Lenalidomide in the treatment of plasma cell dyscrasia: state of the art and perspectives

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Lenalidomide is a 2nd generation immunomodulatory drug (IMiD) that has shown remarkable activity in the treatment of multiple myeloma (MM). In comparison with its parent drug thalidomide, lenalidomide has the advantage of having no neurological toxicity. Two phase III randomized studies validated the role of lenalidomide in combination with dexamethasone (RD) for the treatment of relapsed/refractory MM patients. In both studies, RD induced higher responses compared with dexamethasone alone with a clear advantage in terms of time-to-progression. These results led the US Food and Drug Administration to grant approval to lenalidomide in combination with dexamethasone in patients with MM who have received one prior therapy.

Various trials have tested lenalidomide plus dexamethasone for the treatment of newly diagnosed MM patients, confirming its efficacy. Recently, the MM-015 trial compared melphalan-prednisone-lenalidomide followed by lenalidomide maintenance (MPR-R) with melphalan-prednisone-lenalidomide (MPR) in newly diagnosed elderly MM. The complete response (CR) rate was superior with MPR-R compared to both MPR and MP. MPR-R also significantly prolonged median progression-free survival (PFS), with the greatest advantage in patients aged 65-75 years of age. A landmark analysis from start of maintenance showed that lenalidomide maintenance significantly prolonged PFS as compared to placebo, regardless of age. The immunomodulatory activity of lenalidomide prompted its use in MM patients receiving allogeneic stem cell transplantation (allo-SCT). Only few efficacy and safety data on lenalidomide are available for relapsed/refractory patients receiving immunosuppressive drugs after allo-SCT. Small studies showed a high efficacy of lenalidomide in this setting. Yet, there are some concerns about the risk of acute graft-versus-host disease (GVHD) under this treatment, particularly when lenalidomide is given as maintenance therapy after allo-SCT.

The positive results achieved in MM patients provided the rationale to investigate the role of lenalidomide for the treatment of AL amyloidosis. AL amyloidosis patients have multi-organ dysfunction, which makes them more susceptible to treatment toxicity, and thus have a poor prognosis. Lenalidomide was shown to be beneficial in patients previously treated with chemotherapy/bortezomib and in those refractory to thalidomide. However, this improvement was accompanied by a significant increase in toxicity, especially in patients with a heart condition. In various small trials, lenalidomide combined with alkylator agents induced an up to 77% hematologic response, although a substantial proportion of patients experienced grade 3-4 toxicities.

In the current issue of the Journal, three interesting papers have been published evaluating the role of lenalidomide alone or in combination with steroids and alkylating agents in three different settings of patients with plasma cell dyscrasia.

Coman et al. presented the results of a retrospective multicenter study on MM patients receiving lenalidomide alone or in combination with dexamethasone as salvage therapy after allo-SCT. This study is the largest reported in this setting. Overall response rate was 83%, including 29% of CR. This is quite an impressive result, as all patients enrolled in the study received a median of two treatment lines before allo-SCT, and the majority of them had already been exposed to at least one IMiD or achieved less than a partial response (PR) to IMiDs. These data confirm those reported in previous smaller series and suggest that lenalidomide has higher efficacy compared with thalidomide, comparable to that of bortezomib. The toxicity profile of the treatment was in line with that reported in previous studies and led to dose reductions and treatment interruption in 44% and 17% of patients, respectively.

De novo or exacerbation of pre-existing acute GVHD occurred in one-third of patients and was correlated with the early introduction of lenalidomide after allo-SCT. All cases of GVHD could be controlled, although one patient died from sepsis. The issue of acute GVHD has been raised also by other groups, and in the maintenance setting the risk of acute GVHD outweighed the benefit associated with treatment. However, the occurrence of acute GVHD on treatment was the only factor significantly associated with an improved anti-myeloma response in this trial. This could be due to the potential of lenalidomide to enhance the immunologic graft-versus-myeloma effect. Despite a beneficial impact of the occurrence of acute GVHD on the overall response rate, no benefit in terms of PFS or OS was noted. The authors suggest that the shorter duration of lenalidomide therapy in case of GVHD occurrence could explain in part the absence of improved PFS. Interestingly, only 26% of the patients who had maintained lenalidomide after achieving the best response relapsed, as compared with 56% of those who stopped immediately after achieving the best response. Overall, the results presented by Coman et al. are promising and support the use of lenalidomide in a salvage setting after allo-SCT. However, larger studies are needed to assess the best timing and dosage, and the most appropriate duration of lenalidomide treatment after allo-SCT.

Dimopoulos M et al. assessed the impact of lenalidomide-based therapy on health-related Quality of Life (HRQoL) in 459 patients enrolled in the MM-015 trial. The main results of the MM-015 trial have been recently published (see above). With the increasing availability of effective treatments, the main goal of myeloma therapy should be to improve survival while maintaining a good Quality of Life. Clinical trials are increasingly evaluating HRQoL. In the MM-015 trial, patients were asked to complete HRQoL questionnaires at baseline, after every third treatment cycle, and on completion of treatment. HRQoL improved in all treatment groups during induction therapy. The improvement from baseline was slightly greater in MPR-R patients aged 65-75 years, and the most pronounced improvement was observed in patients receiving lenalidomide maintenance. Overall, changes in HRQoL score from baseline were generally higher in patients who received lenalidomide. These results demonstrate that MPR-R was not only effective and safe in newly diagnosed elderly MM patients, but it was also associated with improved HRQoL. An increasing number of clinical trials are now including maintenance therapy, and survival benefits were reported in both patients eligible and ineligible for transplantation. Because continuous therapy aims to control disease, long-term tolerability of this strategy is crucial. Different trials
assessed thalidomide maintenance, and this approach was not always well tolerated.15-18 Stewart et al. have recently reported that maintenance therapy with thalidomide-prednisone after autologous stem cell transplantation (ASCT) improved the duration of disease control but was associated with worsening of patient-reported HRQoL, without a detectable OS benefit.19 These findings further support the concept that the choice of the most appropriate maintenance treatment should carefully balance the potential benefits and risks associated with this strategy, as none of the novel agents currently approved for maintenance therapy.

In another study presented in this issue of the Journal, Sanchorawala et al. reported the results of a phase II trial of melphalan-lenalidomide-dexamethasone (MLd) for the treatment of AL amyloidosis.14 Various phase II studies showed the efficacy of lenalidomide plus dexamethasone in AL amyloidosis,15 and subsequent studies tested lenalidomide combination with alkylating agents.10,11,15 The tolerability of such combinations was not always acceptable. In the study conducted by Sanchorawala et al., the median age was 70 years. The majority of patients experienced grade 3-4 adverse events, with myelosuppression being the most common toxicity and 85% of patients requiring dose reductions. This high rate of toxicity was not compensated by a significant efficacy advantage. The PR rate was disappointing (43% with 7% CR). Due to these negative results, the trial was stopped. Side effects reported in this trial were greater than those seen in a previous study,20 and this may be attributed to the higher median age of the study population (70 years compared with 57 years in the French study). This combination required dose reductions to prevent grade 3-4 toxicities and induced response rates that were no better than those seen with either melphalan or lenalidomide alone. The combination of lenalidomide-dexamethasone plus cyclophosphamide was better tolerated, although toxicity was not negligible.11 Based on the current data, the combination of lenalidomide and alkylating agents should not be suggested, in particular in elderly and unfit patients. Available data indicate that in AL amyloidosis, as well as in MM, prolonged exposure to lenalidomide may improve patient outcome.21 Trials to assess the value of maintenance therapy in this disease are warranted.

Lenalidomide is currently approved for the treatment of relapsed/refractory MM, and data presented in the allogeneic setting strengthen its role also in heavily pre-treated patients. However, results of first-line therapy suggest that lenalidomide is a valuable option, particularly as maintenance therapy, with the greatest benefit in young fit patients, while gentler approaches with correct and appropriate dose reductions are needed for the frail/unfit population. The efficacy of a treatment should always be balanced against its safety profile, and an effective treatment should be well tolerated and associated with improved Quality of Life.

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