Shortened Platelet Half-life in Multiple Myeloma

By Elke Fritz, Heinz Ludwig, Werner Scheithauer, and Helmuth Sinzinger

Various defects in platelet function have been reported as being associated with multiple myeloma. In 30 myeloma patients and 15 healthy controls, we investigated platelet survival using in vitro labeling of autologous platelets with $^{111}$indium-oxine and measuring the in vivo kinetics of the radioisotope. Significantly shortened platelet half-life in patients averaged 73 hours, while platelet half-life in the healthy controls averaged 107 hours. In myeloma patients, serum levels of thromboxane $B_2$, $\beta$-thromboglobulin, and platelet factor 4 were significantly elevated; aggregation indices were within the pathological range; platelet counts and spleen–liver indices, however, were comparable to those of the healthy control group. No statistical correlation was found between platelet half-life and paraprotein concentrations. Our findings suggest an initial—so far unexplained—intravascular process of platelet activation and consumption that finally manifests in shortened platelet half-life. It seems that overt thrombocytopenia develops only when the compensatory capacity of the bone marrow finally becomes exhausted. Further studies should be able to elucidate the pathophysiologic processes involved.

From the Department of Medicine L II, University of Vienna, Austria.

Supported in part by Austrian Research Grant No. P4999 and the Ludwig Boltzmann Institute for Gerontology, Vienna.

Submitted April 10, 1985; accepted April 8, 1986.

Address reprint requests to Dr H. Ludwig, II. Dept of Medicine, University of Vienna, Garnisongasse 13, A-1090 Vienna, Austria.

$^{111}$Indium-oxine and measuring the in vivo kinetics of the radioisotope. Significantly shortened platelet half-life in patients averaged 73 hours, while platelet half-life in the healthy controls averaged 107 hours. In myeloma patients, serum levels of thromboxane $B_2$, $\beta$-thromboglobulin, and platelet factor 4 were significantly elevated; aggregation indices were within the pathological range; platelet counts and spleen–liver indices, however, were comparable to those of the healthy control group. No statistical correlation was found between platelet half-life and paraprotein concentrations. Our findings suggest an initial—so far unexplained—intravascular process of platelet activation and consumption that finally manifests in shortened platelet half-life. It seems that overt thrombocytopenia develops only when the compensatory capacity of the bone marrow finally becomes exhausted. Further studies should be able to elucidate the pathophysiologic processes involved.

$^{111}$Indium-oxine and measuring the in vivo kinetics of the radioisotope. Significantly shortened platelet half-life in patients averaged 73 hours, while platelet half-life in the healthy controls averaged 107 hours. In myeloma patients, serum levels of thromboxane $B_2$, $\beta$-thromboglobulin, and platelet factor 4 were significantly elevated; aggregation indices were within the pathological range; platelet counts and spleen–liver indices, however, were comparable to those of the healthy control group. No statistical correlation was found between platelet half-life and paraprotein concentrations. Our findings suggest an initial—so far unexplained—intravascular process of platelet activation and consumption that finally manifests in shortened platelet half-life. It seems that overt thrombocytopenia develops only when the compensatory capacity of the bone marrow finally becomes exhausted. Further studies should be able to elucidate the pathophysiologic processes involved.

$^{111}$Indium-oxine and measuring the in vivo kinetics of the radioisotope. Significantly shortened platelet half-life in patients averaged 73 hours, while platelet half-life in the healthy controls averaged 107 hours. In myeloma patients, serum levels of thromboxane $B_2$, $\beta$-thromboglobulin, and platelet factor 4 were significantly elevated; aggregation indices were within the pathological range; platelet counts and spleen–liver indices, however, were comparable to those of the healthy control group. No statistical correlation was found between platelet half-life and paraprotein concentrations. Our findings suggest an initial—so far unexplained—intravascular process of platelet activation and consumption that finally manifests in shortened platelet half-life. It seems that overt thrombocytopenia develops only when the compensatory capacity of the bone marrow finally becomes exhausted. Further studies should be able to elucidate the pathophysiologic processes involved.
The spleen–liver index was determined 18 to 24 hours after reinjection of labeled autologous platelets, using computerized scintigraphy in anteroposterior view. After insertion of regions at interest, the counts registered in the splenic area were divided by the actual counts obtained over the liver to yield a dimensionless index.

The aggregation index, according to Wu and Hoak, a proposed measure of reversible circulating microaggregates, was determined by the method described. Plasma concentrations of β-thromboglobulin and platelet factor 4 were evaluated, using commercially available radioimmunoassay systems (Radiochemical Center, Amersham, U.K., and Abbott, North Chicago, Ill). Plasmatic thromboxane B2 was measured in unextracted plasma samples using the double-antibody technique. Two percent EDTA ensured anticoagulation, and I mg/mL of acetylsalicylic acid served as a blocker of cyclo-oxygenase.

Clinical parameters determined by routine methods included total serum protein concentration as well as serum and urinary M-component, serum calcium and hemoglobin levels, and peripheral platelet count. Additional data checked for possible correlations with the parameters of platelet function were sex, age, duration of the disease, extent of osteolytic bone lesions (determined by x-ray evaluation and whole-body scintigraphy), and estimated tumor cell population, and I mg/mL of acetylsalicylic acid served as a blocker of cyclo-oxygenase.

Statistical evaluation. All data were normally distributed either inherently or after logarithmic transformation. Only results of testing plasma concentrations of thromboxane B2 included semiquantitative values (<70 pg/mL) and were therefore processed as frequencies. Mean values were compared, using Student’s t test; for linear correlations, Pearson’s product-moment correlations were calculated. For coefficients resulting from intercorrelations involving multiple comparisons within a single set of data, the level of significance was corrected according to Bonferroni statistics. The semiquantitative data on thromboxane B2 were compared, using a chi-square test, while correlations were evaluated from Pearson’s contingency correlation coefficients.

Possible influence of renal function on relevant parameters was tested by selecting all patients with serum creatinine findings of ≥20 g/L and determining the magnitude of each data item in relation to the total patient population. Mean coefficients of variation ([X – mean]/SD) were calculated for normally distributed data, while for skewed distributions results were expressed as percentiles.

Because the sample of 15 test series from our 15 healthy subjects was relatively small, we compared the data on platelet half-life in these 15 healthy controls with age- and sex-matched values from a previous comparable study involving 106 controls. No significant difference was detected. Computer-assisted stepwise multivariate regression analysis, cluster and discriminant analysis, and matrix operations necessary to generate the three-dimensional plot were carried out on the IBM 43 41 computer.

RESULTS

Platelet half-life was significantly shorter (P < 10⁻⁵) in multiple myeloma patients than in healthy controls (Table 1). Figure 1 shows the distribution of individual values in these two groups. Platelet half-life in the controls ranged from 95 to 122 hours, with a median of 106 hours. In only seven of the 30 myeloma patients (less than 25%) were the values of platelet half-life within the normal range. In the remaining 23 patients, distribution appears to be skewed to the left, indicating pathological decrease. Median platelet half-life of the total patient group is 75.5 hours, ranging from 30 to 110 hours.

In patients as well as in controls, serial evaluation of radioactivity in whole blood yielded linear functions with varying slopes. Ratios of variances accounted for by the regression model were sufficiently high (r² median, .937; range, .690 to .992) to justify interpolation at 50% of residual radioactivity. Figure 2 gives one example each of the two types of kinetics observed in the patient group. In one patient, platelet half-life was 103 hours; the plot corresponds to those obtained in the control group, and it may well be taken as an example of normal findings. Kinetics in the other patient with a platelet half-life of only 32 hours are obviously pathological. However, the only certain difference is manifested in the steeper slope of the function.

Table 1 makes evident that mean platelet half-life in the patient group is significantly reduced and amounts to only 68% of the mean in the control group, and that no significant differences between the patient and the control group were observed in platelet count and spleen–liver indices. The aggregation index in the control population approaches the expected normal index of 1, while its significant reduction in the patient group indicates the presence of reversible circulating platelet microaggregates. Values for platelet activation parameters were significantly higher in the patient group than in healthy controls.

In three patients, serum creatinine was elevated to 22, 24, and 99 g/L, respectively. Mean coefficients of variation and
percentiles for age, duration of the disease, total serum protein, serum M-component, hemoglobin, serum calcium, bone lesions, bone marrow plasma cell infiltration, tumor load, platelet count, platelet half-life, spleen–liver index, platelet aggregation index, thromboxane $B_2$, $\beta$-thromboglobulin, and platelet factor 4 showed no significant deviations in the two patients with 24 and 99 g/L of serum creatinine, respectively. In the third patient, with 22 g/L of serum creatinine, values for the duration of the disease, total serum protein, serum M-component, serum calcium, tumor load, and bone marrow plasma cell infiltration were significantly higher. His values for platelet half-life and platelet function (spleen–liver index, aggregation index, thrombox-

![Image](https://www.bloodjournal.org)
but also the apparently "normal" subgroup (C) differed significantly from controls in regard to plasma β-thromboglobulin and platelet factor 4. Although platelet survival was shorter than normal in the two patients of subgroup (A), it was not in the shortest bracket. We did not state the highly significant result of comparing platelet half-lives in subgroups (B) and (C) because this outcome is logically trivial.

Multiple searches for possible patterns permitting identification of conditions favorable to or impeding the compensation of accelerated platelet loss remained inconclusive (data not shown).

Bone marrow plasma cell infiltration was determined by differential counts of bone marrow smears from 11 patients with platelet half-life <90 hours and from four patients whose 50% values of platelet clearance were within normal range. Median percentages of plasma cells found in the bone marrow were 29.5 for the first and 12.0 for the second subgroup. The values for all 15 patients ranged from 3% through 91%, the highest percentage determined in the only thrombocytopenic patient included in the sample. Bone marrow plasma cell infiltration correlated significantly with serum calcium, urine M-component, tumor mass per m² body surface, spleen–liver index, and duration of the disease (r between .646 and .784). The inverse correlation with peripheral platelet counts also exceeded the limit of significance (r = .702).

**DISCUSSION**

Theoretically, a pathological shortening of platelet half-life may be traced to one of two basic causes: to an intrinsic

---

**Table 2. Correlations Observed in Patients With Multiple Myeloma**

<table>
<thead>
<tr>
<th></th>
<th>T/2</th>
<th>β-TG</th>
<th>PFA</th>
<th>TxB₂</th>
<th>Serum M-Comp</th>
<th>Urinary M-Comp</th>
<th>Bone Lesions</th>
<th>Ca²⁺</th>
<th>Disease Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet half-life</td>
<td></td>
<td>r = -.772</td>
<td></td>
<td>r = -.783</td>
<td>r = -.852</td>
<td>P &lt; .001</td>
<td>P &lt; .001</td>
<td>P &lt; .001</td>
<td></td>
</tr>
<tr>
<td>Platelet count</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spleen–liver index</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aggregation index</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Thromboglobulin</td>
<td></td>
<td>r = -.722</td>
<td></td>
<td>r = .935</td>
<td>r = -.819</td>
<td>P &lt; .001</td>
<td>P &lt; .001</td>
<td>P &lt; .001</td>
<td>r = -.471</td>
</tr>
<tr>
<td>Platelet factor 4</td>
<td></td>
<td>r = -.783</td>
<td></td>
<td>r = .935</td>
<td>r = -.823</td>
<td>P &lt; .001</td>
<td>P &lt; .001</td>
<td>P &lt; .02</td>
<td></td>
</tr>
<tr>
<td>Thromboxane B₂</td>
<td></td>
<td>r = -.852</td>
<td></td>
<td>r = .819</td>
<td>r = -.823</td>
<td>P &lt; .001</td>
<td>P &lt; .001</td>
<td>P &lt; .001</td>
<td></td>
</tr>
</tbody>
</table>

T/2, platelet half life; β-TG, β-thromboglobulin; PFA, platelet factor 4; TxB₂, thromboxane B₂.

---

**Fig 3.** Interrelations between platelet half-life, thromboxane B₂, and β-thromboglobulin. Front: Low plasma concentrations of thromboxane B₂ and β-thromboglobulin are associated with normal platelet half-life. Rear: The lowest platelet half-lives are observed after smoothing of random errors of measurement.
defect of the platelet, leading to premature destruction in the spleen or at other prominent sites of RES activity, or to an extrinsic defect, ie, environmental conditions effecting accelerated platelet loss. Extrinsic factors, in turn, may also operate by two fundamentally different mechanisms: by either rendering blood platelets more vulnerable to degradation or effecting an abnormally high rate of intravascular platelet consumption. The significantly shortened platelet half-life observed in our myeloma patients cannot be attributed unequivocally to one or the other of these three possible causes.

Both intrinsic impairment due to a disease-associated deviant clone of megakaryocytes, which produces qualitatively inferior, or even defective, platelets, and influences resulting from the distinctly abnormal intravascular environment can be assumed to cause reduced platelet survival in multiple myeloma. Seeing the findings obtained in our study in the light of these hypotheses, it is challenging to weigh their value in providing possible explanations.

Although the absence of correlation between platelet half-life and paraprotein concentration appears to argue against environmental factors, the data collected on serial evaluation of radioactivity in the patients' blood fail to support the assumption of a fraction of pathological platelets being present among normal specimen. If two survival functions with distinctly different slopes were combined, the resulting hyperbolic function would not permit a satisfactory fit of a linear model to the observed data points. The linearity of the clearance function suggests a uniform population of platelets with fairly constant survival times.

When considering external factors that might exert adverse influences on platelet survival in multiple myeloma, chemotherapy constitutes an obvious possibility. However, platelet half-life in patients under treatment did not differ from that in patients not yet treated. The expected negative correlation between duration of the disease and half-life of platelet clearance also could not be confirmed. Neither cytostatic drugs nor possible consequences of steroid treatment appear to be responsible for the shortening of platelet survival in multiple myeloma.

In previous reports on abnormal platelet function in patients with plasma cell dyscrasias, the observed defects were mostly attributed to paraprotein coating of the platelets, which may enhance their tendency to form micro-aggregates or render them more susceptible to destruction. Although our patient collective exhibited highly significant reductions in the aggregation indices (ie, increased amounts of reversible circulating microaggregates), we were unable to confirm the proposed correlation between the amount of serum or urine paraprotein and parameters of platelet function. Nor did stratification into subgroups according to heavy-chain class or light-chain type of the paraprotein molecule yield any significant results. No association of any observed feature of platelet pathology with IgG, IgA, or lambda light chain could be detected.

These findings, however, do not necessarily rule out all influence of the plasma M-component on the platelet population. Even though the total amount of paraprotein seems to be of little relevance as such, detrimental effects from immunoglobulin aggregates, polymers, or free light chains have to be considered. Unlike most of the previous studies, we excluded cases of Waldenström's macroglobulinemia, and the number of our patients with light-chain myeloma was too small to permit drawing specific conclusions in this regard. In this connection it is interesting to note that—in contrast to bone marrow plasma cell infiltration—paraprotein concentration did not correlate with the duration of the disease. As myeloma progresses, the tumor cells, to some extent, lose their capacity to secrete paraprotein, and deviant antibody molecules become more frequent. Possibly it is the quality rather than the quantity of paraprotein that determines the effect it has on the platelet population.

The spleen—liver indices in our patient group did not differ from those observed in healthy controls; there were no indications of extraordinary sequestration or degradation of platelets. Unexpected was the observation that the parameters of platelet activation were significantly increased, even in patients whose platelets still showed normal life spans. On the other hand, in no patient was reduced platelet half-life found concurrently with normal values in all parameters of platelet activation. We ruled out the possibility that the elevated serum levels of platelet factors were due to diminished renal clearance in patients with impaired kidney function.

Our findings do not support the assumption that in multiple myeloma, premature elimination of platelets is due to mere coating or cross-linking of inert platelets, ie, of platelets not activated and not exhibiting release reaction. It rather
appears that initially some intravascular process\textsuperscript{13,14} activating the platelets takes place. Our data suggest that the extent of such a proposed platelet activation has to exceed a certain threshold before it manifests as a measurable shortening of platelet half-life.

A second threshold, in the bone marrow's capacity to compensate for increased platelet consumption, appears to be indicated by the fact that in more than 75\% of our patients, platelet half-life fell below the normal range, while only less than 10\% showed overt thrombocytopenia. Unfortunately, we had not included bone marrow examinations in our investigational plan as a general feature, but in 15 patients—among them one of the two patients with thrombocytopenia—this procedure was performed concurrently with the testing of platelet function. Although the small number of cases does not allow for definitive conclusions, the results merit consideration on theoretical grounds: in general, shortened platelet half-life appears to be associated with larger numbers of myeloma cells in the bone marrow, but there is no necessity to presuppose a linear correlation. Our findings showing that platelet half-life is not correlated with paraprotein concentration permit the following conclusion: if more plasma cells secrete larger amounts of paraprotein, this fact alone does not constitute a greater hazard to the platelet population. However, the significant correlation between high percentage of bone marrow tumor cell infiltration and low platelet count suggests that the progression of the disease may play a key role in the capacity of the bone marrow to provide adequate amounts of platelets in compensation for their premature peripheral elimination.

Even though the magnitude of platelet activation findings depends on the test being used, our interpretations rely on differences between patients and controls observed under identical conditions. The method of determining microaggregates, as proposed by Wu and Hoak, is prone to produce artifacts due to the passive participation of formaldehydefixed platelets in aggregation\textsuperscript{37} so that the indications of platelet aggregation need to be confirmed by independent investigators.

We tentatively propose a model explaining the processes involved in the reduction of platelet half-life and the eventual manifestation of thrombocytopenia in myeloma patients: very early in the course of the disease, some intravascular stimulus appears to activate the platelet population; the extent of the ensuing consumption and possibly also of increased extravascular destruction may be reflected in platelet survival time, leading from a slight or moderate to a pronounced shortening of platelet half-life. There seems to exist, however, the capacity to compensate for this diminution of the platelet pool to a large extent and for relatively long periods. For the continuous platelet loss to become manifest as overt thrombocytopenia, apparently a second event or process must take place: severe bone marrow depression as a consequence of massive infiltration of the bone marrow by myeloma cells.

Future investigations are needed to determine possible agents of intravascular platelet activation, and they should include differential counts of bone marrow smears. The hypothesis of a primarily normal platelet population being affected by environmental influences could be tested by labeling experiments using allogeneic platelets. Should the observed interrelationship between platelet half-life and plasma concentrations of thromboxane B\textsubscript{2} and $\beta$-thromboglobulin be confirmed, simple screening assays included in clinical routine examinations may be sufficient to monitor the risk of thrombocytopenia. It would be of particular interest to include in future studies all thrombocytopenic patients without overt bleeding complications, in order to determine the conditions necessary to compensate for the platelet loss. If the processes involved in the platelet pathophysiology associated with multiple myeloma can be more fully elucidated, more efficient treatment—or even prevention—of overt thrombocytopenia in multiple myeloma may become possible.

REFERENCES

Shortened platelet half-life in multiple myeloma
E Fritz, H Ludwig, W Scheithauer and H Sinzinger

Updated information and services can be found at:
http://www.bloodjournal.org/content/68/2/514.full.html
Articles on similar topics can be found in the following Blood collections

Information about reproducing this article in parts or in its entirety may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#repub_requests

Information about ordering reprints may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#reprints

Information about subscriptions and ASH membership may be found online at:
http://www.bloodjournal.org/site/subscriptions/index.xhtml