The duration of survival of patients with multiple myeloma ranges from a few months to many years (median, 2.5 to 3 years). This range is wide, and both the patient and the physician would like to have a more precise prediction of survival for the individual patient. Furthermore, it is reasonable to consider more aggressive and more toxic therapy for the patient with prognostic factors that indicate a short survival. Alternatively, patients with favorable prognostic factors that suggest a survival of many years would be less inclined to accept an aggressive therapeutic approach with a high morbidity and mortality.

For more than a quarter century, investigators have attempted to identify clinical and laboratory features affecting survival. Carbone et al1 reported that survival in multiple myeloma was longer when the patient had a hemoglobin (Hb) level more than 9 g/dL, a blood urea nitrogen value less than 30 mg/dL, a serum calcium level less than 12 mg/dL, and a good performance status. In an Acute Leukemia Group B (ALGB) evaluation of 189 patients, the Hb, blood urea nitrogen, and calcium levels as well as the clinical performance, presence of proteinuria, and percentage of bone marrow (BM) plasma cells were prognostically important.2 The Medical Research Council3 also noted an unfavorable effect on survival of patients with myeloma whose blood urea nitrogen value was increased and whose Hb and serum albumin concentrations were low. In a Mayo Clinic study of 219 patients with multiple myeloma, the initial serum creatinine and calcium levels were the most significant variables affecting survival at 2 years. The Hb level made only a modest contribution. The concentration of monoclonal protein (M-protein) in the serum did not contribute to prediction of survival or death at 2 years. There was also no difference in survival in patients who had IgG myeloma compared with those who had IgA myeloma (31 months vs 28 months, respectively).4

The morphologic characteristics of the myeloma cell have been studied for features affecting survival. In 1948, Bayrd5 reported that none of 10 patients with myeloma who had poorly differentiated plasma cells survived a year, whereas 4 of 7 patients with well-differentiated plasma cells were living 2 to 6 years after diagnosis. In another study, the demonstration of plasmablastic morphology was associated with a median survival of 10 months, whereas other morphologic features were associated with a survival of 35 months.6 In an Eastern Cooperative Oncology Group (ECOG) study of 239 patients with multiple myeloma treated with multiple alkylating agents (vincristine, BCNU, melphalan, cyclophosphamide, and prednisone [VBMC-P-based chemotherapy]), the median survival was 25.6 months for patients with plasmablastic morphology and 39.8 months for those with other subtypes (P = .003). In the first year after diagnosis, 24% of patients with a plasmablastic morphology died and 12% with the other subtypes died.7 Tumor-cell grading (well-differentiated v poorly differentiated plasma cells) was an important prognostic factor among 320 patients with multiple myeloma in the German Myeloma Treatment Group trial M Mol.8

The Durie-Salmon clinical staging system9 is based on a combination of factors that correlate with the myeloma cell mass. The median duration of survival is approximately 5 years for patients with stage IA disease and 14.7 months for those with stage IIIB disease. However, this clinical staging system is unreliable in many instances and has significant shortcomings, especially in the designation of bone lesions.

The time of response to chemotherapy affects survival. Hansen et al10 reported that patients whose serum M-protein value decreased by 0.6 g/dL or more within 2 months after beginning chemotherapy had a median survival of 13 months, whereas those who responded slowly had a median survival of 62 months. Boccadoro et al11 also noted that patients with rapid response to therapy and a high plasma cell labeling index (PCLI) had a much shorter duration of response and survival.

The uncorrected β2-microglobulin (β2-M) level is one of the most significant prognostic factors in multiple myeloma. Cuzick et al,12 in a study of 476 cases of multiple myeloma, reported that the uncorrected β2-M level at the time of presentation was the single most powerful prognostic variable. The addition of the Hb level made only a modest contribution. In addition, the β2-M level during follow-up is also predictive of subsequent survival for the first 2 years of follow-up. The β2-M level does not provide a good guide to long-term survival.13

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Interleukin-6 (IL-6) is a major growth factor and stimulates in vitro and in vivo plasma cell growth. This finding is supported clinically by the fact that anti–IL-6 monoclonal antibodies (MoAbs) block myeloma cell proliferation in vivo and result in reduction of symptoms and manifestations of the disease.\textsuperscript{14} IL-6 was a significant univariate predictor of survival in 42 cases of multiple myeloma.\textsuperscript{15} In a study of 210 patients with multiple myeloma from Finland, a sensitive sandwich-type enzyme-linked immunosorbent assay (ELISA) technique detected an elevated IL-6 level in 42% of patients. On univariate logistic regression analysis, elevated serum levels of IL-6 were associated with an increased 3-year mortality ($P = .002$). Thus, elevated serum IL-6 levels were associated with a poor prognosis in this group of patients with myeloma.\textsuperscript{16} IL-6 induces synthesis of C-reactive protein (CRP). CRP levels decrease after the infusion of anti–IL-6 MoAbs. Therefore, it appears that serum CRP levels are a reflection of IL-6 activity. Alternatively, in this issue of Blood, Ballester et al\textsuperscript{17} state that IL-6 is not a major growth factor for multiple myeloma. They report that high levels of IL-6 secretion from BM cultures of patients with multiple myeloma defined a subgroup of patients with low tumor burden, as determined by lower serum $\beta_2$-M levels, a lower percentage of BM plasma cells, a higher synthetic rate of M-protein production, and low proliferative levels. Patients with high IL-6 secretion had lower levels of $\beta_2$-M (median, 2.5 mg/L) than those with low IL-6 levels (median, 5.2 mg/L). Similarly, patients with high IL-6 secretion had lower percentages of BM plasma cells (median, 23.5%) than those with low IL-6 levels (median, 66%). Furthermore, there was no difference in survival between patients with low and those with high IL-6 secretion. The investigators propose that IL-6 is a major differentiation factor.

Bataille et al\textsuperscript{18} reported that the median duration of survival was 6 months for patients with CRP and $\beta_2$-M levels $\geq 6$ mg/L but 54 months when both values were less than 6 mg/L. An elevated lactate dehydrogenase level is also a predictor of poor prognosis. In a study of 391 patients with multiple myeloma, 11% had an elevated lactate dehydrogenase level. This was associated with extraosseous disease, a high tumor mass, and a poor response to chemotherapy, and the resulting median survival was 9 months.\textsuperscript{19} One must be cautious because granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF) can produce elevated lactate dehydrogenase levels in the absence of tumor progression. This effect may be due to increased marrow turnover induced by G-CSF or GM-CSF.\textsuperscript{20} CD4$^+$ T cells are commonly reduced in myeloma, whereas the CD8 level is normal or increased. San Miguel et al\textsuperscript{21} reported that a CD4 T-cell level less than $700 \times 10^6$/L was associated with a higher stage of myeloma and a shorter duration of survival. The expression of CD38 on circulating lymphocytes is a typical feature of myeloma. Omedé et al\textsuperscript{22} found a median survival of 14 months in patients with a CD38$^+$ lymphocyte value of $0.45 \times 10^6$/L, whereas those with a CD38$^+$ lymphocyte level less than $0.45 \times 10^6$/L had a survival of 32 months.

A study of 107 patients with newly diagnosed multiple myeloma at the Mayo Clinic from 1984 through 1986 showed that PCLI levels of thymidine kinase, $\beta_2$-M, serum albumin, CRP, and age were all significant univariate prognostic factors. A multivariate analysis showed that only PCLI and $\beta_2$-M levels had independent prognostic significance.\textsuperscript{23} The survival curves were better separated by the PCLI and $\beta_2$-M level than by other combinations of variables. Among the nine patients younger than 65 years with low PCLI and low $\beta_2$-M levels, eight were alive almost 6 years after starting chemotherapy. These good-risk patients could not be identified by standard clinical or laboratory features.

The median duration of survival was 16 months for our 34 patients with a high PCLI (>1%) and $\beta_2$-M levels (>2.7 mg/mL) and 71 months for the 15 patients with low values ($P < .0001$). Unfortunately, more than half (58 patients) had high values for either variable, and the median duration of survival was 40 months. Age, thymidine kinase value, CRP level, plasmablastic morphology, and serum creatinine level were not significant after the PCLI and $\beta_2$-M levels were considered. With the PCLI removed from the model, $\beta_2$-M and thymidine kinase values were the only independent prognostic factors. The CRP value did not provide independent prognostic significance. Our patients with a thymidine kinase value $\geq 7$ U/L had a short median survival of 1 year; all but 1 of 13 patients died in the first 2 years. However, only a small number of patients had elevated thymidine kinase levels. In short, the PCLI and $\beta_2$-M levels measured at diagnosis were independent factors, and the addition of thymidine kinase and CRP values did not add useful additional prognostic information. The PCLI measures the proliferative rate of the plasma cells, whereas the $\beta_2$-M level is an indication of tumor mass. It is obvious that PCLI and $\beta_2$-M levels must be considered when interpreting the results of clinical trials.\textsuperscript{24}

Increased levels of soluble IL-6 receptor (sIL-6R) have been found in patients with myeloma. The sIL-6R molecule is synthesized by plasma cells and probably by other cells as well because its level appears to be independent of myeloma cell tumor burden. It can act as an agonist for myeloma cell proliferation by binding serum IL-6, the central growth factor in myeloma, and transferring it to the plasma cell surface. There it binds to gp130, forming a high-affinity receptor that initiates a signal to the nucleus to begin DNA replication and cell proliferation. In the presence of equivalent amounts of IL-6, sIL-6R can amplify myeloma cell production 10-fold.

The sIL-6R level was measured in 420 patients with multiple myeloma who entered an ECOG trial. The PCLI, $\beta_2$-M and CRP levels, age, stage, sex, performance status, creatinine, Hb, calcium, and albumin levels, type of serum and urine M-protein, and the percentage of BM plasma cells were evaluated. With the Cox proportional hazards model, higher levels of serum sIL-6R were associated with shorter survival ($P = .002$). Seventy-nine patients with an sIL-6R level $\geq 300$ ng/mL had a median survival of 29 months compared with 43 months for 341 patients with sIL-6R levels less than 300 ng/mL.

A multivariate analysis of 388 cases with complete information showed independent prognostic significance for PCLI $\geq 2\%$, sIL-6R values greater than 300 ng/mL, performance
status greater than 1 ($P < .006$), creatinine value $\geq 2$ mg/dL, and $\beta_2$-M level $\geq 4$ $\mu$g/dL ($P < .05$). $\alpha$-IL-6R levels did not correlate with PCLI. The addition of sIL-6R to PCLI and $\beta_2$-M allowed improved prognostic classification, doubling the proportion of patients identified as high risk. In patients with elevation of two or more of the following three factors—PCLI greater than 2%, $\beta_2$-M greater than 4.0 $\mu$g/dL, or sIL-6R greater than 300 ng/mL—the estimated 2-year survival was 41% at 2 years and the median survival was 18 months; when none of the three factors was increased, the estimated 2-year survival was 83% and the median survival was not yet reached. Similarly, survival was long when this classification was used for patients who were considered candidates for an autologous BM or peripheral stem cell transplant: age less than 65 years, performance status less than 2, and creatinine level less than 2 mg/dL.\textsuperscript{24}

Controversy exists with regard to the prognostic value of the expression of common acute lymphoblastic leukemia antigen (CALLA). It was initially reported that the expression of this marker was associated with a poor prognosis,\textsuperscript{25} whereas other investigators have reported that it is of no value in prognosis.\textsuperscript{21} In another of our studies, which examined levels of CD10—expression of CALLA using the J5 antibody—we found no difference in survival whether or not plasma cells expressed CD10. Similarly, we found that expression of CD56 did not result in statistically different durations of survival for patients with multiple myeloma.

Increased levels of $\alpha_1$-antitrypsin, an acute-phase protein, indicate a shorter survival.\textsuperscript{26} Neopterin has been reported as an indicator of disease severity in multiple myeloma. The median survival of patients with high values was 20 months, whereas survival was 63.9 months for those with low values.\textsuperscript{27} Low plasma cell acid phosphatase levels have been associated with poorer survival—1.7 years with low values versus 2.8 years with higher scores.\textsuperscript{28} Flow cytometric analysis of oncoprotein expression in myeloma using MoAbs to six oncoproteins ($\alpha$-myc, $\alpha$-fos, $\alpha$-neu, pan-ras, bcl-2, and p53 variant) and two tumor suppressor gene products (Rb and p53 wild) showed that 82% of 63 patients had increased expression of at least one oncoprotein. Those with more than two oncoproteins had evidence of progressive disease.\textsuperscript{29}

The search for more accurate prognostic factors continues. This is necessary for the identification of patients for whom more aggressive therapy is indicated. It is also essential to have well-defined prognostic factors when evaluating any therapeutic approach for multiple myeloma.

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Why better prognostic factors for multiple myeloma are needed [editorial] [see comments]

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