A high bone marrow plasma cell labeling index in stable plateau-phase multiple myeloma is a marker for early disease progression and death

David P. Steensma, Morie A. Gertz, Philip R. Greipp, Robert A. Kyle, Martha Q. Lacy, John A. Lust, Janice R. Olford, Matthew F. Plevak, Terry M. Therneau, and Thomas E. Witzig

The plasma cell labeling index (PCLI) is a measure of plasma cell proliferative activity and is an important prognostic factor in newly diagnosed multiple myeloma (MM). Occasionally patients have been observed with stable, plateau phase MM with minimal numbers of residual light-chain-restricted monoclonal plasma cells, but a high PCLI. No data are available on the outcomes for such patients. Data from 57 patients with plateau phase MM and a marrow PCLI of more than 1.0% were compared with 105 matched control patients with MM with a marrow PCLI of less than 1.0%. All patients had less than 10% total plasma cells on marrow aspirate and biopsy. The median time to progression and overall survival were 8 months and 20 months, respectively, in the high PCLI group versus 39 months and 56 months, respectively, in the low PCLI group (P < .0001). These findings suggest that a high PCLI in patients with apparently stable, plateau phase MM is an adverse parameter that may predict a short time to disease progression and death. (Blood. 2001;97:2522-2523) © 2001 by The American Society of Hematology

Introduction

Patients with multiple myeloma (MM) treated with chemotherapy typically enter a plateau phase, defined as a period of stability in which the disease is present but relatively inactive.1,2 Accurate knowledge of the prognosis of these patients would help clinicians plan the frequency of follow-up evaluations and assist in decisions regarding maintenance therapy.

We have occasionally observed patients with stable, plateau phase MM who have been treated with chemotherapy and have a small number of light-chain–restricted plasma cells, but a high marrow plasma cell labeling index (PCLI). The PCLI is a powerful and independent predictor of survival in newly diagnosed MM; however, the clinical significance of a high PCLI in a small number of monoclonal marrow plasma cells is unknown.3-6 We studied whether the PCLI is a prognostic indicator in patients with plateau phase myeloma who have a minimal burden of light-chain–restricted plasma cells.

Study design

The medical records of all patients with typical MM who underwent a bone marrow aspirate and biopsy at the Mayo Clinic, Rochester, MN, between 1984 (the year of introduction of the bromodeoxyuridine PCLI technique at our institution) and January 1999 were reviewed. The Institutional Review Board of the Mayo Clinic approved this study, and all included patients gave approval for review of their medical records.

We identified patients with stable MM who had a high PCLI (at least 1.0%) and minimal plasma cell burden. To minimize sampling error, minimal plasma cell burden was strictly defined as less than 10% plasma cells on the bone marrow aspirate, biopsy, and PCLI assay. Patients obviously relapsing at the time of marrow sampling who were not truly in plateau phase (ie, those with new bone lesions or rapidly increasing M protein) were excluded. In all cases the PCLI had been determined on a single marrow aspirate and biopsy. The median time to progression (defined as a 25% increase in serum and/or urine M protein, a new lytic bone lesion, or a new plasmacytoma) and until death.

Results and discussion

From 8927 PCLI assays performed for suspected or known plasma cell disorders during the 16-year study period, we identified 57 patients with stable MM, a high PCLI, and minimal plasma cell burden. An age- and gender-matched control group of 105 patients did not differ from the 57 cases in terms of serum M protein, hemoglobin, creatinine, level of urine M protein, or ethnicity (Table 1). The level of serum M protein was slightly higher in the control group with the low PCLI. The time from initial diagnosis of multiple myeloma to the date of the PCLI assay during stable plateau phase was identical in the 2 groups (23 months).

Disease progression data were available for 51 of 57 cases and 98 of 105 controls. Survival data were available for all 57 cases and 104 of 105 controls. The patients with high PCLI had a shorter time to disease progression (8 vs 39 months, P < .0001) and shorter survival (20 vs 56 months, P < .0001) compared with the low PCLI control group (Figure 1). Of the 57 patients with high PCLI, 16 patients were being observed off-treatment at the time of...
marrow sampling, and 41 patients were receiving some form of maintenance therapy; there was no difference in progression or survival time between these 2 subgroups. Among the patients with high PCLI, the patients who progressed in 12 months or less had a median PCLI of 1.60%, whereas those who took longer than 12 months to progress had a median PCLI of 1.25%.

Many prognostic factors have been determined in MM. The PCLI reflects the proliferative activity of the malignant clone in MM and is one of the most important prognostic indicators in newly diagnosed patients. Patients fortunate enough to enter a stable phase after receiving induction chemotherapy have been characterized as having a low PCLI. We studied patients with a high PCLI and observed this to be an adverse prognostic sign, even in those patients with apparent stable, plateau phase MM and minimal residual plasma cell burden. The constellation of a high PCLI, but low plasma cell number, is uncommon; only 57 such patients were detected during 15 years of bromodeoxyuridine PCLI assays at our institution.

This retrospective study is limited by the lack of uniformity in the way the study patients were treated during induction, during the stable phase, and after disease progression. Another group of investigators has reported the median duration of the plateau phase in MM to be 22 months; this value is intermediate to the median time to progression observed in our high PCLI and low PCLI groups (8 months and 39 months, respectively).

It is unclear why the low PCLI control group in our study had a slightly higher amount of serum M protein, which might have reflected earlier progression in the control group. In spite of this, the group with high PCLI progressed more rapidly. The finding that patients with high PCLI progress and die earlier than similar patients with a low PCLI indicates that these patients should be considered for clinical trials of novel agents or early high-dose therapy with stem cell rescue, if appropriate. Clinicians should be vigilant for early progression in this group of patients.

### Table 1. Clinical and laboratory characteristics of cases and controls

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cases (n = 57)</th>
<th>Controls (n = 105)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>58</td>
<td>60</td>
<td>.69</td>
</tr>
<tr>
<td>Gender, male %</td>
<td>61</td>
<td>62</td>
<td>.95</td>
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<tr>
<td>Ethnicity, white %</td>
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<td>β₂-microglobulin, mcg/mL (n)</td>
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<td>2.20 (55)</td>
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<td>C-reactive protein, mg/dL (n)</td>
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<td>0.42 (24)</td>
<td>.78</td>
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<tr>
<td>Hemoglobin, g/dL (n)</td>
<td>12.1 (53)</td>
<td>12.0 (99)</td>
<td>.60</td>
</tr>
<tr>
<td>Creatinine, mg/dL (n)</td>
<td>1.1 (54)</td>
<td>1.0 (100)</td>
<td>.97</td>
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<tr>
<td>Mean urine M protein, g/dL (n)</td>
<td>0.56 (45)</td>
<td>0.28 (59)</td>
<td>.26</td>
</tr>
<tr>
<td>Mean serum M protein, g/dL (n)</td>
<td>1.24 (44)</td>
<td>1.71 (83)</td>
<td>.03</td>
</tr>
</tbody>
</table>

Laboratory studies were drawn within 30 days of the bone marrow plasma cell labeling index. Cases had a PCLI of at least 1.0%, and controls had a PCLI of less than 1.0%.

### Figure 1. Time to disease progression and death correlates with the bone marrow plasma cell labeling index in plateau phase MM. In patients with stable, treated MM and less than 10% residual monoclonal plasma cells, progression-free survival (A) and overall survival (B) are significantly worse in patients with a high PCLI in comparison to those with a low PCLI (median, 8 versus 39 months [P < .0001] and 20 versus 56 months [P < .0001], respectively).

### References


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