Circulating Matrix Metalloproteinase-9 Levels as a Biomarker of Disease

To the Editor: Nikkiola et al. (1) have recently addressed the prognostic value of serum levels of matrix metalloproteinase 9 (MMP-9), collagenase 1, and collagenase 3 in patients with advanced melanoma. Specifically, the serum levels of MMP-9 were determined by ELISA, Western blot, and gelatin zymography analysis. They have found that patients with high serum levels of MMP-9 had poorer overall survival than patients with lower serum MMP-9 levels, and high MMP-9 levels were found to be associated with metastasis, high alkaline phosphatase levels, and liver metastases. Therefore, they have concluded that serum MMP-9 could have clinical value in identifying patients at increased risk for melanoma progression. There is evidence, however, indicating that their MMP-9 results in serum do not reliably reflect the circulating levels of MMP-9. Measurement of MMP-9 levels in serum has been reported as artificially high compared with the results obtained from plasma samples (2–4). In addition, there is no correlation between MMP-9 levels in serum and in plasma. In summary, preanalytic conditions and other methodologic issues are of major importance when assessing MMPs in clinical samples (5). Therefore, there is strong evidence indicating that serum samples should not be used to measure circulating MMP-9 levels as a diagnostic or as a prognostic marker of disease (6).

Raquel F. Gerlach
Department of Morphology, Estomatology, and Physiology
Dental School of Ribeirao Preto
University of Sao Paulo
Ribeirao Preto, Brazil

Jose E. Tanus-Santos
Department of Pharmacology
Faculty of Medicine of Ribeirao Preto
University of Sao Paulo
Ribeirao Preto, Brazil

References

In Response: We thank Prof. Tanus-Santos for his criticism on our article “High serum levels of matrix metalloproteinase-9 and matrix metalloproteinase-1 are associated with rapid progression in patients with metastatic melanoma” published in Clinical Cancer Research on July 15, 2005 (1).

We conclude that matrix metalloproteinase (MMP)-1, MMP-9, and MMP-13 have important roles at different phases of metastatic spread and that serum MMP-9, in particular, could be of clinical value when identifying patients at high risk for progression. Our original work was sent to Clinical Cancer Research in June 2003. At that time, there were only few studies about prognostic markers in metastatic melanoma and research activity has been increasing in recent years.

We agree that there might be some methodologic concerns in our work. In this study, however, our aim was not to find the most optimal laboratory method, but to see whether serum marker measurement might have a prognostic role in addition to computed tomography scans in stage IV melanoma patients who already had a diagnosed disease. In spite of Prof. Tanus-Santos’ criticism, there are more than 40 recently published articles in which correlation between serum MMP levels and prognosis or survival in patients with cancer has been found (2–4). Most studies have also shown that serum MMP levels are clearly increased among cancer patients when compared with healthy controls (2).

Some conversation about the optimization of the measurement of blood MMP levels has been engaged already, but Tanus-Santos et al. recommend in their recent article that plasma samples should be used to measure MMP activities and that serum samples should not be used. There are also some controversial studies about MMP measurements in tumor and plasma samples. Curran et al. (5) have shown that tumor tissue MMP profile is an independent prognostic indicator in colorectal cancer, but Waas et al. (6) did not find any correlation between plasma proMMP-2 and proMMP-9 activities and prognosis of patients with colorectal cancer. What is important in marker studies on the clinical aspect is that the same method is used throughout the study. Tanus-Santos et al. do not recommend the use of serum samples because, in that way, artificially higher levels of MMPs would be measured. From the clinical point of view, however, no disease-specific level of MMP-9 can be pointed out and if MMP-9 value is used in clinical practice, the measurements should be followed individually only and together with computed tomography scans. If we study the value variation during a patient’s disease progression, the absolute low or high value is not important—it is more important to follow the trend. This can be seen, for example, when using serum or plasma measurements of other markers, such as Ca15-3 in breast cancer, which can be “normal” even when breast cancer is metastatic.

As an individual study, we think that our work provides at least a guideline about the importance of MMP-9 in cancer progression. Obviously, more work is needed to confirm our results and to develop the measurement of MMPs in clinical
practice. Because of the different measuring methods, it is probably not recommended to compare the MMP levels such as those between different studies.

Pia Vihinen
Department of Oncology and Radiotherapy, Turku University Hospital, Turku, Finland

References
Circulating Matrix Metalloproteinase-9 Levels as a Biomarker of Disease

Raquel F. Gerlach and Jose E. Tanus-Santos


Updated version
Access the most recent version of this article at:
http://clincancerres.aacrjournals.org/content/11/24/8887

Cited articles
This article cites 11 articles, 4 of which you can access for free at:
http://clincancerres.aacrjournals.org/content/11/24/8887.full.html#ref-list-1

Citing articles
This article has been cited by 2 HighWire-hosted articles. Access the articles at:
/content/11/24/8887.full.html#related-urls

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.