Pretreatment Tumor Mass, Cell Kinetics, and Prognosis in Multiple Myeloma

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One-hundred fifty patients with multiple (plasma cell) myeloma had pretreatment tumor mass staging, and 79 also had measurement of the pretreatment labeling index (L1%). There were clear differences in survival by pretreatment stage of disease. The pretreatment L1% of bone marrow plasma cells was an independent prognostic factor both in single factor and multivariate regression analyses, including myeloma stage (p < 0.02). Other important prognostic factors (multivariate) included performance status, serum creatinine, presence of Bence Jones protein, age, and k/λ subtype. A L1% of < 1% was associated with long survival in each patient group. Patients with benign gammopathy had excellent survival and very low labeling indices. A pretreatment L1% of >3% in high cell mass patients with a high total number of DNA synthesizing cells (S) conferred a very poor prognosis (p = 0.002). This subgroup of patients with high S values also had a high incidence of central nervous system relapse (27%), Bence Jones proteinuria, and elevated serum uric acid levels. We conclude that the pretreatment labeling index provides helpful prognostic information in addition to tumor mass staging.

A number of factors, such as renal function, hemoglobin, serum calcium, presence of urinary Bence Jones protein, immunoglobulin type, extent and type of bone lesions, serum albumin, and performance status, at the onset of disease are known to be important in relation to survival in patients with multiple myeloma.1–3 A staging system has been introduced to facilitate categorization of patients in the evaluation of treatment protocols.4 Even this subdivision of patients into stages I, II, and III (low, intermediate, and high tumor cell mass) plus stratification (A or B) for serum creatinine ≥2.0 mg/100 ml, has not entirely accounted for all prognostic differences. Several studies4–8 have suggested that rapid response has a poor prognosis. It therefore seemed that the kinetics of tumor growth and regression in individual patients might have prognostic importance.

In the present study, the pretreatment tritiated thymidine labeling index (LI)9 and direct measurement of myeloma cell mass were carried out as previously described10 and correlated with subsequent response to treatment and survival. The relationship to other known prognostic factors as well as unusual facets of the disease, such as central nervous system relapse, plasma cell leukemia, and extra medullary disease, were also analyzed.

MATERIALS AND METHODS

Patients

Between 1972 and 1978, 150 patients with plasma cell myeloma evaluated at the University of Arizona had measurements of pretreatment myeloma cell mass. Of the 150 patients, 120 had in vitro measurement of M-component synthetic rate, plasma volume measurement, and other baseline information sufficient to directly measure myeloma cell mass, as described below. In 30 patients, clinical staging1 was the basis for calculation of the myeloma cell mass. Seventy-nine patients had both direct measurement of myeloma cell mass and an in vitro tritiated thymidine labeling index performed. Multiple (plasma cell) myeloma was defined as by the Chronic Leukemia-Myeloma Task Force of the National Cancer Institute.9 Early deaths were included. For purposes of comparison, 8 additional patients with IgG benign gammopathy, as previously defined,10 were included in the kinetic analysis.

Of the 79 myeloma patients who had pretreatment labeling index determinations, 50 had IgG myeloma, 19 had IgA myeloma, and 10 had pure Bence Jones myeloma. Forty-seven patients were stage III (high cell mass), 24 were stage II, and 8 were stage I.1 A complete inventory of presenting clinical features as well as subsequent details of response to therapy were collated and stored in a computer file. Initial recorded features were those obtained prior to all treatment (including chemotherapy, radiation therapy, transfusion, plasma pheresis, and treatment for hypercalcemia or renal failure). Features recorded included hemoglobin, total neutrophil count, platelet count, scaled bone lesions,1 serum creatinine, serum and/or urinary M (monoclonal) component level (g/100 ml in the serum of g/day in the urine), urinary albumin (g/day), serum calcium, serum uric acid, immunoglobulin type, percentage of bone marrow plasma cells, presence or absence of bone marrow fibrosis, age, sex, serum albumin, and performance status, as well as initial presence or subsequent development of heart or lung disease, splenomegaly, biopsy-proven amyloidosis, central nervous system involvement, plasma cell leukemia, or extra medullary disease.11

Therapy consisted of courses of melphalan or cyclophosphamide plus prednisone in an intermittent or pulse fashion, or in the more recent patients, these agents plus BCNU, Adriamycin, or vincristine at the initiation of therapy. During the period of study, no significant differences in response rate or early survival have been noted with the various treatment protocols used.12 The patients received supportive treatment, such as local radiation therapy or treatment for hypercalcemia, when required. Patients were followed serially using a computerized system for initial staging and calculation of myeloma cell mass changes with chemotherapy.13–15 Response was assessed in terms of changes in total body myeloma cell number.
Measurement of Total Body Myeloma Cell Number

The in vitro M-component synthetic rate was measured as previously described. Bone marrow samples for in vitro studies were obtained either prior to the start of therapy or at least 3 wk after pulse treatment. In this study, 43 patients had serial measurement of in vitro M-component synthesis rate (e.g., pretreatment and at remission). The values for synthetic rate, expressed as pg/cell/day, varied by less than ±10%. The total body synthetic rate for the M component was based on either in vivo radioiodinated immunoglobulin turnover data or calculated from the serum M-component concentration, plasma volume, and predicted fractional catabolic rate, using the equations of Waldmann and Strober. All patients had radioiodinated albumin plasma volume determinations done initially and serially. The total protein content of serum and urine samples was measured by the biuret technique of Gornall, Bordawill, and David. Cellulose acetate electrophoresis and densitometry, immunoelectrophoresis, and immunoglobulin quantitation by radial immunodiffusion were performed on all serum samples. Myeloma cell mass was calculated from the total body and in vitro M-component data, as previously described. All patients had IgG subtyping performed to identify myeloma subtype IgGt, which has a higher fractional catabolic rate. No patient with IgG myeloma is included in this study.

The techniques used for the measurement of myeloma cell mass in patients with IgA myeloma were entirely analogous to those reported previously for IgG myeloma. An IgA radioimmunoassay, using the standard sandwich radioimmunoassay technique, was utilized for measuring IgA production in short-term tissue culture. The range of in vitro IgA M-component synthesis rate for different patients was 4.0–26 pg/cell/day.

In the patients with Bence Jones proteinuria only, myeloma cell mass was calculated using previously reported equations.

Calculation of the Total Body M-Component Synthetic Rate and Total Body Myeloma Cell Number (TBMC)

The total body synthetic rate for the M-component was calculated from the fractional catabolic rate for the specific immunoglobulin, its concentration in the serum, plasma volume, and body weight. In IgG myeloma cases, the equation of Waldmann and Strober for the calculation of f was used, as described in our previous kinetic analysis. TBMC was derived from the calculated total M-component synthetic rate and the measured cellular M-component synthetic rate per myeloma cell in vitro, as described previously.

Myeloma Cell Labeling Index (LI) Measurement

A 1–3-ml specimen of bone marrow was aspirated aseptically into a syringe containing heparin. One-quarter volume of 3% was added to the sample in order to sediment the red cells. The supernatant plasma, which was contained in the marrow cells, was transferred to a sterile centrifuge tube and diluted to 45 ml with Hank’s balanced salt solution with 10% fetal calf serum (HBSS-FCS) and centrifuged for 10 min at 600 g at room temperature. The cell button was then resuspended in HBSS-FCS, and the centrifugation and cell washing procedure was repeated two times. A 2-ml aliquot of the washed cell suspension was placed in a sterile plastic tissue culture tube and warmed to 37∞C in a waterbath. Five microCuries of tritiated thymidine (specific activity, 40–60 Ci/mmmole) was added to the cell suspension. After 1 hr of incubation, the suspension was washed free of the unincorporated tritiated thymidine by two additional centrifugations and washes with HBSS-FCS. The cell preparations were free of clumping, and at the completion of the incubation, viability was from 98% to 100%. Slides for autoradiography and microscopic examination were prepared with a cytocentrifuge. After methanol fixation, autoradiographs were prepared for exposure by dipping in Kodak NTB-3 emulsion and further processed using our previously published method of high-speed scintillation autoradiography (HSARG). Routinely, duplicate slides were exposed for 6 hr and 24 hr with and without scintillator and compared on an ongoing basis (every few batches of slides processed) with conventional autoradiography using isotope of specific activity 18 Ci/mmmole and exposed for 7 days at 2∞C. No significant differences were found in final labeling indices. Readings of slides processed using the HSARG technique and exposed for 24 hr were used in this analysis.

Standard developing techniques were used, and the slides were stained with acid Giemsa stain. Autoradiographs prepared in this fashion were of exceedingly high quality with a background median grain count of less than 35 gr/100 cells. All marrow cells that were morphologically in the lymphoid-plasma cell series were defined as myeloma cells. Special care was taken in staining and microscopic examination to assure that plasma cells could be distinguished morphologically from early red cell precursors. Cells containing at least 5 gr over the nucleus were considered labeled. One-thousand cells were counted in order to determine the myeloma cell LI, which was expressed as a percentage. The median grain count of labeled myeloma cells measured with this LI technique was in the class of greater than 50 gr/cell nucleus. Statistical considerations regarding threshold grain counts and relation to background were as described by Clarkson, Okhita, Ota, and Fried.

As described previously, a simple extrapolation from the LI and tumor cell number data was the calculation of the total number of labeled myeloma cells in the body (the size of the compartment of DNA-synthesizing tumor cells), TBLMC, or S. TBLMC (S) equals TBMC x LI. For purposes of calculating the TBLMC (S), only patients with direct measurements of cell mass (from immunosynthetic measurements as opposed to clinical staging) were utilized.

Statistical Methods

The method of Kaplan and Meier was used to calculate actuarial survival curves, and tests of their differences were based on a generalized Wilcoxon test or Breslow test. To further assess differences in some of the survival durations, the logrank test was
be seen that overall there is superior survival for patients with pretreatment LI% of <1% ($p = 0.02$). This effect can be noted in terms of both early deaths and survival beyond the median. In Fig. 3, the effect of pretreatment LI% on survival in the high cell mass category of patients is outlined. The survival of the 18 patients with a pretreatment LI% of <1% is significantly superior to that for the other two categories ($p = 0.06, \Delta; p = 0.002, \square$).

For patients with intermediate and low cell mass, the number of patients and deaths in the different categories did not allow for completely reliable comparisons of survival duration. However, there was a definite trend toward longer survival duration in patients with an LI% of <1%; median survival 67.5 mo compared to 41.0 mo ($p = 0.04$) for groups with a LI% of ≥1%. This trend was supported by the finding of excellent survival and an LI% of <1% in 8 of 8 patients with benign monoclonal gammopathy. In 6 of these 8 patients, the LI% was very low, being <0.5%.

To evaluate the combined effect of the labeling index and cell mass on survival, calculation of the total number of DNA-synthesizing myeloma cells in the body (see Materials and Methods) was carried out for

![Myeloma Stage and Survival Duration](image)

**Fig. 1.** Displayed are the Kaplan-Meier survival curves for 150 patients with multiple myeloma categorized by stage. (a) Stage IA, (A) stages IIA and B (only 3 stage IIIB patients), (e) stage IIIA, and (f) stage IIIIB. Stage IA survival is not significantly different to stages IIA and B ($p = 0.62$), but is significantly different to stages IIIB ($p = 0.01$). Stages IIA and B are significantly different to stage IIIB ($p = 0.07$) and stage IIIA ($p = 0.07$) and stage IIIIB ($p = 0.002$). Stages IIIB and IIIA are significantly different ($p = 0.02$).

also performed$^{24}$ (Table I). However, unless otherwise stated all, $p$ values for survival differences listed in the text are based on the Wilcoxon or Breslow tests. Differences in response rates were tested by the chi-square test or Fisher Exact test, where appropriate.$^{25,26}$

A nonlinear regression procedure developed by Cox was used to determine the combination of patient characteristics related to survival duration.$^{27}$ A logistic regression procedure was used to determine which patient characteristics were important in predicting 50% or greater tumor regression.$^{28}$ Regression coefficients were estimated in a step-wise fashion. The mean value was used for patient characteristics that were not available. Using the methods of Livingston, Ambus, George, Freireich, and Hart,$^{29}$ duplicate autoradiographs were counted and compared. It was concluded that twofold differences were statistically significant ($p < 0.05$).

**RESULTS**

Figure 1 shows the relationship between myeloma stage and survival. From the durations of median survival, it can be seen that there is a progressively poorer survival with increase in stage. Shown in Figs. 2 and 3 are the survival plots for patients with different pretreatment LI% values. the LI% cut-off values were chosen to maximize separation in survival duration, response duration, or response rates. In Fig. 2, it can

![Labeling Index and Survival Duration](image)

**Fig. 2.** The Kaplan-Meier survival curves for patients with low labeling index (LI% < 1%—□) and a high labeling index (LI% ≥ 1%—△) are displayed. The difference between the curves is significant ($p = 0.02$).
Fig. 4. Displayed are the Kaplan-Meier survival curves for 79 patients with pretreatment measured myeloma cell mass and labeling index determinations. The number of DNA-synthesizing cells has been calculated (see Materials and Methods) and patients divided into $S$ values of $<1.0 \times 10^{11}$ cells (A) and $1.0 \times 10^{11}$ cells (A), based on a significant survival difference ($p = 0.002$).

Since the subgroup of patients with high cell mass ($>1.2 \times 10^{12}$ cells/sq m) plus high labeling index ($>3\%$) had not previously been recognized, a search was made for any special clinical features that might identify this subgroup. Of the 15 such patients, the M-component was IgG type in 5, IgA in 6, and Bence Jones in only 4. Nine patients were stage IIIA and 6 patients were stage IIIB (serum creatinine $\geq 2.0$ mg/100 ml). These latter 6 patients were also hypercalcemic. There were 9 men and 6 women with an age range of 33 to 68 yr. There were 2 relatively young patients, aged 33 and 39, respectively.

A special feature of the subgroup was the incidence of central nervous system (CNS) relapse, which occurred in five high cell mass patients. In two of these five patients, the CNS relapse occurred at the time of systemic remission. The CNS relapse was documented in all instances by the presence of myeloma cells on cytocentrifuge smear (Wright stained) and in three patients with $S$ values of $<1.0 \times 10^{11}$ cells, the median survival for patients with high cell mass was 5.3 mo, as compared to 30.5 mo for the patient group with a high cell mass, but a labeling index of $<1\%$ ($p = 0.002$ for this difference).

To further assess the significance of the differences in survival duration by stage, labeling index, and number of DNA-synthesizing cells ($S$), the $p$ values obtained using the Wilcoxon test and logrank test were compared. The Wilcoxon test emphasizes the early survival, whereas the logrank test is weighted toward long-term survival (Table 1). It was found that the Wilcoxon $p$ values consistently indicated a higher level of significance, indicating that the major differences were in early survival. This was particularly true for labeling index and $S$ value, but also for disease stage.
Table 2. Optimal Cox Model Relating Pretreatment Characteristics to Survival Duration

<table>
<thead>
<tr>
<th>Pretreatment Characteristic</th>
<th>Code Used in Cox Model</th>
<th>Median Survival in Months</th>
<th>p Value for Survival Differences</th>
<th>Relative* Risk Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Performance status†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥70%</td>
<td>1</td>
<td>75</td>
<td>0.001</td>
<td>4.76</td>
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<tr>
<td>69%–40%</td>
<td>2</td>
<td>45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>39%–10%</td>
<td>3</td>
<td>27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10%</td>
<td>4</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cell mass * LI%‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Cell mass ≤1.2; LI% &lt; 1%</td>
<td>1</td>
<td>67.6</td>
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<td></td>
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<tr>
<td>2. Cell mass ≤1.2; LI% ≥ 1%</td>
<td>2</td>
<td>41.0</td>
<td>0.001</td>
<td>3.33</td>
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<tr>
<td>3. Cell mass &gt; 1.2; LI% ≥ 1%</td>
<td>4</td>
<td>15.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nephrotic Status§</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td>48</td>
<td>0.001</td>
<td>1.90</td>
</tr>
<tr>
<td>Yes</td>
<td>2</td>
<td>27</td>
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<td>Age (yr)</td>
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<td>&lt;55</td>
<td>1</td>
<td>47</td>
<td>0.10</td>
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<tr>
<td>55–64</td>
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<tr>
<td>≥65</td>
<td>3</td>
<td>30</td>
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<tr>
<td>κ/λ Subtype</td>
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<td></td>
</tr>
<tr>
<td>λ</td>
<td>1</td>
<td>42</td>
<td>0.03</td>
<td>1.68</td>
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<tr>
<td>Hemoglobin (g/100 ml)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥8.5</td>
<td>2</td>
<td>45</td>
<td>0.03</td>
<td>1.62</td>
</tr>
<tr>
<td>&lt;8.5</td>
<td>1</td>
<td>21</td>
<td></td>
<td></td>
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</table>

*Represents the ratios of the poor/good λ/λ₀ coefficients for each patient characteristic, allowing comparison of the relative prognostic importance in the Cox model equation. The larger the value for the ratio, the greater the prognostic difference between the good and poor subcategories.

†Performance status is expressed using Karnofsky scaling system. In multivariate analyses, performance status cross-correlates with serum creatinine level.

‡The myeloma cell mass * labeling index (LI%) groupings are based on the median survival data. The middle two groups are given the same code because of the similar survival. In multivariate analyses, cell mass * LI% category cross-correlates with S value (number of DNA synthesizing cells).

§The coding of patients by 'nephrotic' status (presence or absence of persistently ≥0.5 g/24 hr albumin in urine) has a slight statistical advantage over coding for just presence or absence of Bence Jones protein.

instances also by high levels of M-component in the cerebrospinal fluid.

To evaluate the interaction of LI% with other known prognostic variables, multivariate regression analyses were carried out. Table 2 shows the optimal Cox's model relating pretreatment characteristics to survival duration. It is important to point out that this model is optimal from a statistical standpoint, but was only one of several similar models resulting in significant correlations using slightly different data input. For example, as a single parameter, LI% was significantly correlated with survival duration (p < 0.05) irrespective of cell mass, performance status, serum creatinine, and all the other parameters in the multivariate analysis. Likewise, S (the product of LI% and number of myeloma cells in the body) was highly correlated with survival duration (p = 0.002). To facilitate comparison with our prior staging system, it was elected to use the cell mass * LI% categories listed in Table 3. This enabled identification of the subgroup of patients with high cell mass plus LI% of >1% with especially poor survival who had not been previously recognized.

Table 3 lists the major predictors of survival duration, including performance status (Karnofsky scale), myeloma cell mass * LI% category, nephrotic status, age, κ/λ subtype, and hemoglobin level (negative correlation). In the Cox model the λ/λ₀ ratio expresses the "instantaneous risk of death;" the higher the value the poorer the prognosis. The relative importance of the major prognostic factors is summarized in Table 3 in which the multivariate p values and the ratios of Cox hazard functions enable one to quantitate the relative prognostic significance. It is of considerable interest that the cell mass * LI% categories, based on statistically significant survival differences (p = 0.001), allow separation of patients into three major groups: (1) stage I or II with LI% < 1%; (2) stage I or II with LI% ≥ 1% or stage III with LI% < 1%; and (3) stage III with LI% ≥ 1%.

As indicated in the footnote for Table 3, one could substitute serum creatinine for performance status in the multivariate regression analysis with almost no change in the statistical significance. In a comparable way, the values for S (number of cells synthesizing DNA in the body) could be substituted for the cell
mass * LI% categories. Additional cross-correlates of S and cell mass * LI% category were presence or absence of Bence Jones protein in the urine (high S values correlating with presence of Bence Jones protein) and serum uric acid level (high S and uric acid levels cross-correlating).

Since LI% clearly influenced survival, response to initial induction chemotherapy was also evaluated, as shown in Table 4. As can be seen, there were no statistically significant differences (p > 0.20). There were sufficiently frequent follow-up M-component data to determine the exact time to remission, and remission duration in 67 of the 79 evaluated patients. Table 5 illustrates the shorter median survival of those patients reaching maximum regression within 6 mo as compared to those requiring longer for maximal induction. From multivariate regression analyses of both response to induction therapy and survival duration, it was possible to determine the features of this subgroup of patients with rapid regression, but short duration. Patients with high S values or high cell mass with a LI% of >1% and λ (lambda) light chain subtype, Bence Jones proteinuria (alone or in addition to a serum M-component), or high serum uric acid (>8.0 mg/100 ml) were all likely to fall into this group with rapid regression but short survival (p < 0.02). Conversely, poor performance status, advanced age, and severe anemia (see Table 3) correlated with lack of response plus poor survival. Unfortunately, except for these categories of patients with poor survival, response to induction chemotherapy could not be reliably predicted. An overall logistic model could predict response or lack of response in only 40% of the cases. This confirmed our prior conclusion that inherent drug sensitivity or other unknown factors were the major determinants of response, although high S values predicted for short response duration.

Table 4. Labeling Index (LI%) Prior to Treatment and Subsequent Response to Therapy*

<table>
<thead>
<tr>
<th>LI%</th>
<th>No.</th>
<th>%</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;3%</td>
<td>4</td>
<td>16%</td>
<td>11</td>
<td>44%</td>
</tr>
<tr>
<td>1%-3%</td>
<td>4</td>
<td>17%</td>
<td>8</td>
<td>33%</td>
</tr>
<tr>
<td>&lt;1%</td>
<td>3</td>
<td>10%</td>
<td>15</td>
<td>50%</td>
</tr>
</tbody>
</table>

*No difference in response rates: p > 0.20.

DISCUSSION

The findings presented in Fig. 1 with respect to myeloma stage and survival confirm our previous observations and subsequent observations of other investigators. However, in the 3 yr since this staging classification was developed, it has become clear that there can be a range of response to therapy within each of the cell mass categories. Obviously, a major determinant of prognosis is the actual drug sensitivity of the predominant myeloma clone. Using a recently developed in vitro myeloma stem cell colony assay, we have been evaluating this factor and found considerable variability in inherent drug sensitivity. However, the current studies show that the labeling index of the bone marrow cells prior to the initiation of therapy is an additional important prognostic factor.

The most important finding from our study was the degree of correlation between the pretreatment labeling index and survival duration. In addition to overall correlation as a single parameter (Fig. 2), there was particular significance in the high cell mass category (Fig. 3), as well as in multivariate regression analyses including all other known major prognostic factors (Tables 2 and 3). When the labeling index information was incorporated with the cell mass data and expressed as total number of DNA-synthesizing cells (S), as shown in Fig. 4, a whole subgroup of patients with high S values (≥1 × 10⁴ cells/sq m) and short survival duration was identified. Cross-correlates of both S value and cell mass labeling index category were the presence of Bence Jones proteinuria and/or an elevated serum uric acid level. However, the cell mass * labeling index information enabled clearer separation of patients into prognostic categories. From the comparison of the Wilcoxon and logrank test p values, it was clear that a predominant effect of labeling index and S value was on early survival (Table 1). After the deaths within the first 6 mo, the survival curves were almost parallel (Figs. 2–4).

The fact that a high pretreatment labeling index did not always confer a poor prognosis may have been because a percentage of patients with a high pretreatment growth fraction reach a plateau level before accumulating a life-threatening tumor burden. We have previously noted and reported this phenomenon whereby a patient studied serially pretreatment had a ~50% fall in LI% as the plateau phase was reached.
This type of subgroup would be expected to have a relatively good survival. The preponderance of high labeling in the lower cell mass groups as noted by us and Drewinko, Brown, Humphrey, and Alexanian suggests that this is a major pattern.

The finding of a consistently very low labeling index (<0.5%) within the group of patients with stable benign monoclonal gammopathy was particularly interesting. In the absence of other more reliable markers, as may frequently be the case, the use of the labeling index to distinguish benign monoclonal gammopathy from myeloma may prove to be more readily applicable than looking at electron microscopic morphology or acid phosphatase staining, as has recently been proposed.

A notable feature of the group of patients with high S values (total number of DNA-synthesizing cells) was the incidence of leptomeningeal central nervous system involvement. This type of nervous system involvement with malignant plasma cells and a high level of M-component in the cerebrospinal fluid (CSF) has previously been considered to be quite rare. Less than 10 cases of this type have been well documented in the literature, but have had a very poor prognosis. Since it appears that IgG, monomeric IgA, and free light chain can enter the cerebrospinal fluid directly from the systemic circulation without any evident central nervous system involvement, it is important to note that in two of our cases, significant elevation in CSF M-component was noted at a time the peripheral disease was in remission and there were very low levels of serum M-component. Failure to look routinely for malignant plasma cells in CSF cytocentrifuge smears and measure CSF M-component levels may account for the low reported incidence of leptomeningeal myeloma.

The multivariate regression analyses of both survival duration and response provided additional information about this subgroup of patients with poor prognosis. As shown in Table 4, the pretreatment labeling index did not affect the likelihood of response; however, it did affect the likelihood of time to maximum regression as shown in Table 5. The group of patients with rapid initial regression and poor survival also fell into the subgroup of patients with high S values (high cell mass labeling index category). Lambda (\(\Lambda\)) light chain type, the presence of Bence Jones protein in the urine, and an elevated serum uric acid level (>8.0 mg/100 ml) identified this subgroup. A rapid rate of regression has long been felt to represent a poor prognostic sign; however, the kinetic features have not been well defined. The high S values in our study correlated both with rapid regression and short remission duration and survival (Table 5). The details of this pattern plus the converse pattern consisting of lack of response plus poor survival in patients with poor performance status, advanced age, and severe anemia has been further analyzed and is being reported elsewhere. It should be noted that the correlation between lambda (\(\Lambda\)) subtype and poor prognosis supports prior observations, particularly in patients with Bence Jones myeloma. The correlation with an elevated uric acid most likely reflects both higher growth rates and intrinsic cell loss. Unusually, high spontaneous myeloma cell loss has been noted by Drewinko in patients with relapsing disease.

Implications of the findings in this report are several. The pretreatment labeling index would appear to provide information that is clinically useful and not directly obtainable from previously recognized prognostic factors, including our own staging system. The subgroup of patients with both high cell mass and high labeling index would appear to deserve special attention with respect to possible more aggressive therapy both to achieve remission and maintain remission without central nervous system relapse. The findings fit in well with recent observations that intensive induction schedules would seem to particularly benefit patients who have high cell mass myeloma, although not necessarily providing any extra benefit in the low cell mass categories. While it might potentially be of value to include cycle-active drugs for treatment of high cell mass, high labeling index myeloma patients, it is essential that such drugs be known to have a greater effect on cycling myeloma cells than normal hematopoietic progenitors.

The findings of a consistently very low labeling index in the patients with benign gammopathy suggests that the labeling index value may be a useful test in identifying this group of patients. We are currently analyzing the use of the labeling index prospectively in relation to other potential differential criteria, such as the plasma cell acid phosphatase stain.

Our studies thus indicate the prognostic importance of myeloma cell kinetics. It is hoped that further studies will provide additional useful information relating clinical disease stage to both kinetics and drug sensitivity in individual patients.

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Pretreatment tumor mass, cell kinetics, and prognosis in multiple myeloma

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