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The Intergroupe Francophone du Myélome experience with thalidomide

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The Intergroupe Francophone du Myélome (IFM) has conducted studies of thalidomide as treatment for relapsed or refractory multiple myeloma (MM) and as first-line therapy. One study comparing two doses of thalidomide (100 vs 400 mg/d) in relapsed patients has not yet been analyzed. Another study testing low-dose thalidomide in combination with melphalan and prednisone (MP) in elderly patients (>75 years) with newly diagnosed MM is ongoing. Three studies are presented here. Of these, one phase 2 study in relapsed/refractory patients has already been published; the other two have been presented in meetings only.

Thalidomide alone in patients with advanced multiple myeloma

A phase 2 study was conducted to evaluate the efficacy of thalidomide monotherapy in patients with advanced MM.[1] Study end points included response rates, event-free survival rates, and predictive factors for survival. Eighty-three patients were enrolled in the study, with a median age of 64 years. All had active disease and had previously received from two to six lines of chemotherapy (median, three). At the start of treatment, 69% had received at least one autologous transplantation.

The starting thalidomide dose was 400 mg/d, which was then escalated in some patients and reduced in others, but the median dose evaluated remained 400 mg/d. Serum levels of monoclonal immunoglobulin fraction (M component) were measured. Thirteen percent of the patients had a reduction in the M component of greater than 75%. Partial response occurred in 35% of patients, and minimal response occurred in 18%. Disease was stable in 16% of patients, and 18% progressed. The total response rate was 66% (54 of 83 patients) (Figure 1).

Prognostic factors for poor outcomes included IgA isotype, platelet count $<80\times10^9$/L, and serum albumin <30 g/L at the start of therapy. Among patients without these risk factors, 1-year survival was 87%, but this dropped to 40% for patients with at least one risk factor. A higher dose of thalidomide was associated with better outcomes. Patients who received more than 34.4 grams of thalidomide during the first 90 days of treatment had better overall survival and event-free survival than patients who received lower doses.[1]

Thalidomide as maintenance therapy after transplant

A randomized study of maintenance therapy with thalidomide after autologous transplantation was conducted.[2] The study enrolled 780 patients with MM who were younger than 65 years with either no or only one risk factor for poor outcome. Risk factors included β2 microglobulin levels >3 mg/L or deletion of chromosome 13. Patients initially received the following treatments:

- three to four cycles of vincristine + doxorubicin (Adriamycin®) + dexamethasone (VAD) therapy
- a first autologous transplant prepared with melphalan 140 mg/m^2
- a second autologous transplant prepared with melphalan 200 mg/m^2

After the second autologous transplant, some patients were excluded from continuation because of disease progression or severe toxicity. Patients without disease progression 2 months after the second transplant were randomized to receive either no maintenance treatment (arm A), maintenance with pamidronate 90 mg IV/mo (arm B), or maintenance with thalidomide plus pamidronate (arm C). A total of 588 of 780 patients (75%) were randomized to the three maintenance arms: 197 patients in arm A, 194 in arm B, and 197 in arm C. There was no significant difference

in prognostic factors among the three arms. At randomization, there was no difference among the patients in response to VAD treatment or in the number of patients with more than 90% reduction of the M component after two autologous transplantations.

The 3-year progression-free survival rate in the thalidomide plus pamidronate group was 56% versus 34% in arm A and 37% in arm B. The differences between arms A and C or B and C were statistically significant ($p<0.01$). When comparing progression-free survival rates between patients who received thalidomide (arm C) and those who did not (arms A and B), the difference in response is even more significant ($p<0.002$). Preliminary results demonstrate no difference in overall survival among the three study arms, possibly because of the effectiveness of the salvage therapy. For all three study arms, survival is >75% at 3 years after double autologous transplantation.

The tolerability of thalidomide was also analyzed. The initial dose was 400 mg/d, but the protocol was amended to lower the dose to 100 mg/d because of toxicity. Of the first 165 patients enrolled in arm C, thalidomide was discontinued in 60 (36%), most of whom received the 400-mg dose. The median duration of treatment was 12 months.

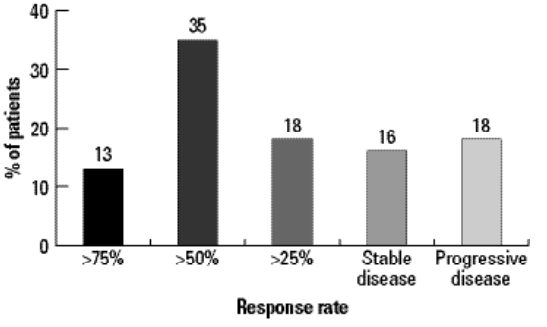

Figure 1. Response rate with thalidomide 400 mg/d showing the percentage of patients who had >75%, >50%, and >25% reduction in the M component as well as those with stable disease (SD) and progressive disease (PD). The median survival for all patients was 391 days.[1]

Thalidomide plus chemotherapy in newly diagnosed multiple myeloma

A three-arm study was initiated to compare standard MP therapy with thalidomide in newly diagnosed patients between the ages of 65 and 75 years.[3] Treatment arms include standard MP (12 courses of treatment at 6-week intervals) (arm A; n=153), standard MP plus thalidomide ≤400 mg/d (arm B; n=95), and a combination therapy regimen as follows: two courses of VAD followed by cyclophosphamide 3 g/m^2, and two courses of melphalan 100 mg/m^2 (arm C; n=92), as shown in Figure 2.

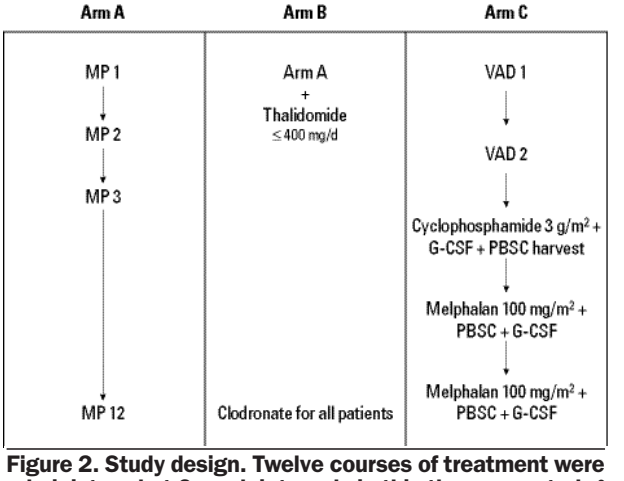

Figure 2. Study design. Twelve courses of treatment were administered at 6-week intervals in this three-arm study.[3] MP = melphalan and prednisone; VAD = vincristine, doxorubicin (Adriamycin®), and dexamethasone; G-CSF = granulocyte colony-stimulating factor; PBSC = peripheral blood stem cell.

Final results have not been analyzed for this ongoing trial, but an interim analysis was conducted on 340 patients. There were no significant differences in hematologic toxicity between the MP and MP plus thalidomide treatment arms (Table 1). There was a slight increase in the incidence of infection among patients who received MP plus thalidomide. The incidence of peripheral neuropathy was 36%, which is similar to results from other studies. Patients with a history of deep vein thrombosis (DVT) were excluded from the study. The incidence of DVT was 5% in arm A, 12% in arm B, and 6.5% in arm C. There were no deaths associated with DVT. The median time of onset of DVT was 3 months in the MP plus thalidomide arm.

Response to treatment is presented in Figure 3.

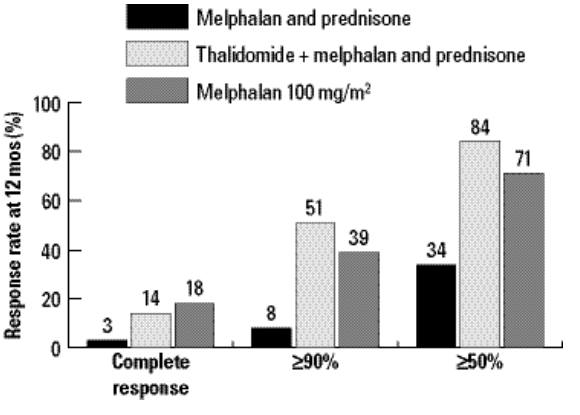

Figure 3. Interim response rates in patients aged 65 to 75 years. The response to melphalan plus prednisone (MP) therapy was lower than expected, but additional analysis will be provided. Results for MP plus thalidomide therapy are similar to those from other studies.[3]

Table 1. Toxicity incidence with MP and MP plus thalidomide.[3]

	MP (N=153)	*MP + thalidomide* (N=99)*
	Toxicity (grade 3/4)	
Neutropenia	32%	41%
Thrombocytopenia	14%	9%
Anemia	18%	14%
Infection	11%	17%
Infection-related death	2%	2%

**A total of 36 patients (36%) developed peripheral neuropathy. MP: melphalan plus prednisone.*

Response to MP therapy was lower than expected. Since this was an interim analysis, the response rates for the MP plus thalidomide arm will have to be confirmed, but they are similar to those seen in other studies of thalidomide combination therapy. Additional analysis will be presented upon the study's completion.[3]

Conclusion

Studies conducted by the IFM demonstrate that thalidomide is effective as maintenance therapy and as first-line therapy in newly diagnosed patients. Although the studies presented here are ongoing, initial results for thalidomide monotherapy and combination therapy show promising results and warrant further study.

References

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