The term “multiple myeloma” was coined more than 100 years ago, based on a patient who was noted to have multiple sites of bone-based plasmacytomas or myelomas on postmortem examination. However, in the modern era of gene expression profiling and advanced diagnostics, the word “multiple” could just as easily refer to the heterogeneous nature of the disease that we collectively call multiple myeloma. In this issue of Blood, Kapoor and colleagues from the Mayo Clinic,1 and Reece and colleagues from the Canadian Leukemia Group,2 both report on the impact of high-risk FISH abnormalities on response and response duration in the context of myeloma. Given the move toward individualized therapy based on risk, these studies are critically important in helping to identify the relative utility of lenalidomide among a group of patients whose outcomes are historically quite poor.

However, interpretation of these 2 trials has its challenges and leaves the clinician with both good and bad news. First, the bad news: risk does matter. Kapoor et al leave the reader with no doubt that, though the fraction of high-risk patients is lower than one would expect from a general population study (25% according to the IFM experience), patients with poor-risk myeloma have a significantly shorter duration of remission than standard risk patients. While these data exemplify the phrase “tyranny of small numbers”, similar data has been presented by the SWOG group in their phase 3 trial of lenalidomide/dexamethasone (LD) versus dexamethasone (D).3 While LD was superior to D, patients who received LD with high-risk criteria had a shorter remission than patients who received LD and had standard risk, though LD was superior to D regardless of risk (B. Barlogie, personal written communication, February 2009). While we accept that bortezomib is able to overcome high-risk features when combined with melphalan in the VISTA trial,4 in the transplant eligible population, this has been largely measured in terms of overall response rate. Data on progression-free survival (PFS) and overall survival (OS) in the induction setting for high-risk patients (IFM1 and GEIMMA1 data) is currently pending.

Now for the good news: risk may matter less. Reece et al evaluate the impact of risk in a relapsed myeloma trial and define high risk as the presence of deletion 13, t(4:14), or del 17p using FISH data. But are all these equally poor? Deletion of 13q was found to be significant as a prognostic marker when isolated by metaphase cytogenetics,5 but when present as the sole FISH abnormality, it was not noted to have an impact on survival.6 Similarly, t(4:14) patients with this abnormality and a low β2M were not noted to have a significant survival decrement in an IFM analysis.7 In the current report, the median β2M was 3.3, suggesting that half of the 28 patients in the analysis did not have poor-risk disease. This leaves the del 17p group, who generally do have poor outcomes regardless of the choice of therapy, and unfortunately, this is no different for LD-treated patients.

So what is the answer? Does risk matter, and can we all agree on how to define it? The simple answer is yes on both accounts. Risk does still matter, and it is unlikely in the high-risk setting that single agents are going to be the solution. Combination therapy with maintenance will likely be the minimum if we are to make significant improvements in PFS and OS for this group of patients. Second, the definitions of high risk are agreed upon for now. From the International Myeloma Working Group, there is a consensus document that codifies the currently agreed upon risk assessment, and the published version will provide support and data that will summarize how to best classify newly diagnosed patients.8

In the relapsed setting, this is less clear. It is clear that we likely eliminate the highest risk patients from analysis in relapsed trials simply because they do not survive long enough to receive salvage therapy. Thus, highest risk patients are likely best evaluated in the induction setting as an inherent selection bias has already set in by the time we get to relapsed trials.

It is clear from both trials that response rate alone is not sufficient to gauge the efficacy of a given approach in the context of high-risk disease. Both papers show no real difference between the overall response rate (ORR) for standard or high-risk patients except in the

**References**

highest risk, those with del 17p had a lower overall response rate. Further improvements for this high-risk group will require prospective assessment, not only of response rate (which should no longer be an acceptable primary end point for randomized phase 3 induction trials) but also time to progression (TTP), CR duration, and ultimately OS among a group of patients treated in a similar fashion. This is the only way we can correctly identify the impact of risk stratification in an era of novel therapies, and the only way by which we can make myeloma therapy less risky.

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Comment on Lee et al, page 589

Ablative RT protects immune responses

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In this issue of Blood, Lee et al provide a rationale for engaging the immune system by treating tumors with large, single-fraction radiation doses. Advances in the technical aspects of radiation oncology have included improved tumor imaging, conformal treatment planning, and millimeter precision in radiation treatment delivery. However, optimal dose fractionation and integration of radiation therapy with other therapeutic modalities are undergoing redefinition. For selected cancer histologies and clinical presentations, conventional treatment approaches of delivering multiple daily fractions of radiation to relatively large volumes over intervals of 8 weeks or longer are evolving, due to the use of highly conformal hypofractionated stereotactic body radiation therapy (SBRT) or single fraction stereotactic radiosurgery (SRS). Such treatments are often less disruptive to patients’ lives and appear to offer radiobiologic benefits, particularly for the treatment of cancers considered “radiation-resistant.” Hypofractionated radiation therapy has been advanced for the treatment of metastatic malignant melanomas, renal carcinomas, and sarcomas with generally favorable clinical responses, but wide acceptance of such an approach for treating primary tumors has been less enthusiastic, pending further experience with normal tissue late effects in patients. Recent SBRT applications have included aggressive therapy of lung and prostate cancers.1,2

In the work presented by Lee et al, ablative radiation therapy delivered in a single fraction was observed to reduce tumor burden at the primary site and in distant metastases in an animal tumor model by engaging the immune system through T-cell responses. In contrast, fractionated radiation therapy or the addition of adjuvant chemotherapy abrogated the radiation-induced immune responses.3 These observations in the murine model have clinical counterparts in the occasional tumor responses attributed to abscessal effects (outside the irradiated volume), and demonstrated to have an immunologic basis in an experimental model.4

Studies of radiation-induced immune modulation have identified critical roles for antigen presentation to dendritic cells leading to T-cell activation. Calreticulin has been recognized as a radiation-inducible protein, and roles in apoptosis, antigen presentation, and signaling dendritic cells have been attributed to this protein.5,6 The report of differential effects of ablative radiation therapy as compared with fractionated radiation therapy or with the addition of adjuvant chemotherapy on T-cell responses offers critical clinical implications to be considered in the design of future combined modality therapeutic strategies. Can it be that the incremental progress anticipated from combining modalities is actually counterproductive in clinical settings conducive to a favorable immune response associated with radiation therapy? Does radiation fractionation or poorly sequenced adjuvant chemotherapy destroy the very cells responsible for a beneficial immune response?

The results described in the murine melanoma model suggest just that. Large single fractions of radiation therapy proved most compatible with a robust immune response. The addition of multiple fractions of radiation therapy over 2 weeks or adjuvant chemotherapy impaired the response, possibly by destroying the very cells responsible for antigen recognition, presentation, and T-cell stimulation. Although this report is unlikely to result in a substantial change in the current clinical approach to cancer treatment, there may be the opportunity to identify clinical settings for testing such a new paradigm.

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Risky business in myeloma

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