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CASE REPORT

Sunitinib Induced Cytopenia in Metastatic RCC

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Introduction

Most malignant kidney tumors are renal tubular epithelium derived adenocarcinomas and referred to as renal cell carcinoma (RCC). Kidney cancer accounts for 3-4% of adult cancers and one third of the overall cases of RCC are diagnosed at the advanced stages of the disease [1-3]. RCC is a chemo-radioresistant cancer. Therefore, immunomodulatory agents and tyrosine kinase inhibitors (TKI) are commonly used in the treatment of mRCC.

Sunitinib is an oral TKI with activity against vascular endothelial growth factor receptor (VEGFR) as well as with an inhibiting activity against many other tyrosine kinase receptors, including c-KIT, FLT3 platelet derived growth factor receptors (PDGFR) [4].

Although effective in the treatment of RCC, sunitinib may cause fatigue, nausea, diarrhea, stomatitis and myelosuppression. Apart from myelosuppression, side effects are usually tolerable. However myelosuppression may be severe enough to require dose reductions or discontinuation of the therapy [5]. Suggested dose levels of Sunitinib are 50 mg, 37.5 mg and 25 mg. Doses reduced for toxicity should not be reescalated.

We aimed at presenting four cases of Sunitinib induced myelosuppression, in which we continued the therapy with dose modifications and recovery from myelosuppression was observed during the follow up period.

Case Presentation

Case 1

A 72-year-old male patient. RCC metastatic to the lungs at the time of diagnosis. The patient developed Grade 1 leukopenia, anemia and thrombocytopenia in the third month of the therapy with Sunitinib. The sunitinib dose was reduced to 37.5 mg. In the sixth month of therapy, in spite of a Grade 2 leukopenia and neutropenia, a complete response was obtained in the lung lesions. Any further reduction in the Sunitinib dose was not carried out due to the significant clinical response. The patient is still progression free in the 37th month of the therapy with sunitinib 37.5 mg.

Case 2

A 66-year-old female patient. Sunitib was initiated due to the recurrence of the abdominal tumor, 4 years after the diagnosis of RCC. She developed Grade 2 thrombocytopenia in the fourth month of the therapy with Sunitinib. Sunitinib treatment was continued at dose reduced to 37.5 mg. The resolution of cytopenia occurred 2 months later. The patient was progression free during the next 7 months. The overall duration of the therapy with Sunitinib was 11 months. The therapy was switched from sunitinib to everolimus due to the disease progression of abdominal masses.

Case 3

A 61-year-old male patient. Lung metastasis was detected 7 years after the diagnosis of RCC and sunitinib

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was started. Although he developed Grade 2 leukopenia and thrombocytopenia and Grade 2 neutropenia in the 3rd month of the therapy with sunitinib, the medicine was continued at dose of 50 mg during the next 16 months. The patient developed Grade 3 anemia, Grade 2 leukopenia and neutropenia and Grade 1 thrombocytopenia in the 19th months of the treatment. Therefore the dose was reduced to 37.5 mg. The patient has received sunitinib at dose of 37.5 mg during the last 6 months and no progression was detected during this period of follow up.

Case 4

A 42-year-old male patient. Cranial metastasis was detected 11 years after the diagnosis of RCC. He developed Grade 3 leukopenia, neutropenia, anemia and Grade 4 thrombocytopenia leading to the discontinuation of the therapy with sunitinib, 18 months after the initiation of therapy. Later on, sunitinib was resumed at dose of 37.5 mg. However, due to the recurrence of Grade 2 leukopenia and neutropenia, sunitinib was continued with a dosing schedule of two weeks off and two weeks on. After the resolution of cytopenia at this level of dose, dosing schedule was readjusted as 4 weeks on and 2 weeks off and the patient was progression-free during the next 9 months then the therapy was switched from sunitinib to everolimus as a consequence of cranial metastasis.

Discussion

TKIs are used in the management of cancer, in an increasing frequency [6]. The high efficacy and easy administration of TKIs allow a longer duration of treatment in comparison to the standard chemotherapeutic regimens, which in turn highlights the importance of the side effects.

One of the most serious side effects of TKIs is myelosuppression. *In vitro* studies revealed that the inhibitory activity of sunitib against c-KIT and FLT3 kinases was higher than the other TKIs [7]. However, the exact mechanism of myelosuppression is not fully understood. In addition to sunitinib, myelosuppression is also associated with the use of sorafenib or pazopanib [8,9]. The results of a meta-analysis performed by Funokoshi, et al. have supported this association. This meta-analysis included 8526 patients from 60 studies. The incidence of neutropenia or thrombocytopenia were found to be higher with sunitinib in comparison to sorafenib and pazopanib. The same studies also revealed the associations between sunitinib and all grades (Grade 1,2,3,4) and high grades (Grade 3,4) neutropenia and thrombocytopenia and all grades anemia (Grade 1,2,3,4) [10].

In a study comparing INF to sunitinib, sunitinib was found to be associated with leukopenia, neutropenia, anemia and thrombocytopenia in all grades, in more than the half of the patients. Transient Grade 3 or Grade 4 neutropenia and thrombocytopenia may be observed in patients who receive sunitinib more than 6 months [11].

Gradual dose reductions of 12.5 mg are recommended in case of intolerance and hematological toxicity and discontinuation of the therapy is recommended in case of the emergence of Grade 3 or 4 toxicity [5]. However, due to the high level of efficacy of sunitinib in RCC, many centers continue sunitinib therapy with dose modifications. We continued the therapy with sunitinib with dose modifications and observed the resolution of the toxicity during the follow up of the patients and by this means, these patients achieved a long term progression free survival.

Conclusion

Sunitinib is a highly efficient agent in the treatment of metastatic RCC. In case of sunitinib induced toxicity, the management of toxicity should be considered first. This may serve to preserve other treatment options as well as to increase the length of progression free survival.

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