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# Thalidomide–Dexamethasone as Primary Therapy for Advanced Multiple Myeloma

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**The value of thalidomide–dexamethasone was assessed in 26 consecutive, previously untreated patients with multiple myeloma of high tumor mass. All showed Hgb < 8.5 g/dL, serum calcium > 11.5 mg/dL, or both. The response rate was 73%, frequency of early death < 3 months was 5%, projected median survival was 30 months, and projected median remission time was 25 months. There were no occurrences of grade 3 or 4 neutropenia or thrombocytopenia, so that serious infection occurred in only 12% of patients. Thalidomide–dexamethasone was useful for these patients with advanced disease because of the high response rate and acceptable survival, with a low frequency of serious complications. Am. J. Hematol. 79:194–197, 2005.** © 2005 Wiley-Liss, Inc.

**Key words: multiple myeloma; thalidomide; dexamethasone**

## INTRODUCTION

Multiple myeloma is a generalized malignancy of plasma cells associated with diverse clinical features including bone lesions, hypercalcemia, anemia, and renal failure. The presence of hypercalcemia or severe anemia has signified advanced disease with extensive bone marrow infiltration, high frequencies of renal failure, pathologic fractures, and short survival [1]. Primary therapy for such patients has usually consisted of a program such as VAD [vincristine–doxorubicin by continuous infusion through central venous catheter with intermittent oral dexamethasone] or, at our center since 1994, a similar combination with added high-dose cyclophosphamide (HCVAD) [2]. The latter has been associated with severe neutropenia for 7–10 days and an increased risk of infection and catheter-related complications. Recently, the combination of thalidomide–dexamethasone (TD) induced remission in approximately 70% of previously untreated patients with low or intermediate tumor mass [i.e., without hypercalcemia or severe anemia] and with acceptable side effects [3,4]. We assessed the same combination in 26 consecutive, newly diagnosed patients with high tumor mass who had been excluded from our previous trial with TD. TD appeared superior to previous programs because of the high response rate and reasonable survival and its low frequency of serious complications.



## PATIENTS AND METHODS

### Patients and Treatment

Between October 2000 and September 2003, we treated 26 patients with advanced multiple myeloma with the combination of thalidomide and dexamethasone. Thalidomide was prescribed in an oral dose of 100 mg q hs and increased by 50 mg every 7 days to a maximum dose of 300 mg, depending on side effects. Dexamethasone was given in an oral dose of 20 mg/m$^2$ each morning after breakfast on days 1–4, 9–12, and 17–20, followed by 10 days without therapy prior to the next cycle. In order to reduce the risk of deep venous thrombosis, either therapeutic low molecular weight heparin or warfarin was prescribed, the latter to maintain INR at 2.0–3.0. Treatment was continued for at least 2 cycles until preparation for intensive therapy.

Partial response (PR) was defined as >75% reduction of serum myeloma protein production and/or >95%

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reduction of Bence Jones protein, and reduction of marrow plasmacytosis to <5%; complete remission (CR) required disappearance of serum and urine myeloma protein by immunofixation with normal marrow differential, confirmed by repeat study at least 3 months later. Relapse was defined as the earliest of >25% increase in myeloma protein from lowest level, new lytic bone lesion, or marrow plasmacytosis >10%. The life-table method was used to calculate survival from start of therapy and remission duration from onset of remission to relapse.

Early intensive therapy within 1 year, supported by autologous blood stem cells, was considered for all patients using criteria described previously [5,6], and was given to 54% of patients. Eligibility required age <70 years, acceptable performance status (Zubrod/WHO score $\leq 2$), adequate cardiac and pulmonary functions, collection of $>2\times10^6$ $CD34^+$ mononuclear cells/kg by apheresis, and sufficient socioeconomic resources for hospitalization and living near the treatment center for >4 weeks.

## RESULTS

### Clinical Features

All patients showed features of high tumor mass defined by virtue of corrected serum calcium >11.5 mg/dL and/or Hgb <8.5 g/dL. Clinical data is summarized in Table I.

### Response to Treatment

The frequency of response was 73% including CR in 15%. Remission was achieved rapidly after a median 1.2 months so that the myeloma had responded in >90% of responsive patients within 2 months. In all responding patients, there was improvement of bone pain, correction of anemia, and improved performance. Among 16 patients with evaluable cytogenetics, an abnormal pattern was present in 10 patients; of 7 patients with deletion of chromosome 13, 5 patients achieved remission. Among our 26 patients, 14 patients (54%) received intensive therapy; the combined frequency of conversion of partial to complete remission and of resistant disease to partial remission was 50%, similar to that observed previously [5,6].

**TABLE I. Clinical Features and Outcomes of Patients Treated With Thalidomide–Dexamethasone**

| | |
|---|---|
| No. of patients | 26 |
| Median age (range, years) | 58 (31–81) |
| Hgb (median, g/dL) | 7.8 |
| Calcium (%) | |
| >13.0 mg/dL | 19 |
| >11.5 mg/dL | 39 |
| Creatinine >2.0 mg/dL (%) | 15 |
| $B_2M$ >5.5 mg/L (%) | 60 |
| Outcomes | |
| Response rate (%) | 73 |
| Partial response (%) | 58 |
| Complete response (%) | 15 |
| Survival (median no. of months) | >30 |
| Remission (median no. of months) | >25 |

### Survival and Remission

The projected median survival was >30 months and projected remission time >25 months. Figure 1 depicts survival and remission for two groups of patients with advanced disease that were not comparable, the current set of 26 patients treated with thalidomide–dexamethasone, and the second of 50 patients (with more frequent hypercalcemia and renal failure) who received an intensive cyclophosphamide–VAD-based combination from 1994 to 2000.

### Side Effects

Early death within 3 months occurred in 2 patients (8%, both with non-neutropenic pneumonia). No patient developed grade 3 or 4 neutropenia or thrombocytopenia, DVT occurred in 2 patients with subtherapeutic anti-coagulation, and hospitalization was required for 3 patients with infection or DVT (Table II). Other side effects such as nausea, fatigue, constipation, neuropathy, and skin rash occurred infrequently and were usually mild and reversible.

## DISCUSSION

Thalidomide is an effective drug for multiple myeloma, as described first in patients with disease resistant to multiple prior therapies [7], confirmed by

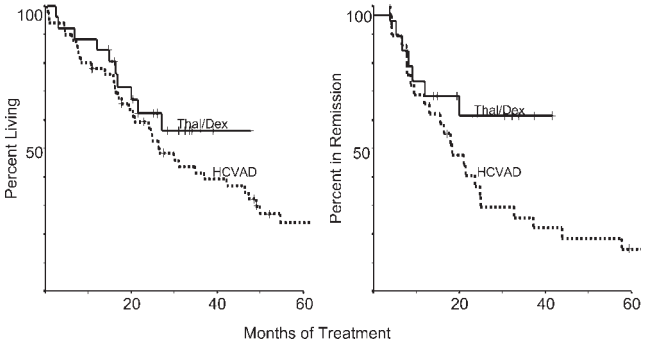


**Fig. 1. Survival of all patients (left panel) and remission time of patients with responsive disease (right panel) after treatment with TD or with a previous combination of cyclophosphamide combined with VAD between 1994 and 2000.**

**TABLE II. Number of Patients With Side Effects Among 26 Patients Treated With Thalidomide–Dexamethasone**

| | Toxicity grade | |
|---|---|---|
| | 1–2 | 3–4 |
| Neutropenia | 2 | 0 |
| Thrombocytopenia | 0 | 0 |
| Infection | 4 | 3 |
| Fatigue | 15 | 1 |
| Nausea | 0 | 1 |
| Constipation | 9 | 0 |
| Neuropathy | 2 | 1 |
| Rash | 2 | 0 |
| DVT | 0 | 2 |

others [8,9], and with frequencies of response in the 25–30% range. While the mechanism of action for thalidomide remains unknown, there is evidence for myeloma cell apoptosis in vitro and inhibition of both angiogenesis and plasma cell adhesion [10].

Among patients with previously resistant disease, intermittent high-dose dexamethasone alone has induced remission in approximately 25% of patients, and in 40–50% of patients when combined with thalidomide [11,12]. Either thalidomide or dexamethasone alone has induced remission in 30–45% of previously untreated patients [3,4,13], and the combination achieved disease response in 72% of patients with low or intermediate tumor mass, including 12% with complete remission [4]. The frequency of deep venous thrombosis was reduced from 15% to less than 5% with prophylactic anticoagulation in therapeutic dose. The high response rate and acceptable tolerance with rational prevention of side effects has justified TD as the treatment of choice for most patients with newly diagnosed multiple myeloma.

In this report, we describe the value of TD in 26 consecutive patients with multiple myeloma of high tumor mass who had been excluded from our previous trials. Outcomes in terms of response rate, survival, and remission time resembled those observed previously with a previous regimen for patients with advanced disease [2]. With TD, severe neutropenia, thrombocytopenia, and catheter-related complications were not observed, so that serious infection and hospitalization were less frequent. Consequently, thalidomide–dexamethasone provided an equally effective, less toxic, more convenient, and less costly initial treatment program for newly diagnosed patients with advanced multiple myeloma, as observed previously for those with less advanced disease [4].

TD also permitted the rapid collection of autologous blood stem cells with Neupogen alone in preparation for intensive consolidation treatment. When intensification was possible, the frequency of meaningful benefit of approximately 50% was similar to that observed previously among comparable patients who received high-dose therapy [5,6].

Effective new agents should be assessed in combination with TD in attempts to improve response rate, complete remission rate, and shorten the time to remission prior to intensification. Bortezomib, an inhibitor of cell proteasome activity, successfully induced remission in 28% of patients with resistant multiple myeloma as a single agent [14] and in 57% of patients when combined with thalidomide–dexamethasone [15]. Considering our positive results with TD for patients with previously untreated myeloma of all stages, the value of added bortezomib is worthy of assessment.

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