Prognosis Value of the Monoclonal Blood Plasma Cells in Multiple Myeloma

To the Editor:

We have read with interest the paper of Witzyg et al. about the prognostic value of peripheral blood clonal plasma cells (PBPC) in patients with multiple myeloma (MM). We have recently evaluated the presence of PBPC at diagnosis in 49 MM patients. Plasma cell leukemia cases were excluded (>20% or >2,000/μL plasma cells in PB).2

We have also studied the relationship with other clinical and biologic variables, including age and stage (Durie and Salmon system), performance status according to the Eastern Cooperative Oncology Group scale, the presence of bone lesions, bone marrow plasmacytosis, and serum concentrations of creatinine and β2 microglobulin. The expression of Ki67, a monoclonal antibody that detects cells in cycle, was evaluated in both bone marrow and PBPC. In addition, patients were evaluated for response to therapy and survival.

Mononuclear cells were isolated from PB by ficoll-hypaque density gradient centrifugation and cytospins were stored at −20°C until immunostaining was performed. Sequential double immunoenzymatic staining was applied as described previously, using an immunoperoxidase sandwich technique with Ki67 and the alkaline phosphatase/antialkaline phosphatase method to detect κ and λ Ig light chains. The proportion of PBPC that expressed the same light chain isotype as the patient M protein was evaluated by two independent observers examining 2,000 mononuclear cells from cytocentrifuge slides. The Ki67 proliferative index was estimated using bone marrow plasma cells. In patients with PBPC we found that the plasma cells of PB can be used to determine the Ki67 proliferative index with results equivalent to the bone marrow plasma cells.

Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>LPC Group</th>
<th>HPC Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (%)</td>
<td>(BPC &lt;1%)</td>
<td>(BPC &gt;1%)</td>
<td></td>
</tr>
<tr>
<td>Mean age (range)</td>
<td>69 (42-87)</td>
<td>71 (51-91)</td>
<td>NS*</td>
</tr>
<tr>
<td>M-component type</td>
<td>22 (71%)</td>
<td>14 (70%)</td>
<td>NS†</td>
</tr>
<tr>
<td>Other</td>
<td>9 (29%)</td>
<td>6 (30%)</td>
<td></td>
</tr>
<tr>
<td>ECOG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-2</td>
<td>22 (71%)</td>
<td>5 (25%)</td>
<td></td>
</tr>
<tr>
<td>3-4</td>
<td>9 (29%)</td>
<td>15 (75%)</td>
<td></td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I or II</td>
<td>18 (58%)</td>
<td>4 (20%)</td>
<td>NS†</td>
</tr>
<tr>
<td>III</td>
<td>13 (41%)</td>
<td>16 (80%)</td>
<td></td>
</tr>
<tr>
<td>Lytic bone lesions</td>
<td>22 (71%)</td>
<td>14 (70%)</td>
<td></td>
</tr>
<tr>
<td>=3 osteoporosis</td>
<td>9 (29%)</td>
<td>6 (30%)</td>
<td></td>
</tr>
<tr>
<td>Creatinin (mg/dL)</td>
<td>1.13 (0.6-6.4)</td>
<td>1.55 (0.6-7.1)</td>
<td>NS*</td>
</tr>
<tr>
<td>CD56†</td>
<td>13 (42%)</td>
<td>8 (40%)</td>
<td>NS†</td>
</tr>
<tr>
<td>CD56‡</td>
<td>18 (58%)</td>
<td>12 (60%)</td>
<td></td>
</tr>
<tr>
<td>% Infiltration</td>
<td>31.07 ± 17.35</td>
<td>53.44 ± 22.45</td>
<td>P &lt; .01*</td>
</tr>
<tr>
<td>KI67</td>
<td>2.16 ± 2.7</td>
<td>6.53 ± 5.27</td>
<td>P &lt; .01*</td>
</tr>
<tr>
<td>β2 microglobulin</td>
<td>4.34 ± 2.65</td>
<td>8.88 ± 8.66</td>
<td>P &lt; .01*</td>
</tr>
<tr>
<td>Response</td>
<td>14/21 (67%)</td>
<td>2/17 (12%)</td>
<td>P &lt; .05†</td>
</tr>
</tbody>
</table>

Comparisons between groups were made by the non-parametric Mann-Whitney test (†) for quantitative variables and the χ² test for qualitative variables (†).

Abbreviation: NS, nonsignificance (P value >.05).

The mean percentage of PBPC was 0.87% of the mononuclear fraction (range, 0% to 14%). A cut-off point of 1% was chosen because it was as predictive as the mean value and easier to use.

The patients were classified into two groups: with high number of PBPC (group HPC, >1%) and a lower number (group LPC, <1%). Table 1 presents the distribution of the biologic and clinical variables according to the number of PBPC.

The method of Kaplan and Meier was used to compute the survival curves and to estimate median survival. The differences in survival curves were tested with the log rank statistic method. An evaluation of survival using the cut-off value is summarized in Fig 1A. The patients in the HPC group presented a median survival of 6 months, which was significantly shorter than in the LPC group (>18 months).

The interaction between the number of PBPC and other single parameters was estimated. We found statistically significant correlations between HPC and advanced Salmon-Durie stage and poor per-
of them also being anti-HCV ± negative) NHL patients and also in possible that HCV infection may induce a chronic B-cell prolifera-

tion in MM, 5 was also similar.

antigen, which was postulated to contribute to the leukemic expres-

Valencia, Spain

paring other clinical characteristics, including age, advanced lytic

There were no significant differences between patient groups com-

with respect to the group with LPC (U-Mann Whitney, 
P

x

performance status (χ² test, P < .01). Moreover, the β2 microglobulin

levels, percentage of bone marrow plasma cells, and bone marrow

or peripheral blood plasma cell proliferative index were increased

in the group with HPC, with a significant difference being observed

with respect to the group with LPC (U-Mann Whitney, P < .01).

There were no significant differences between patient groups com-

paring other clinical characteristics, including age, advanced lytic

bone lesions, creatinin levels, and type of treatment. Loss of CD56

antigen, which was postulated to contribute to the leukemic expres-

in MM, 5 was also similar.

Because there was a strong correlation between HPC and stage

III of MM, a separate analysis of survival was made including only

patients in stage III. Statistically significant differences in survival

were observed as complete series (Fig 1B). In addition, HPC before

treatment was associated to a low response rate (χ² test, P < .05).

In conclusion, the methodology described allows us to easily iden-

tify and quantify circulating plasmatic cells in an important propor-

tion of MM patients, as well as to establish the proliferative index

of disease. We confirm the adverse prognostic implications of PPBC

in MM observed by Witzyg et al. 1 In our series, the proportion of

PPBC identified a subgroup of MM characterized by advanced stage,

poor status performance, high proliferative index, and short survival.

F. Tarin
M. Orero
A. Miguel Garcia

REFERENCES


Lack of Preferential Localization of Tumoral Mass in B-Cell Non-Hodgkin’s Lymphoma Associated With Hepatitis C Virus Infection

To the Editor:

The possible association between hepatitis C virus (HCV) infection and B-cell–type non-Hodgkin’s lymphoma (NHL) has previously been suggested. 1-4 HCV tropism for hepatocytes and also, according to recent data, for the salivary gland ductular cells 5 may imply the existence of some preferential sites of neoplasia.

We report here the clinical and virologic features of 150 patients with B-cell–type NHL (71 men) consecutively seen at either a hematology or internal medicine outpatient clinic at our university hospital. Only subjects at first diagnosis of lymphoma were included in the study. Biopsy material was classified according to the Working Formulation for Clinical Usage. 6 The NHL grade was low, intermediate, or high in 37%, 49%, and 14%, respectively. All patients underwent clinical examination, routine blood analysis, chest x-ray or CT chest scan, abdominal ultrasonography and/or abdominal CT scan, and bone marrow biopsy. They were classified according to the Ann Arbor staging system 7 and 27% of patients were stage I, 35% were stage II, 18% were stage III, and 21% were stage IV. One hundred and fifty healthy, anti-HCV–negative, age- and sex-matched subjects and 80 Hodgkin’s lymphoma (HL) patients were also studied as controls. Twenty-six NHL patients were anti-HCV positive (RIBA II; Chiron, Emeryville, CA), 34 were HCVRNA positive using one-tube nested polymerase chain reaction (PCR), 1,8 and 37 (25%) were anti-HCV- and/or HCVRNA positive. The latter prevalence was significantly higher than that observed in healthy subjects (25% v 1%) and HL patients (25% v 8%; P < .01) as well as in the general Italian population (approximately 1.3%).

Samples of peripheral blood mononuclear cells (PBMC) were also tested by HCV PCR using previously described methods. 19 HCV RNA sequences were detected in PBMC in 30 of 34 (90%) serum HCVRNA-positive, in 3 of 15 (20%) serum HCVRNA-negative (2 of them also being anti-HCV–negative) NHL patients and also in neoplastic lymph node and bone marrow samples in 5 cases in whom this material was available. The results of HCV genotyping, performed with previously described methods in serum and/or PBMC samples, 10,11 are shown in Table 1. In particular, in 3 patients a mixed infection (1b + 2) was detected in PBMC and only HCV type 1b in serum. No significant differences were observed between HCV-positive and HCV-negative patients with respect to the extra-

nodal sites of the neoplasia (Table 2) as well as to the range of age and the grade of lymphoma. In particular, among patients with low-grade, intermediate-grade, or high-grade NHL, HCV-positive subjects were 14 of 56 (25%), 18 of 73 (25%), and 5 of 21 (24%) respectively.

We previously showed the existence of a high prevalence of HCV infection in patients with both mixed cryoglobulinemia-associated and idiopathic B-cell–type NHL, suggesting that HCV may play a role in lymphomagenesis in humans. 12-15 This study further confirms these previous results as well as the almost constant involvement of the lymphatic system by HCV infection. No specific or more probable extranodal tumor localization were identified in HCV-positive patients when compared with non-HCV–associated forms of NHL, suggesting that systemic and not local factors may trigger malignant lymphoproliferation. In this respect, the possibility that direct infec-

tion of lymphatic cells, probably in association with extralymphatic HCV epitope stimulation, plays a role in lymphomagenesis ought to be taken into account and deserves further analysis. 13 The demonstration of HCVRNA sequences in lymphoid cells from the great majority of HCV-positive NHL patients tested, even in the absence of serum HCV markers, is not sufficient to demonstrate the validity of this hypothesis. However, it does point in the same direction. The identification in lymphoid cells of genotypes not detectable in serum suggests clustering into extrahepatic sites of more lymphotrophic types, which may have pathogenetic relevance. In synthesis, it is possible that HCV infection may induce a chronic B-cell prolifera-
Prognosis Value of the Monoclonal Blood Plasma Cells in Multiple Myeloma

F. Tarin, M. Orero, A. Miguel Garcia, A. Miguel-Sosa, M. Sanchez, J. Marco and F. Carbonell

Updated information and services can be found at: http://www.bloodjournal.org/content/89/8/3065.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