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From cell biology to therapy: lenalidomide in untreated multiple myeloma

Multiple myeloma (MM) is a disorder of malignant plasma cells that is characterised by the presence of a monoclonal immunoglobulin in serum and urine. It represents 10% of haematological malignancy and accounts for more than 16 000 deaths every year in Europe.[1]

Immunomodulatory drugs (IMiDs) are a series of compounds that were developed with use of the first-generation IMiD thalidomide as the leading compound. CC-5013 (lenalidomide, Revlimid®) is derived from the parent compound by the addition of an amino (NH_2) group at position 4 of the phtaloyl ring of thalidomide and removal of one of the carbonyl groups.[2]

It was originally selected for its increased potency as inhibitor of TNF· production and its absence of teratogenicity in preliminary screening.[3]

Lenalidomide is the leading IMiDs® compound that is being tested, and it has now been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) for use in combination with dexamethasone in patients with MM who have received at least one previous treatment.

Newly diagnosed multiple myeloma

Lenalidomide plus dexamethasone

A phase II trial assessed the efficacy and safety of lenalidomide plus dexamethasone as initial therapy. 34 patients with MM were given lenalidomide 25 mg orally every day (days 1-21) and dexamethasone 40 mg (days 1-4, 9-12, and 17-20) on each 28-day cycle.[4,5] After four cycles, patients were allowed to proceed to stem-cell harvest and autologous transplantation; treatment beyond four cycles was allowed at the investigator discretion, with dexamethasone dose reduced to 40 mg on day 1-4 of each cycle. Overall, 13 patients proceeded to stem-cell transplantation after a median of four lenalidomide-dexamethasone cycles (range 4-13), whereas 21 patients continued with treatment for a median of 19 cycles (range 2-30). Assessment of response after 4 months of therapy showed that the combination was highly effective: 91% of patients achieved at least a PR; CR was recorded in 18% of patients and 56% showed at least a VGPR. Moreover, response was very rapid with median time to response of 1 month. In the 21

patients who did not undergo transplantation, the depth of remission improved over time: 67% of patients achieved at least a VGPR, with 24% achieving CR. Responses were durable. After a median follow-up of 36 months, median TTP was not reached in the transplant group and was 32.4 months in the non-transplant group. The 2-year PFS was 59% in the non-transplant group and increased to 83% in patients undergoing transplantation. The 3-year OS for the whole group was 88%.

Treatment with lenalidomide and dexamethasone was well tolerated. The most common grade 3-4 adverse events were fatigue (21%) and neutropenia (21%). Myelosuppression was minimal in this trial, which probably reflects the better bone-marrow reserve in patients previously untreated than in those with previous treatments. With routine use of prophylactic aspirin every day, a low incidence of thromboembolic events was recorded (3%).[4]

The efficacy of lenalidomide plus dexamethasone induction therapy, was confirmed by preliminary results of a Phase III study comparing this combination with dexamethasone alone in newly diagnosed patients.[6] The study was planned to enrol 500 patients, but the number was cut off at 198, due to external data affecting acceptability of the high-dose dexamethasone as control arm. Lenalidomide was given at 25 mg daily on day 1 to 28 in 35-day cycles, for three induction cycles and then on day 1 to 21 in 28-day maintenance cycle. Dexamethasone was given at 40 mg on days 1-4-9-12 and 17-20 during induction and on days 1-4 and 15-18 during maintenance.

The combination therapy was superior to dexamethasone alone, in terms of response rate (85.3 vs 51.3%; p=0.001) and 1-year PFS (77 *vs.* 55%; p=0.002).

A recent phase III study (E4A03) compared the combination of lenalidomide (25 mg per day on days 1-21 every 28 days) plus low-dose dexamethasone (40 mg on days 1, 8, 15, and 22 every 28 days) with the standard combination of high-dose dexamethasone (40 mg days 1-4, 9-12, and 17-20 every 28 days) in 445 newly-diagnosed patients with MM.[7] Major grade 3 or higher toxic effects, including thrombosis (25% *vs.* 9%) and infections (16% *vs.* 6%), were significantly higher in the high-dose dexamethasone group than in the lenalidomide plus low-dose dexamethasone group. Survival was significantly better with lenalidomide plus low-dose dexamethasone (1-year survival 96% *vs.* 87%; p<0.001). Increased mortality in the high-dose dexamethasone group was due to disease progression and increased toxic effects. Since the differences were confirmed in both younger and elderly patients, this study has major implications for the use of high-dose dexamethasone in the treatment of patients with newly diagnosed MM.

Another phase II trial assessed the safety and efficacy of the combination of lenalidomide 25 mg (days 1-21 of a 28-day cycle) in combination with low-dose dexamethasone (40 mg once per week) and clarithromycin 500 mg twice a day.[8] 72 patients were enrolled in the study. The combination yielded a high overall response rate (90%), with 53% achieving a CR or near CR. Grade 3-4 neutropenia was recorded in 19% of patients and was significantly related to values of creatinine clearance.[9] Nine (12.5%) patients developed thromboembolic complications, five of which were definitively associated with aspirin interruption, suggesting again the need of antithrombotic prophylaxis and the potential efficacy of low doses of aspirin.[10]

Given the favorable results and the increasing use of lenalidomide as initial therapy, the interest has come up about the impact of this drug on stem-cell mobilization, and conflicting data have emerged. Rajkumar and colleagues obtained adequate stem-cell harvest in all

patients who underwent autologous stem-cell transplant, and suggest this combination as a useful conditioning regimen before transplant.[4]

The BiRD (Biaxin®/Revlimid®/dexamethasone) regimen did not impede stem-cell mobilization or engraftment after autologous transplantation.[8,11] Opposite results were obtained in three different retrospective studies.[12-14] In Kumar's analysis, induction treatment with lenalidomide was associated with reduced stem-cell harvest compared with other therapies (vincristine-doxorubicin-dexamethasone combination, dexamethasone alone, or thalidomide plus dexamethasone). The reduction was more significant among patients mobilized with G-CSF. Age and length of previous treatment were thought to contribute to poor mobilization: all patients given Lenalidomide plus dexamethasone who failed to mobilize stem cells were older than 67 years of age and had received more than 7 months of therapy before stem-cell collection.[12] Similar results were published by Mazumder *et al.*[13] and Paripati and colleagues;[14] in both reports approximately 40% of patients failed to harvest stem-cells after induction therapy with Lenalidomide plus dexamethasone and treatment with G-CSF. However, 25% of them achieved subsequent successful mobilization following cyclo-phosphamide therapy.[12] These preliminary negative results need to be verified in larger prospective studies. Based on these data, it would be useful to plan stem-cell mobilization after a limited number of monthly Lenalidomide cycles, and following cyclophosphamide chemotherapy.

MP plus lenalidomide

On the basis of encouraging results from trials with the combination of lenalidomide and dexamethasone, phase I-II trials testing oral MP with different lenalidomide doses (MPR) in newly-diagnosed elderly patients with MM have been designed.[15,16] In the Italian study, the MTD of the combination was defined with lenalidomide 10 mg per day (days 1-21) plus melphalan 0.18 mg/kg per day and prednisone 2 mg/kg per day (days 1-4) every 4 weeks for a total of nine cycles. Maintenance therapy was planned with lenalidomide 10 mg orally every day for 21 days, every 4-6 weeks. At this dose, 81% of patients showed at least a PR, including 47.6% of patients with at least a VGPR and 23.8% who showed an immunofixation-negative CR. 1-year EFS was 92% and 1-year OS was 100%. Response rates and EFS did not differ significantly between patients with or without a chromosome 13 deletion or chromosomal translocation (4;14). The major side-effects of the combination were related to haematological toxic effects, primarily neutropenia (52%) and thrombocytopenia (24%). Major grade 3-4 non-haematological adverse events were febrile neutropenia and vasculitis (9.4%); no neurological toxic effects were recorded and the frequency of thromboembolism was low (4.8%) with aspirin prophylaxis. These findings were confirmed in a subsequent study, which defined the MTD as melphalan 5 mg/m^2 and prednisone 60 mg/m^2 in combination with lenalidomide 10 mg.[16]

Conclusions

In newly-diagnosed patients, induction therapy with lenalidomide plus low-dose dexamethasone seems to be a promising combination with a more favourable profile of toxic effects.[7] In elderly patients, the combination of lenalidomide with standard MP regimen appeared to be an active combination with high dose response rate, low incidence of non-hematological side-effects, and prolonged survival.

Lenalidomide appeared to be able to induce a significant response rate and to extend TTP even in patients with MM that is relapsed/refractory to thalidomide and in patients with

negative prognostic features like del(13) and t(4;14). Its oral formulation avoids the need of indwelling catheters, reduces the numbers of hospital visits, and improves quality of life for patients.

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