Extended survival in advanced and refractory multiple myeloma after single-agent thalidomide: identification of prognostic factors in a phase 2 study of 169 patients

Bart Barlogie, Raman Desikan, Paul Eddlemon, Trey Spencer, Jerome Zeldis, Nikhil Munshi, Ashrof Badros, Maurizio Zangari, Elias Anaissie, Joshua Epstein, John Shaughnessy, Dan Ayers, Dan Spoon, and Guido Tricot

This report of a phase 2 trial of thalidomide (THAL) (200 mg/d; 200 mg increment every 2 weeks to 800 mg) for 169 patients with advanced myeloma (MM) (abnormal cytogenetics (CG), 67%; prior autotransplant, 76%) extends earlier results in 84 patients. A 25% myeloma protein reduction was obtained in 37% of patients (50% reduction in 30% of patients; near-complete or complete remission in 14%) and was more frequent with low plasma cell labeling index (PCLI) (below 0.5%) and normal CG. Two-year event-free and overall survival rates were 20% ± 6% and 48% ± 6%, respectively, and these were superior with normal CG, PCLI of less than 0.5%, and β_2-microglobulin of 3 mg/L. Response rates were higher and survival was longer especially in high-risk patients given more than 42 g THAL in 3 months (median cumulative dose) (landmark analysis); this supports a THAL dose-response effect in advanced MM. (Blood. 2001;98:492-494)

Introduction

Thalidomide (THAL) represents the first new class of active agents in the treatment of multiple myeloma (MM) since the introduction of melphalan and glucocorticoids more than 3 decades ago.[1] Its possible antitumor mechanisms in MM include a direct effect on MM and/or bone marrow stromal cells,[2] modulation of MM stromal cell adhesion,[3] suppression of MM cell–sustaining cytokines,[4] antiangiogenic effects by repression of vascular endothelial growth factor and basic fibroblast growth factor pathways,[5] and immunomodulation such as induction of T_{H1} T-cell response with secretion of interferon-γ and interleukin-2.[6] More recently, synergistic apoptotic signaling of THAL and dexamethasone has also been observed.[7]

We now report on the follow-up of all 169 patients enrolled in a phase 2 trial for advanced and refractory MM.

Study design

Between December 1997 and December 1998, 169 consecutive eligible patients with extensively pretreated and progressive MM were enrolled in a phase 2 trial. THAL (50-mg capsules) (Celgene, Warren, NJ) was started at a daily dose of 200 mg and escalated by 200 mg every 2 weeks to 800 mg according to tolerance. Patients with cardiopulmonary or renal dysfunction were not excluded; liver function tests could not exceed twice the upper limit of normal. All patients were enrolled at a single institution and provided written informed consent in keeping with institutional and Food and Drug Administration guidelines.

Baseline and follow-up laboratory tests were performed as previously outlined.[1] Patients kept a diary to document the occurrence and severity of toxicities. Follow-up visits were scheduled every 3 months, and more than 90% of patients adhered to this.

Study endpoints included paraprotein responses (PPRs) in serum and/or urine of at least 25%, 50%, 75%, or 90%; complete remission (CR) was defined by absence of monoclonal protein on immunofixation analysis.[1] Patients with a PPR less than 25% and those discontinuing treatment before response could be assessed (minimum of 4 weeks of therapy) were considered to have failed treatment; all results were evaluated on an intent-to-treat basis. Relapse criteria have been previously reported.[1]

Survival distributions (Kaplan-Meier) were compared by means of the log-rank test.[8,9] Multivariate modeling of bivariate responses was performed by means of logistic regression and stepwise selection methods. Similarly, multivariate modeling of event-free (EFS) and overall survival (OS) employed stepwise selection and proportional hazard regression models.[10] The percentage of change in laboratory measures was calculated from baseline to 90 days post–THAL administration. Wilcoxon rank sum tests were used to compare the percentage-change distributions of patients with 50% or greater reduction in paraprotein levels and of patients with less than 50% reduction.

Results and discussion

Patient characteristics and percentages consisted of the following: age older than 60 years in 40% of patients, β_2-microglobulin (B2M) greater than 3 mg/L in 50%, abnormal cytogenetics (CG) in 67% (deletion 13 in 37%), longer than 5 years of prior therapy in 20%, and longer 2 years of prior therapy in 72%. Seventy-six percent had received at least 1 and 53% had received 2 or more cycles of prior high-dose therapy with stem cell support. THAL could be escalated to 400 mg, 600 mg, and 800 mg in 87%, 68%, and 56% of patients, respectively. No treatment-related deaths were observed; 58% developed toxicities greater than grade 2 which affected the central nervous system in 25% (mainly sedation and somnolence; confusion; depression; tremor), gastrointestinal tract in 16% (mainly constipation; infrequently nausea or vomiting), and peripheral nerves (sensory neuropathy) in 9%. These toxicities

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were related to both intensity and cumulative dose of THAL administered (data not shown). Fewer than 2% of patients developed deep venous thrombosis (Doppler) or cytopenia.

A PPR of 25% was observed in 37% of patients; a PPR of 50% in 30%; and a PPR of 90% in 14% (Figure 1). Of patients exhibiting 25% PPR, 70% achieved that response within 2 months and 90% within 4.5 months. PPRs of 25% were more frequent with normal CG (52% vs 28%; $P = .003$) and with low PCLI (44% vs 10%; $P < .001$). Importantly, 14% of patients experienced their best response ever on THAL. THAL-induced PPRs were associated with significant reductions in bone marrow plasmacytosis and B2M as well as improvement in hemoglobin and uninvolved immunoglobulin M levels (data not shown).

Twenty-four patients remain on study. Reasons for study removal were disease progression in 105 patients, toxicity in 28, and other reasons in 12. With a median follow-up of 22 months among 84 alive patients, 2-year EFS and OS rates are 20% ± 6% and 48% ± 6%, respectively (Figure 1).

On multivariate analysis, EFS and OS were superior with normal CG, PCLI lower than or equal to 0.5%, and B2M lower than or equal to 3 mg/L, permitting distinction of 4 risk groups (see Figure 1). When results were re-examined without CG and PCLI, which are usually not available in the standard practice setting, B2M greater than 3 mg/L and C-reactive protein (CRP) greater than 7 mg/L emerged as key adverse variables for OS and EFS. Better prognosis was not associated with no prior transplant or longer time lapse since transplant.

To evaluate a possible dose effect of THAL on clinical outcome, a 3-month landmark analysis was performed. Patients given more than 42 g THAL in 3 months (median cumulative dose) had a higher response rate (25% PPR) (54% vs 21%; $P < .001$) and superior 2-year survival (63% ± 8% vs 45% ± 13%; $P < .001$); this was especially the case among patients with at least 1 of 3 adverse prognostic features present (Table 1; Figure 1). Responders (25%, 3-month landmark) had superior 2-year EFS and OS rates (34% and 69%, respectively) compared with nonresponders (20% and 47%, respectively; $P < .001$ and $P = .01$, respectively).

These data extend, in twice as many patients with longer follow-up, our earlier observations in 84 patients.[1] Considering the high-risk study cohort, the EFS and OS rates of 26% and 48%, respectively, 2 years after initiation of treatment are impressive. In fact, 38% of patients had received salvage treatment with dexamethasone (32 patients) or combination chemotherapy (dexamethasone and 4-day continuous infusions of cyclophosphamide, etoposide, and cisplatin [DCEP],[11] 33 patients) and progressed when THAL was initiated.

Results similar to ours have since been reported with THAL alone and in combination with dexamethasone.[12-17] Anticipating a THAL dose-response effect in a patient population with such advanced MM, our study called for dose escalation according to tolerance. Indeed, a dose-response effect was apparent in the high-risk subgroup defined by abnormal CG, B2M, and PCLI. However, prospective investigations are needed to determine, separately in early and advanced MM, the optimal THAL dose and schedule.

Table 1. Higher thalidomide dose benefits patients with high-risk disease

No. risk factors*	Thalidomide dose of more than 42 g/3 mo	No. patients	PPR by at least 25%	*P*	% alive at 2 y	*P*
≤ 1	yes	55	45	.01	74	NS
	no	36	19		66	
≥ 1	yes	28	43	.02	42	.01
	no	30	13		20	

*Risk factors are β2-microglobulin > 3 mg/L, plasma cell labeling index > 0.5%, and abnormal cytogenetics.

We had previously not observed a consistent antiangiogenic effect of THAL using serial microvessel density measurements of anti-CD34 monoclonal antibody–stained bone marrow biopsies.[1] This may not be surprising since the major effect of an antiangiogenesis agent should be prevention of new microvessel formation rather than destruction of existing blood vessels. Many of the multiple mechanisms already demonstrated in vitro may be operative in different patient subsets or even in MM subpopulations in the same patient.[7] Gene array technology is uniquely suited to unravel the mechanisms of action of THAL and its congeners in vivo.[18]

The virtual lack of myelosuppression makes THAL an ideal drug for combination with cytotoxic agents earlier in the disease. Such trials are currently in progress. Deep venous thrombosis,[19] hypothyroidism, and bradycardia were more frequent in patients randomized to THAL.[20]

In conclusion, THAL has definite activity in refractory MM. Its role in the up-front management of newly diagnosed MM and as maintenance therapy is under investigation. Issues of pharmacokinetics, dose intensity and scheduling, mechanism of action, and drug combinations need to be addressed.[21] Since THAL's activity in MM may involve, among other things, an antiangiogenic mechanism, this malignancy lends itself well to investigation of strictly antiangiogenic agents such as angiostatin and endostatin, shown to possess remarkable antitumor activity in the human severe combined immunodeficiency disease model of MM (J. Epstein, personal communication, May 2000).

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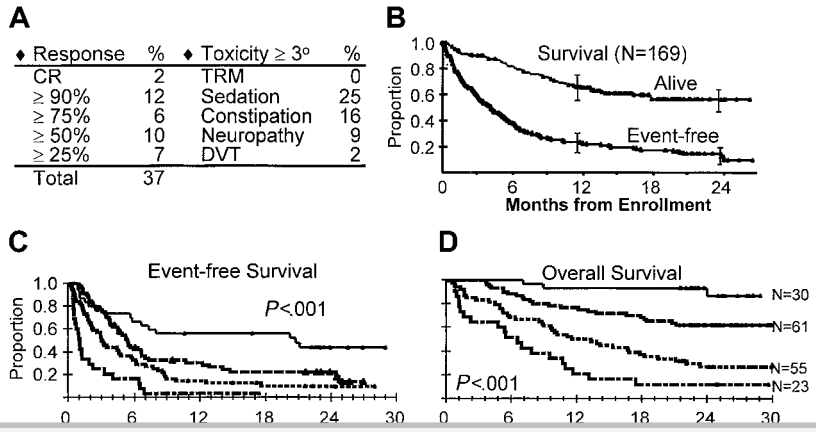

Figure 1. Response, toxicity, and survival. (A) Response rates and grade 3 toxicities; (B) EFS and OS. (C) EFS and (D) OS according to the number of unfavorable prognostic factors present prior to thalidomide. Risk discrimination on the basis of abnormal CG (EFS hazard ratio [HR] 2.15, $P < .001$; OS HR 2.53, $P = .002$); plasma cell labeling index (PCLI) greater than 0.5% (EFS HR 1.86, $P = .002$; OS HR 1.82, $P = .009$); and B2M greater than 3 mg/L (EFS HR 1.54, $P = .016$; OS HR 2.99, $P < .001$). Solid lines indicate no risk factors; dashed line, 1; dotted line, 2; and dash-dotted line, 3 risk factors. Additional unfavorable variables that are only univariately significant included the following for EFS: albumin level less than 3.5 g/dL, $P = .003$; and BM plasmacytosis greater than 30%, $P = .001$. Additional unfavorable variables that are only univariately significant included the following for OS: albumin level less than 3.5 g/dL, $P < .001$; BM plasmacytosis greater than 30%, $P = .05$; hemoglobin level less than 10 g/dL, $P < .001$; creatinine greater than 1.5 mg/dL, $P < .001$; and platelet count fewer than 100 000 μL, $P = .007$. TRM indicates

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