The Intergroupe Francophone du Myélome experience with thalidomide

The Intergroupe Francophone du Myé-
lobe (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 ana-
lyzed. Another study testing low-dose thali-
domide in combination with melphalan and
prednisone (MP) in elderly patients (>75
years) with newly diagnosed MM is ongo-
ing. Three studies are presented here. Of
these, one phase 2 study in relapsed/refrac-
tory patients has already been published;
the other two have been presented in meet-
ings only.

Thalidomide alone in patients
with advanced multiple
myeloma

A phase 2 study was conducted to eval-
uate the efficacy of thalidomide monother-
apy 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 reduc-
tion 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
<80x10^9/L, and serum albumin <30 g/L at
the start of therapy. Among patients with-
out 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 sur-
vival and event-free survival than patients
who received lower doses.1

Thalidomide as maintenance
therapy after transplant

A randomized study of maintenance ther-
apy 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 + dox-
orubicin (Adriamycin®) + dexamethasone
(VAD) therapy
• a first autologous transplant prepared
with melphalan 140 mg/m²
• a second autologous transplant prepared
with melphalan 200 mg/m²
After the second autologous transplant,
some patients were excluded from contin-
uation 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 thali-
domide plus pamidronate (arm C). A total of
588 of 780 patients (75%) were random-
ized to the three maintenance arms: 197
patients in arm A, 194 in arm B, and 197 in
arm C. There was no significant difference

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Thalidomide in the Treatment of Multiple Myeloma
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.

**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. Treatment arms include standard MP (12 courses of treatment at 6-week intervals) (arm A; \(n=153\)), standard MP plus thalidomide \(\leq 400\) 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.

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.
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.

**Table 1. Toxicity incidence with MP and MP plus thalidomide.\(^3\)**

<table>
<thead>
<tr>
<th>Toxity (grade 3/4)</th>
<th>MP (N=153)</th>
<th>MP + thalidomide* (N=99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>32%</td>
<td>41%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>14%</td>
<td>9%</td>
</tr>
<tr>
<td>Anemia</td>
<td>18%</td>
<td>14%</td>
</tr>
<tr>
<td>Infection</td>
<td>11%</td>
<td>17%</td>
</tr>
<tr>
<td>Infection-related death</td>
<td>2%</td>
<td>2%</td>
</tr>
</tbody>
</table>

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

**References**