EDITORIAL

A kinder, gentler way: control of the proliferative tumor compartment, not cosmetic complete response, should be the goal of myeloma therapy

In this issue of Leukemia, Arzoumanian et al.[1] advocate a new clinical end point for multiple myeloma (MM) therapy: suppression of the abnormal karyotype. It is an impressive summary of the analysis of metaphase cytogenetics in 2000 patients with MM treated at the University of Arkansas for Medical Sciences. It establishes a new paradigm for evaluating relapsed MM and clearly demonstrates that relapsed MM may be effectively divided into different groups with markedly different outcomes, in much the same way that untreated MM has been divided into different molecular[2,3] and prognostic groups.[4] To put their findings in context, it is helpful to review the natural history of plasma cell neoplasia.

Multiple myeloma is characterized by the progressive accumulation of malignant plasma cells in the bone marrow causing anemia and bone destruction. It is often preceded by a stable and limited monoclonal expansion of benign plasma cells in the bone marrow that do not cause any end-organ damage. In examining isolated plasma cells, we are unable to identify genetic or gene expression features that distinguish malignant from benign monoclonal gammopathy. In practice, therefore, a combination of clinical features, including temporal stability, minimal plasmacytosis (less than 10% of bone marrow mononuclear cells) and lack of end organ damage, is used to identify benign monoclonal gammopathy. This condition has been variously termed 'benign monoclonal gammopathy', 'monoclonal gammopathy of unknown etiology', 'essential hyperglobulinemia' and 'dysimmunoglobulinemia',[5–8] although the generally accepted term is now 'monoclonal gammopathy of undetermined significance'.[9] This latter, rather awkward historical term derives from a time when the natural history of this condition was not known, and reflects the inability to distinguish either pathologically or molecularly, benign from malignant plasma cells. In patients in whom MM is relapsing from a (complete) remission, we are again faced with the dilemma of distinguishing benign (or more appropriately, minimally malignant) from aggressively malignant plasma cells.

In contrast to the situation for relapsed MM, a great deal of effort has been focused on stratifying untreated MM into different groups with more uniform outcomes. These include staging systems (Durie–Salmon and International Staging System) that quantitate tumor mass (level of monoclonal gammopathy and β2-microglobulin) and extent of host end-organ damage (lytic bone lesions, anemia and hypoalbuminemia) as a measure of tumor burden and aggressivity.[10,11] More powerful are classifications based on genetics, which seek to identify different molecular subtypes of MM. Although primarily designed based on underlying genetics, these classification systems also have important prognostic implications. The genetics of MM has been divided into primary and secondary events. The primary events are thought to be immunoglobulin gene translocations involving 4p16 (FGFR3/MMSET), 16q23 & 20q11 & 8q24 (c-maf, mafB and mafA), 6p21 & 11q13 (cyclin

D3 and cyclin D1), and hyperdiploidy (mainly trisomies of chromosomes 3, 5, 7, 9, 11, 15, 19 and 21).[12] Of these, the 4p16 and 16q23 translocations have a poor prognosis (that we expect is also shared by the mafA and mafB translocations). Secondary genetic events include activating mutations of ras, translocations of MYC, deletion of chromosome 13 and deletion of p53, with the latter two associated with a poor prognosis. Translocations of 4p16 and 16q23 and deletion of p53 are strongly associated with deletion of chromosome 13 (>78% of cases), so that in a multivariate analysis including all these genetic abnormalities, deletion of chromosome 13 was not identified as an independent prognostic factor.[13] However, genetic factors alone do not allow sufficient discrimination, and in a large study of 1000 patients from the Intergroupe Francaise du Myelome, it was found that the addition of β2-microglobulin to t(4;14) and deletion of p53 provided the most robust prognostic model.[13]

Finally, the addition of a measure of plasma cell proliferation provides a final independent prognostic factor. This can be done prospectively on bone marrow aspirates using 5-bromo-2-deoxyuridine incorporation *in vitro* (the Plasma Cell Labeling Index (PCLI), with a cutoff of 1%), and as with cytogenetic abnormality (CA), an elevated PCLI in patients in plateau phase MM is associated with a poor prognosis.[14] More recently, proliferation has been measured retrospectively on bone marrow biopsies using a double immunohistochemical stain for nuclear Ki67 and surface CD138 (with a cutoff of 4%).[15] Not surprisingly, an elevated Ki67 correlated with the presence of abnormal metaphase karyotype (CA) (82% of patients with an elevated Ki67 index vs 43% in the remaining patients), furthermore, Ki67 index was elevated in 93% of the patients with hypodiploidy, whereas no correlation was found with hyperdiploidy. In view of recent studies using array-based comparative genomic hybridization, it is clear that almost all MM patients have genetic changes that should be evident with conventional cytogenetics.[16,17] The failure to detect metaphase karyotype abnormalities in an MM patient does not mean the MM tumor is cytogenetically normal, but is attributed to a failure to stimulate the MM cells to divide *in vitro*, and provide appropriate metaphase nuclei for analysis. Therefore, the detection of CA in relapsing MM patients by Arzoumanian *et al.* is a measure of both the MM tumor burden and their intrinsic proliferative ability, perhaps accounting for its powerful prognostic impact.[1]

This report from the Arkansas group is significant for what it does not say. It does not say that suppression of the myeloma clone is critical for long-term survival. Their conclusion is that it is sufficient simply to suppress abnormal karyotypes. After leading the field for the last two decades in the pursuit of ever-higher complete responses, this is a seemingly remarkable admission, although perfectly consistent with their recent publications and editorials.[18,19] It is becoming increasingly clear that the qualitative impact of a complete response is dependent on the treatment employed, with the most significance given to complete responses following high-dose
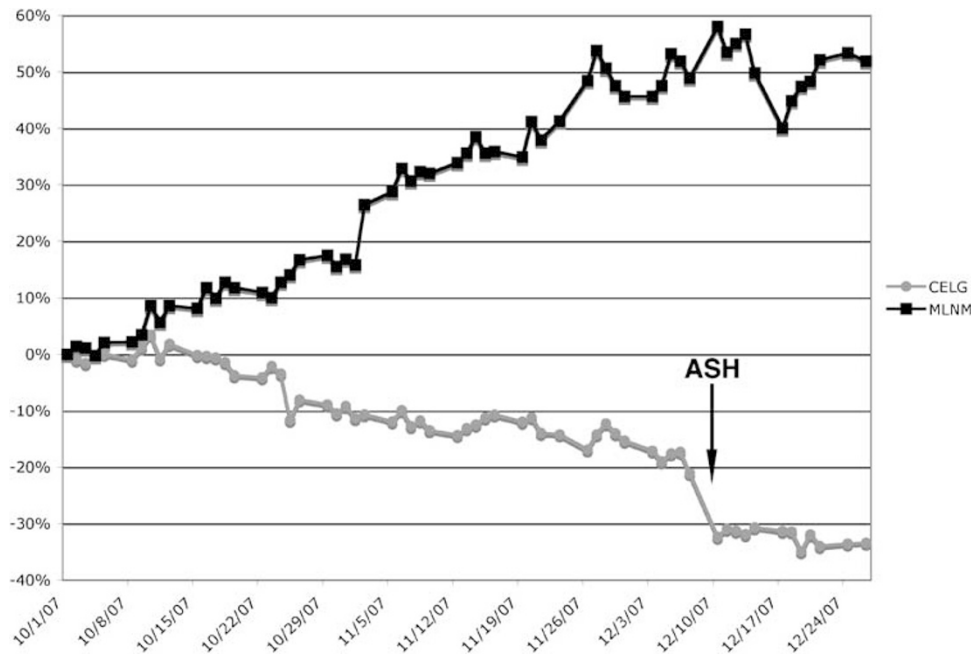
Figure 1 Percentage change in stock price of Celgene (CELG) and Millenium Pharmaceuticals (MLNM) around the time of the 2007 annual meeting of the American Society of Hematology (ASH).

melphalan, and the least significance to complete responses to glucocorticoids. There are insufficient data to conclude about the quality of complete responses to thalidomide, lenalidomide or bortezomib, although I am willing to hazard a guess that we will find thalidomide and lenalidomide somewhat closer to melphalan, and bortezomib closer to glucocorticoids. A lack of information has not prevented the field from single-mindedly pursuing the 'cosmetic' complete response, defined as one that makes the principal investigator look good, but does not provide meaningful benefit to the patient (and in fact may be harmful). The seductive allure of the cosmetic complete response propels the investigator's career, attracts patients to clinical trials, facilitates presentation and publication of clinical trials, helps pharmaceutical companies raise capital and compels stock analysts to trade pharmaceutical stocks. The irony of the situation was highlighted following the 2007 annual meeting of the American Society of Hematology.

Surrounding the time of this meeting, the price of Celgene (the manufacturer of thalidomide and lenalidomide) stock fell 30%, and the price of Millenium Pharmaceuticals (the manufacturer of bortezomib) stock rose 50% (Figure 1). It is of course impossible to pinpoint all of the factors that play into the valuations of stocks, but it is notable that the sharp drop in Celgene stock followed the oral presentation[20] of the results of the E4A03 study comparing lenalidomide with high or low-dose dexamethasone. The oral presentation contained response rate data not present in the published abstract including a complete response + very good partial response (CR + VGPR) after four cycles of 46 vs 26% ($P < 0.001$), that was presumably disappointingly low for some analysts, despite the fact that there is a significant difference in the 2-year probability of survival of 75 vs 87% ($P < 0.009$). The obvious conclusion is that response rate after four cycles is not a good surrogate for long-term survival, although this view is apparently not rewarded by the financial markets. In contrast, Jesus San Miguel[21] presented the results of the VISTA trial showing significantly better response rates, progression-free survival and overall survival

with melphalan, prednisone and bortezomib treatment compared to melphalan and prednisone treatment. This was accompanied by a complete response rate of close to 30% and is very encouraging, although one could argue that the dramatic increase in the complete response was not accompanied by an equally dramatic prolongation of overall survival.

Hopefully the results of these and other clinical trials, together with the careful analysis of patient outcomes studied with correlative studies similar to those described by Arzoumanian et al. will temper the thoughtless enthusiasm for cosmetic complete response, and help to identify other valuable surrogates of long-term disease survival, such as the suppression of cytogenetic abnormalities as reported here.

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