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Thalidomide plus oral melphalan for advanced multiple myeloma: a phase II study

Thalidomide exerts synergistic or additive effects when combined with other drugs. This study reports the toxicity and efficacy of the combination of thalidomide plus oral melphalan in 27 patients with advanced multiple myeloma. We found that this combination induces a high response rate and a long progression-free survival without significantly increasing thalidomide-related toxicity.

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There are few therapeutic options available for patients with relapsed-refractory multiple myeloma (MM). Since the first report by Singhal *et al*.,[1] attention was focused on thalidomide or thalidomide combined with dexamethasone or chemotherapy. Unfortunately, there was a significant increase in side effects, mainly deep venous thrombosis and myelosuppression, in association with combination therapy.[2,3] We report our experience using thalidomide and oral melphalan in patients with advanced MM.

From May 2000 to July 2002 in our tertiary care institute and in the main medical institutions of the Marche region (Italy) 27 patients with relapsed-resistant MM were treated with thalidomide plus melphalan. Patients with poor performance status and/or cardiopulmonary, renal and liver diseases were not excluded whereas patients with severe mental disorders or severe peripheral or central neuropathy were not enrolled. All patients signed a written informed consent form. The starting dose of thalidomide was planned to be 100 mg p.o. daily at bedtime, escalated weekly by 100 mg increments up to a maximum dose of 600 mg, in the absence of severe side effects. Thalidomide was stopped only because of severe side effects or disease progression. Melphalan was administered intermittently at a dose of 0.20 mg/kg/day p.o. for four days every 28 days for at least one course after greatest response was achieved or until severe toxicity developed. No patients received antithrombotic prophylaxis. Responses to therapy were assessed as reductions of paraprotein in serum and/or urine of at least 25%, 50% and 75% without the appearance of new skeletal lesions or an increase in bone marrow plasma cells. Complete response (CR) was defined according to EBMTR/IBMTR criteria.[4] Toxicity was assessed according to the Word Health Organization (WHO) criteria.

Forty percent of patients were aged >70 years; more than 2 prior regimens had been administered to 56%, prior high-dose therapy with stem cell support to 41% and prior therapy with melphalan to 96% of patients β2-microglobulin concentration was > 3 mg/L in 63% and the disease had been present for longer than 3 years in 30% of patients.

Paraprotein decreases of ≥ 50% and ≥ 75% were obtained in 59% and 15% of patients, respectively (Table 1). Remarkably, 3 out of 4 patients who had a maximal response had no monoclonal paraprotein detectable by immunofixation. The median time to remission was 6 weeks. The main side effects were constipation (82%), somnolence (41%), fatigue (22%), sensory peripheral neuropathy (56%), deep venous thrombosis (11%) and grade 3 leukopenia (30%). However, no severe infections occurred. After a median follow-up of 15 months (range 6-32), 9 patients (33%) had disease progression and 6 (22%) had died. The 2-year progression-free survival (PFS) and overall survival (OS) were both 61%.

As a single agent thalidomide produces an overall response rate of 30% and a 2-year event-free survival (EFS) of 20% in patients with heavily pretreated MM. Some studies have demonstrated that thalidomide may restore the sensitivity of myeloma cells to apoptosis induced by drugs, preventing the interaction between tumor cells and stromal cells.[5,6] We found

Table 1. Response to treatment.

Paraprotein response	No. (%)
≥ 75%	4 (15)*
≥ 50%	12 (44)
≥ 25%	6 (22)
Stable disease	4 (15)
Progressive diseas	1 (4)
Response ≥ 50%	16 (59)

**3 patients with absence of myeloma protein by immunofixation.*

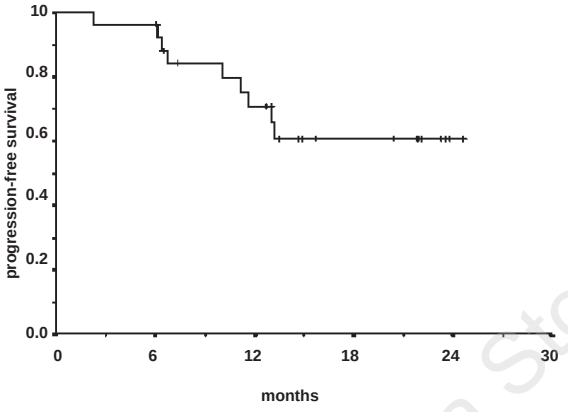

Figure 1. Progression-free survival (PFS) of the 27 patients treated with thalidomide plus oral melphalan.

that thalidomide with oral melphalan was active in 80% of patients of whom approximately 60% achieved a ≥ 50% reduction of myeloma protein. Of note, 3 patients obtained a *true* complete remission. Moreover, performance status improved quickly, the median response time being 6 weeks.

Thalidomide with chemotherapy produced response rates ranging from 73% to 84% but toxicity, mainly myelosuppression and severe infections, was much higher than that observed in our study.[3,7] Compared with thalidomide alone or thalidomide plus dexamethasone, the combination of thalidomide-melphalan does not seem to worsen non-hematologic toxicity whereas leukopenia appears more frequently and is occasionally dose limiting. The frequency of DVT (11%) was higher than the 2% reported during thalidomide treatment alone[8] and similar to that during treatment with thalidomide plus dexamethasone[9] or plus chemotherapy[3] in advanced MM. The 2-year PFS of 61% reported in our study is an impressive result.

Despite the need for comparative investigations, the PFS obtained with the combination of thalidomide-melphalan seems superior to that reported with thalidomide plus dexamethasone[2,9,10] and similar to that observed with thalidomide combined with more toxic chemotherapies.[7]

Barlogie *et al*. reported a 2-year OS of 48% in patients treated with thalidomide alone.[8] Thus, a 2-year OS of 61% appears noteworthy in a group of patients characterized by short-term poor prognosis with conventional chemotherapy.[10]

In conclusion, we found that the combination of thalidomide plus oral melphalan induces an high response rate and a long PFS without a significant increase of thalidomide toxicity. Consequently, the combination of thalidomide plus oral melphalan warrants further investigation in the context of controlled studies.

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