic cranial lesion, and osteolytic destruction of the left hip joint with involvement of new skeletal sites (Figure 2). With these data we decided to stop therapy with sunitinib. The patient continued with somatostatin analogs at a dose of 30 mg every 28 days. He died in May 2009 due to neurological complications.
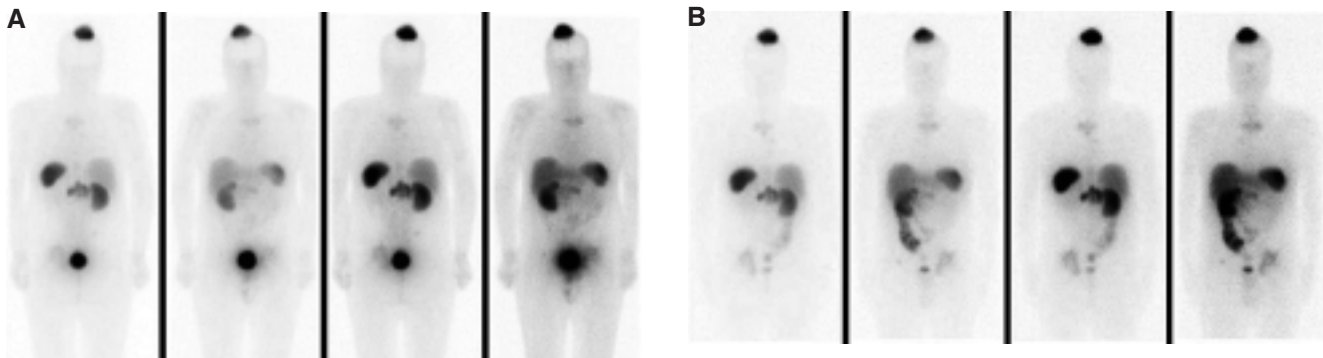

Figure 1 - OctreoScan: high receptor density in the lesions of the skull, dorsal and lumbar spine, and left sacral region (A, after 4 hours; B, after 24 hours).
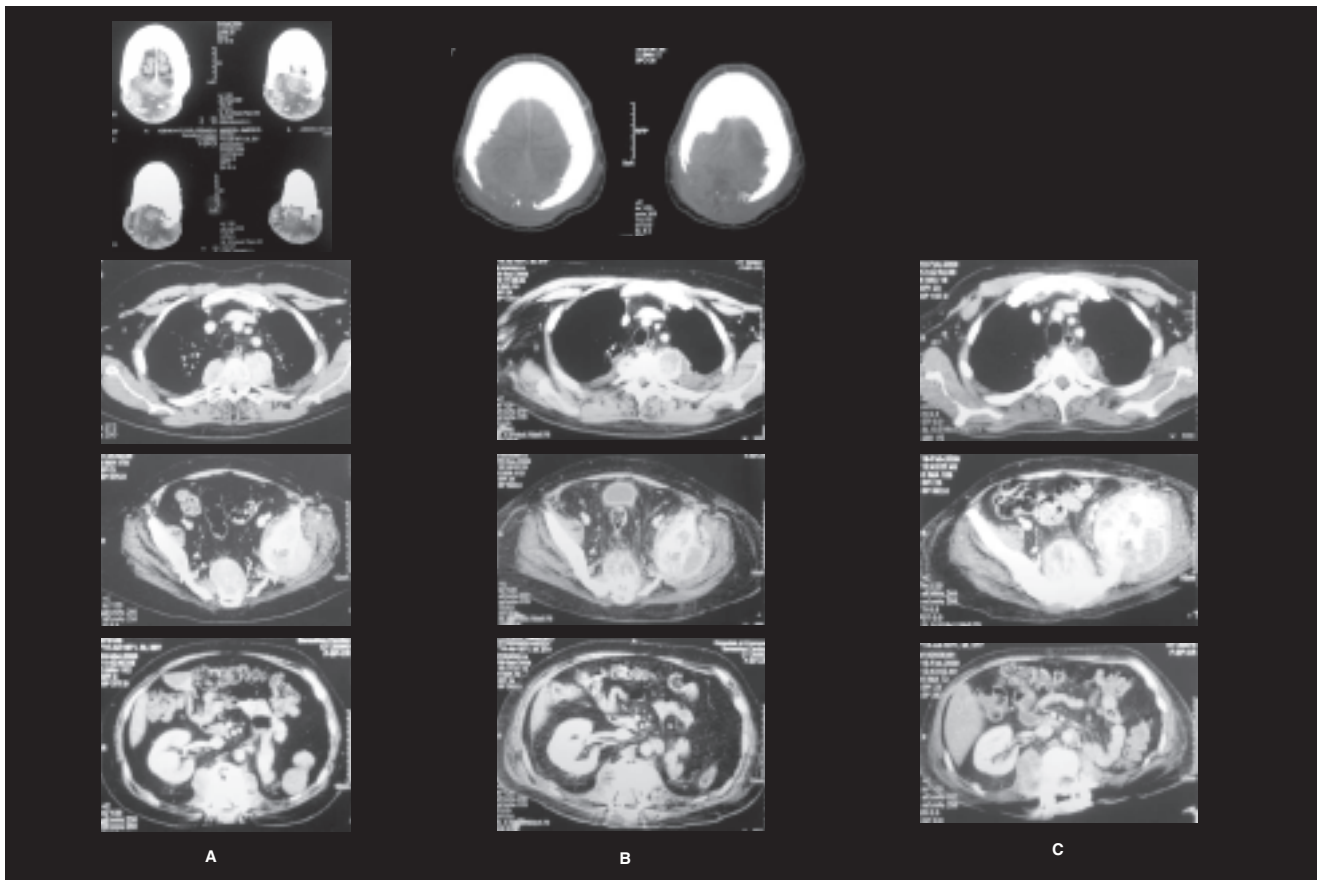
Figure 2 - CT scan. A) before treatment with sunitinib (chromogranin A 4481 ng/mL, NSE 7.3 ng/mL). B) After 3 cycles of sunitinib (chromo-granin A 1620 ng/mL, NSE 8.9 ng/mL). C) After 6 cycles of sunitinib (chromogranin A 1451 ng/mL, NSE 20.40 ng/mL).

Notes: patient with histologically proven advanced paraganglioma for which no other therapy was possible. Karnofsky performance status 70. Adequate bone marrow, liver, renal and thyroid function. Echocardiogram showed no heart problems. Toxicity was graded using the National Cancer Institute Common Toxicity Criteria. Tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines[7].

Discussion

Paraganglioma is a tumor deriving from the extra-adrenal chromaffin tissue. It can originate from the sympathetic nervous system and is then mostly located in the retroperitoneum. Functional tumors in the chest also occur. Tumors of parasympathetic derivation usually develop in the head and neck region as nonfunctioning carotid body tumors[8]. Paraganglioma is a relatively rare tumor that may release catecholamines, causing symptoms typical of pheochromocytoma[9,10], including severe cardiovascular complications[11-13]. Ten percent of paragangliomas are childhood tumors. This tumor has been reported to occur in a variety of sites: the upper para-aortic region in 46% of cases, lower para-aortic region in 29%, bladder and chest in 10%, and head and neck in 2% of cases[14] [AUTHORS: Change OK?]. Nearly 5% of abdominal paragangliomas produce peptides[8]. Forty percent of paragangliomas are malignant, compared to 10% of pheochromocytomas. In malignant cases catecholamine secretion is rare[14], so the clinical diagnosis of paraganglioma may be difficult to make and the tumor becomes manifest only at an advanced stage.

The palliative treatment options for patients with advanced paragangliomas are limited. Chemotherapy (cyclophosphamide, vincristine, dacarbazine) should be considered in the management of symptomatic patients and may result in objective improvement in the control of blood pressure[15]. Radionuclide therapy may improve symptoms and biochemical marker levels, but the results in the control of tumor bulk are less favorable, with responses being frequently short-lived. In a phase II study, patients with metastatic neuroendocrine tumors were treated with temozolomide and thalido-

mide[16]; 68% of patients achieved stabilization of the disease with a median response duration of 13.5 months (range, 2-31 months). Although 90% of neuroendocrine tumors express somatostatin receptors[17], somatostatin analogs rarely result in tumor regression[18,19], except in low-grade tumors characterized by a high receptor density and a low proliferation index[20]. Recently, everolimus (RAD001, Afinitor, Novartis), a compound that inhibits mTOR (mammalian target of rapamycin) signaling, was used in 4 patients with progressive malignant paragangliomas or pheochromocytomas in addition to other therapies, with relatively disappointing outcomes[21].

Finally, the high vascularity of neuroendocrine tumors has triggered research into angiogenesis inhibition by means of targeted therapy with sunitinib[22]. Overexpression of VEGF and its receptors has been observed in endocrine tumors, suggesting that autocrine activation of the VEGF pathway may promote tumor growth[23]. A number of other signaling pathways have been implicated in neuroendocrine tumors, which also express platelet-derived growth factor, insulin-like growth factor-1, basic fibroblast growth factor, transforming growth factor α and β, epidermal growth factor, stem-cell factor, and their receptors[6].

In the case reported, the toxicity profile was similar to that observed in other trials[5,6,24]. The most common adverse events were constitutional, such as fatigue and anorexia, or digestive, such as nausea and diarrhea. Grade 3 neutropenia, thrombocytopenia and anemia may be due to the advanced stage of disease and to previous systemic therapy[24]. Usually, neutropenia (without fever) and thrombocytopenia clear up during off-treatment periods[25]. In patients with grade 3 neutropenia or thrombocytopenia persisting after the 2 weeks off treatment, sunitinib treatment should be delayed or the dose reduced, as was done in the present case with the use of a 2/1 schedule of sunitinib at a 25-mg daily dose[26].

Signs and/or symptoms related to hypothyroidism (fatigue, muscle pain, difficulty concentrating, sleepiness, cold intolerance, anorexia) resolved with the replacement of levothyroxine and periodic monitoring of TSH serum levels. Hypothyroidism associated with sunitinib treatment was observed in 84% of cases[27]. In the case reported, no ultrasound abnormalities of the thyroid were observed.

Stomatitis often occurs during the second week of treatment[25]. Oral miconazole gel 2% mouthwash combined with oral fluconazole 100 mg daily for 2-3 weeks improved the symptoms in our patient.

Inhibition of tyrosine kinase receptors, which are widely expressed in the skin, may result in a range of chronic cutaneous side effects such as folliculitis, splinter hemorrhages, hair depigmentation, and hand-foot syndrome[25]. This syndrome generally presents as dysesthesia, tingling and erythema in the affected areas, which may progress to burning pain with dryness, cracking, desquamation, ulceration and edema[25]. We observed a moderate grade of hand-foot syndrome that did not limit our patient's ability to perform normal daily activities. He took sunitinib in the evening to reduce the severity of the syndrome, because the peak plasma concentration of the molecule is reached during rest.

We also observed the characteristic herpes simplex of the trunk during the whole treatment with sunitinib. It was controlled with oral acyclovir 200 mg every 4 hours for a week, sometimes also 2 consecutive weeks. In our opinion this kind of cutaneous manifestation is not due to sunitinib therapy but to the immunocompromised state of cancer patients.

The disease progression observed on CT scan at the same time as a moderate increase in plasma NSE may have been due to a number of factors: a change in differentiation of the tumor cells, the possible tolerance of VEGF receptors to sunitinib, the dose and schedule of administration of the molecule. With regard to the latter, we should mention that the patient completed only 4 cycles out of 6, with a long recovery between one cycle and the next because of his poor state of health.

In the second and third cycles the patient was given 25 mg daily 4/2, and in the following cycles 25 mg daily 2/1 (Table 1). The choice to shift from 50 to 25 mg daily and from a 4/2 to a 2/1 schedule was prompted by severe myelosuppression and the patient's overall weakness (fatigue, fever >38 °C, infection, hemorrhage, nausea and vomiting refractory to antiemetic therapy), which necessitated a long recovery period[26]. With the 25 mg daily and 2/1 schedule of sunitinib, the patient achieved prolonged drug exposure without major side effects. An important issue is the appropriate dosage of sunitinib to produce significant antitumor activity in advanced metastatic tumors, keeping the toxicity within limits. Because of the toxicity of the drug we decided to go directly from 50 to 25 mg daily and from 4/2 to 2/1, excluding an intermediate dose of 37.5 mg, which, given the poor condition of the patient, was considered too high.

Table 1 - Cycles of sunitinib

1. 50 mg daily for 4 weeks and 2-week off period. Hematuria, fever, herpes simplex: cycle interrupted after 19 days.

2. 25 mg daily for 4 weeks and 2-week off period. Complete.

3. 25 mg daily for 4 weeks and 2-week off period. Acute hematological toxicity, candidosis, depressive syndrome: cycle interrupted after 3 weeks.

4. 25 mg daily for 2 weeks and 1-week off period. Complete.

5. 25 mg daily for 2 weeks and 1-week off period. Complete.

6. 25 mg daily for 2 weeks and 1-week off period. Complete.

The mechanism of action of sunitinib in neuroendocrine tumors remains unclear. Inhibitors of the VEGF pathway are generally thought to exert their antitumor effects indirectly by targeting endothelial cells and inhibiting tumor angiogenesis[6,28]. Objective responses of sunitinib were observed at doses ≥50 mg daily in patients with highly vascularized tumors[5]. Nonetheless, sunitinib and other inhibitors of the VEGF pathways should have to exert a dose-independent antitumor activity [AUTHORS: This is unclear. Please check and consider rephrasing].

Finally, we want to say a few words about treatment response evaluation by CT scan. A tumor's response to treatment is traditionally evaluated on the basis of morphological features[29]. The RECIST guidelines[7] are based on unidimensional tumor size and do not reflect the biological changes of solid tumors induced by targeted therapy with sunitinib or similar molecules[30]. This differs from the Southwest Oncology Group (SWOG) criteria[31], where radiological responses are based on bidimensional tumor size[32], and also from evaluation by FDG PET [33] or non-FDG PET imaging[34], where tracer uptake in some cases shows a significant decrease despite radiologically increasing tumor size and significant clinical improvement[35].

In the case reported here, the last CT scan showed a dramatic increase in the size of the metastatic bone lesions, probably due to fluid expansion in response to tumor necrosis induced by sunitinib, with the only exception of a contemporary increase of plasma NSE and the progression of the disease. [AUTHORS: The link with the first part of the sentence is unclear. Please check and consider rephrasing]

In conclusion, sunitinib malate is a fascinating targeted molecule also for the treatment of advanced neuroendocrine tumors[36], with evidence of short-term responses paralleled by significant clinical improvement as in our patient. Sunitinib may be associated with significant toxicity, in which case reduction of the daily dose and a different schedule of administration should be considered. Specific plasma markers are important for assessment of the tumor's behavior. Finally, response evaluation by CT scan should take into account tumor necrosis from treatment with sunitinib or other related molecules.

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