

CCO Independent Conference Coverage of the 2006 Annual Meeting of the American Society of Clinical Oncology*

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Lowering Thalidomide Dose Reduces Toxicity, Maintains Efficacy in Refractory or Relapsed Multiple Myeloma Patients

- Multicenter, prospective, randomized, noninferiority trial
- Intergroupe Francophone du Myelome 01-02 Study

Summary of Key Conclusions

In patients with relapsed/refractory multiple myeloma, lowering thalidomide dose from 400 mg/day to 100 mg/day did not affect treatment outcomes

Thalidomide better tolerated at lower dosage

- Less severe somnolence, constipation, peripheral neuropathy

No significant difference in 1-year overall survival between groups

Nevertheless, hypothesis of noninferiority of 100 mg/day dose not confirmed

Suggests 100 mg/day thalidomide may be appropriate starting dose in relapsed/refractory patients

Background

Efficacy of thalidomide in relapsed/refractory multiple myeloma well established

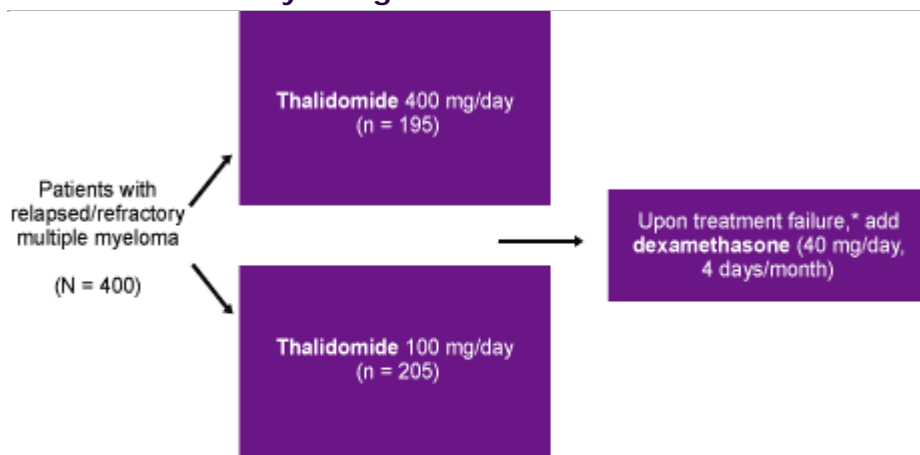
High incidence of thalidomide toxicity associated with cumulative exposure or dose intensity

Minimum effective thalidomide dose unknown

- Outcomes not affected by mean thalidomide dose during first 3 months of treatment

Current study aimed to evaluate safety, efficacy of lower dose thalidomide

Schematic of Study Design



All patients received pamidronate (90 mg/month).

*Treatment failure: stable disease after 3 months or disease progression.

Eligibility

Inclusion criteria

- Relapsed/refractory multiple myeloma after 2 previous lines of therapy or after 1 previous line of therapy with alkylating agent with no other treatment options
- Relapse after 1 line of intensive treatment
- Oral anticoagulation in patients with prior deep vein thrombosis

Enrollment: December 2000 - October 2004

Baseline Characteristics

Arms well matched

| <i>Characteristic</i> | <i>Thalidomide 400 mg/day (n = 195)</i> | <i>Thalidomide 100 mg/day (n = 205)</i> |
|--|---|---|
| Median age, yrs | 68 | 69 |
| Median interval from diagnosis to randomization, mos | 36 | 36 |
| Prior therapy, % | | |
| ≥ 2 lines of therapy | 45 | 46 |
| 1 line chemotherapy | 13 | 17 |
| Intensive treatment | 57 | 52 |
| Serology, mg/L | | |
| Median creatinine | 10 | 10 |
| Median CRP | 5 | 5 |
| Median β 2M | 3.7 | 3.5 |
| ISS stage, % | | |
| I | 41 | 44 |
| II | 31 | 27 |
| III | 28 | 29 |
| Ch13 deletion (n = 209), % | 52 | 44 |

β 2M, beta-2 microglobulin; CRP, C-reactive protein; ISS, International Staging System; Ch13, chromosome 13.

Description of Current Analysis

Statistical analysis on intent-to-treat per-protocol analyses

Primary endpoint

 1-year overall survival

Secondary endpoints

 Overall response rate (ORR)

 Time to treatment failure (dexamethasone introduction)

 Progression-free survival

 Safety

Main Findings

Noninferiority hypothesis not confirmed based on per-protocol population, however

Clinical outcomes comparable with 100 mg/day vs 400 mg/day thalidomide

 1-year overall survival, 73% \pm 3% vs 69% \pm 3% for 400 mg/day and 100 mg/day, respectively

| <i>Outcomes at Year 1</i> | <i>Thalidomide 400 mg/day, % (n = 205)</i> | <i>Thalidomide 100 mg/day, % (n = 195)</i> |
|---------------------------|--|--|
| Proportion alive | 44 | 39 |

| <i>Outcomes at Year 1</i> | <i>Thalidomide 400 mg/day, % (n = 205)</i> | <i>Thalidomide 100 mg/day, % (n = 195)</i> |
|-----------------------------|--|--|
| Thalidomide alone | 29 | 18 |
| Thalidomide + dexamethasone | 15 | 21 |
| Deaths | 27 | 31 |
| Withdrawn | 29 | 30 |

Significantly higher ORR in higher-dose group after 3 months

| <i>Response at Month 3</i> | <i>Thalidomide 400 mg/day, % (n = 181)</i> | <i>Thalidomide 100 mg/day, % (n = 183)</i> |
|----------------------------|--|--|
| Progression | 24.7 | 44.6 |
| SD | 13.8 | 17.7 |
| Minor response | 33.3 | 22.6 |
| PR | 25.3 | 13.4 |
| Very good PR | 2.3 | 1.1 |
| CR | 0.6 | 0.5 |
| ORR | 62.0* | 38.0 |

SD, stable disease; PR, partial response; CR, complete response.

*P < .001 vs 100 mg/day dose.

No significant difference in ORR for combination therapy, regardless of thalidomide dose

| <i>Response at Month 3 of Thalidomide + Dexamethasone</i> | <i>Thalidomide 400 mg/day, % (n = 90)</i> | <i>Thalidomide 100 mg/day, % (n = 119)</i> | <i>P Value</i> |
|---|---|--|----------------|
| Progression | 39.0 | 42.1 | NS |
| SD | 16.9 | 12.1 | NS |
| Minor response | 23.4 | 32.7 | NS |
| PR | 18.2 | 12.1 | NS |
| Very good PR | 2.6 | 0.9 | NS |
| CR | 0 | 0 | NS |

NS, not significant.

Lower dose of thalidomide better tolerated

Significant for grade 2-4 adverse effects

No difference in incidence of deep vein thrombosis

| <i>Side Effect</i> | <i>Thalidomide 400 mg/day (n = 193)</i> | <i>Thalidomide 100 mg/day (n = 202)</i> | <i>P Value</i> |
|--------------------|---|---|----------------|
| Somnolence, % | | | |
| All cases | 75 | 61 | .004 |
| Grades 2-4 | 33 | 13 | < .0001 |

| <i>Side Effect</i> | <i>Thalidomide 400 mg/day (n = 193)</i> | <i>Thalidomide 100 mg/day (n = 202)</i> | <i>P Value</i> |
|--------------------------------|---|---|----------------|
| Peripheral neuropathy, % | | | |
| All cases | 74 | 60 | .004 |
| Grades 2-4 | 32 | 20 | .003 |
| Deep vein thrombosis, n | | | |
| All cases | 20 | 20 | NS |
| Thalidomide alone | 11 | 12 | NS |
| Thalidomide + dexamethasone | 9 | 8 | NS |
| Constipation, % | | | |
| All cases | 89 | 74 | .0003 |
| Grade 2-4 | 40 | 28 | .0006 |

Reference

Yakoub-Agha I, Doyen C, Hulin C, et al. A multicenter prospective randomized study testing non-inferiority of thalidomide 100 mg/day as compared with 400 mg/day in patients with relapsed/refractory multiple myeloma: results of the final analysis of the IFM 01-02 study. Program and abstracts of the 42nd Annual Meeting of the American Society of Clinical Oncology; June 2-6; Atlanta, Georgia. Abstract 7520.

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