ANSWERING REVIEWERS

July 4, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 3865-review.doc).

Title: The role of bevacizumab in malignant tumor growth and its adverse effects: a review

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The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated
2 Revision has been made according to the suggestions of the reviewer
Reviewer(1) 1. It has already been done. All the ''Abstract'' summarizes the key points of this review. Also, the following text has been added in the ''Introduction'' as suggested (page 3, six last lines)
''The topic of this study, currently, attracts much interest in clinical oncology and experimental research. VEGF by promoting angiogenesis favours tumor growth, while its inhibition results in tumor limitation. The novel anti-angiogenic agent bevacizumab is a recombinant humanized monoclonal antibody against VEGF activity. This targeted therapy is presently used mainly in metastatic colorectal cancer combined with chemotherapy.''
2. A summary has been added at the end of the paper as conclusions (page 16,17).
''Conclusions
*VEGF promoting angiogenesis favours tumor growth. Bevacizumab, which is a recombinant humanized monoclonal antibody against VEGF activity, inhibiting the angiogenesis restricts malignant cell growing and thus it prevents tumor spread. It has been recently used as target therapy in combination with chemotherapy, mainly in advanced colorectal cancer with hepatic or other metastasis, secondly in breast cancer inspite of the debate and occasionally in pancreatic cancer (but without proven efficiency), ovarian tumors, small-cell lung cancer, renal cancer and prostate cancer. Increasing research in experimental studies also attracts great interest for its use in other advanced malignancies. This novel biological agent is, generally safe and well-tolerated. However, there are rare, though serious side effects and complications that should be considered***.''**
3. I think it is better to be the ''Experimental use- perspectives'' as separate part stressing the large research effort on this topic, but still before the clinical use. The ''Clinical application'' constitutes a separate section and refers to clinical trials not in experimental studies.
4. I agree that Bevacizumab binds to VEGF, not to its receptors. The opposite was done by mistake (I am apologized) and it has been corrected by changing the phrase (page 8, last paragraph)
''As a result, even small doses of the drug (0.3 mg/kg B.W.) may be bound with VEGF preventing the incorporation with its receptors and thus inactivating all VEGF efficiency.''
Reviewer(2) According to the suggestion four new lines have been added in page 6 and the corresponding three new references (Ref, 12,13,14).
''The role of VEGF in other diseases such as allergic and immune-mediated diseases has been well-established[12,13]. The

potential positive effect of other biological drugs (specific immunotherapy) such as TNF-a inhibitors upon the mechanisms of action of VEGF has also been debated[14].''

12. Ciprandi G, Murdaca G, Colombo BM, De Amici M, Marseglia GL. Serum vascular endothelial growth factor in allergic rhinitis and systemic lupus erythematosus. Hum Immunol 2008; 69 :510-512.

13. Ciprandi G, Colombo BM, Murdaca G, De Amici M. Serum vascular endothelial growth factor and sublingual immunotherapy. Allergy 2008; 63: 945-946.

14. Murdaca G, Spanò F, Miglino M, Puppo F. Effects of TNF-a inhibitors upon the mechanisms of action of VEGF. Immunotherapy 2013; 5: 113-115.

Reviewer(3) According to the first suggestion the following text has been added in page 10

''A large randomized multi-centre control trial showed that the addition of bevacizumab in the treatment with capecitabine plus or minus mitomycin improved significantly the progression-free survival (PFS) without inducing further major toxicity; only the expected modest adverse events including proteinuria, hypertension, arterial thromboembolism and hemolytic uremic syndrome. However, it did not improve response rate (RR) or overall survival (OS); overall quality of life (QOL) was similar. Furthermore, there were 11 treatment-related deaths: one in the capecitabine group (sepsis); seven in the capecitabine- bevacizumab group (hemorrhage, myocarditis, bowel perforation, sepsis); and three in the capecitabine- bevacizumab- mitomycin group (hemorrhage, pulmonary embolism, neutropenic colitis)[35].''

According to the second suggestion the following text has been added at the end of page 13; also, the suggested four new references (56-59)

''Bevacizumab has also been used in primary and metastatic brain tumors mainly in glioblastomas[55]. It has been researched extensively in patients with primary brain malignant gliomas and has been approved as second line chemotherapy alone or in combination with irinotecan following first or second recurrence after radiotherapy and temozolomide[56-58]. Furthermore, the efficacy and safety of combining bevacizumab with standard-of-care therapy in patients with newly diagnosed glioblastoma multiforme of the brain is currently being studied by AVAGLIO phase III randomized trial[59].''

56. Vredenburgh JJ, Desjardins A, Herndon JE 2nd, Marcello J, Reardon DA, Quinn JA, Rich JN, Sathornsumetee S, Gururangan S, Sampson J, Wagner M, Bailey L, Bigner DD, Friedman AH, Friedman HS. Bevacizumab plus irinotecan in recurrent glioblastoma multiforme. J Clin Oncol 2007; 25: 4722-4729.

57. Kreisl TN, Kim L, Moore K, Duic P, Royce C, Stroud I, Garren N, Mackey M, Butman JA, Camphausen K, Park J, Albert PS, Fine HA. Phase II trial of single-agent bevacizumab followed by bevacizumab plus irinotecan at tumor progression in recurrent glioblastoma. J Clin Oncol 2009; 27: 740-745.

58. Friedman HS, Prados MD, Wen PY, Mikkelsen T, Schiff D, Abrey LE, Yung WK, Paleologos N, Nicholas MK, Jensen R, Vredenburgh J, Huang J, Zheng M, Cloughesy T. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. J Clin Oncol 2009; 27: 4733-4740.

59. Chinot OL, de La Motte Rouge T, Moore N, Zeaiter A, Das A, Phillips H, Modrusan Z, Cloughesy T. AVAglio: Phase 3 trial of bevacizumab plus temozolomide and radiotherapy in newly diagnosed glioblastoma multiforme. Adv Ther 2011; 28: 334-340.''

Reviewer (4,5) 1. It has been corrected: bound (Abstract-line 7), posphorylation (page 4).

2. It has been added schematic drawing for the mechanism action of VEGF- bevacizumab (page 7).

3. It has been corrected (page 8): *''As a result, even small doses of the drug (0.3 mg/kg B.W.) may be bound with VEGF preventing the incorporation with its receptors and so inactivating all VEGF efficiency.''*

4. The main clinical trials have been highlighted in the bevacizumad FDA and EMA approval by adding (page 10,11,12) with the relevant new references (37-46).

''The U.S. Food and Drug Administration (FDA) in February 2004 based on a pivotal study approved bevacizumab for the first-line treatment of patients with metastatic carcinoma of the colon and rectum. In this study, 833 patients were randomly allocated to irinotecan, 5-FU, and leucovorin (LV) either alone (the IFL regimen) or with bevacizumab (5

mg/kg every 2 weeks). In the group with bevacizumab, overall survival was significantly longer (median, 20.3 months versus 15.6 months) as well as the progression-free survival and response rate [24]. Later on June 20, 2006, the FDA approved bevacizumab administered in combination with FOLFOX4 (5-fluorouracil, leucovorin, and oxaliplatin) as a second-line treatment for metastatic carcinoma of the colon or rectum. It was based in the Eastern Cooperative Oncology Group (ECOG) open-label, multicenter, randomized, three-arm, active-controlled trial. In this study, 829 patients with recurrence following prior chemotherapy were randomly allocated to bevacizumab (10 mg/kg, as a 90-minute i.v. infusion on day 1, every 2 weeks) with FOLFOX4, or FOLFOX4 alone. In the group with bevacizumab, there was a statistically significant and clinically meaningful improvement in overall survival (13.0 months versus 10.8 months) in patients whose disease had progressed after adjuvant chemotherapy with 5-FU and irinotecan and in patients with advanced or metastatic disease who had received prior 5-FU and irinotecan. The administration of bevacizumab was beneficial in any sub group, well tolerated and with no impact on quality of life[37].

A recent phase II study adding bevacizumab to capecitabine plus irinotecan (XELIRI) found an acceptable tolerability and improvement outcome as first-line treatment for metastatic colorectal cancer[38].

An updated meta-analysis and systematic review of 10 randomized controlled trials including 1366 patients has identified the additional benefits of BEV to cytotoxic chemotherapy in overall survival (OS) and progression-free survival (PFS) in metastatic colorectal cancer[39].

However, there is controversy to the aforementioned, in a large phase III trial among 2,672 patients with stages II to III colon cancer. By adding bevacizumab to modified FOLFOX6 (mFOLFOX6; ie, infusional/bolus fluorouracil, leucovorin, and oxaliplatin) as adjuvant treatment for 1 year, it does not significantly prolong disease free survival[40].

The development of bevacizumab-induced hypertension as biomarker did not predict radiological response or survival in patients with poor-risk colorectal liver-only metastases unsuitable for upfront resection[41].

Overall survival, disease-free survival, and local control showed favourable trends in patients with stage II/III rectal cancer treated with neo-adjuvant bevacizumab with chemoradiotherapy followed by surgery[42]. Another study with neo-adjuvant oxaliplatin, bevacizumab, continuous infusion 5-FU, and radiation in rectal cancer was terminated early because of significant gastrointestinal toxicity[43].

Bevacizumab has been used as first line treatment early in advanced cancer and in patients with Stage III unresectable or Stage IV adenocarcinoma of the colon or rectum[44,45].

A retrospective analysis of a large USA managed database has estimated lower cost of treatment containing bevacizumab rather than cetuximab[46].''

5. For the pharmaco-economic approach, it has been added (page 12) with the relevant new references (50-54).

''Results of trial E2100 led to the initial approval of bevacizumab as first-line therapy for patients with metastatic breast cancer in the U.S.A. in February 2008. However, based on results from subsequent trials, the U.S. FDA Oncologic Drugs Advisory Committee (ODAC) revoked its approval in July 2010[50-52]. The drug costs about $90,000 (£58,000; €68,000). The drug had not been shown to be safe and effective in metastatic breast cancer, since several studies did not show influence in overall survival and also benefits overcoming the drug's serious and potentially life-threatening side effects.

Despite the FDA decision, it was not withdrawn in Europe by the European Medicines Agency (EMA), but the prescribing practice has been reduced[50]. A recent survey highlights the discord between the opinion of the oncologists and the FDA's recent decision[53]; likewise there is another controversy with FDA decision[54].''

References and typesetting were corrected

English editing has been done by a doctor native speaker of English. Thus, the quality of language has been improved. I guarantee myself for this linguistic revision.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology.*

Sincerely yours,

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