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Case Report 1. Sunitinib malate in patients with pre-existing haematological abnormalities

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1. Introduction

Sunitinib malate is an inhibitor of multiple tyrosine kinases, including those of vascular endothelial growth factor (VEGF) and platelet derived growth factor (PDGF) receptors.[1] It has been recently approved for the first-line treatment of advanced renal-cell carcinoma (RCC) due to its superiority compared to cytokines,[2] which have been the standard of care in this disease up to now. Sunitinib is well tolerated, with fatigue, diarrhoea, stomatitis and skin toxicity being the most common side effects.[2] Leucopenia and thrombocytopenia have also been reported in more than 50% of patients, although Grade 3 and 4 haematological toxicities are rare. Furthermore, adequate bone marrow function has been required for inclusion in all studies of this agent.[2,3] As a result, data on the use of sunitinib in patients with pre-existing haematological abnormalities are lacking. We hereby report a case of advanced RCC treated successfully with sunitinib in spite of pre-existing thrombocytopenia and leucopenia.

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2. Case Report

A 70-year-old male underwent a left radical nephrectomy for a renal mass in January 2005. Macroscopic examination showed a 6 cm mass on the upper pole of the kidney. Histology revealed a Grade II clear-cell RCC, without invasion of the capsule or major vessels (pT1b). No lymph nodes were removed during the operation (Nx).

The patient was followed up with 6-monthly abdominal CT scans and chest X-rays. Two years after the operation a $5\times3\times3$ cm mass was found on abdominal CT scan, consistent with local recurrence. In addition, the spleen was considerably enlarged, but no focal lesions were detected. Platelet count was at 52 000/mm^3. There was also mild anaemia (haemoglobin 11.7 g/dl) and leucopenia (WBC 3800/mm^3). The patient was asymptomatic (ECOG PS: 0), while corrected calcium and LDH were within normal limits. Thrombocytopenia was investigated with a blood smear, bone marrow aspirate and biopsy. No evidence of bone marrow infiltration or other specific abnormalities were found. A diagnosis of hypersplenism of unknown cause was made.

Surgery was not considered a viable option in this patient for two reasons. First, the tumour mass was considered too large and was in a difficult anatomical location for radical resection. Second, the preexisting

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thrombocytopenia increased the risk of bleeding during or after surgery.

The patient was started on sunitinib at a dose of 37.5 mg/day for 4-weeks followed by 2 weeks off (4/2 schedule). Full blood counts were obtained every two weeks. Treatment was interrupted only for Grade 3 haematological toxicity and was restarted after recovery at Grade 2. The patient has been treated for 5 months and is still on treatment.

During treatment, platelet nadir was 42 000/mm^3 and neutrophil nadir was 700/mm^3. Additional toxicities were dermatitis grade 1 and stomatitis grade 1. There was one treatment interruption for 5 days due to Grade 3 thrombocytopenia and one treatment delay for a week due to Grade 3 thrombocytopenia and neutropenia. Ganulocyte-colony stimulating factor was used once to accelerate neutrophil recovery. No serious adverse events occurred. Following 2 cycles of treatment there was a 20% reduction of the maximal diameter of the local recurrence.

3. Discussion

Sunitinib has been associated with haematological toxicity, but Grade 3/4 neutropenia or thrombocytopenia are rare. Clinical sequelae due to haematological toxicity are even rarer. In most studies, leucocyte counts above 4000 and platelet counts above 100 000 are required for inclusion. As a result, patients with mild haematological abnormalities would not be treated with sunitinib, which is the most active first-line agent in advanced RCC.

Our patient belonged to the good prognosis group, according to the recent analysis of 375 patients receiving first-line treatment with sunitinib, which showed a median progression-free survival of 14.8 months for this group of patients.[4] Taking into consideration the expected benefit and the low risk of significant haematological toxicity we decided to treat him using sunitinib at a lower dose than the usual 50 mg dosage. Our decision was justified by the lack of significant worsening of his thrombocytopenia or leucopenia, no significant treatment delays, but also a reduction in the size of his tumour.

Recent data have suggested an association between exposure to the drug and efficacy of treatment.[5] Based on the good tolerability of the dose we used, it could be argued that an escalation to the standard dose of 50 mg under close monitoring could be attempted. Nevertheless, such a decision should be weighed against the possibility of increased haematological toxicity and continuing benefit from treatment.

4. Conclusion

This case demonstrates that treatment with sunitinib can be offered to patients with pre-existing haematological abnormalities. Close monitoring is essential in order to avoid excessive toxicity, which could lead to clinical sequelae.

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Conflict of interest

None declared.

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