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*Commentary*

# Prognostic Factors in Plasma Cell Myeloma

(A COMMENT ON: SCARFFE JH, ANDERSON H, PALMER MK, CROWTHER D. Prognostic significance of pretreatment serum $\beta_2$-microglobulin levels in multiple myeloma. *Eur J Cancer Clin Oncol* 1983, **19**, 1361–1364)

CLINICIANS are interested in the clinical and laboratory variables which help in the prediction of survival prognosis for patients with neoplasms. An understanding of these prognostic factors is important in the stratification of patients for randomization in clinical trials, in the analysis of results, and in discussing the significance of the disease with a patient. An analysis of prognostic factors may also identify a subgroup who are not benefited by current treatment policies and lead to the testing of new approaches for this subgroup.

The development of extensive computer files of clinical and laboratory data on patients with plasma cell myeloma, and statistical methods for analyzing the effect of variables on prognosis, has resulted in numerous reports. The principle variables which affect the survival of myeloma patients are those associated with: (1) the myeloma cell mass, (2) renal function, (3) the myeloma growth rate and (4) certain intrinsic properties of myeloma cells in different patients.

Many prognostic factors correlate strongly with the myeloma cell mass, which is estimated by dividing the total amount of M-protein produced in a patient per 24 hr by the amount of M-protein produced per myeloma cell during the same period [1]. By correlating the estimated myeloma cell mass with certain clinical manifestations, Durie and Salmon devised a useful clinical staging system [2]. They found that patients with marked anemia (Hg <8.5 g/dl), hypercalcemia (serum calcium >12.0 mg/dl), multiple osteolytic lesions or very high M-protein synthesis rates all had high myeloma cell numbers. Patients with one or more of these features were classified as having stage III disease. Patients with all of the following features had a low number of myeloma cells, and were called stage I: Hg >10.0 g/dl, normal serum calcium, normal bones or a solitary lytic lesion, low M-protein production rates and a serum albumin >3.0 g/dl. Patients with intermediate values were classified as stage II. These criteria enable clinicians to classify patients into groups with high, intermediate and low myeloma cell masses on the basis of easily measured clinical features of the disease. In an article in this issue, Scarffe *et al.* (pp. 000–000) point out that serum beta-2-microglobulin ($\beta_2$m), corrected for renal function, correlates strongly with myeloma cell mass. Corrected serum $\beta_2$m values provide an independent estimate of myeloma cell mass, and may prove to be helpful in evaluating the stage and response to treatment of patients with myelomas which produce only light chains and those secreting little or no M-protein [3].

Renal function is an important prognostic factor which is independent of the myeloma cell mass. Patients who present with renal insufficiency (BUN >30 mg/dl or serum creatinine >2.0 mg/dl) have a poor prognosis regardless of whether the estimated myeloma cell mass is low, intermediate or high. For this reason, each stage is subclassified as A for those without and B for those with renal insufficiency.

The growth rate of the plasma cell tumor is a strong predictor of survival. The M-protein doubling time has been used as a measure of growth rate and has been shown to correlate well with survival [4]. Patients with rapidly growing tumors (short M-protein doubling times) have the worst prognosis. Determining the percentage of marrow plasma cells engaged in the synthesis of DNA with tritiated thymidine (labelling index, LI) provides another assessment of growth rate. Myeloma patients with an LI of less than 1% survive significantly longer than those with values greater than 1% [5, 6]. The pretreatment LI of marrow plasma cells is an independent prognostic factor which is capable of identifying subgroups of patients with a poor prognosis within each stage. Hobbs [7] noted that myeloma patients who responded rapidly to treatment with melphalan or cyclophosphamide survived for shorter periods than those who responded slowly.

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An explanation for this finding is that the rate of decrease in the serum M-protein is probably directly related to the myeloma growth fraction. Since cells exposed to an alkylating agent do not die until the next cell division is attempted, one would expect tumors with a high growth fraction to regress more rapidly than those with smaller numbers of proliferating cells. Tumors with a high growth fraction which regress rapidly would also be expected to regrow rapidly and to be associated with shorter survival. Durie *et al.* [5] confirmed that patients who achieved maximum tumor regression in less than 6 months after starting treatment had shorter remissions and overall survival than those who responded more slowly. The rapid responders also had a higher LI than the slow responders.

Several intrinsic properties of myeloma cells influence the survival prognosis of a patient. Perhaps the most important of these is the sensitivity of the myeloma cell to the chemotherapeutic agent used to treat the patient. Patients who respond to treatment with a fall in the serum M-protein to less than 50% and light-chain proteinurea to less than 10% of the pretreatment value achieve median survivals about four times longer than non-responders. The type of light chain produced by the myeloma cell also influences survival; those producing lambda light chains have a significantly shorter survival than those producing kappa [5, 8–10]. The DNA content of myeloma cells prior to treatment has been shown to be a prognostic factor which is independent of stage [11]. Myeloma patients with aneuploid tumors at diagnosis were more likely to have advanced stage than those with diploid myeloma cells, and all patients with renal failure had aneuploid tumors. Finally, the ability of myeloma cells to form colonies in the culture system described by Takahashi *et al.* [12] signifies a grave prognosis. Myeloma colonies were detected in cultures of marrow cells from 7 of 44 myeloma patients. The marrow samples which formed myeloma colonies were obtained from patients in the terminal phase of the disease with pancytopenia, a cellular marrow and rapidly progressive disease; 6 of the 7 patients expired within 1–9 months after the marrow was obtained.

These studies have identified groups of myeloma patients with limited survival prognosis. Attempts to devise special treatments for these patients have not been very successful as yet. Continued efforts are required to learn more about the biology of myeloma cells and the factors which determine their response to treatment.

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