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UPDATES IN CLINICAL MEDICINE

Update in Hematology

Anca CIOBANU[a]; Oana CIOCAN[b]; Anca Roxana LUPU[b]

[a]Academy of Medical Science, Bucharest, Romania
[b]Carol Davila University of Medicine and Pharmacy, Hematology Dept, Coltea Hospital, Bucharest, Romania

Multiple myeloma (MM) is an incurable plasma-cell neoplasm. The primary aim of current treatment strategy is to improve long-term outcomes, including progression-free survival (PFS) and overall survival (OS), as well as health-related quality of life (HRQoL), which is affected by treatment effect, toxicity, and change in disease status(1) The introduction of high-dose therapy and stem-cell transplant (HDT-SCT), which is now the standard of care for eligible patients ≤65 years of age, and the novel agents bortezomib, thalidomide, and lenalidomide has been associated with improved overall survival in the past 10 years (1,2).

The use of bortezomib in combination with conventional therapies has resulted in increased CR rates associated with improved outcomes.(1) The phase 3 Velcade study (VISTA) compared bortezomib plus melphalan-prednisone (VMP) versus melphalan-prednisone alone in previously untreated patients with MM who were ineligible for high-dose therapy This study demonstrated that VMP was superior to MP across all response rate and time-to-event efficacy end points and resulted in a very high complete response (CR) rate of 30% (1).

An Italian randomized study with melphalan, prednisone, and thalidomide (MPT) versus melphalan and prednisone (MP) demonstrated a significant difference in progression-free survival (PFS) (3,4). Thalidomide was demonstrated to be effective in patients with relapsing multiple myeloma. This discovery generated an array of studies that confirmed the initial results that approximately 30% of patients with relapsing multiple myeloma respond to thalidomide (2).

In this study, they found that addition of thalidomide to standard MP therapy in elderly myeloma patients had a significant antimyeloma effect in terms of increased proportions of high-quality responses (3,4).

Thalidomide plus dexamethasone has also been evaluated in phase III clinical trials. Thalidomide plus dexamethasone produced better responses compared with dexamethasone or MP whereas survival was reduced compared with MP (3,4).

A phase 1/2 study has shown the combination lenalidomide-bortezomib-dexamethasone in newly diagnosed MM have favorable tolerability during a lengthy period, with no treatment-related mortality (5).

Patients with multiple myeloma are an increased risk of venous and arterial thrombosis. The pathogenesis remains unclear, but probably involves several factors such as activation of procoagulant factors, acquired activated protein C resistance, and inflammation.

Address for correspondence:
Anca Lupu, MD,PhD, Hematology dept, Coleta Hospital, 1, I.C. Bratianu Boulevard, Bucharest
e-mail: ancaroxanalupu@yahoo.com

The risk for venous thromboembolism is high when patients are treated with thalidomide or lenalidomide in combination with dexamethasone or multi-agent chemotherapy and all patients should be treated with thromboprophylaxis, with the exception of patients with a major risk of bleeding (6,7).

In light of the recent randomized clinical trials, aspirin, LMWH, and fixed, low-dose warfarin seem to be effective in thalidomide/ lenalidomide -treated patients. Because 90% of all patients with multiple myeloma have an additional risk factor, most patients should be treated with LMWH. LMWH and fondaparinux, which are considered the optimal thromboprophylaxis according to clinical guidelines (6).

Aspirin should be used in patients with no or only one additional risk factor. For example, in newly diagnosed patients treated with thalidomide and anthracycline, the venous thromboembolism incidence was 58% without any thromboprophylaxis, but decreased to 18% when aspirin was introduced. Several clinical studies on MM patients treated with lenalidomide have used aspirin as thromboprophylaxis with encouraging results, with a venous thromboembolism incidence of 3% to 15% (6).

In conclusion - the introduction of the proteasome inhibitor, bortezomib and the immunomodulatory drugs, thalidomide and lenalidomide, has been associated with improved survival. Combinations of bortezomib or lenalidomide with conventional anti-MM drugs have demonstrated very high overall response rates and quality of response in the front-line setting (5).

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