Clin Transl Oncol (2016) 18:1082–1087
DOI 10.1007/s12094-016-1485-1

RESEARCH ARTICLE

Serum uric acid as a surrogate marker of favorable response to bevacizumab treatment in patients with metastatic colon cancer

F. Selcukbiricik[1] · M. Kanbay[2] · Y. Solak[3] · A. Bilici[4] · M. Kanıtez[5] · E. Balık[6] · N. M. Mandel[1,7]

Received: 27 October 2015 / Accepted: 7 January 2016 / Published online: 19 January 2016

Abstract Bevacizumab is a monoclonal antibody which is a vascular endothelial growth factor inhibitor. It obscures vascularization of tumor tissue and damages intratumoral microcirculation. The damaged intratumoral microcirculation leads to tissue hypoxia and results in increase of uric acid level. The main aim of our study was to investigate the relationship between uric acid change and response to bevacizumab therapy. This study included a total of 158 patients with metastatic colorectal cancer who had received bevacizumab therapy. The number of male patients was 100 (63.3 %) while female patients number was 58 (37.7 %). The median age was 61 (29–83). There was relationship between increase of uric acid level of third month uric acid level and stable disease ($p < 0.001$). There was a significant overall survival increased in the group with increased uric acid level ($p < 0.001$). The decline of CEA level was related to uric acid level ($p < 0.022$). In conclusion, this study is the first showing significant increases of serum uric acid in patients with metastatic colorectal cancer who favorably responded to chemotherapy with bevacizumab. But further studies are justified to test whether monitoring uric acid levels might predict clinical outcomes of patients with metastatic colorectal cancer.

Keywords Bevacizumab · Uric acid · Hypoxia · Metastatic colorectal cancer · Carcinoembryonic antigen · Survival

✉ F. Selcukbiricik
fsbiricik@yahoo.com

[1] Department of Medical Oncology, Faculty of Medicine, Koc University, Istanbul, Turkey

[2] Department of Nephrology, Faculty of Medicine, Koc University, Istanbul, Turkey

[3] Department of Nephrology, Sakarya Education and Research Hospital, Korucuk, Turkey

[4] Department of Medical Oncology, Faculty of Medicine, Medipol University, Istanbul, Turkey

[5] Department of Medical Oncology, Hamidiye Sisli Education and Research Hospital, Istanbul, Turkey

[6] Department of General Surgery, Faculty of Medicine, Koc University, Istanbul, Turkey

[7] Department of Medical Oncology, VKV American Hospital, Istanbul, Turkey

Introduction

Bevacizumab is a humanized monoclonal antibody which binds to vascular endothelial growth factor (VEGF) and prevents the binding of VEGF with its receptors, VEGFR-1 (Flt-1) and VEGFR-2 (Flk-1/KDR). Normally VEGF receptors are found on the surface of endothelial cells. VEGF plays a critical role in angiogenesis. In cancer tissues, increased expression of VEGF is associated with increased microvascular density, tumor growth, metastasis, and a poor prognosis. Bevacizumab has been approved as the first or second-line chemotherapy for the treatment of a number of advanced solid cancers such as colorectal cancer (CRC), breast cancer, non-small cell lung cancer, ovarian cancer, and renal cell cancer [1–4].

Recent years witnessed the resurgence of the interest in uric acid research. Uric acid has been implicated, albeit not unequivocal in some conditions, as a causative factor in hypertension, renal disease, atherosclerosis [5, 6], and the main pathophysiologic factors responsible for these effects were believed to be increased oxidative stress and resultant inflammation in hyperuricemic subjects.

Some data have accumulated regarding the role of increased serum uric acid levels in impairment of the microcirculation. Elevated serum uric acid has been shown to be associated with impaired microcirculation in a number of vascular beds including coronary and retinal microcirculation [7, 8]. However, a recent study did not confirm these preliminary results in that microcirculation in the skin was not associated with serum uric acid levels in a general population [9]. In fact, several other studies showed strong association of microvascular endothelial function deteriorates with increasing serum uric acid levels in several patient cohorts [10, 11].

On the other hand, it still remains to be seen if impaired microvascular function may lead to uric acid elevation in the serum. Uric acid is consistently overproduced by ischemic tissues and exerts immunomodulatory effects [12]. It has been put forward that uric acid and/or its precursors might behave as injury signals which are able to mobilize endothelial progenitor cells in acute renal ischemia [13, 14]. Although uric acid levels have been associated with some cancer types such as lymphoma, there were no documented relationship between uric acid levels and drugs especially bevacizumab.

Determination of effectiveness of bevacizumab therapy in metastatic colon cancer can be done by serial measurements of serum CEA and radiologic evidence for regression of tumoral tissues [15]. We hypothesized that since uric acid is associated with issue level ischaemia and bevacizumab is an inhibitor of neovascularization, effective inhibition of generation of new microvascular beds in the tumoral tissue leads to ischaemia and consequently increased serum uric acid levels. In sum, elevation of serum uric acid levels in the course of the bevacizumab treatment may be a surrogate marker of the effectiveness of bevacizumab treatment. Thus, we undertook an observational cohort study in which patients with metastatic CRC undergoing bevacizumab therapy to investigate whether any association between therapeutic effectiveness and serum uric acid levels exists.

Statistical analysis

Statistical analyses were performed using SPSS software (version 21. Inc., Chicago, IL, USA). The distribution of continuous variables for normality was tested with a one-sample Kolmogorov–Smirnov test and data were presented as mean ± standard deviation (SD) or median and interquartile ranges, as appropriate. Categorical variables were reported as frequencies and group percentages. Differences between survivor and exitus patients with normally and non-normally distributed variables were evaluated by the unpaired *t* test, and Mann–Whitney *U* test, respectively, as appropriate. The Wilcoxon signed-rank test was used to compare the change in serum uric acid values between baseline and after 3rd month of bevacizumab therapy. The Pearson correlation test was used to assess the strength of association between change in serum uric acid and CEA levels. A p value <0.05 was considered as statistically significant.

Materials and methods

This was an observational cohort study. Patients with metastatic CRC irrespective of their previous treatment status were recruited from outpatient register between 2008 and 2014. The following patient characteristics were obtained from patients' charts after written informed consent had been obtained from patients or their relatives: age, gender, histopathology, date of diagnosis, type of chemotherapy and targeted therapy, date of last visit, responses to treatment and survival. Also was detected uric acid and carcino embryonic antigen levels 0, 3, 6 and 12 months. The eligibility criteria consisted of who received as a targeted therapy bevacizumab therapy at diagnosis or following whichever organ metastasis and survival time >3 months. Patients with insufficient disease information, chronic kidney failure, diabetes mellitus, hypertansion, gout, receiving allopurinol, and thiazide type diuretics and who received patients targeted therapy except bevacizumab were excluded from the study. Response evaluation was made every 3 months. In addition, response evaluation was made according to response evaluation criteria in solid tumors-1.1 (RECIST-1.1) criteria as partial response, stable disease and progressive disease. Also was made response evaluation association UA levels and overall survival analysis.

All patients received bevacizumab treatment as part of a chemotherapeutic regimen varying between patients. The regimens included FOLFOX (consisting folinic acid, 5-FU, and oxaliplatin), FOLFIRI (folinic acid, 5-FU, and irinotecan) and XELOX (capecitabine and oxaliplatin). Chemotherapeutic regiments were given individual patients at discretion of the caring medical oncologist based on patient characteristics. However, bevacizumab was a part of all three chemo regimens. The dose and administration scheme of bevacizumab were as follows: 5 mg/kg per course and it was as follows 7.5 mg/kg per course for XELOX regimen.

The cut-off value for each biological baseline parameter was defined as follows serum uric acid levels were determined by using an enzymatic colorimetric method (Cobas Integra Uric Acid Casette; Roche Diagnostics, Indianapolis, IN) on an autoanalyzer (Cobas Integra 400; Roche Diagnostics) and serum CEA level was determined with the two-sided radio-immunometric assay by using the

IRMA-coat CEA kits (Byk Sangtec Diagnostica GmbH & Co. KG, Dietzenbach, Germany). The CEA and CA 19–9 values of the patients at the time of diagnosis and following treatment were determined. The normal value for CEA was 0.52–6.3 ng/mL for males and 0.42–4.8 ng/mL for females among smokers and 0.37–3.3 ng/mL for nonsmokers.

Results

Characteristics of the study population

Demographic and clinical characteristics of the study population are summarized in Table 1. The mean age was 60 ± 11 years in the survivor and 60 ± 12 years in the exitus groups, respectively. There were no differences in terms of age, gender and follow-up time between groups. On the other hand, progressive disease as non-response to chemotherapy was significantly different between survivor and exitus groups as expected (Table 1).

The chemotherapy regimens were consisting of bevacizumab and FOLFOX or FOLFIRI or XELOX. There were no significant differences between the groups in terms of chemotherapy regimens (Table 1).

The effect of bevacizumab therapy on serum uric acid levels

Baseline serum uric acid values were similar between exitus and survivor groups. We found a significant difference in serum uric acid levels 3 months after starting bevacizumab treatment ($p = 0.009$) whereas serum uric acid levels did not change significantly in the exitus group ($p = 0.53$; Table 2). Change (Δ uric acid) in serum uric acid levels between baseline and the third month of the follow-up period was significant only in the survivor patients (Fig. 1; Table 2).

The number of patients who do not respond to bevacizumab treatment (non-responsive group) were 73 (46.2 %). Although baseline serum uric acid levels were similar between non-responsive and responsive groups, serum uric acid levels at 3rd month after initiation of bevacizumab treatment were significantly higher in non-responsive group ($p < 0.0001$; Table 3). Change in serum

Table 1 Demographic and clinical characteristics of the study population

	Survivor ($n = 124$)	Exitus ($n = 34$)	p value
Age			
Mean ± SD	60 ± 11	60 ± 12	0.79
Follow-up (months)			
Median (min–max)	26 (2–77)	20 (1–108)	0.62
Gender (M/F)	80/44	20/14	0.54
Response to therapy			
Progressive disease	39 (32)	34 (100)	<0.001
Non-progressive disease	83 (68)	–	
Chemotherapy regimens			
5-FU + Bevacizumab	2 (1.6)	–	
FOLFOX + Bevacizumab	62 (50)	15 (44.1)	0.39
FOLFIRI + Bevacizumab	52 (41.9)	14 (41.2)	
XELOX + Bevacizumab	8 (6.5)	5 (14.7)	

FOLFOX is chemotherapy regimen, consisting folinic acid, 5-FU, oxaliplatin

FOLFİRİ is chemotherapy regimen, consisting folinic acid, 5-FU, irinotecan

XELOX is chemotherapy regimen, consisting capecitabine, oxaliplatin

Table 2 Correlation between survival and uric acid levels

	Exitus (+) ($n = 34$)	Exitus (−) ($n = 124$)	p value
Baseline uric acid	4.5 (3.8–5.6)	4.1 (3.8–4.9)	0.283
Uric acid after 3rd month of bevacizumab therapy	4.0 (3.7–6.1)	4.9 (4.0–7.1)	0.009
Δ uric acid	−0.45 ((−1.5)–0.9)	0.70 ((−0.75)–3.0)	0.012
p value*	0.531	<0.001	

Data are shown as median (25th–75th percentile). Analysis between groups, Mann–Whitney U test ($p < 0.05$); analysis of change within a group, Wilcoxon signed-rank test (* $p < 0.05$) were used

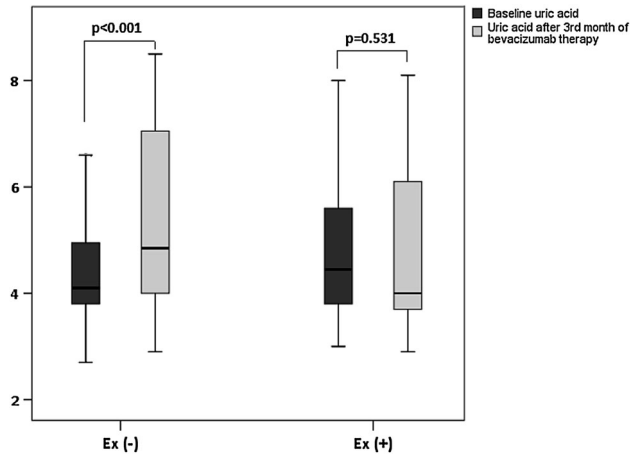

Fig. 1 Baseline and 3 months after serum uric acid level in survived and deceased patients

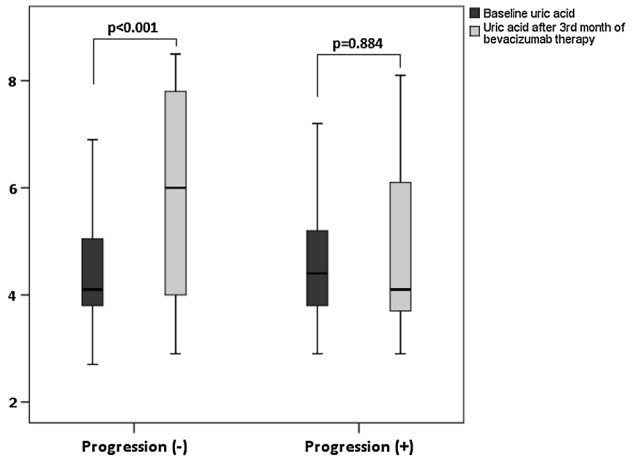

Fig. 2 Baseline and 3 months after serum uric acid level in survived and progressed and nonprogressed patients

uric acid levels between baseline and the 3rd month of the follow-up period was significant only in non-responsive group ($p < 0.0001$; Fig. 2; Table 3). In addition, we found a negative correlation between change (Δ CEA) in serum CEA levels and the change (Δ uric acid) in serum uric acid levels ($r = -0.222$, $p = 0.006$). In addition, Δ uric acid levels were significantly lower in patients with increased CEA levels after 3 months follow-up ($p = 0.02$; Fig. 3).

Discussion

The most striking result of this study was that change in serum uric acid (increase) could predict the favorable response to bevacizumab treatment in patients with metastatic CRC. We hypothesized that in patients who favorable responded to bevacizumab therapy, generation of new microvascular beds to existing tumoral tissues could effectively be prevented by bevacizumab treatment. This relative discrepancy between tumoral tissue and supplying vascular tissue produced local ischemia and hyperuricemia ensued. Negative significant correlation between change of uric acid and change of serum CEA levels also supported this association. Thus, hyperuricemia appeared as a

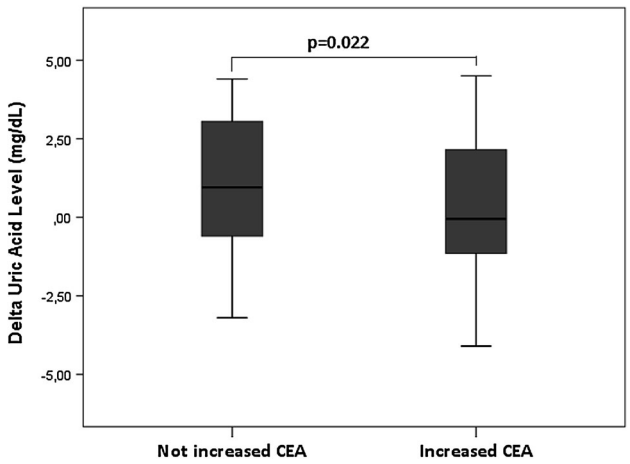

Fig. 3 According to carcinoembryonic antigen and delta uric acid level in survived and deceased patients

surrogate marker for the efficacy of bevacizumab treatment in patients with metastatic CRC.

Several lines of evidence pointed to the causative role of increased serum uric acid levels in endothelial dysfunction showed that serum uric acid was independently associated with endothelial function even in the general population [16, 17]. Microvascular dysfunction, another term related

Table 3 Correlation between response and uric acid levels

	Progression (+) ($n = 73$)	Progression (−) ($n = 83$)	p value
Baseline uric acid	4.4 (3.8–5.2)	4.1 (3.8–5.1)	0.654
Uric acid after 3rd month of bevacizumab therapy	4.1 (3.7–6.1)	6.0 (4.0–7.8)	<0.001
Δ uric acid	−0.30 ((−1.50)–1.20)	0.90 ((−0.45)–3.20)	0.001
p value*	0.884	<0.001	

Data are shown as median (25th–75th percentile). Analysis between groups, Mann–Whitney U test ($p < 0.05$); analysis of change within a group, Wilcoxon signed-rank test (*$p < 0.05$) were used

to impaired endothelial dysfunction in the microvasculature, was also shown to be related to increased serum uric acid levels. Coronary and retinal microvasculature was particularly affected by elevated serum uric acid levels [6, 7]. However, a recent population based study did not show such an association in dermal microvessels. It was speculated that all vascular beds are not the same in that different vascular beds may have different features of the myogenic control, a major mechanism accounting for the autoregulation of blood flow. Thus, it is possible that elevated serum uric acid may be associated with impaired microvasculature while not affecting dermal vessels.

Detrimental role of elevated serum uric acid and possible mechanisms on microvascular function was discussed in detail elsewhere, but little is known if the reverse is also true [11]. Microvascular dysfunction can lead to hypoxia of the organ or tissue supplied by the corresponding micro vessels. This has been studied well in coronary microvasculature [18]. Moreover, this microvascular dysfunction has been related to increased serum uric acid levels albeit it is difficult to ascertain which one was the initiator based on the study designs [19].

Uric acid has been shown to be increased in response to tissue ischaemia. Patschan et al. [12] showed in an experimental model in which mice were subjected to acute renal ischaemia showed a transient surge in serum uric acid levels. Some also argued that uric acid behaves as a danger signal in case of ischemia in several vascular beds [14].

Several randomized trials have shown the efficacy of adding bevacizumab to traditional chemotherapeutic regimens [20]. VEGF functions in angiogenesis by regulating both vascular proliferation and permeability. Bevacizumab blocks generation of new vessels, so-called neovascularization, in the tumor tissues via inhibiting of the function of VEGF. When deprived of nurturing vascular supply new tumor tissue does not develop. We hypothesized that if bevacizumab is effectively prevents neovascularization of the tumor tissue, hypoxia would ensue and serum uric acid levels would increase.

In fact, results of this study confirmed our hypothesis in that in patients who favorably responded to bevacizumab treatment showed a significantly more change in serum uric acid compared with patients in whom bevacizumab was found to be ineffective. In addition, serum CEA levels were also showed a negative correlation supporting the role of serum uric acid as a surrogate marker of the effectiveness of bevacizumab treatment.

The limitations to our study include that this is a retrospective analysis that has the associated issues of potential selection patient, incomplete data collection, and lack of pathology review. In addition, it should be keep in mind that high uric acid level may be as a result of tumor lysis syndrome. Attempts to address these concerns were made and several efforts to obtain complete patient information from medical records including such as phosphor and potassium.

In conclusion, this study is the first showing significant increases of serum uric acid in patients with metastatic CRC who favorably responded to chemotherapy with bevacizumab.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interests.

Informed consent It is human study and all participants have given inform consent.

References

1. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med. 2004;350(23):2335–42.
2. Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, et al. Paclitaxel–carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med. 2006;355(24):2542–50.
3. Miller K, Wang M, Gralow J, Dickler M, Cobleigh M, Perez EA, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med. 2007;357(26):2666–76.
4. Rini BI, Halabi S, Rosenberg JE, Stadler WM, Vaena DA, Archer L, et al. Phase III trial of bevacizumab plus interferon alfa versus interferon alfa monotherapy in patients with metastatic renal cell carcinoma: final results of CALGB 90206. J Clin Oncol. 2010;28(13):2137–43.
5. Kanbay M, Ikizek M, Solak Y, Selcoki Y, Uysal S, Armutcu F, et al. Uric acid and pentraxin-3 levels are independently associated with coronary artery disease risk in patients with stage 2 and 3 kidney disease. Am J Nephrol. 2011;33(4):325–31.
6. Kanbay M, Solak Y, Dogan E, Lanaspa MA, Covic A. Uric acid in hypertension and renal disease: the chicken or the egg? Blood Purif. 2010;30(4):288–95.
7. Gullu H, Erdogan D, Caliskan M, Tok D, Kulaksizoglu S, Yildirir A, et al. Elevated serum uric acid levels impair coronary microvascular function in patients with idiopathic dilated cardiomyopathy. Eur J Heart Fail. 2007;9(5):466–8.
8. Yuan Y, Ikram MK, Jiang S, Lin H, Ren L, Yan H, et al. Hyperuricemia accompanied with changes in the retinal microcirculation in a Chinese high-risk population for diabetes. Biomed Environ Sci. 2011;24(2):146–54.
9. Wijnands JM, Houben AJ, Muris DM, Boonen A, Schram MT, Sep SJ, et al. Uric acid and skin microvascular function: the Maastricht study. J Hypertens. 2015;33(8):1651–7.
10. Matheus AS, Tibiriçá E, da Silva PB, de Fátima Bevilácqua da Matta M, Gomes MB. Uric acid levels are associated with microvascular endothelial dysfunction in patients with type 1 diabetes. Diabet Med. 2011;28(10):1188–93.
11. Kanbay M, Sánchez-Lozada LG, Franco M, Madero M, Solak Y, Rodriguez-Iturbe B, et al. Microvascular disease and its role in the brain and cardiovascular system: a potential role for uric acid as a cardiorenal toxin. Nephrol Dial Transplant. 2011;26(2):430–7.
12. Patschan D, Patschan S, Gobe GG, Chintala S, Goligorsky MS. Uric acid heralds ischemic tissue injury to mobilize endothelial progenitor cells. J Am Soc Nephrol. 2007;18(5):1516–24.
13. Miller WL, Thomas RA, Berne RM, Rubio R. Adenosine production in the ischemic kidney. Circ Res. 1978;43:390–7.
14. Shi Y, Evans JE, Rock KL. Molecular identification of a danger signal that alerts the immune system to dying cells. Nature. 2003;425:516–21.
15. de Andrade DP, Lima JP, Lima AD, Sasse AD, dos Santos LV. Bevacizumab in metastatic colorectal cancer and carcino-embryonic antigen kinetics: case report and review of literature. Anticancer Drugs. 2011;22(Suppl 2):S15–7.
16. Kanbay M, Huddam B, Azak A, Solak Y, Kadioglu GK, Kirbas I, et al. A randomized study of allopurinol on endothelial function and estimated glomular filtration rate in asymptomatic hyperuricemic subjects with normal renal function. Clin J Am Soc Nephrol. 2011;6(8):1887–94.
17. Maruhashi T, Nakashima A, Soga J, Fujimura N, Idei N, Mikami S, et al. Hyperuricemia is independently associated with endothelial dysfunction in postmenopausal women but not in premenopausal women. BMJ Open. 2013;3(11):e003659.

18. Lanza GA, Crea F. Primary coronary microvascular dysfunction: clinical presentation, pathophysiology, and management. Circulation. 2010;121(21):2317–25.
19. Xia S, Deng SB, Wang Y. Clinical analysis of the risk factors of slow coronary flow. Heart Vessels. 2011;26(5):480–6.
20. Petrelli F, Coinu A, Ghilardi M, Cabiddu M, Zaniboni A, Barni S. Efficacy of oxaliplatin-based chemotherapy + bevacizumab as first-line treatment for advanced colorectal cancer: a systematic review and pooled analysis of published trials. Am J Clin Oncol. 2015;38(2):227–33.