Increased mean corpuscular volume as a predictor of response during bevacizumab treatment

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SUMMARY

Background: *Remission during sunitinib (a multikinase inhibitor and antiangiogenic drug) treatment correlates with appearance of macrocytosis. There are some suggestions that bevacizumab, an antiangiogenic drug, may result in macrocytosis as well. There are no published data available on the influence of bevacizumab on macrocytosis. This paper attempted to answer the question: does bevacizumab induce macrocytosis being a predictor of the response?*

Methods: *Between August 2008 and August 2011, 53 patients (29 male and 24 female) were treated with bevacizumab in the combination with chemotherapy at the Oncological Department, University Hospital in Krakow, Poland. Efficacy of bevacizumab was assessed on the basis of the computer tomography scans performed every 3 months within the period of 12 months. Concurrently, mean corpuscular volume (MCV) was evaluated and correlated to the response of the treatment.*

Results: *The percentage increase of MCV compared to baseline at 3, 6, 9 and 12 months was 3.7%, 9.2%, 8.7% and 11.8% respectively. The mean value of baseline MCV was 85.3 fl. The mean value of MCV at 3, 6, 9 and 12 months was 90.5 fl, 93 fl, 91.8 fl and 93.1 fl respectively. Macrocytosis did not occur in our study but an increase of MCV was observed within bevacizumab therapy. It was closely related to the response of the treatment. It seems that an increase of MCV can be a predictive agent of bevacizumab response.*

Conclusion: *Bevacizumab does not induce macrocytosis. Increased MCV after treatment with bevacizumab is related to the treatment response. MCV can be a predictor of the response during bevacizumab treatment. A small number of the observed patients requires further investigations.*

Key words: *Antibodies, Monoclonal, Humanized; Erythrocyte Indices; Antineoplastic Agents; Treatment Outcome*

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INTRODUCTION

Bevacizumab is a humanized monoclonal antibody binding and neutralizing all isoforms of vascular endothelial growth factor (VEGF). VEGF is the most powerful pro-angiogenic factor. Multikinase inhibitor – sunitinib is the next antiangiogenic drug. Remission in the course of treatment with sunitinib correlates with appearance of macrocytosis (1). Mean corpuscular volume (MCV) ranges from 82 to 92 fl. Macrocytosis was defined as mean corpuscular volume above 100 fl (2).

The aim of our study was to evaluate the correlation between bevacizumab response and MCV serum level. The study was based on the assumption that both sunitinib and bevacizumab are the antiangiogenic agents and may have similar predictor factors.

MATERIAL AND METHODS

Fifty-three patients (29 male and 24 female) were treated with bevacizumab in the combination with chemotherapy at the Oncological Department, University Hospital in Krakow, Poland in the period from August 2008 to August 2011. Bevacizumab was administered intravenously every 2 or 3 weeks with chemotherapy. Doses of bevacizumab ranged from 5-15 mg/kg of a body mass.

Efficacy of bevacizumab was assessed on the basis of the CT scans performed after 3, 6, 9 and 12 months of treatment. Response to the treatment was estimated according to RECIST scale. Simultaneously, a mean corpuscular volume was evaluated: at the baseline and then every 3 months during the period of 12 months. The correlation between the response to the treatment and MCV was estimated every 3 months.

RESULTS

Seven patients (13.2%) among 53 treated with bevacizumab were excluded from the assessment due to missing data on MVC and 1 patient (1.9%) was excluded because of his premature death. Finally, 45 patients treated with bevacizumab in the combination with chemotherapy were evaluated. The mean patients' age was 53 years.

Table 1 shows patients' baseline characteristics.

MCV was evaluated every 3 months during the period of 12 months. Gradual increase of mean corpuscular volume in comparison to baseline value was observed.

Table 2 shows an increase of mean corpuscular volume within bevacizumab therapy.

In the control CT scans performed at 3, 6, 9 and 12 months of bevacizumab treatment, progression of the disease was revealed in 28 patients (62.3%) and stabilization in 6 patients (13.3%). Further 6 patients (13.3%) have continued treatment with bevacizumab until now. The next 5 patients (11.1 %) discontinued treatment due to toxicity.

Reasons for completion of the treatment with bevacizumab are presented in Table 3.

Table1. Patients' baseline characteristics treated with bevacizumab in the combination with chemotherapy in our study

	characteristcs
number of patients	N= 45 patients
male : female (%)	21 : 24 (46,7% : 53.3%)
mean age (range) at	53 years (32 years -80 years)
localization of cancer	colorectal cancer - 31 (68.9%) breast cancer – 6 (13.4%) renal cancer – 3 (6.7%) lung cancer -2 (4.4%) breast and colon cancer – 2 (4.4%) ovarian cancer – 1 (2.2%)
mean corpuscular volume (MCV)	microcytic – 15 (33.3%) normocytic – 27 (60%) increased – 3 (6.7%) macrocytic – 0 (0%)
number of cycles of bevacizumab (range)	336 cycles (2 – 25 cycles)
line of treatment with bevacizumab	I line – 20 (44.4%) II line – 13 (28.9%) III line – 9 (20%) IV and further line – 3 (6.7%)
concurrent medications with macrocytosis as side effects	YES – 17 (37.8%) NO - 28 (62.2%)

Table 2. Values of mean corpuscular volume (MCV) within bevacizumab therapy

Baseline MCV (mean value)	85.3 fl
N = number of patients after 3 months of treatment with bevacizumab	45 (100%)
MCV after 3 months (mean value)	90.5 fl
increase of MCV (%)	3.7%
N = number of patients after 6 months of treatment with bevacizumab	21 (46.7%)
MCV after 6 months (mean value)	93 fl
increase of MCV (%)	9.2%
N = number of patients after 9 months of treatment with bevacizumab	13 (28.9%)
MCV after 9 months (mean value)	91.8 fl
increase of MCV (%)	8.7%
N = number of patients after 12 months of treatment with bevacizumab	3 (6.7%)
MCV after 12 months (mean value)	93.1 fl
increase of MCV (%)	11.8%

Tabel 3. Reason of completion of treatment with bevacizumab

reason of completion of treatment with bevacizumab	number of patients N= 45 (100%)
progression of disease	28 (62.3%)
stabilization of disease	6 (13.3%)
general deterioration	2 (4.5%)
pulmonary embolism	1 (2.2%)
exacerbation of ischaemic heart disease	1 (2.2%)
intracranial haematoma	1 (2.2%)

DISCUSSION

Myelodysplastic syndromes, vitamin B12 and folic acid deficiency anemia, liver disease, hypothyroidism, alcoholism and pregnancy are the most common reasons for occurrence of macrocytosis (1,2). Also, anticancer drugs such as: cladribine, methotrexate, hydroxyurea, cyclophosphamide and capecitabine induce macrocytosis (3-5). Macrocytosis interferes with DNA synthesis by a variety of mechanisms. Among others, these are: inhibition of folate metabolism, nucleotide synthetic pathways, incorporation of nucleotide analogs with subsequent DNA strand breakage or inhibition of DNA polymerase (1). Defective DNA synthesis can impair nuclear maturation while cytoplasmic development continues resulting in macrocytic erythrocytes.

A few data on the correlation between response to some tyrosine kinase inhibitors (imatinib, sunitinib) and macrocytosis occurrence have been published so far (1, 6-8). In case of other tyrosine kinase inhibitors such as: sorafenib and erlotinib – macrocytosis does not occur (7, 8). The probability of macrocytosis increases with the duration of treatment. Macrocytosis develops at average after 3 cycles, which usually means 17 weeks of therapy with sunitinib (1). Macrocytosis was diagnosed regardless the type of neoplasm when sunitinib was used (1, 6-8). Sunitinib-induced macrocytosis is reversible with drug discontinuation (7). Macrocytosis seems to be a predictive factor for response to the therapy. Bevacizumab-humanized monoclonal antibody is an antiangiogenic drug partly similar to sunitinib. Insufficient data does not explain the presence of macrocytosis / increased MCV and potential correlation with the results of bevacizumab treatment.
In the presented study, macrocytosis did not occur during bevacizumab therapy. But, an increase of mean corpuscular volume was demonstrated. It was closely related to the response to the treatment with bevacizumab. It seems that an increasing mean corpuscular volume can be a predictive factor of bevacizumab response. However, considering heterogeneity of the sample (37% of the patients received concurrently capecitabine which causes macrocytosis) and a small number of patients enrolled to the analysis, further investigations with numerous patients are recommended.

CONCLUSIONS

Bevacizumab does not induce macrocytosis. Increased MCV after treatment with bevacizumab is related to the treatment response. Increased MCV can be a predictor of the response during bevacizumab treatment. A small number of the observed patients requires further investigations.

Conflict of interest

We declare no conflicts of interest.

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