

Thalidomide and dexamethasone for resistant multiple myeloma

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Summary. Between November 1998 and April 2000, the combination of thalidomide and dexamethasone was evaluated in 47 consecutive patients with multiple myeloma that was resistant to prior high-dose dexamethasone-based therapies. Remission was observed in 22 patients (47%), including six patients with complete remission. Side-effects were frequent, mild and usually reversible, but deep vein thrombosis occurred in 8% of

patients. Survival and remission times were longer among patients treated for previous resistant disease rather than for resistant relapse. This experience supports the use of thalidomide–dexamethasone in myeloma patients with resistant disease and justifies further trials in newly diagnosed patients.

Keywords: multiple myeloma, thalidomide, dexamethasone.

Multiple myeloma is a generalized disease of malignant plasma cells with a median survival of approximately 4 years. The marked variability in lifespan depends on the stage of disease at diagnosis, the occurrence, degree and duration of remission, and the frequency and duration of further disease control with new agents. Recently, Singhal *et al* (1999) described a response rate of 28% with thalidomide in patients with resistant myeloma or who relapsed despite multiple prior agents, subsequently confirmed by others (Weber *et al*, 1999; Rajkumar *et al*, 2000). When dexamethasone was combined with thalidomide for similar patients, approximately half of patients achieved remission (Weber *et al*, 1999; Dimopoulos *et al*, 2001). In this report, we update our experience to include long-term outcomes of remission and survival, and identify those with primary resistant disease as more likely to benefit from this combined therapy.

PATIENTS AND METHODS

Patients and treatment. Between November 1998 and April 2002, 47 consecutive patients with multiple myeloma that was resistant to, or who relapsed following prior therapies, were treated with the combination of thalidomide and dexamethasone (TD). The median age was 48 years (range 31–77 years); the median months from therapy was

36 months; serum β_2 microglobulin (B_2M) exceeded 4.0 mg/l in 34% of patients. Seventy-seven per cent of patients had received at least two prior regimens, including thalidomide alone in 24% and intensive therapy supported by autologous stem cells in 11%. Thalidomide was prescribed at a dose of 200 mg p.o., at bedtime (h.s.), increased by 100 mg increments every 7 d in the absence of side-effects, to a maximum of 600 mg. Dexamethasone was given concurrently at 20 mg/m² p.o. each morning on d 1–5 and repeated every 15 d. Patients with responsive disease continued daily thalidomide (100–150 mg/h.s.) with dexamethasone for 5 d each month. Written informed consent was obtained from all patients.

All eligible patients had myeloma that had been resistant to a prior regimen with intermittent high-dose dexamethasone (20 mg/m² on d 1–4, 9–12, 17–20) [VAD (vincristine, adriamycin, dexamethasone), cyclophosphamide-pulse dexamethasone, pulse dexamethasone alone]; 11 patients also showed disease resistance to thalidomide alone. Partial response (PR) to treatment was defined as > 75% reduction of serum myeloma protein production and/or > 90% reduction of Bence Jones protein excretion; complete remission (CR) required disappearance of serum myeloma protein by immunofixation and < 5% bone marrow plasma cells. Relapse was defined as the earliest of > 25% increase in myeloma protein from lowest level, new lytic bone lesions, marrow plasmacytosis to > 10% or hypercalcaemia.

Chi-squared tests were used to assess differences in frequencies of response. The life-table method was used to calculate survival from start of therapy or from onset of

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remission (Kaplan & Meier, 1958). The landmark analysis was used to compare survival of patients responsive or unresponsive to treatment (Anderson *et al*, 1983). Differences were compared by the log-rank test (Peto *et al*, 1977).

RESULTS

Response to treatment

Response to treatment was observed in 22 patients (47%), including six patients with CR. The median time to remission was 2 months, with 95% of responding patients achieving remission within 5 months. The mean daily dose of thalidomide over the first 2 months was similar at 270 mg/d for responsive and unresponsive patients; more than 90% of patients who achieved remission received a mean daily dose of 400 mg or less.

Survival and remission

The median survival for all patients from start of TD was 38 months. With a landmark analysis using a guaranteed survival of 3 months based on the time required for remission in 80% of patients, survival was significantly longer for responsive than for unresponsive patients (Fig 1). The landmark analysis excluded one early death and one unresponsive patient who was lost to follow-up within 3 months; four patients who responded after 3 months were included among unresponsive patients.

Side-effects

Side-effects were frequent, mild and usually reversible, including constipation (51%), paresthesias (47%), skin dryness or rash (27%), fatigue or somnolence (21%), and thrombotic complications (8%). There was no haematological toxicity of grade 2 or higher. Grade 3 toxicities included numbness/tingling of feet in four patients (8%), skin rash in

two patients (4%), ileus in one patient (2%) and deep venous thrombosis in four patients (8%), including a non-fatal pulmonary embolism in one patient.

Prognostic factors

No clinical feature correlated with frequency of remission. Frequencies of remission were similar among patients with relapsing or resistant disease (44% vs 50%), with or without prior resistance to thalidomide alone (46% vs 48%), and among patients with less or more than 2 years of prior therapy (44% vs 48%). Survival and remission times were longer among patients treated for primary resistant disease in comparison with relapsing disease (Figs 1 and 2).

DISCUSSION

For patients with resistant multiple myeloma, thalidomide is an active drug, as first shown by Singhal *et al* (1999) and confirmed by others (Weber *et al*, 1999; Rajkumar *et al*, 2000). Response frequencies ranged from 25% to 32% based on criteria that differed slightly among the different groups, with remission times that have remained uncertain. The mechanism of action has remained unknown as there is evidence for direct myeloma cell apoptosis *in vitro*, as well as other potential effects such as inhibition of angiogenesis and of plasma cell adhesion (Hideshima *et al*, 2000).

Because intermittent high-dose dexamethasone alone has been effective in approximately a quarter of similar patients with resistant disease and in 40% of newly diagnosed patients (Alexanian *et al*, 1992), the combination with thalidomide was assessed. The frequency of remission among patients with resistance to prior therapies was approximately 50% higher than the frequency observed with thalidomide alone, despite use of stricter criteria for defining remission. Of major importance were the frequent

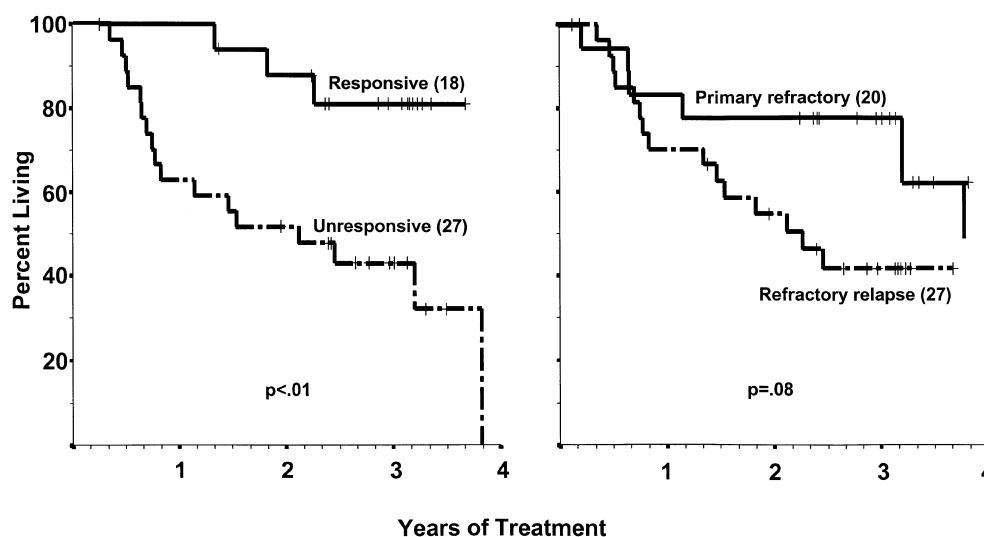


Fig 1. Survival for patients with disease responsive ($n = 18$) or resistant ($n = 27$) to thalidomide-dexamethasone by landmark analysis using a guaranteed survival of 3 months (left panel), and survival for patients with prior resistant ($n = 20$) or relapsing ($n = 27$) disease (right panel).

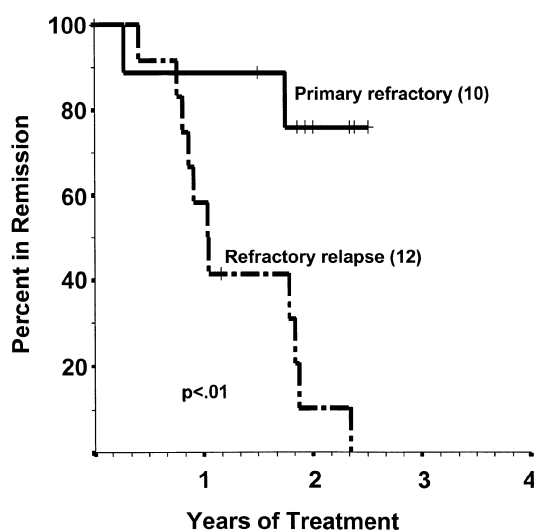


Fig 2. Remission times for responding patients with prior resistant ($n = 10$) or relapsing ($n = 12$) disease.

and marked antitumour effects observed even after prior resistance to thalidomide and dexamethasone given separately, as well as after intensive therapy supported by autologous stem cell transplantation. Response rates appeared higher than those described for comparable patients who received more intensive therapies, such as VAD-based regimens, but with less toxicity. These observations support the potential for a meaningful reduction of multiple myeloma with rational combinations of drugs that had been ineffective when given previously. *In-vitro* studies have shown that the addition of dexamethasone to thalidomide enhances antimyeloma activity in a dose-responsive manner (Hideshima *et al*, 2000).

While combination therapy was more effective, side-effects were frequent but mild in degree. Within our dose range, there was less relationship of dose to response in contrast to more frequent side-effects with higher doses. Of concern was the occurrence of deep venous thrombosis in 8% of patients that was not prevented by coumadin 1.0 mg/d or aspirin, but has been prevented by therapeutic doses of coumadin that maintain an International Normalized Ratio of 2.0–3.0 (Weber *et al*, 2002). Certain hypercoagulable risk factors may identify those at risk for thrombosis who may be more likely to benefit from anticoagulant prophylaxis in therapeutic doses. Other side-effects, such as constipation, fatigue and skin dryness, were usually preventable and always reversible, but a mild degree of sensory neuropathy persisted in 15% of patients.

The primary focus of this study was to assess long-term outcomes, such as remission and survival times, as well as to identify prognostic groups that were more likely to benefit. The longer remission and survival among patients with primary resistant disease, in comparison with relapsing disease, were also similar to those observed after VAD or intensive therapy supported by autologous stem cell transplantation (Alexanian *et al*, 1994). Remission times

among patients with disease that converted from resistant to responsive were also similar to those of newly diagnosed patients who responded directly to initial therapy. These findings support the use of TD as soon as resistance to standard therapy is recognized, including in patients who have received dexamethasone or transplant-supported therapies.

The encouraging activity of thalidomide–dexamethasone for primary resistant myeloma justifies further trials with this programme in newly diagnosed patients, with therapeutic anticoagulation to prevent deep venous thrombosis. This oral programme was devoid of myelosuppression and permitted rapid collection of autologous blood stem cells with neupogen alone, in preparation for intensive consolidation treatment, which is more likely to convert partial to complete remission (Alexanian *et al*, 2001).

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