Thalidomide/dexamethasone in myeloma: a double-edged sword

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In this issue of Blood, Ludwig and colleagues show that TD may result in treatment-related mortality in elderly patients with multiple myeloma.

Thalidomide was introduced for multiple myeloma (MM) in 1998. Its mode of action makes it a suitable candidate to combine with corticosteroids. Hence, it has been combined with dexamethasone or melphalan/prednisolone (MP) as upfront treatment for patients who are not eligible for high-dose therapy. Peripheral poly-neuropathy (PNP) and deep venous thrombosis (DVT) are serious clinical side effects. Dexamethasone has long been used as an oral schedule of repeating 4-days blocks. In the study by Ludwig et al, the clinical effects of thalidomide plus dexamethasone (TD), in a slightly modified schedule derived from the Eastern Cooperative Oncology Group (ECOG), is compared with classical MP in patients with MM who were not transplant candidates.

The toxicity of TD is 2-sided and strongly depends on age: thalidomide-associated DVT and dose-related PNP directly affect the quality of life, and these effects may have an even stronger impact in the elderly MM patient. Dexamethasone has many unwanted side effects, such as mineralocorticoid disturbances, psychiatric disease, hormonal imbalance, and an increased risk of infections. These and other clinical symptoms have long been accepted because of the rapid disease reduction affected by this potent corticosteroid. The lesson from the Ludwig trial is that TD can result in excess early mortality in patients over 75 years of age with poor performance status, in particular from infections that are presumed linked to dexamethasone.

While there are good reasons to consider dexamethasone for myeloma treatment, the standard-dose regimen has too long been taken for granted. Recently, an ongoing trial by the ECOG (E4A03), which compared lenalidomide with standard-dose versus low-dose dexamethasone, reported that standard-dose dexamethasone is associated with higher early mortality in the first year as compared with low-dose. These data indicate that standard-dose dexamethasone in older patients is a poor choice during early treatment when disease control has not yet been established. Along the same line, an initial high dose of thalidomide should be avoided because of a risk of early mortality in older patients as observed by the Nordic Myeloma Study Group.

Thalidomide, bortezomib, and lenalidomide have changed the spectrum of MM treatment. They induce a fast improvement of disease-related symptoms and a high response rate, especially when combined with other agents. In an elderly patient with MM, they can be used effectively, provided that excessive toxicity is avoided. The trial reported here indicates prudence is called for in treatment of the older patient, and that adjustment of the dose and schedule of both thalidomide and dexamethasone is desirable. Alternatively, in order to avoid the hazards of dexamethasone and to use the effect of an alkylating agent, thalidomide can be combined at an appropriate dose with MP (MP-T), resulting in good efficacy and less mortality.

REFERENCES

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Comment on Ludwig et al, page 3435
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