

# blood

1992 79: 2174-2176

## **Hyperreactive cellular immunity in multiple myeloma [letter; comment]**

G Reibnegger, H Wachter, M Krainer, H Ludwig, M Herold and H Huber

---

Information about reproducing this article in parts or in its entirety may be found online at:  
[http://bloodjournal.hematologylibrary.org/misc/rights.dtl#repub\\_requests](http://bloodjournal.hematologylibrary.org/misc/rights.dtl#repub_requests)

Information about ordering reprints may be found online at:  
<http://bloodjournal.hematologylibrary.org/misc/rights.dtl#reprints>

Information about subscriptions and ASH membership may be found online at:  
<http://bloodjournal.hematologylibrary.org/subscriptions/index.dtl>



### **HYPERREACTIVE CELLULAR IMMUNITY IN MULTIPLE MYELOMA**

*To the Editor:*

The demonstration of hyperreactive T cells in patients with multiple myeloma by Massaia et al<sup>1</sup> is of particular interest for the understanding of the functional activity of the immune system in this disorder. Our data on neopterin serum concentrations in

patients with multiple myeloma<sup>2</sup> point to immunologic activation in this disease and, in addition, indicate prognostic importance of this activation marker.

Neopterin is synthesized in human monocytes and macrophages from guanosine triphosphate (GTP) after stimulation by interferon- $\gamma$ ,<sup>3</sup> because the key enzyme of pteridine biosynthesis, GTP cyclohy-

drolase I, is regulated by interferon- $\gamma$ .<sup>4</sup> Neopterin has been identified as a useful *in vivo* indicator of the state of activation of the cellular immune system.<sup>5</sup> In malignant diseases, increased neopterin levels in serum or increased neopterin urinary excretion have been shown to be an important indicator for an unfavorable course of the disease.<sup>6-10</sup>

We have measured serum neopterin levels by immunoassay and interleukin-6 (IL-6) levels by bioassay in 44 patients with multiple myeloma.<sup>2</sup> Both neopterin and IL-6 showed a significant positive correlation with tumor stage. By univariate survival analysis using the product-limit approach, both neopterin ( $P = .0001$ ) and IL-6 ( $P = .025$ ) were significant predictors of survival. However, when tumor stage was included in a multivariate proportional hazards model for survival, only neopterin and stage were jointly significant; whereas for IL-6 only a tendency towards additional predictive information not reaching statistical significance was observed. In several tested multivariate models, including a variety of potentially predictive markers such as stage, hemoglobin, renal function, and others, neopterin remained a significant predictor. The findings are compatible to data obtained in other cancers in which neopterin has been shown to be of important prognostic value independent of many other prognostic variables.<sup>6-10</sup>

Our data indicate that the predictive information obtained by IL-6, which is an important paracrine growth factor in multiple myeloma, may in part be already contained in the tumor stage. In contrast, the predictive value of neopterin, which is regarded to be

a marker for activation of early events of cellular immunity, remained significant in the multivariate models because neopterin data provide information on a different aspect of the disease.

In conclusion, our data on increased neopterin concentrations in patients with multiple myeloma are compatible with the presence of activated T cells as putative source of endogenous interferon- $\gamma$ , and hence increased neopterin synthesis by macrophages, in such patients. Moreover, our findings of a significant correlation between endogenous neopterin serum levels and prognosis point to the clinical relevance of this activation state, which was demonstrated clearly by Massaia et al.<sup>1</sup>

GILBERT REIBNEGGER  
HELMUT WACHTER  
*Institute of Medical Chemistry and Biochemistry  
University of Innsbruck  
Innsbruck, Austria*  
MICHAEL KRAINER  
HEINZ LUDWIG  
*Department of Medicine II  
University of Vienna  
Vienna, Austria*  
MANFRED HEROLD  
HEINZ HUBER  
*Department of Medicine  
University of Innsbruck  
Innsbruck, Austria*

#### REFERENCES

1. Massaia M, Bianchi A, Attisano C, Peola S, Redoglia V, Dianzani U, Pileri A: Detection of hyperreactive T cells in multiple myeloma by multivalent cross-linking of the CD3/TCR complex. *Blood* 78:1770, 1991
2. Reibnegger G, Krainer M, Herold M, Ludwig H, Wachter H, Huber H: Predictive value of interleukin-6 and neopterin in patients with multiple myeloma. *Cancer Res* 51:6250, 1991
3. Huber C, Batchelor JR, Fuchs D, Hausen A, Lang A, Niederwieser D, Reibnegger G, Swetly P, Troppmair J, Wachter H: Immune response-associated production of neopterin. Release from macrophages primarily under control of interferon gamma. *J Exp Med* 160:310, 1984
4. Werner ER, Werner-Felmayer G, Fuchs D, Hausen A, Reibnegger G, Yim JJ, Pfeleiderer W, Wachter H: Tetrahydrobiopterin biosynthetic activities in human macrophages, fibroblasts, THP-1, and T-24 cells. GTP cyclohydrolase I is stimulated by interferon gamma, and 6-pyruvoyl-tetrahydropterin synthase and sepiapterin reductase are constitutively present. *J Biol Chem* 256:3189, 1990
5. Wachter H, Fuchs D, Hausen A, Reibnegger G, Weiss G, Werner ER, Werner-Felmayer G: Neopterin: Biochemistry—Methods—Clinical Application. New York, NY, Walter de Gruyter, 1991
6. Reibnegger GJ, Bichler AH, Dapunt O, Fuchs DN, Fuith LC, Hausen A, Hetzel H, Lutz H, Werner ER, Wachter H: Neopterin as a prognostic indicator in patients with carcinoma of the uterine cervix. *Cancer Res* 46:950, 1986
7. Lewenhaupt A, Ekman P, Eneroth P, Eriksson A, Nilsson B, Nordstöm L: Serum levels of neopterin as related to the prognosis of human prostatic carcinoma. *Eur Urol* 12:522, 1986
8. Reibnegger G, Hetzel H, Fuchs D, Fuith LC, Hausen A, Werner ER, Wachter H: Clinical significance of neopterin for prognosis and follow-up in ovarian cancer. *Cancer Res* 47:4977, 1987
9. Kawasaki H, Watanabe H, Yamada S, Watanabe K, Suyama A: Prognostic significance of urinary neopterin levels in patients with hepatocellular carcinoma. *Tohoku J Exp Med* 155:311, 1988
10. Abate G, Comella P, Marfella A, Santelli G, Nitsch F, Giore M, Perna M: Prognostic relevance of urinary neopterin in non-Hodgkin's lymphoma. *Cancer* 63:484, 1998

#### RESPONSE

The increased serum neopterin concentrations reported by Reibnegger et al<sup>1</sup> in multiple myeloma patients further confirm that cell-mediated immunity is under pressure in this disorder. It is possible that alerted myeloma T cells are a source of endogenous interferon- $\gamma$  (IFN- $\gamma$ ) that stimulates neopterin production in monocytes and macrophages; resting bone marrow T cells may constitutively release low amounts of IFN- $\gamma$  (2 to 3 U/mL) (personal observation).

We have recently reported high serum neopterin concentrations in 63 multiple myeloma patients at diagnosis.<sup>2</sup> Neopterin showed prognostic importance; median survival for patients with high values was 20 months, whereas it was 63.9 months for patients with low values ( $P < .003$ ).<sup>2</sup> Neopterin data are an additional evidence for the negative correlation between the activation state of cell-mediated immunity and the tumor progression in multiple myeloma.<sup>3,4</sup> To explain this contradictory correlation, one can specu-

late that the immune system is unproductively engaged by the tumor cells. Although negative, these relationships point out the presence of specific interactions between T and tumor cells that can be exploited to generate productive antitumor activity, ie, by CD3 and/or interleukin-2 stimulations.

It is really important that neopterin remained a significant predictor in a multivariate analysis. By exploring the status of cell-mediated immunity (a feature extrinsic to the tumor cell clone), neopterin provides prognostic informations that are different and complementary to that provided by factors exploring intrinsic features of the tumor cell clone (like the labeling index of bone marrow myeloma cells, the tumor stage, etc). These data suggest

that neopterin is worthy to be included in the staging system of multiple myeloma.

MASSIMO MASSAIA  
ALBERTO BIANCHI  
CARMELA ATTISANO  
MARIO BOCCADORO  
ALESSANDRO PILERI  
*Divisione Universitaria di Ematologia  
Dipartimento di Medicina e Oncologia Sperimentale  
Ospedale Molinette  
Torino, Italy*

#### REFERENCES

1. Reibnegger G, Krainer M, Herold M, Ludwig H, Wachter H, Huber H: Predictive value of interleukin-6 and neopterin in patients with multiple myeloma. *Cancer Res* 51:6250, 1991
  2. Boccadoro M, Battaglio S, Omede P, Palumbo AP, Fusaro A, Frieri R, Gallone G, Polloni R, Mosso R, De Filippi PG, Pileri A: Increased serum neopterin concentrations as indicator of disease severity and poor survival in multiple myeloma. *Eur J Haematol* 47:305, 1991
  3. Dianzani U, Pileri A, Boccadoro M, Palumbo A, Pioppo P, Bianchi A, Camponi A, Fossati G, Battaglio S, Massaia M: Activated idiotype-reactive cells in suppressor/cytotoxic subpopulations of monoclonal gammopathies: Correlation with diagnosis and disease status. *Blood* 72:1064, 1988
  4. Omede P, Boccadoro M, Gallone G, Frieri R, Battaglio S, Redoglia V, Pileri A: Multiple myeloma: Increased circulating lymphocytes carrying plasma cell-associated antigens as an indicator of poor survival. *Blood* 76:1375, 1990
-