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Malignant Lymphomas

Soluble syndecan-1 levels in different plasma cell dyscrasias and in different stages of multiple myeloma

We measured serum levels of syndecan-1 in patients with multiple myeloma (MM), solitary plasmocytoma and monoclonal gammopathy of undetermined significance (MGUS). We then studied serum syndecan-1 levels in MM patients stratified by the Durie-Salmon staging system and the correlation of syndecan-1 levels with well known independent prognostic factors of MM.

haematologica 2004; 89:370-371
(*http://www.haematologica.org/journal/2004/3/370*)

We investigated 67 patients: 13 had monoclonal gammopathy of undetermined significance (MGUS), 4 had solitary plasmocytoma, and 50 had multiple myeloma (MM). All plasma cell dyscrasias were defined by the diagnostic criteria of the American Southwest Oncology Group (SWOG).[1] For comparative analysis of patients the following data and parameters were registered: age, sex, percentage of plasma cells in the bone marrow, immunoglobulin (Ig) class, serum M-protein concentration, serum levels of β2-microglobulin, albumin, calcium, creatinine, total alkaline phosphatase, and C-reactive protein (CRP).

Patients were subdivided by the Durie-Salmon staging system.[2] At the time of evaluation 35 patients with MM had already undergone some form of chemotherapy. The other group of 15 previously untreated MM patients were followed during their chemotherapy. The median follow-up period of the patients was 6 months. Seven patients received ICOMP (idarubicin, cyclophosphamide, vincristine, methylprednisone) therapy, and 8 patients received VAD (vincristine, doxorubicin, dexamethasone) therapy for 6 months. All patients were co-treated with bisphosphonates. Response to therapy was determined by the change in M-protein concentration and the ratio of bone marrow plasma cells 6 months after initiation of chemotherapy. Objective therapeutic response was defined as at least a 50% reduction of serum paraprotein concentration.

The serum concentration of soluble syndecan-1 was measured using a commercially available human syndecan-1 enzyme-linked immunosorbent assay (ELISA) kit (Diaclone Research, Besancon, France).

Results were considered statistically significant when the *p* value was less than 0.05. Comparisons between groups were determined with the Mann-Whitney U-test. Response to treatment was analyzed with multiple logistic regression techniques.

Serum concentrations of syndecan-1 and correlation with other prognostic factors of MM. The median serum syndecan-1 concentrations of patients with MGUS (n=13) and solitary plasmocytoma (n=4) were 77.9 ng/mL (range: 33-122) and 65.6 ng/mL (range: 33.8-94.5), respectively. In contrast, the median syndecan-1 concentration in the group of MM patients (n=50) was 223.8 ng/mL (range: 36-508). Although the numbers of patients with MGUS and solitary plasmocytoma group were low, differences between the median syndecan-1 values were statistically significant.

Table 1. Correlations between serum syndecan-1 and other variables.

	Serum creatinine	*Serum β2-microglobulin*	*Plasma cell content (%) of bone marrow*	*Serum M-component*
N	50	49	49	49
r	0.378	0.379	0.407	0.558
p	0.007	0.007	0.004	<0.001

r: indicates correlation coefficient for syndecan-1 and the designated variable.

Statistically significant differences were also observed in median syndecan-1 levels in the MM group stratified according to Durie-Salmon stage (values given in ng/mL, number of patients and range in parentheses): group I/A: 61 (n=4, 36-102), II/A: 188.6 (n=20, 65.3-344), II/B: 260.6 (n=3, 208-267), III/A: 300.2 (n=12, 157-466), and III/B: 253.5 (n=11, 97.3-508). As shown in Table 1 a clear correlation was found with other well known prognostic factors of MM such as serum creatinine, β_2-microglobulin, monoclonal protein concentration, and bone marrow plasma cell content.

Follow up of MGUS and MM patients. Over a 6-month follow-up period there was no increase in serum syndecan-1 level in the MGUS patients (n=13). Baseline serum syndecan-1 levels were determined before initiation of chemotherapy, whereas follow-up syndecan-1 levels were measured once after 6 months of treatment in the MM patients followed sequentially (=15). As shown in Table 2, there was a significant decrease in the median syndecan-1 level among patients who responded to chemotherapy. In contrast, no change was observed in patients who did not respond to chemotherapy. Syndecans are a family of cell surface proteoglycans.[3] The molecule is expressed on mature plasma cells.[4] Syndecan-1 mediates specific adhesion of myeloma cells to type I collagen and also mediates cell-cell adhesion between myeloma cells.[5-8]

Measured by a semiquantitative method, syndecan-1 levels were elevated in the sera of 7 out of 20 myeloma patients. Higher serum levels of soluble syndecan-1 were associated with higher levels of serum β_2-microglobulin and elevated plasma cell content in the bone marrow.[9] Evaluation of data collected from 138 MM patients showed that the serum syndecan-1 concentration could serve as an independent prognostic parameter in addition to serum β_2-microglobulin and WHO performance status.[10] In our study, patients with MM showed a higher median level of serum syndecan-1 than did patients with MGUS or plasmocytoma. The differences between these groups were significant.

A comparison of serum syndecan-1 levels among the myeloma subgroups also revealed significant differences. A

Table 2. Serum syndecan-1 levels in myeloma patients receiving chemotherapy.

	Baseline Syndecan-1 ng/mL	*Follow-up Syndecan-1 ng/mL*
Responders (n=11)		
Median	258	106
Range	97.3-460	57.3-440
Non-responders (n=4)		
Median	327	361.7
Range	245-466	251-486

correlation was found between the level of serum β_2-microglobulin, monoclonal protein concentration or bone marrow plasma cell content. A significant decrease in median syndecan level was observed in patients responding to chemotherapy, whereas the median syndecan level did not change in non-responders. Our results indicate that there is a marked difference in the serum syndecan-1 levels in different forms of plasma cell dyscrasias. Moreover, the level of syndecan-1 is higher in patients with higher stage MM. Further evaluation of patients is needed to evaluate the role of syndecan-1 in the prognosis of MM.

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Key words: syndecan-1, multiple myeloma, prognostic marker.

Funding: this work was supported by grants ETT 186/2000, 192/2000, 193/2000, OTKA T 33067, 034/892, and FKFP 0150/2001.

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Multiple Myeloma

Oral idarubicin, dexamethasone and vincristine in the treatment of multiple myeloma: final analysis of a phase II trial

This prospective phase II study evaluated a regimen with vincristine, oral idarubicin and dexamethasone (VID) in 74 patients with multiple myeloma. A partial response was achieved in 57% (16/28) of patients with previously untreated disease and in 35% (16/46) with refractory diseases. VID chemotherapy is an effective and tolerable oral alternative in an outpatient setting for these patients.

haematologica 2004; 89:371-373
(*http://www.haematologica.org/journal/2004/3/371*)

The combination of a continuous infusion of doxorubicin and vincristine with high-dose oral dexamethasone (VAD) has become a standard treatment for patients with multiple myeloma but the necessary central venous line causes considerable complications. Therefore, oral alternatives would be preferable. We tested such an alternative (vincristine, idarubicin and dexamethasone) in 74 patients with multiple myeloma.

For this trial, the following inclusion criteria had to be fulfilled: (i) diagnosis of multiple myeloma according to the British Columbia Cancer Agency Criteria; (ii) at least stage II disease according to the staging system of Durie and Salmon, and (iii) refractory disease (i.e. unresponsive to previous therapy) or previously untreated disease.

Vincristine was administered as an intravenous bolus injection on day 1 (2 mg). Idarubicin was given as a capsule, 10 mg/m^2 per day p.o., on days 1-4 (total dose 40 mg/m^2 per course). Dose escalation (up to 13 mg/m^2/d) and dose reduction (to 8 mg/m^2/d) was possible. Dexamethasone was given at a dose of 40 mg p.o. on days 1-4, 9-12, and 17-20. Courses were repeated starting on day 29 to reach a total of 6-8 courses. An interim report of this trial was published in 1997.[1] Response was defined by European Group for Blood and Marrow Transplantation (EBMT) criteria. Seventy-six patients were registered, but two patients were excluded after registration: one had been previously treated with idarubicin and dexamethasone and one died from pre-existing pneumonia on day 3. The remaining 74 patients (Table 1) received a total of 322 courses of VID, and a median of 4 (interquartile range 3-6). Patients with refractory disease had been heavily pretreated (Table 1). Twenty-one patients (9/46 with refractory, 12/28 with previously untreated disease) received autologous stem cell transplants; their survival data were censored at the time of transplantation. Five patients died within two months of entering the study (*early death*, two from sepsis in neutropenia in the first course) and one patient was lost to follow-up after the first course. These patients were counted as failures in the efficacy evaluation. Complete informa-