Prognosis in monoclonal proteinaemia

Schaar, C.G.

3 Serum syndecan-1 in newly diagnosed monoclonal proteinaemia

Schaar CG[1], Vermeer HJ[2], Wijermans PW[3], Huisman W[4], le Cessie S[5], Kluin-Nelemans JC[6]

Haematologica/The Hematology Journal 2005; 90: 1437-1438
(Letter to the editor)

1. Comprehensive Cancer Centre West, Leiden
2. Department of Clinical Chemistry, Haga Hospital, location Leyenburg, The Hague
3. Department of Haematology, Haga Hospital, location Leyenburg, The Hague
4. Department of Clinical Chemistry, Medical Centre Haaglanden, location Westeinde, The Hague
5. Department of Medical Statistics, Leiden University Medical Centre, Leiden
6. Department of Haematology, University Medical Centre Groningen, Groningen
All in The Netherlands

Abstract

Serum syndecan-1 was investigated in 189 patients with newly diagnosed monoclonal proteinaemia (MM (66), MGUS (54), provisional MGUS (no bone marrow examination performed; 69)) and 36 controls. Syndecan-1 levels ranged widely between all diagnostic categories and were of limited discriminatory value (sensitivity 68%, specificity 78%) in newly diagnosed monoclonal proteinaemia.

In the large majority of patients with newly diagnosed monoclonal proteinaemia (M-proteinaemia) there is no evidence for the presence of multiple myeloma (MM), plasmacytoma, amyloidosis, macroglobulinaemia or other haematological malignancy. Therefore, the need for an easily obtainable serum discriminatory marker is felt. The best-known serum marker to distinguish between these categories is the M-protein concentration it self, but much overlap exists[1]. Serum syndecan-1 (CD-138) is an independent prognostic marker in MM and is expressed on pre-B-cells, lost during differentiation and re-expressed on normal and malignant plasma cells[2,3].

We investigated the discriminatory value of serum syndecan-1 in 189 patients with newly diagnosed M-proteinaemia registered prospectively in a population-based registry. During a three-year period 1464 patients with newly diagnosed M-proteinaemia or MM were entered. Information on patient characteristics, laboratory tests results, M-protein-related diagnosis, comorbidity, results of bone marrow examination and skeletal x-rays, and therapy were documented annually. A serum sample at first diagnosis was frozen at –80 ºC. The set-up and contents of this registry have been described previously[4]. From 867 patients with serum available, 189 were evaluable for the present study. The other 678 sera were excluded for the following reasons: other haematological malignancy present, insufficient clinical data concerning the stage of disease, the serum was not taken at diagnosis or an insufficient amount was left for the syndecan-1 determination. The diagnoses of MM and MGUS were made according to the criteria by Durie and Salmon [5]. In the absence of clinical evidence of MM or other haematological malignancy and a low M-protein concentration (<20 g/l) the patient is often diagnosed with MGUS and a bone marrow examination is not considered to be necessary[6]. For precise definition therefore, MGUS was divided in two categories: 'definite' MGUS (confirmed by bone marrow examination) and 'provisional' MGUS (no bone marrow examination performed). Control sera were used from patients without M-proteinaemia, confirmed by protein electrophoresis.

Syndecan-1 was determined using an enzyme-linked immunosorbent assay (Diaclone Research, Besançon, France). Median values of laboratory parameters for different diagnostic categories were compared using Mann-Whitney's test or Kruskall-Wallis test when appropriate. Survival curves were made using the Kaplan Meier method and compared with the log-rank test. Analyses were performed using SPSS 12.0 for Windows.

Serum syndecan-1 levels of all diagnostic categories with newly diagnosed M-proteinaemia are shown in Figure 1 and Table 1. The median levels were highest in MM with significant differences between the diagnostic categories ($p<0.0001$), however, a wide overlap exists. These results are in accordance with two studies on smaller series comparing serum syndecan in MGUS and MM[7,8]. In contrast to Seidel but in accordance with Maisnar, we could not demonstrate a relation between serum syndecan-1 levels and MM stages (Table 1; $p=0.06$)[2;7]. Using a cut-off value of 166 ng/ml (e.g. the mean level + 2SD of normal human sera; information on kit leaflet) sensi-

tivity and specificity were respectively 68% and 78%. Like Seidel et al we confirmed the prognostic significance of high serum syndecan levels at diagnosis in patients with MM[2]. Median time of follow-up for patients with MM still alive was 8.1 (0.9-10.2) years. Patients with MM and high serum syndecan-1 levels (≥166 g/l; n=45) showed a median survival of 1.3 years compared to 4.7 years in 21 MM-patients with lower serum syndecan-1 levels (p=0.0018). In a Cox regression analysis corrected for M-protein isotype and Salmon and Durie stage, elevated serum syndecan remained of prognostic importance with a hazard ratio of 3.6 (95% CI 1.7-7.6).

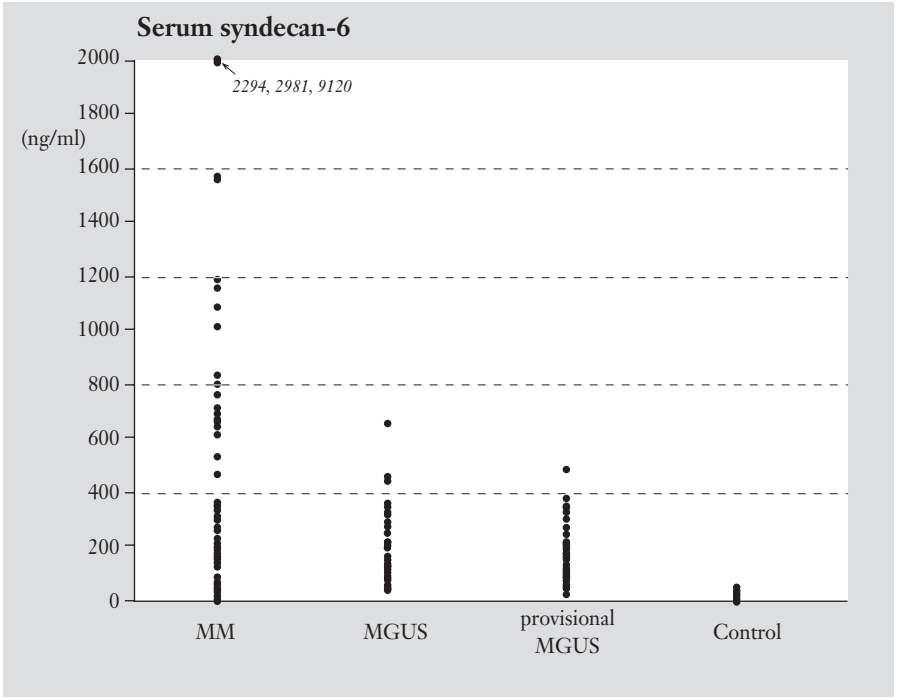

Figure 1. **Serum syndecan levels in 226 patients with newly diagnosed M-proteinaemia.**

Abbreviations: MM: Multiple myeloma,
MGUS: definite MGUS,
prov MGUS: provisional MGUS.

Median serum syndecan-1 levels in ng/ml (range): Multiple Myeloma 226 (3-9120);
MGUS: 128 (50-656); Provisional MGUS 91 (22-494), Controls 5 (0-52).

Table 1. **Median serum values (ranges) of syndecan-1 in newly diagnosed patients with M-proteinaemia.**

Category	N	Syndecan-1 (ng/ml)
Multiple myoma (all)	66	226 (3-9120)
• MM stage I	24	194 (3-667)
• MM stage II	5	290 (160-1019)
• MM stage III	37	238 (30-9120)
MGUS	54	128 (50-656)
Provisional MGUS*	69	91 (22-494)
Control Patients	36	5 (0-52)

*) MGUS without confirmatory bone marrow examination

During an 8.8 (4.3-10.7) year follow-up of all patients alive with definite MGUS or provisional MGUS (n=123) MM developed in only two patients at respectively 6 and 12 months. One patient had a low (83 ng/ml) and one a high (176 ng/ml) level of serum syndecan.
In conclusion, serum syndecan-1 is an important prognosticator for patients with MM, but this marker is of no discriminatory value in patients with newly diagnosed M-proteinaemia.

Acknowledgements

We thank Mrs W. Kloosterman (Comprehensive Cancer Centre West, Leiden) for her assistance in collecting all the serum samples.

Reference list

1. Ong F, Hermans J, Noordijk EM et al. Development of a 'Myeloma Risk Score' using a population-based registry on paraproteinemia and myeloma. Leuk Lymphoma 1997;27:495-501.
2. Seidel C, Sundan A, Hjorth M et al. Serum syndecan-1: a new independent prognostic marker in multiple myeloma. Blood 2000;95:388-392.
3. Dhodapkar MV, Abe E, Theus A et al. Syndecan-1 is a multifunctional regulator of myeloma pathobiology: control of tumor cell survival, growth, and bone cell differentiation. Blood 1998;91:2679-2688.
4. Ong F, Hermans J, Noordijk EM et al. A population-based registry on paraproteinaemia in The Netherlands. Comprehensive Cancer Centre West, Leiden, The Netherlands. Br J Haematol 1997;99:914-920.

5. Durie BGM, Salmon DE. A clinical staging system for multiple myeloma. Correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival. Cancer 1975;36:842-854.
6. Kyle RA, Therneau TM, Rajkumar SV, Offord JR, Larson DR, Plevak MF, et al. A long-term study of prognosis in monoclonal gammopathy of unknown significance. New Engl J Med 2002;346:564-569.
7. Maisnar V, Touskova M, Maly J et al. Importance of selected laboratory indicators in the differential diagnosis and monitoring of multiple myeloma. Vnitr Lek 2002;48:290-297.
8. Janosi J, Sebestyen A, Mikala G et al. Soluble syndecan-1 levels in different plasma cell dyscrasias and in different stages of multiple myeloma. Haematologica 2004;89:370-371.