Serum levels of OPG, RANKL and RANKL/OPG ratios in newly-diagnosed patients with multiple myeloma. Clinical correlations

Serum levels of OPG and RANKL and their clinical correlations were analyzed in 66 newly–diagnosed patients with multiple myeloma (MM). RANKL and RANKL /OPG ratios were significantly increased in advanced clinical stages and high grade myeloma bone disease (MBD), while OPG showed a tendency to decrease. Renal failure modified the expression of OPG. RANKL and RANKL/OPG ratios are informative markers for myeloma tumor burden and MBD.

Haematologica 2007; 92:1000-1001

OPG/RANKL system is a critical regulator of bone metabolism. A serious imbalance of the system has been found in multiple myeloma (MM). Myeloma cells participate directly in this process. They induce RANKL expression by the bone marrow stromal cells and osteoblasts and most probably produce certain amounts of RANKL themselves. On the other hand myeloma cells bind, internalize and degrade OPG,[1] and inhibit the activity of osteoblasts. While the experimental data for OPG/RANKL system in MM are well-founded, there are few clinical studies on the problem in MM patients.

To contribute to the understanding of the role of OPG/RANKL system in myeloma patients, we analyzed the serum levels of OPG and RANKL in 66 newly–diagnosed patients with MM and 32 healthy controls, their expression in the clinical stages and grades of myeloma bone disease (MBD), the influence of renal failure on their levels and their correlations with basic parameters of disease activity. Mean age of the patients was 61.3±9.2 years, 29 males and 37 females. Fifty-three percent were in clinical stage III (ISS). Renal failure (RF) was confirmed in 40.9% and MBD in 84.8% (graded according to the Merlini scale). Analyses were carried out with ELISA (Biomedica, Vienna kits). Statistical analyses were carried out using the Mann-Whitney test, one-way ANOVA and Spearman's correlations. OPG levels were significantly higher in MM patients compared with the controls, but the OPG/creatinin ratio eliminates the difference. Literature reports three possible types of results: low levels of OPG,[2-4] high[5-7] and no difference with controls.[8] In MM patients, the levels of RANKL and RANKL/OPG ratio were more than two times higher than controls (p<0.001). This agrees with most other studies.[4,8,9] OPG shows a tendency to decrease in the advanced clinical stages (NS) and in high grade MBD (S). The lowest OPG level was measured in patients with severe bone lesions (4.26±0.36 pmol/L). RANKL and RANKL/OPG ratios significantly increase in advanced clinical stages and in patients with severe bone lesions. They are highest in clinical stage III and in MBD grade 2+3 (Table 1). Reasonably OPG and OPG/creatinin ratios correlate reversely with MBD and bone marrow infiltration. RANKL and RANKL/OPG ratios have positive correlations with the clinical stage, grade of MBD, percentage of bone marrow infiltration and LDH. The strongest correlation was found between the RANKL/OPG ratio and MBD (Table 2). OPG is high in early clinical stages and in patients with minimal bone lesions because, as in the patients with MGUS and benign osteoporosis, osteoblast function is still coupled to the intensified osteoclast function. Its decrease as the disease evolves is a result of the suppressive effects of myeloma cells. In advanced clinical stages, RANKL and RANKL/OPG ratios rise significantly. Other studies observed differences between each clinical stage, between clinical stage I and MGUS, and between MGUS and healthy controls.[8] They are elevated even in myeloma patients without bone lesions, and are significantly higher in patients with multiple bone lesions.[9] Not surprisingly, significant positive correlation between RANKL and extent of MBD have also been found by other investigators.[10]

Renal failure (RF) has a specific influence on OPG/RANKL system. MM patients have significantly higher levels of OPG, RANKL and RANKL/OPG ratios compared with controls. But patients with *severe bone lesions + RF* have significantly lower OPG compared with the group with *minimal or no bone lesions + RF* (4.92±0.62 pmol/L *vs.* 9.97±2.42 pmol/L; p<0.05). We interpret this finding as the skeletal response to the combined but opposite effects of renal insufficiency and osteolytic activity produced and/or induced by myeloma cells. In advanced clinical stages, although RF progresses, OPG is significantly lower because of the accumulation of the myeloma tumor mass. RANKL and RANKL/OPG ratios are very informative markers of MBD and myeloma tumor burden. OPG level in MM is influenced by many factors and has specific dynamics, depending on the counter-active signals for its production and inhibition.

Table 1. Serum levels of OPG, RANKL and RANKL/OPG ratio in patients with multiple myeloma and controls.

Groups	*N*	*OPG pmol/L X±Sx*	*RANKL pmol/L X±Sx*	*RANKL/OPG X±Sx*
Controls	32	3.77±0.33	0.203±0.031	0.053±0.003
MM patients	66	5.36±0.46*	0.458±0.046*	0.114±0.013*
Clinical stage I+II	31	5.85±0.67	0.329±0.050	0.086±0.019
Clinical stage III	35	4.93±0.63	0.571±0.416*	0.139±0.018*
MBD gr "0 + 1"	30	6.69±0.86	0.300±0.025	0.057±0.006
MBD gr "2 + 3"	36	4.26±0.36*	0.589±0,076*	0.162±0.021*
Creatinin <166 μmol/L	39	4.51±0.33	0.392±0.047	0.089±0.003
Creatinin >166μmol/L	27	6.60±1.00	0.552±0.088	0.150±0.025*

**difference significant at p<0.05.*

Table 2. OPG /RANKL system in multiple myeloma –clinical correlations.

Parameter	*OPG pmol/L*		*OPG/creatinin*		*RANKL*		*RANKL/OPG*	
	p	*r*	*p*	*r*	*p*	*r*	*p*	*r*
Stage	NS		NS		<0.001	+0.423	<0.001	+0.499
MBD	<0.05	-0.323	<0.001	-0.521	<0.001	+0.557	<0.001	+0.651
BM inf.	NS	–	<0.001	-0.530	0.004	+0.346	<0.001	+0.427
β2 mg	<0.05	+0.375	NS	–	NS	–	NS	–
LDH	NS	–	NS		0.001	+0.397	<0.001	+0.421

Veselina Goranova-Marinova, Stefan Goranov, Pavel Pavlov, Todorka Tzvetkova**

*Clinic of Hematology, University Hospital "Sv.Georgi"-Plovdiv; *Central Clinical Laboratory, University Hospital "Sv. Georgi", Plovdiv, Plovdiv, Bulgaria*

Correspondence: Veselina Goranova-Marinova, Clinic of Hematology, University Hospital"Sv.Georgi"-Plovdiv, 15 A Vasil Aprilov blv, Plovdiv 4002, Bulgaria. Phone: international +359.32602481. Fax: international +359.32602481. E-mail: vesselina_goranova@yahoo.com

References

1. Standal T, Seidel C, Hjertner O, Plesner T, Sanderson RD, Waage A, et al. Osteprotegerin is bound internalized and degraded by multiple myeloma cells. Blood 2002; 100: 3002-7
2. Lipton A, Ali SM, Leitzel K, Chinchilli V, Witters L, Engle L, et al. Serum osteoprotegerin levels in healthy controls and cancer patients. Clin Cancer Res 2002;8:2306-10
3. Seidel C, Hijerther Q, Abilgaard N, Heickendorff L, Hjorth M, Westin J, et al. Serum osteoprotegerin levels are reduced in patients with multiple myeloma with lytic bone disease. Nordic Myeloma Study Group. Blood 2002; 98:2269-71
4. Terpos E, Szylo R, Apperley JF, Hatjiharissi E, Politou M, Meletis J, et al. Soluble receptor activator of nuclear factor κ B ligand (RANKL) - osteoprotegerin ratio predicts survival in multiple myeloma: proposal for novel prognostic index. Blood 2003;102:1064-9
5. Politou M, Terpos E, Anagnostopoulos A, Szydlo R, Laffan M, Layton M, et al. Role of receptor activator of nuclear factor κ B ligand (RANKL), osteoprotegerin and macrophage inflamatory protein 1-alpha (MIP1a) in monoclonal gammopathy of undetermined significance (MGUS). Br J Heamatol 2004;126:686-9
6. Kraj M, Owczarska K, Sokołowska U, Centkowski P, Poglód R, Kruk B. Correlation of osteoprotegerin and sRANKL concentrations in serum and bone marrow of multiple myeloma patients. Arch Immunol Ther Exp 2005; 53:454-64.
7. Corso A, Dovio A, Rusconi C. Osteoprotegerin serum levels in multiple myeloma and MGUS patients compared with age, sex- and age-matched healthy controls. Leukemia 2004;18:1555-78
8. Kyrtsonis MC, Vassilakopoulos TP, Siakantaris MP, Kokoris SI, Gribabis DA, Dimopoulou MN, et al. Serum syndecan -1, basic fibroblast grouth factor and osteoprotegerin in myeloma patients at diagnosis and during the course of the disease. Eur J Hematol 2004;72:252-8.
9. Jakob C, Sterz J, Kleeberg L. Serum total-RANKL is elevated in patients with multiple myeloma, increases with ISS stage and decreases under induction therapy. Blood 2005; 11[Abstract 2511].
10. Heider U, Langellotz C, Jacob C, Zavrski I, Fleissner C, Eucker J, et al. Expression of receptor activator of nuclear factor κB ligand on bone marrow plasma cells correlates with osteolytic bone disease in patients with multiple myeloma. Clin Cancer Res 2003;63:5438-45.