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Retrospective study of thalidomide plus dexamethasone versus conventional chemotherapy in the relapsed multiple myeloma patient and the study of melphalan and prednisone versus melphalan, prednisone, and thalidomide

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Thalidomide shows promise in the treatment of multiple myeloma (MM). Questions remain, however, about its efficacy compared with conventional chemotherapy.

Retrospective study: thalidomide versus conventional therapy

A retrospective study compared the clinical outcome of patients treated with combination thalidomide plus dexamethasone therapy with that of a control group treated with conventional chemotherapy.[1] The study's objectives were to assess the long-term toxicity of low-dose thalidomide and to determine whether combination thalidomide plus dexamethasone was as effective as conventional chemotherapy. The dosage regimen included continuous thalidomide 100 mg/d plus dexamethasone 40 mg/d for 4 days per month. A total of 120 patients whose disease had relapsed or who were refractory to chemotherapy treatment received the combination thalidomide plus dexamethasone regimen. Characteristics for the treatment group were compared with those of a matched control group (Table 1) of 120 patients who received chemotherapy. Matching criteria included disease stage at diagnosis and β2 microglobulin status.

Initial treatment response

The initial response rate for all patients who received combination thalidomide plus dexamethasone was 52% compared with 45% for patients who received conventional chemotherapy (Figure 1). Response was rapid, with a median time to response of 4 months. Figure 2 presents the maximum response time and demonstrates that approximately one-half the patients had a delayed response, with maximum response achieved for all patients at about 18 months. Survival curves were estimated using stratified Kaplan-Meier analysis according to the number of previous chemotherapy lines administered. Curves were compared using the log-rank test. When comparing progression-free survival and overall survival, the thalidomide plus dexamethasone regimen produced slightly better outcomes than conventional chemotherapy (Figure 3).

First salvage response

A multivariate analysis using a Cox regression analysis model revealed that β2 microglobulin status and more than one prior chemotherapy treatment significantly affected progression-free survival and overall survival. As a result, a response analysis was repeated only for the patients who had received one line of chemotherapy (first salvage). A total of 52% of patients in the treatment and control groups had received one line of chemotherapy, and 48% had received two or more. In the first salvage analysis, 62 patients received combination thalidomide plus dexamethasone, and 60% had prior high-dose chemotherapy; 82 patients received conventional chemotherapy, and 18% had received high-dose chemotherapy.

The first salvage response rate was 56% in the combination thalidomide plus dexamethasone group and 46% in the conventional chemotherapy group. The difference in response rates was not statistically significant and was similar to the first analysis that included all patients. Progression-free survival and overall survival rates between the two groups in the first salvage analysis were significantly different, however. The combination thalidomide plus dexamethasone therapy group reached a median of 17 months of progression-free survival compared with a median of 11 months for the conventional chemotherapy group (p=0.0024). The probability of survival at 3 years is projected to be 60% for the thalidomide plus dexamethasone group compared with 26% for the conventional

Table 1. Patient characteristics.[1]

	Thal-Dex N=120	*CC N=120*
Median age (y)	63	60
Stage at diagnosis*		
IIA	41%	41%
IIIA	48%	48%
B	11%	11%
β2 microglobulin*		
<3.2	48%	48%
≥3.2	52%	52%
Resistant disease	25%	29%
Untested-relapse	75%	71%
Entered the study after:		
1 line of chemotherapy	52%	68%
≥2 lines of chemotherapy	48%	32%

**Matching criteria.*
Thal: thalidomide; Dex: dexamethasone; CC: conventional chemotherapy.

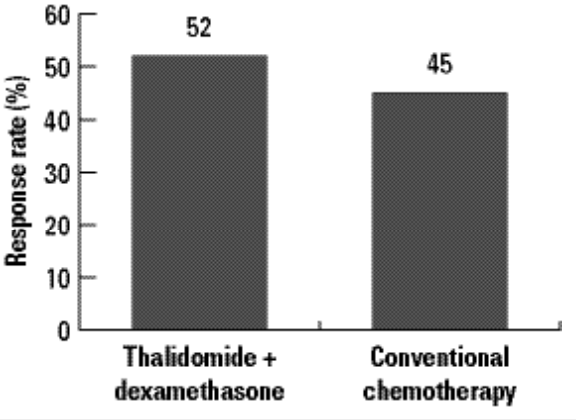

Figure 1. Initial response rates for thalidomide plus dexamethasone versus conventional chemotherapy. The results demonstrated a superior response for the thalidomide plus dexamethasone combination.[1]

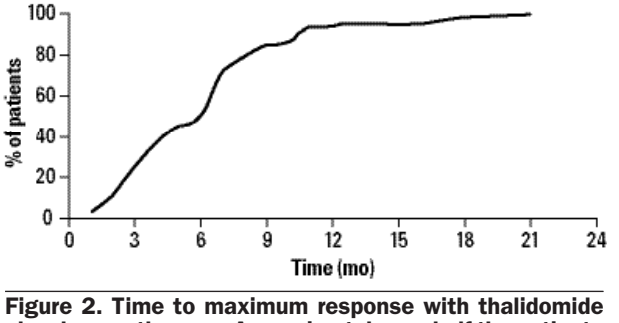

Figure 2. Time to maximum response with thalidomide plus dexamethasone. Approximately one-half the patients treated with combination thalidomide plus dexamethasone therapy responded within 6 months. Maximum response was achieved for all patients approximately 18 months after initiation of therapy.[1]

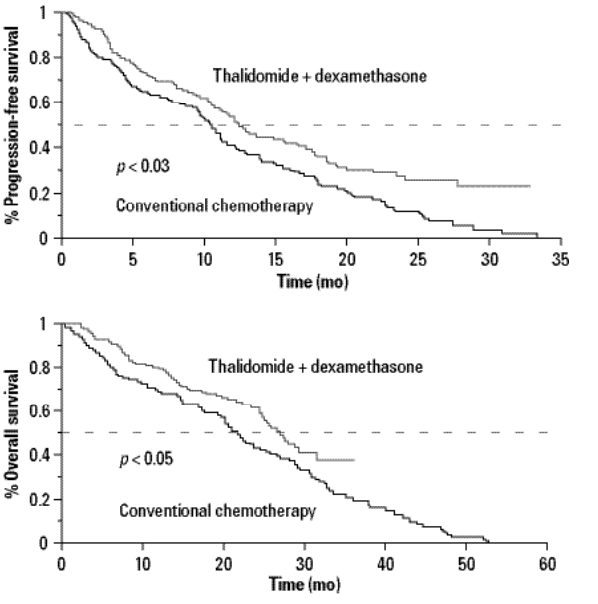

Figure 3. Progression-free and overall survival. Median progression-free survival and overall survival rates were superior in the thalidomide plus dexamethasone group compared with the conventional chemotherapy group. This analysis included all patients.[1]

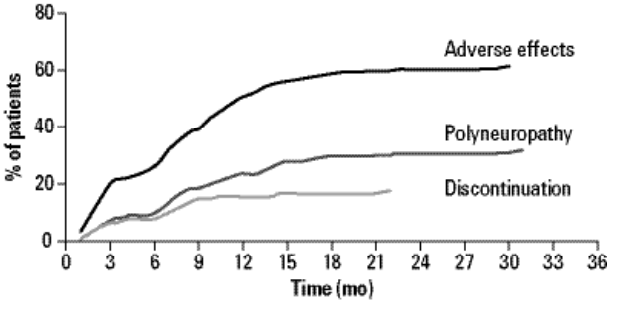

Figure 4. Time to onset of adverse events with combination thalidomide plus dexamethasone. Therapy was discontinued in 18% of patients because of adverse events; polyneuropathy occurred in approximately 27% of patients.[1]

chemotherapy group (p=0.0016). These results are similar to those of patients who received two or more lines of chemotherapy. Among those patients, progression-free survival was 11 months for patients who received combination thalidomide plus dexamethasone therapy and 9 months for patients who received conventional chemotherapy. There was no difference in overall survival between the two groups (median 19 months). As first salvage therapy, the combination of thalidomide plus dexamethasone was superior to conventional therapy, but it was equivalent to conventional chemotherapy as second or third salvage therapy.

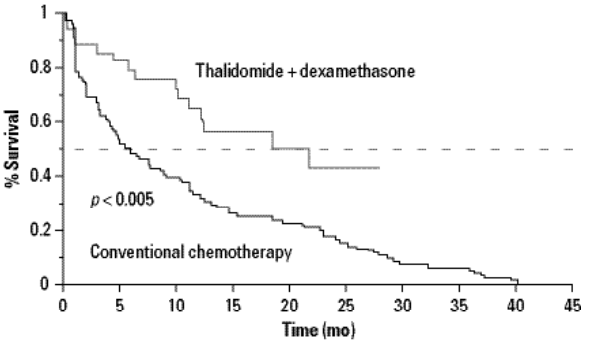

Figure 5. Survival after relapse in both treatment groups. Thalidomide may produce superior survival rates because it is not myelotoxic but does delay disease progression. Subsequent chemotherapy treatment can therefore be delayed.[1]

Adverse events

The most common adverse events reported among patients who received combination thalidomide plus dexamethasone were neuropathy (19%), constipation (18%), sedation (13%), confusion (8%), and deep vein thrombosis ([DVT] 2%). Treatment was discontinued in 18% of patients. Toxicity was graded according to World Health Organization (WHO) criteria (0 = none; 4 = worst).[2] Grade 1 toxicity occurred in 84% of patients, grade 2 in 12%, and grade 3 in 4%. Time to onset of adverse events is presented in Figure 4.

Therapeutic implications

The difference in survival between patients who received one line of chemotherapy and those who received two or more may occur because thalidomide can be administered without producing myelotoxic effects. This effect postpones the need for chemotherapy and delays the progression of resistant disease. Figure 5 presents survival rates after relapse among patients who received only one line of chemotherapy. The difference in survival is significant ($p<0.005$). Although the results presented here are from a retrospective, non-randomized analysis, they suggest that thalidomide plus dexamethasone as first salvage therapy produces superior results compared with conventional chemotherapy.[1]

Melphalan, prednisone, and thalidomide versus melphalan and prednisone therapy

A randomized study of combination melphalan, prednisone, and thalidomide (MPT) compared with melphalan and prednisone (MP) therapy is currently being conducted by the Italian Multiple Myeloma Study Group (Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto [GIMEMA] Multiple Myeloma Working Party). The study population includes patients with MM who are older than 65 years. The MPT regimen includes melphalan 4 mg/m^2 and prednisone 40 mg/m^2 for 7 days per month for six courses plus thalidomide 100 mg/d continuously until relapse. The MP regimen includes melphalan 4 mg/m^2 and prednisone 40 mg/m^2 also for 7 days per month for six courses.

Table 2. Patient characteristics (MPT vs MP).

	MPT N=89	*MP N=88*
Median age (y)	71	73
Stage at diagnosis		
IIA	44%	43%
IIIA	47%	49%
B	9%	8%
Median β2 microglobulin (mg/L)	3.4	3.6
M protein		
IgG	58%	64%
IgA	32%	21%
BJ	10%	15%

MPT: melphalan, prednisone, and thalidomide; MP: melphalan and prednisone; IgG: immunoglobulin G; IgA: immunoglobulin A; BJ: Bence-Jones proteins.

Table 3. Incidence of adverse events: MPT vs MP.

	MPT		*MP*	
	WHO grade		*WHO grade*	
	1-2	*3-4*	*1-2*	*3-4*
Hematologic	29%	18%	35%	25%
Constipation	28%	7%	—	—
Neurologic	32%	9%	11%	—
Cardiac	17%	3%	3%	4%
Cutaneous	15%	2%	3%	—
Infection	14%	10%	12%	1%
Thromboembolism	19%		4%	
Early death	5%		5%	

MPT: melphalan, prednisone, and thalidomide; MP: melphalan and prednisone; WHO: World Health Organization.

Results

The two groups of patients in this study have similar demographic and historical characteristics (Table 2). Adverse events stratified by WHO severity are presented in Table 3. In the interim analysis, the rates of thromboembolism and serious infection were high for MPT therapy. As a result, the protocol was amended to add enoxaparin as prophylactic treatment for DVT. A total of 28 patients who received enoxaparin had no

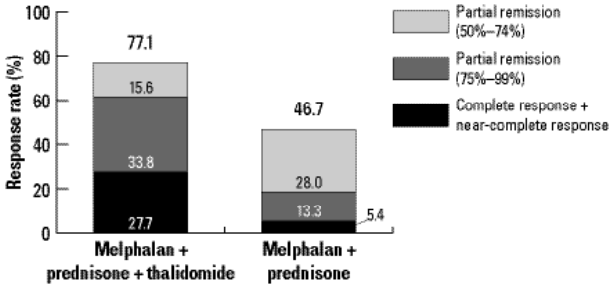

Figure 6. Response to MPT and MP. Complete response was statistically significantly better for patients receiving MPT therapy (p<0.001).

arterial occlusion or pulmonary thromboembolism. Of the 61 patients who received no prophylactic therapy, arterial occlusion was seen in 1.6% and thromboembolism in 4.9%. Among patients who received enoxaparin, the incidence of DVT was 7.1% compared with 21.3% among patients who received no prophylaxis. At 24 months, more than 40% of patients discontinued treatment with MPT, primarily because of neurotoxicity. Although the doses of each agent administered are considered low, adverse events were still problematic.

The response to therapy was favorable (Figure 6). MPT therapy, with a response rate of 77.1%, was superior to MP, with a response rate of 46.7%. The percentage of complete responses was also higher for MPT therapy (27.7%) compared with MP therapy (5.4%) (p<0.001). The value "13.3%" is the percentage of partial remission with MP (Figure 6). Overall survival was similar among the two treatment arms, with 78.7% of patients in the MPT group and 68.2% of patients in the MP group surviving at 33 months. Although it is too early to evaluate survival rates, response has been related to survival in all studies so far.

Conclusion

Thalidomide plus dexamethasone is particularly beneficial to patients with relapsed MM who have received one line of prior chemotherapy. The lack of myelotoxicity associated with thalidomide, along with its effects in delaying disease progression, make it an appropriate choice for first salvage therapy. Among patients taking melphalan plus prednisone, the addition of thalidomide produces significantly superior response to therapy compared with melphalan plus prednisone. Adverse events are problematic, however. The addition of prophylactic therapy to prevent DVT and thromboembolism is recommended. While the results presented here are preliminary, it appears that thalidomide provides improvement in survival rates.

References

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