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CASUISTRY

Experience with sunitinib in hormone-resistant metastatic prostate cancer that is unresponsive to docetaxel

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Abstract

Introduction: Systemic treatment options for patients with hormone-refractory prostate cancer (HRPC) that progress despite the use of Docetaxel are very limited. One of the options of compassionate use currently available is the use of Sunitinib. We present a joint preliminary experience with the use of Sunitinib in this clinical case.

Patients and methods: A series of eight cases is presented, which sets forth a prospective multicentre experience with Sunitinib in patients with hormone-refractory metastatic and progressive prostate cancer, previously treated with at least a regimen of Docetaxel-based chemotherapy. Other alternative chemotherapy regimes had already been tried in some patients. The primary objective of our study was the PSA response rate and our secondary objective was the progression-free period. We administered a dosage of 50 mg/day for four-week cycles, followed by a two-week rest per cycle, until we reached a total of eight cycles or up to clinical progression or intolerable toxicity.

Results: In four cases, the PSA dropped to below 50% of the baseline level at the beginning of the treatment, and five patients presented some decrease in PSA. The progression-free time was 16.4 weeks. Toxicity arising from the treatment was moderate and manageable.

Conclusions: Despite the limits of this experience, we can say that Sunitinib appears to be an active and safe option in patients with hormone-refractory prostate cancer that is resistant to chemotherapy with Docetaxel.

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PALABRAS CLAVE
Sunitinib;
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Resistencia a quimioterapia

Experiencia con sunitinib en cáncer de próstata metastásico hormonorresistente sin respuesta a docetaxel

Resumen

Introducción: Las opciones de tratamiento sistémico para los pacientes con cáncer de próstata hormonorrefractario (CPHR) que progresan a pesar del uso de docetaxel son muy limitadas. Una de las opciones de uso compasivo disponibles en la actualidad es el empleo de sunitinib. Presentamos una experiencia preliminar conjunta con el uso de sunitinib en esta circunstancia clínica.

Pacientes y métodos: Se presenta una serie de 8 casos que refleja una experiencia multicéntrica prospectiva con sunitinib en pacientes con cáncer de próstata metastático, hormonorrefractario y en progresión, previamente tratados con al menos un régimen quimioterápico a base de docetaxel. En algunos pacientes ya se habían ensayado otros regímenes quimioterápicos alternativos. El objetivo primario de nuestro estudio fue la tasa de respuesta de PSA, y el objetivo secundario el tiempo libre de progresión. Se administró una dosis de 50 mg/día durante ciclos de 4 semanas, seguidos de 2 semanas de descanso por ciclo, hasta alcanzar un total de 8 ciclos o hasta la progresión clínica o toxicidad intolerable.

Resultados: En 4 casos el PSA descendió por debajo del 50% del nivel basal al inicio del tratamiento, y 5 pacientes presentaron algún descenso del PSA. El tiempo libre de progresión fue de 16,4 semanas. La toxicidad derivada del tratamiento fue moderada y manejable.

Conclusiones: A pesar de lo limitado de esta experiencia, podemos decir que sunitinib parece una opción activa y segura en pacientes con cáncer de próstata hormonorrefractario y resistente a quimioterapia con docetaxel.

Clinical problem

Systemic treatment options for patients with hormone-refractory prostate cancer (HRPC) that progress despite the use of Docetaxel are very limited. One of the options of compassionate use currently available is the use of Sunitinib. We present a joint, preliminary, multicentre and prospective non-randomized experience that is not funded by any pharmaceutical company. It is an observational experience that assesses the compassionate use of Sunitinib in hormone-refractory prostate cancer that is resistant to chemotherapy and which is in progression in 8 patients.

Design of the study

All the patients were affected by metastatic cancer and had progressed despite hormone treatment and at least one regimen of Docetaxel-based chemotherapy (Taxotere®; Sanofi-Aventis, Bridgewater, NewJersey). In some patients, other alternative chemotherapy regimens had been tested. Treatment with Sunitinib was established in all the patients due to clinical needs and as compassionate use. The primary objective of our study was the PSA response rate and the secondary objective was the progression-free period.

They all presented a baseline PSA increase in series controls of at least two-week intervals between them, and in all the cases, their last PSA was greater than 10 ng/ml. The "*Eastern Cooperative Oncology Group (ECOG) performance status*" was between 0 and 2. Likewise, they all had good heart function, without arrhythmia or uncontrolled hypertension. None of the patients received prior treatment with radionuclides that affected more than 50% of the bone marrow. Kidney and haematopoietic functions were likewise normal in all the cases. None of the patients had presented episodes of bleeding in the four previous weeks or cardiovascular morbidity in the previous six months. Moreover, no radiotherapy treatment was given in the four weeks prior to the initiation of treatment.

The patients initially received 50 mg of Sunitinib daily on 1-28 days every six weeks, until one of the following circumstances occurred: a total of 8 cycles was achieved, there was tumour progression, unacceptable toxicity or withdrawal of the patient's consent. In the design of the trial, we considered that to be included in the analysis, only a total of 2 Sunitinib dose reductions due to toxicity be permitted, initially up to 37.5 mg daily and subsequently 25 mg daily. In cases with grade 3 or 4 toxicity, the treatment would be suspended until the patient had fully recovered or the toxicity had improved to grade 1, continuing with the following corresponding reduced dosage level. Patients that interrupted their treatment for more than three weeks were not included in the analysis.

Results achieved

A total of 8 patients were included, with a mean age of 71 years. The means PSA at the beginning of the treatment was 584 ng/ml (table 1). All the patients had received at least one line of chemotherapy that included Docetaxel and 6 (75%) had also received a second line of chemotherapy with Oxaliplatin and Capecitabine. None of the patients included presented another area of metastasis besides the bone.

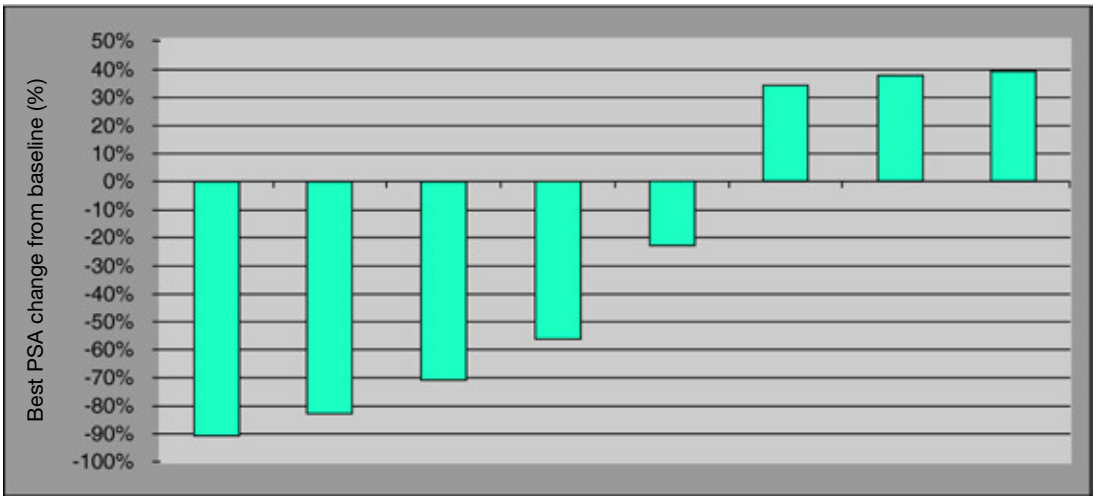

Figure 1 Change relative to the PSA for each patient on the baseline value achieved by treatment with Sunitinib.

Five of our patients showed a decrease in PSA for a period of at least six weeks. Four of the patients achieved a decrease of at least 50% Three patients increased their PSA level despite following treatment with Sunitinib (fig. 1). In patients with response/stabilization, the progression-free interval was 16.4 weeks (12-18 weeks). We did not find a correlation between the response to prior chemotherapy and the response to Sunitinib in our cohort study.

Asthenia, diarrhoea, anaemia and thrombopenia were the most relevant toxicities recorded. Side effects considered as serious (grade 3 or 4) were not very frequent in our series, given that only one patient presented grade 3 digestive toxicity in the form of diarrhoea. The rest were minor. Five patients (62.5%) presented asthenia (1 grade 1, 4 grade 2), 1 patient (12.5%) presented anaemia (grade 1) and 4 patients (50%) presented diarrhoea (1 grade 1, 2 grade 2 and 1 grade 3). There were no deaths due to the treatment with Sunitinib. None of our patients interrupted their treatment for more than 3 weeks.

Table 1 Characteristics of the patients

AGE	
Mean	71.25 years
Range	54-82 years
No. prior chemotherapies	
Mean	1.75
Range	1-2
No. prior hormone therapies	
Mean	3
Range	2-4
Initial PSA	
Mean	584.5 ng/ml
Range	167-1288 ng/ml
Area of Metastasis	
Bone	8
Other	0

Commentary

Sunitinib (Sutent®, Pfizer, New Jersey, USA) is an oral multiselective inhibitor of various membrane receptors of tyrosine kinase, which includes all the known receptors of VEGFR (-1, -2, and -3) and PDGFR (-α, and –β), as well as RET, KIT and FLT-3. Sunitinib is currently approved for the treatment of first line patients with renal cell cancer and for the treatment of patients with gastrointestinal stromal tumours (GIST) whose treatment with Imatinib has failed or who are intolerant. Through the inhibition of VEGFR and PDGFR, Sunitinib has a antiangiogenic action mechanism and it acts directly against the proliferation of the tumour cells through its action on the other type tyrosine kinase membrane receptors.[1]

Notice was recently given of a preclinical trial in which Sunitinib, both as a single agent and in combination with Docetaxel, significantly inhibits the growth and increases the apoptosis markers of the PC3 prostate cancer cell lines implanted in murine xenografts.[2] Based on these hopeful preclinical results, the first results of a stage I/II trial on Sunitinib as a single agent during a cycle (4 weeks "on" / 2 weeks "off") followed by the standard combination of Docetaxel and Prednisone plus Sunitinib were disclosed at the ASCO 2007 congress. The treatment was administered to patients with CPMHR in the first line of treatment after progression to complete hormonal blockage.[3]

We evaluated the safety and activity of Sunitinib in single-drug therapy in highly pretreated patients with hormone-refractory prostate cancer and in progression with Docetaxel. 50% of the patients achieved a decrease in PSA of more than 50% of the base level. Two patients (25%) presented an increase in PSA after the first cycle of treatment, then subsequently experienced a decrease in the PSA level of up to 70% in one of the two cases. This barely described phenomenon is know as "flare" and exemplifies how probably treatment with Sunitinib should not be suspended after the first cycle in spite of an increase in PSA being determined in the first control.

This case selection and method is very limited, however the progression-free interval in the responders is similar to that published by Sonpavde et al.[4] This group found disease-free survival of 19.4 weeks. The toxicity recorded in these patients was easily manageable and it was necessary to reduce the dosage to 37.5 mg in 3 patients (37.5%). We believe that the addition of Sunitinib to the normal treatment of these patients with prednisone (which may help to overcome some of the side effects of Sunitinib, such as asthenia, vomiting or anorexia) may better control the symptoms of the disease, thus achieving an improvement in the quality of life of the patients and greater progression-free survival.

Conclusions

Sunitinib shows activity in the context of hormone-resistant prostate cancer in highly pretreated patients, who present a very manageable toxicity profile and with very interesting progression-free survival data, which is why we believe it is justified to continue with the study of this drug in this difficult clinical context.

Conflict of interest

The authors declare that they have no conflict of interest.

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