ABSTRACT

Background

Sunitinib is approved for treatment of advanced renal cell carcinoma (rcc). Based on a clinical observation that patients receiving sunitinib developed macrocytosis, we undertook a study to further define this observation.

Methods

In a retrospective review of rcc patients treated at a single centre, data on treatment duration, hematology parameters, concomitant medications, vitamin B12 and folate levels, and thyroid function were recorded.

Results

The 43 patients reviewed had received a median of 5 cycles of sunitinib. Overall, 21 patients (49%) developed macrocytosis after a median of 3 cycles. Of the 9 patients that received 2 or fewer cycles, none developed macrocytosis. Among patients with macrocytosis, 9 (43%) had anemia at the time macrocytosis was first documented. In patients who did not develop macrocytosis, 82% showed a trend of increasing mean corpuscular volume.

Conclusions

Treatment with sunitinib in patients with rcc can cause macrocytosis. The frequency of macrocytosis increases with duration of treatment. The mechanism of sunitinib-associated macrocytosis remains to be elucidated.

KEY WORDS

Renal cell carcinoma, sunitinib, macrocytosis

1. INTRODUCTION

Sunitinib is an oral multi-targeted tyrosine kinase inhibitor with activity against the vascular endothelial growth factor and platelet-derived growth factor receptors. Phase iii trial results showed that, compared with interferon, sunitinib improves progression-free survival in metastatic renal cell carcinoma (mRCC) 1. Sunitinib has become the standard first-line therapy for mRCC.

In an early cohort of mRCC patients treated with sunitinib at one institution, several patients were observed to develop an increase in red blood cell (RBC) mean corpuscular volume (MCV). To investigate the development of this macrocytosis, a retrospective review was conducted of all rcc patients treated with sunitinib at the centre over a 15-month period.

2. PATIENTS AND METHODS

After approval for the study was obtained from the Capital Health Research Ethics Board, we performed retrospective chart review of all patients with mRCC who received sunitinib at the QEII Health Sciences Centre in Halifax between August 2005 and November 2006. Patients were treated primarily with the standard daily dose of sunitinib 50 mg, 4 weeks on followed by 2 weeks off. Dose reductions and changes in the schedule were made based on toxicity according to clinical trial protocols or the standard of care.

Results of complete blood counts, including RBC indices, were recorded before treatment; on days 1, 14, and 28 of the first cycle; and on days 1 and 28 of subsequent cycles. Patients were categorized as having macrocytosis when their RBC MCV exceeded the laboratory-specific upper limit of normal. The highest MCV reached was recorded. If available, folate and vitamin B12 levels and thyroid studies were noted. Concurrent medications and prior therapy for rcc were ascertained. Descriptive statistics were used to analyze the data.

3. RESULTS

The study cohort consisted of 43 patients (30 men, 13 women) with mRCC. Table 1 shows baseline patient characteristics. Before starting sunitinib, 10 patients...
(23%) had a microcytic MCV, 33 (77%) had a normocytic MCV, and no patient had a macrocytic MCV (Figure 1). Anemia was present in 24 patients (56%).

Patients were treated for a median of 5 cycles (range: 1–19 cycles) or 30 weeks (range: 6 to 86+ weeks). Of the 43 patients, 34 (79%) received 3 or more cycles. Overall, 21 patients (49%) developed macrocytosis after a median of 3 cycles or 17 weeks (Figure 2).

Of the 22 patients who did not develop macrocytosis, 18 (82%) showed a trend of increasing MCV during sunitinib therapy. Among those 18 patients, 3 were documented as having received RBC transfusions or medications (iron supplementation), which theoretically could have contributed to an increase in MCV. Figure 3 shows the increase in MCV before and on sunitinib in all patients. Among the 21 patients who developed macrocytosis, 9 (43%) were anemic at the time. Another 9 (43%) went on to develop anemia later.

The use of other medications that could contribute to macrocytosis was infrequent. One patient took trimethoprim–sulfamethoxazole concurrently with sunitinib and famciclovir 8 months before the onset of macrocytosis.

Thyroid studies were available in only 12 of the 21 patients who developed macrocytosis. In 5 of the 12, thyroid levels were normal. Of the 7 patients with abnormal thyroid indices, 2 had hypothyroidism, and 2 had hyperthyroidism and were taking methimazole. More subtle thyroid abnormalities were seen in 3 patients. One had a level of thyroid-stimulating hormone (TSH) at the low end of normal and a slightly elevated level of free T4 hormone; 2 patients had normal TSH levels, but a slightly low level of free T4 or T3 hormone.

Vitamin B12 levels were available for 7 of the 21 patients in whom macrocytosis occurred, and 2 of those 7 had low vitamin B12 levels. In those 2 cases, vitamin B12 level had not been determined at baseline when the MCV was normal. Serum folate levels were available in 8 of the 21 patients with macrocytosis, and all levels were normal.

4. DISCUSSION

In this retrospective review of 43 patients treated with sunitinib for mRCC, half the patients developed macrocytosis. This series is the second-largest of four to identify macrocytosis in patients treated with sunitinib for mRCC. The proportion of patients developing macrocytosis while on sunitinib has varied between these series. Some of this variation may relate to differences in duration of therapy.

In our cohort, macrocytosis developed after a median of 3 cycles or 17 weeks of therapy, and none

![Figure 1](image1.png)  
**Figure 1** Macrocytosis before and during sunitinib therapy.

![Figure 2](image2.png)  
**Figure 2** Time to development of macrocytosis.

![Figure 3](image3.png)  
**Figure 3** Macrocytosis over time. MCV = mean corpuscular volume.
of the 9 patients who received 2 or fewer cycles developed macrocytosis. In another series of patients with a median treatment duration of 9 months (range: 3–23 months), in which patients treated for fewer than 3 months were excluded, 67% of the patients developed macrocytosis. The same study also demonstrated an ongoing and statistically significant increase in MCV from baseline to 3 months on treatment, and from 3 months on treatment to the end of therapy. A series reporting MCV values of 105 fL (range: 100–124 fL) in 10 of 40 patients did not specifically describe the duration of treatment, but a duration of only up to 30 weeks was graphically depicted. Collectively, these findings suggest time dependence of the sunitinib-associated increase in MCV.

Of the 21 patients in our study who developed macrocytosis, 43% were anemic at the time macrocytosis developed. In a general population, approximately 60% of patients presenting with macrocytosis do not have anemia. However, several of our patients went on to develop anemia during the study period, so that 86% of those with macrocytosis eventually became anemic. Rini et al. reported that hemoglobin remained relatively stable in their patients who developed macrocytosis; however, at all reported time points, median hemoglobin values were below the lower limit of the reference range, suggesting that anemia was common.

Common causes of macrocytosis include medications, vitamin B12 and folate deficiency, thyroid disease, liver disease, alcohol, myelodysplastic and other bone marrow disorders, and reticulocytosis. Although available data were limited by the retrospective nature of our study, no consistent abnormalities in thyroid function or folate level were apparent. Notably, when many of these patients were started on sunitinib, hypothyroidism was not recognized as a sunitinib-related toxicity and was therefore not monitored.

Vitamin B12 was low in only 2 of the patients that were evaluated for that vitamin. Data on alcohol consumption was not obtained. Significant liver or bone marrow disorders are not likely causes in this cohort, many of whom were treated on a clinical trial, which would not have included patients with significant dysfunction in those systems. Other medications cannot explain macrocytosis in this cohort.

Despite the incompleteness of the data, no consistent or compelling association appeared to suggest an alternative cause of macrocytosis. Our findings do not demonstrate an association of macrocytosis with vitamin B12 deficiency during sunitinib therapy as identified in two earlier series of 6 and 40 patients. The largest study to date, although also limited by a retrospective design, likewise did not identify an association of vitamin B12 deficiency with observed macrocytosis in patients with and without hypothyroidism.

Anti-neoplastic drugs—including methotrexate, cladribine, hydroxyurea, cyclophosphamide, and capecitabine—have been associated with macrocytosis. Macrocytosis attributable to those agents is often a result of interference with DNA synthesis by a variety of mechanisms, including inhibition of folate metabolism or nucleotide synthetic pathways, incorporation of nucleotide analogs with subsequent DNA strand breakage, or inhibition of DNA polymerase. Defective DNA synthesis can impair nuclear maturation while cytoplasmic development continues, resulting in macrocytic erythrocytes. These mechanisms are less plausible for sunitinib, which acts through multi-targeted tyrosine kinase inhibition rather than through interference with DNA synthesis. Imatinib, which inhibits the receptor tyrosine kinase c-Kit in gastrointestinal stromal tumours, has also been associated with macrocytosis. Sunitinib also inhibits c-Kit, and c-Kit inhibition has been postulated to possibly be the common link in macrocytosis induced by these two agents (although other mechanisms are also possible).

The present study has limitations as discussed earlier, most of which relate to the retrospective design. One strength of the attribution of macrocytosis to sunitinib itself by Rini et al. is the observation that, after discontinuation of sunitinib, several patients showed a decrease in MCV. Unfortunately, similar data were not recorded for our cohort; anecdotally, however, a similar pattern was observed.

5. CONCLUSIONS

Macrocytosis was observed to develop in half our patients treated with sunitinib for mRCC. Allowing for a retrospective design, no consistent associations with abnormalities in thyroid function or deficiencies in vitamin levels were evident. Considering possible effects of varying durations of treatment, the observed frequency of macrocytosis in our cohort was consistent with that in previously reported series. Departing from the earliest reports of macrocytosis during sunitinib therapy, which suggested an association with vitamin B12 deficiency, our results would support consideration of an alternative mechanism.

6. CONFLICT OF INTEREST DISCLOSURE

The authors declare that no financial conflict of interest exists.

7. ACKNOWLEDGMENTS

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8. REFERENCES


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