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# Multiple Myeloma: What's New

Brian G. M. Durie, MD

In the current issue of *CA*, Drs. Zaidi and Vesole provide a summary of new perspectives for multiple myeloma as we move into the new millennium. Since the first reports of “mollities and fragilitas ossium” (soft and fragile bones) by Macintyre, Bence Jones and Solly in the mid-1840s, multiple myeloma has remained a debilitating disease that is difficult to treat.<sup>1</sup> However, over these 150 years, progress has been made, especially in the past 25 years, with an accelerated pace in the past 5–10 years. It is interesting to note that the first case descriptions of myeloma coincide with the beginning of the Industrial Revolution in Europe when synthetic dyes (mauve being the first) and organic chemicals were first introduced into the environment.<sup>2</sup>

To this day, the exact gene–environment interactions which contribute to the etiology of myeloma remain elusive. Gene polymorphisms and mutations related to chemical metabolism, immune responsiveness, and susceptibility to infectious diseases are important with respect to exposures and stress factors encountered during life.<sup>3</sup> New technologies, especially molecular genetics, have already led to a dramatic increase in the understanding of the biology and pathogenesis of myeloma as reviewed by Zaidi and Vesole. It is reasonable to anticipate that a refined molecular classification of myeloma will lead to the identification of several discrete myeloma disease entities, or subtypes, comparable to the non-Hodgkin's lymphomas. This will allow both physicians and patients to select treatment in a more rational and targeted fashion.

But what about a patient diagnosed in 2001? Classical staging and prognostic factors such as serum  $\beta_2$  microglobulin, serum albumin, C-reactive protein, and bone marrow chromosome analysis (including fluorescent in situ hybridization or FISH) provide excellent information for identification of “active myeloma” and the need for therapy.<sup>4</sup> Likewise, careful assessment of clinical data can be used to accurately identify patients with monoclonal gammopathy of undetermined significance (MGUS), or related entities who can safely be monitored without systemic therapy.

For those who need immediate therapy, important new choices are available. Despite the widespread use of high-dose chemotherapy with transplantation, the true role of this expensive approach is unclear. Results of the only US randomized trial will be available in 2003. As summarized by Zaidi and Vesole, the French experience indicates potential survival benefit with high-dose therapy and autologous stem cell support. The questions remain: Which patients benefit the most and which do not? Is there clinically meaningful improvement in survival and/or quality of life? Must transplant be performed early or is later use acceptable? Since we don't currently have definite answers to these questions, the “appropriate” use of high-dose therapy is more of an art than a science. Approximately 50% of patients with symptomatic myeloma can achieve excellent, “complete” remissions with high-dose therapy. This is the most compelling reason to perform autologous transplantation.

For patients without symptoms, high-dose therapy is an aggressive preemptive strategy designed to lead to prolonged remission and possibly survival. Use of transplantation in this setting requires careful patient–physician discussion. This is particularly necessary if mini-allogeneic transplantation,

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with its current toxicities and uncertain benefits, is proposed as part of an initial consolidation approach. For patients with poor risk features, such as chromosome 13 abnormalities, who do not derive much additional benefit from high-dose autologous therapy, early mini-allogeneic or non-ablative transplant may be helpful. New approaches are required for this patient subgroup.

A major disappointment is that long-term follow-up of high-dose therapy reveals that only a small percentage of patients (approximately 5–10%) are still alive after 10 years. Since the median survival for good-risk patients with conventional (*non-high-dose*) therapy is 6–7 years, the added impact with transplantation is small, particularly considering the financial and quality-of-life implications.

So, what new approaches can really make a difference? Thalidomide (alone or in combination) is the first drug to offer true hope of survival benefit in more than three decades. Patients with life-threatening refractory myeloma have had their lives extended by 1 or 2 years.<sup>5,6</sup> Using the combination of thalidomide plus dexamethasone pulses as frontline induction, over 75% of patients achieve initial response. This is remarkable and makes tangible the prospect of real progress toward prolonged remission or even cure with

this and/or related biologic agents. Thalidomide analog (Celgene®), IMiD 501 already shows promise in Phase I trials. The proteasome inhibitor, PS-341 (Millennium®) has produced impressive responses in refractory disease patients in Phase II studies. About a dozen additional agents are currently in clinical trials.

True optimism is, therefore, appropriate. However, progress takes time to allow assessment of long-term benefit. Nonetheless, with the improvements in quality of life from bisphosphonates and growth factors, such as erythropoietin (Procrit®), the transition from life with myeloma to life without myeloma is closer to becoming a reality with each new drug and observation about the nature of the disease.

Most likely, progress will be achieved step by step with new targeted therapy for specific molecular subgroups of myeloma patients. The success with imatinib mesylate (Gleevec®) for chronic myelogenous leukemia has intensified the search for similar targeted approaches. It is possible that such therapies are close at hand in the form of IMiDs and/or PS-341 analogs, or maybe further searching is required. But at the start of the new millennium there is new confidence that longer survivals and better quality of life are achievable goals.

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