[haematologica reports]
2005;1(11):14-15

Thalidomide plus dexamethasone as initial therapy for multiple myeloma: overview of Mayo Clinic and Eastern Cooperative Oncology Group experience

ROBERT A. KYLE
S. VINCENT RAJKUMAR

Mayo Clinic,
200 First Street SW,
Stabile Building, 6th Floor
Rochester, Minnesota 55905
Phone: 507.284.3039
Fax: 507.266.9277
E-mail: rajkumar.vincent@mayo.edu

Dexamethasone has been shown to produce a response in at least 45% of patients who are newly diagnosed with multiple myeloma (MM) and in approximately one quarter of patients with relapsed or refractory disease.[1,2] A synergistic effect between dexamethasone and thalidomide has been identified, which is illustrated by the efficacy of this combination in relapsed MM.[3] Studies of thalidomide and dexamethasone used to treat patients who are newly diagnosed with MM have yielded response rates from 64% to 72%.[4,5] These results and others suggest that the combination of thalidomide and dexamethasone is an effective treatment choice for patients with MM.

Thalidomide plus dexamethasone versus dexamethasone

The Eastern Cooperative Oncology Group (ECOG)[6] conducted a randomized phase 3 trial to compare the response and toxicity of thalidomide plus dexamethasone versus dexamethasone alone as first-line therapy for patients newly diagnosed with MM. Patients were randomized to either thalidomide plus dexamethasone or dexamethasone alone for four monthly cycles (Figure 1). Patients who had a response of any type or whose disease stabilized were continued in the study for 4 months and were then offered autologous stem cell transplant. Those whose disease progressed at any time were removed from the study.

The dosage regimen included daily oral thalidomide 200 mg and dexamethasone 40 mg administered on days 1 through 4, 9 through 12, and 17 through 20. All patients received either pamidronate or zoledronic acid at monthly intervals. The primary study end point was best response at 4 months, defined as a 50% reduction in urine M protein levels or a 90% reduction in serum M protein if that was the only assessable measurement. Results were calculated using serum protein electrophoresis and urine protein electrophoresis of an aliquot of urine concentrated from a 24-hour collection.

Results

As of November 2004, the study included 207 patients. No measurable disease was found at baseline in six patients, who were declared ineligible. Assessable response data were available for 198 patients (Figure 2). An overall response rate of 58% was reported for patients who received thalidomide plus dexamethasone compared with 42% for patients who received dexamethasone alone (p=0.0164). The response in 13 patients was evaluated using quantitative immunoglobulin or urine light chain levels. The best response rates were 69% in the thalidomide plus dexamethasone group and 51% in the dexamethasone-only group. This measurement included serum M protein levels determined by quantitative values in two patients who had no measurable urine M protein. The median time to response was rapid, occurring at 1.1 months for both treatment groups. Disease progression occurred in 3% of patients who received thalidomide plus dexamethasone and in 5% of patients who received dexamethasone alone. Event-free and overall survival rates have not yet been determined.

Adverse events data were available for 201 patients. Deep vein thrombosis (DVT) occurred in 18% of patients who received thalidomide plus dexamethasone and in 3% of patients who received dexamethasone alone. Rash was uncommon. Sinus bradycardia occurred in one patient receiving the thalidomide regimen. Peripheral neuropathy was expected, but rates were low because patients were treated for only 4 months. As expected, toxicity was higher in the thalidomide group (34%) compared with the dexamethasone-only group (17%). Toxicity levels in the thalidomide group were considered significant. The total adverse event rate for the thalidomide plus

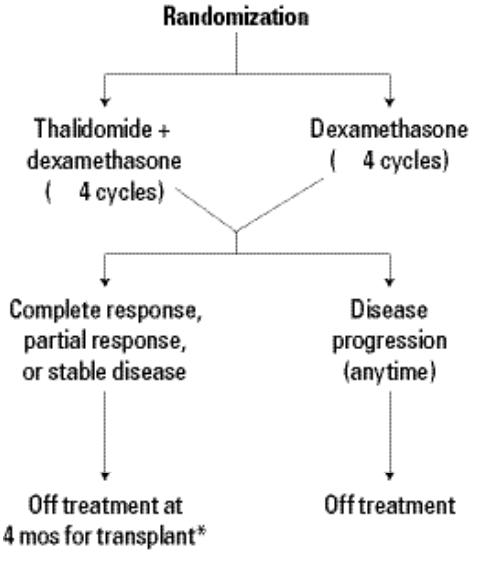

Figure 1. Phase 3 study design. Patients received thalidomide plus dexamethasone or dexamethasone alone for 4 months. Those who had a response of any kind or whose disease stabilized were offered autologous stem cell transplantation. Patients whose disease progressed were removed from the study.[6] *Treatment beyond 4 months was permitted at the physician's discretion.

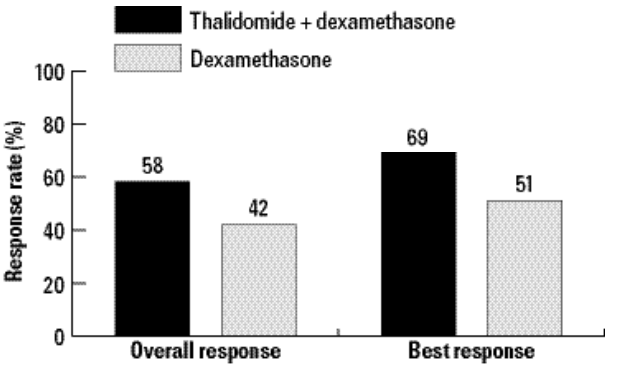

Figure 2. Response rates. Patients who received thalidomide plus dexamethasone had higher overall and "best response" rates than patients who received dexamethasone alone. Best response was defined as a 50% reduction in urine M protein levels or a 90% reduction in serum M protein.[6]

dexamethasone group was 46% compared with 20% for dexamethasone alone. Nonhematologic toxicities of grade 3 or higher were 68% for the thalidomide plus dexamethasone regimen and 43% for dexamethasone alone. The death rate over the 4-month treatment cycle was 7% for the thalidomide regimen and 11% for dexamethasone alone.[6]

Conclusion

Thalidomide plus dexamethasone is an effective induction therapy in newly diagnosed MM. The response to thalidomide plus dexamethasone was superior to dexamethasone alone but must be balanced with the risk of added toxicity associated with thalidomide. Results were comparable with conventional vincristine + doxorubicin (Adriamycin®+dexamethasone therapy. We recommend prophylactic anticoagulant therapy to decrease the incidence of DVT when using thalidomide. A future strategy is to continue with a phase 3 study of lenalidomide, a derivative of thalidomide, plus dexamethasone. Lenalidomide has shown promising results in the treatment of relapsed or refractory myeloma in two phase 3 clinical trials.

References

1. Alexanian R, Dimopoulos MA, Delasalle K, Barlogie B. Primary dexamethasone treatment of multiple myeloma. Blood 1992; 80: 887–90.
2. Barlogie B, Vesole DH, Jagannath S. Salvage therapy for multiple myeloma: the University of Arkansas experience. Mayo Clin Proc 1994; 69:787–95.
3. Hideshima T, Chauhan D, Shima Y, Raje N, Davies FE, Tai YT, et al. Thalidomide and its analogs overcome drug resistance of human multiple myeloma cells to conventional therapy. Blood 2000; 96:2943–50.
4. Rajkumar SV, Hayman S, Gertz MA, Dispenzieri A, Lacy MQ, Greipp PR, et al. Combination therapy with thalidomide plus dexamethasone for newly diagnosed myeloma. J Clin Oncol 2002; 20: 4319–23.
5. Weber D, Rankin K, Gavino M, Delasalle K, Alexanian R. Thalidomide alone or with dexamethasone for previously untreated multiple myeloma. J Clin Oncol 2003; 21:16–9.
6. Rajkumar SV, Blood E, Vesole DH, Shepard R, Greipp PR. Thalidomide plus dexamethasone versus dexamethasone alone in newly diagnosed multiple myeloma (E1A00): results of a phase III trial coordinated by the Eastern Cooperative Oncology Group. Blood 2004; 104:205. Abstract.