

Editorial

Prognostic Factors in Multiple Myeloma: It's in the Genes

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Introduction

These are very exciting times in myeloma research. Genetic analysis has identified immunoglobulin gene translocations in two-thirds of patients, with t(4;14)(p16;q32) and t(11;14)(q13;q32) each present in about 15% of patients (1, 2). Gene expression profiling has identified clusters of genes associated with different stages of the disease and will no doubt deluge investigators with potential prognostic markers (3). Elegant cell biology experiments have provided new models for studying the interaction of MM² in the bone marrow microenvironment (4), and new targets, both in the MM cell, and the microenvironment have been identified (5). Drugs that target the microenvironment (bisphosphonates) have become a mainstay in our treatment of patients (6). Perhaps the most exciting development, however, is the identification of active drugs with novel mechanisms of action, the most advanced in clinical trials being thalidomide (and its analogues; Ref. 7) and the proteasome inhibitor PS-341 (8). After ~30 years in which there were only two agents (alkylating agents and glucocorticoids) with appreciable anti-myeloma activity, it appears as though we may be on the verge of an onslaught of active agents that will need to be evaluated, alone and in combinations, in well-designed clinical trials. This represents a considerable challenge to the myeloma research community. It took >20 years to establish that combination chemotherapy was not significantly better than melphalan and prednisone (9). Hopefully with the advances in biology and the availability of new *in vitro*, xenograft and transgenic animal models, we will establish the place of these new agents in our armamentarium more quickly. This will probably require some changes in the way we conduct clinical trials, starting with disease-focused Phase I/II trials, then moving directly to large, international, multi-institutional Phase III trials. Key to this effort is the availability of prognostic factors that will allow us to objectively evaluate the different populations treated and more importantly will identify patients who do not benefit from our current therapy and should be offered experimental therapy from the outset.

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² The abbreviations used are: MM, multiple myeloma; FISH, fluorescence *in situ* hybridization; BM, bone marrow.

³ S. Ely and P. L. Bergsagel, unpublished observations.

Traditional prognostic factors in MM measure plasma cell proliferation (plasma cell labeling index, Ki-67), plasma cell mass (clinical stage, plasmacytosis), or the status of the patient (hemoglobin, calcium, creatinine, albumin). The most consistently powerful prognostic marker is β 2-microglobulin that in one variable measures a combination of cell proliferation, cell mass, and renal function. Genetic factors are also important prognostic factors, perhaps the most important being the loss of all or part of chromosome 13 (detected either by interphase FISH or conventional cytogenetics), and hypodiploidy (detected by conventional cytogenetics; Ref. 10). The problem with some of these factors is that they are not universally available. One of the most established plasma cell labeling index involves special handling and incubation of the BM aspirate followed by immunofluorescent microscopy and is available only at specialized centers. Recently, a simple immunohistochemical assay that measures proliferation restricted to the plasma cells in the BM biopsy has been developed (plasma cell proliferation index) and promises to provide an accurate measure of plasma cell proliferation that can be widely used. Similarly, conventional cytogenetics, although generally available, is not generally useful because it requires successful stimulation of the MM cells *in vitro* to obtain metaphase chromosomes, and informative karyotypes are obtained in only ~30% of patients.

The two factors that are widely available and have shown up repeatedly as important independent prognostic factors are β 2-microglobulin and deletion of 13q14 detected by interphase FISH analysis. Using these two variables, the Intergroup Francophone du Myeloma divided patients into a group with two favorable variables (20% of patients) with median survival not reached at 110 months, one favorable variable (50% of patients) with median survival 47 months, and no favorable variables (30% of patients) with median survival 25 months (11). Promising for the future is the identification of prognostic markers that appear to identify different disease entities within MM. A follow-up study from the Intergroup Francophone du Myeloma using interphase FISH analysis to detect immunoglobulin heavy chain gene translocations found that patients with t(4;14) (13% of patients) have a poor overall survival (23% at 80 months) and do not appear to achieve lasting disease control with high-dose chemotherapy (2). In contrast, patients with t(11;14) (16% of patients) had an especially good prognosis with this therapy (88% at 80 months). Survival for both of these subgroups was independent of deletion 13. The other patients in the study with (29%) or without (42%) deletion 13 represented intermediate prognoses (46 and 68% at 80 months, respectively). The power of these prognostic markers is that they identify homogeneous groups of patients with a shared pathogenesis for whom rational targeted therapy may be developed. In particular, the t(4;14) is associated with ectopic expression of receptor tyrosine kinase fibroblast growth factor receptor 3 (12) and may be successfully targeted with small molecule tyrosine kinase inhibitors *in vitro* (unpublished). Hopefully, clinical trials of these agents in t(4;14) MM will begin in the near future, and we may optimistically

expect that they will show activity similar to targeting the tyrosine kinase abl in t(9;22) leukemia.

In this issue of *Clinical Cancer Research*, Filipits *et al.* [9: 820–826, 2002] have used immunohistochemistry on a retrospective collection of MM patients' BM biopsies and determined that low expression of p27KIP1 (CDKN1B) is an adverse prognostic factor that is independent β 2-microglobulin and chromosome 13 deletion. One might expect that as an inhibitor of cyclin-dependent kinases that regulate G₁ to S-phase progression of the cell cycle, low p27 may simply be another way of identifying the plasma cells that are cycling. Although most lymphomas show an inverse correlation between p27 and proliferation, mantle cell lymphoma and a subset of diffuse large cell lymphoma do not (13). The authors did not find an association with Ki-67 and p27KIP1 expression in MM, suggesting some dysregulation or other biological functions of p27 in MM. Additional biological studies will be required to determine whether modulating p27 levels may exert an anti-MM effect or if its loss is simply a marker of a more aggressive tumor. Translocations of cyclin D1, cyclin D3, and other mechanisms that result in the ectopic expression of cyclin D1 are present in almost one-half of patients with MM (3), emphasizing the importance of the D-type cyclin pathway in MM and stimulating a closer look at the cyclin-dependent kinase inhibitors, particularly in the other half of patients.

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