

## CLINICAL OBSERVATIONS

Comment on Brenner et al, page 2521, and Kumar et al, page 2516

## The road to cure in multiple myeloma

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For the past several decades, multiple myeloma (MM), the second most common hematologic malignancy, has been considered a fatal disease with a median survival of 5 years. However, recent advances in the understanding of the molecular pathogenesis of MM have led to new treatment strategies.

Thalidomide, bortezomib, and lenalidomide, which target the tumor cell in its bone marrow microenvironment and overcome cell adhesion-mediated drug resistance to conventional therapies,<sup>1</sup> were first shown to be active alone and in combination with dexamethasone in patients with relapsed refractory MM. Subsequently, each has been combined with dexamethasone for transplantation candidates and with melphalan and prednisone for nontransplantation candidates with newly diagnosed disease.<sup>2,3</sup> Remarkably, thalidomide and dexamethasone is a Food and Drug Administration (FDA)-approved treatment of newly diagnosed disease, while lenalidomide/dexamethasone, bortezomib, and bortezomib/pegylated doxorubicin are now FDA-approved treatment options for previously treated MM. Although these agents have achieved high frequency and extent of response and resulted in a treatment paradigm shift in MM, we still did not know whether these new therapeutic options and high response rates would alter the natural history of disease and translate to significantly longer survival rates.

In this issue of *Blood*, 2 publications demonstrate that the survival of patients with MM has significantly improved with the introduction of novel therapies. Brenner et al demonstrate for the first time that the overall 5-year relative survival rates in MM have increased from 28.8% to 34.7% between 1990-1992 and 2002-2004. The most significant change occurred in younger patients (age < 50 years), with 5- and 10-year survival rates of 56.7% and 41.3%, respectively, in 2002-2004. In a second study, Kumar et al demonstrate that patients who relapsed after stem-cell transplantation (SCT) and were treated with thalidomide, bortezomib, or lenalidomide had a significantly improved median survival of 30.9 months, compared with only 14.8 months for those who did not receive those agents.

Importantly, they also show that the overall survival of patients with newly diagnosed MM has improved by 50% over the past decade. These 2 studies provide exciting evidence that improvement in the treatment of patients with MM using SCT and novel agents such as thalidomide, bortezomib, and lenalidomide leads to prolonged survival. Progress in SCT and enhanced supportive care occurred in the early to mid-1990s, whereas thalidomide was introduced into clinical trials in 1998, followed by bortezomib and lenalidomide in 2001-2002. Therefore, the major impact of bortezomib and lenalidomide and other novel agents recently approved by the FDA for use in MM, such as pegylated liposomal doxorubicin in combination with bortezomib, is not reflected in these 2 studies, and future improvements are expected. Moreover, although the lack of survival benefit in older patients (> 60 years

old) in the Brenner et al study is disappointing, new combinations of melphalan and prednisone with thalidomide, bortezomib, or lenalidomide offer great promise for improved outcomes in these patients as well.

We have come a long way from the time when patients diagnosed with MM had limited options of only palliative chemotherapy; we now have several effective novel target agents to be used alone or in combination, as well as multiple promising emerging therapies. The precedent of combination therapies curing cancer is exemplified in childhood acute lymphocytic leukemia (ALL), Hodgkin and non-Hodgkin lymphoma, and testicular cancer. In MM, the future is bright, as we evaluate rationally based combinations of novel agents to achieve prolonged disease-free survival and potential cures.

*Conflict-of-interest disclosure:* The authors declare no competing financial interests. ■

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## CLINICAL OBSERVATIONS

Comment on Bacher et al, page 2527, and Gale et al, page 2776

## Who's dancing with FLT3?

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FLT3 mutations may influence prognosis in acute myeloid leukemia (AML), but the context in which they occur may be just as important.

Mutations of the receptor tyrosine kinase FLT3 are present in approximately 30% of patients with newly diagnosed AML.<sup>1</sup> These mutations come in 2 forms, the first being the internal tandem duplication (FLT3/ITD) mutations, localized to the juxtamembrane region of the receptor, and the second being the point mutations located in the tyrosine kinase domain (FLT3/TKD). The FLT3/ITD mutations, which are the most common type, have clearly been shown to have a strong negative impact on clinical

outcome, while the prognostic influence of an FLT3/TKD mutation is still uncertain.

Several lines of laboratory data now suggest that FLT3 mutations by themselves do not cause AML.<sup>2</sup> Rather, these mutations represent a single (albeit relatively common) event in a complex dance of mutations eventually leading to transformation. The interaction between the FLT3 mutation and other genetic lesions presumably influences the nature of the leukemia, which is reflected in its clinical behavior. In support of this concept, 2 articles in