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Role of von Willebrand factor levels in the prognosis of stage IV colorectal cancer: Do we have enough evidence?

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TO THE EDITOR

Cancer patients usually present a prothrombotic condition. Several clotting-related proteins, such as von Willebrand factor (vWF), presenting higher plasma concentrations in these patients, may play a key role in this process. Moreover, some of those proteins are currently being characterized as response rate and overall survival markers in metastatic colorectal cancer (MCRC). In this comment article, we discuss the last piece of evidence that supports the use of vWF as a prognostic indicator in MCRC patients, provided by a paper recently published by Wang *et al*., in the *World Journal of Gastroenterology*. Summarizing, although vWF should be seriously considered as potential future prognostic and predictive indicator in colorectal cancer, more dynamic and better designed studies in longer series of patients should be conducted before standardizing its universal use among these patients.

Wang *et al*.[1], have recently published an encouraging paper in the World Journal of Gastroenterology regarding the possible and novel use, as a prognostic factor, of vWF plasma levels in MCRC.

As the authors expose, cancer patients often show an imbalance between coagulation and fibrinolysis systems, which results in their prothrombotic condition[2-6]. Several clotting-related proteins, such as vWF, presenting higher plasma concentrations in these patients[7-11], may play a key role in this process. Moreover, some of those proteins are currently being characterized as response rate and overall survival markers in MCRC[12-16].

Accordingly, the data shown by Wang *et al*.[1], seem to indicate that plasma vWF concentrations are increased among colorectal cancer patients and correlate with tumor stage. In addition, those vWF higher levels may be related to significantly poor prognosis of subjects presenting metastasis.

However, although authors are aware of the important variability of vWF levels in humans due to the presence of a variety of diseases like diabetes mellitus, connective tissue disease, cardiovascular dysfunctions, thrombo-embolic events, acute infections, and other conditions like age or gender[17-20], patients suffering any of those illnesses were not apparently excluded from the study nor controlled by those factors in the multivariate analysis.

More strikingly, even though platelets are partially responsible for vascular endothelial growth factor (VEGF) levels[21-25], and VEGF is considered the most potent activator of the endothelium (main vWF producer), neither platelet count nor VEGF levels were measured and included in the statistical analysis.

Other issue that remains unclear in this article is whether the chemotherapy (CMT) regime used (5-fluorouracil alone or in combination with irinotecan, oxaliplatin or capecitabine) in each group of patients could have accounted for the differences observed between the survival curves for individuals presenting vWF ¡ Ý160% and those with levels below that threshold. Thus, in order to avoid the possible bias, the CMT regime administered to each patient should have also been taken into account in the multivariate statistical analysis.

Finally, given the fact that the CMT could catalyze the original risk for progression and death in these patients due to its alleged antiangiogenic effect, measuring vWF concentrations during treatment may modify the prognostic value of this protein.

According to this, in the University Clinic of the University of Navarra, 64 colorectal cancer patients were enrolled from 2002 and 2004. Blood samples were taken dynamically before and after fluoropirimidine-based CMT in 32 patients presenting metastasis, and stored until further processing. vWF, VEGF, plasminogen activator inhibitor

(PAI) 1, D-dimer, fibrinogen levels and platelet count were measured before and after CMT using standardized techniques. Gender, age, ECOG performance status, tumor burden, CMT course, and regime and CEA/CA 19.9 levels were also considered for the statistical analysis. Patients received a median of 3 cycles of CMT (range: 2-10) between both blood samples. After a median follow-up of 10 mo, baseline levels of vWF >202% showed an associated hazard ratio (HR), for death higher than patients with vWF ¡Ü202%, with tendency to the statistical significance ($P = 0.08$). Meanwhile, post-CMT vWF levels above 189% were related to a fourfold HR for progression with respect to those subjects showing concentrations ¡Ü189% after CMT treatment. These results were adjusted for the rest of the different protein levels measured, age, gender, ECOG performance status, tumor burden, and CMT course and regime.

In conclusion, although vWF and other coagulation/fibrinolysis factors should be seriously considered as potential future prognostic and predictive indicators in colorectal cancer, more dynamic and better designed studies in longer series of patients should be conducted before standardizing their universal use among these patients.

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