Thalidomide for the Treatment of Myelodysplastic Syndrome in Taiwan: Results of a Phase II Trial

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Abstract. *Background: Thalidomide inhibits angiogenesis and exerts complex immunomodulatory activities. This phase II study aimed to examine the efficacy of thalidomide in Taiwanese patients with myelodysplastic syndrome (MDS). Patients and Methods: Sixty patients [intention to treat group (ITT)] with MDS were treated with thalidomide (100 mg/day, increased by 100 mg/day weekly to a maximum of 400 mg/day) for 12 weeks. Forty-two patients of the ITT group were considered as comprising the evaluable population (EP). Results: Thalidomide resulted in hematological improvement (HI) in 28% of ITT analysis and in HI in 40% of the EP. Thalidomide was more effective for MDS patients with low to intermediate-1 International Prognostic Score System scores. The response rates were 7% for ITT and 10% for EP patients. Only two patients exhibited a cytogenetic response. Net reduced levels of vascular endothelial growth factor and basic fibroblast growth factor cytokines were observed in the peripheral blood and the bone marrow of thalidomide-treated patients. Conclusion: Low-dose thalidomide is an effective and safe treatment for patients with low-risk MDS.*

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The myelodysplastic syndromes (MDS) are a heterogeneous collection of hematological disorders characterized in most patients by cytopenia as the result of progressive bone marrow failure (1). MDS is regarded as a preleukemic disorder from which a substantial proportion of patients progress to acute myeloid leukemia (AML). Bone marrow transplantation is the only treatment for MDS that has the potential to induce long-term remission; allogeneic stem cell transplantation and chemotherapy have been shown to improve survival in some patients (2, 3). However, the treatment goal in the majority of patients with MDS remains palliation, in which the increase in quality of life and reduction in the likelihood of progression to AML are the main objectives.

Thalidomide exerts a broad spectrum of pharmacological and immunological effects, such as down-regulation of tumor necrosis factors alpha (TNF-α) (4, 5), up-regulation of adhesion molecules (6), and inhibition of angiogenesis (7). Treatment with thalidomide has been shown to improve anemia and long-term survival for patients with MDS (8-14). We conducted a single-arm, multicenter, open label, phase II clinical study of thalidomide for Taiwanese patients with MDS. The primary endpoint was to determine the hematological improvement (HI). Secondary endpoints of the study included determining the response to and the toxicity of thalidomide in these patients. Other hematological and immunological features that may indicate sensitivity to thalidomide, including levels of TNF-α, interferon gamma (IFN-γ), interleukin-6 (IL-6), vascular endothelial growth factor (VEGF), and those of basic fibroblast growth factor (bFGF) in the peripheral blood and bone marrow of patients with MDS were also investigated.

Patients and Methods

Eligibility criteria. This phase II, single-arm, non-comparative, and open label clinical trial was conducted across seven centers in Taiwan between September 2004 and November 2007. Inclusion criteria were diagnosis of MDS of the following subtypes according to the French-American-British criteria: Refractory anemia (RA), RA with ringed sideroblasts (RARS), chronic myelomonocytic leukemia (CMML), and refractory anemia with excess blasts (RAEB). Patients were required to meet one of the following hematological criteria: i). Pre-transfusion hemoglobin ≤10 g/dl; ii). pre-transfusion platelet count ≤50,000/mm^3; iii). absolute neutrophil count ≤1,000/mm^3. None of the patients had received any therapy for MDS for at least 30 days prior to the study, with the exception of supportive care with transfusions. Patients with a diagnosis of malignant condition or infection were excluded, as were patients who had undergone previous thalidomide treatment. This protocol was approved by the local Ethic Review Boards, and written informed consent was obtained from all patients.

The primary endpoint was HI. HI included erythroid response (HI-E), platelet response (HI-P), and neutrophil response (HI-N). A major HI-E was defined as an increase in hemoglobin (Hb) greater than 2 g/dl for patients with Hb <11 g/dl, and as transfusion independence for patients who were transfusion-dependent prior to treatment; a minor HI-E was defined as an increase of 1 to 2 g/dl in Hb for patients with pre-treatment Hb <11 g/dl, and as a 50% decrease in packed red blood cell requirement for transfusion-dependent patients. A major HI-P was defined as an absolute increase of >30,000/μl for patients with a platelet count <100,000/μl, and as stabilization of platelet count and platelet transfusion independence for platelet transfusion-dependent patients; a minor HI-P was defined as a 50%, or greater increase in platelet count with a net increase greater than 10,000/μl but less than 30,000/μl, for patients with a pre-treatment platelet count less than 100,000/μl. For HI-N, a greater than 100% increase or an absolute increase of greater than 500/μl, whichever was greater, for patients with an absolute neutrophil lower than 1500/μl before therapy, was defined as a major response; a minor response was defined as an absolute neutrophil increase of at least 100% but an absolute increase of less than 500/μl.

The secondary objectives of the study included the response rate and the toxicity of this regimen in these patients. The response rate was defined as the sum of the proportions of patients graded as having complete remission (CR) or partial remission (PR). Moreover, cytogenetic response and changes in the levels of TNF-α, IFN-γ, IL-6, VEGF, and bFGF in the peripheral blood and bone marrow were assessed in these patients.

Treatment. Patients received 50 mg of thalidomide orally twice daily during the study period. The dose of thalidomide was escalated weekly by 100 mg/day, if no grade 3 non-hematological toxicity occurred, until the dose reached 400 mg/day. All eligible patients were enrolled into the thalidomide treatment group. Patients were on thalidomide for 12 weeks and were followed-up for treatment response every 4 weeks for up to 16 weeks. The two study populations were the intention-to-treat (ITT) population and the evaluable population (EP). The ITT group was defined as those patients who were exposed to at least one study regimen. The EP was the subset of the ITT patients who completed baseline evaluation and had at least one post-treatment evaluation.

Table I. *Summary of patients' demographics and characteristics.*

Demographic characteristic		Total (N=60)
Age (years)	N	60
	Mean (SD)	60.24 (17.21)
	Median (IQR)	61.91 (25.47)
	Min-Max	18.8-89.85
Sex	Male N (%)	43 (71.7%)
	Female N (%)	17 (28.3%)
Weight (kg)	N	57
	Mean (SD)	64.75 (9.47)
	Median (IQR)	66.00 (10.00)
	Min-Max	41.50-86.90
Height (cm)	N	53
	Mean (SD)	162.40 (7.08)
	Median (IQR)	162.00 (10.00)
	Min-Max	148.00-176.00
BMI (kg/m^2)	N	53
	Mean (SD)	24.58 (3.57)
	Median (IQR)	24.54 (3.95)
	Min-Max	16.94-35.12

SD: Standard deviation; IQR: interquartile range, BMI: body mass index.

Results

Overall, 43 (71.7%) male and 17 (28.3%) female patients were enrolled in this study. The demographic characteristics of the 60 MDS patients are summarized in Table I. The duration of MDS was defined as the time between the day of diagnosis of MDS and the first day the study drug was given. The average duration of MDS was 132.87±385.78 days. In terms of MDS types, 24 patients (40.0%) had RA, 3 patients (5.0%) had RARS, and 33 patients (55.0%) had RAEB. The majority (91.7%) of patients had pre-transfusion hemoglobin ≤10 g/dl (Table II). Treatment duration and the mean daily dose of thalidomide are summarized in Table III. The mean treatment duration was 105.73±69.22 days and the mean daily dose was 204.52±84.13 mg/day (Table III).

HI response. Overall, 17 (28%) out of the 60 patients of the ITT group achieved an HI, 6 (10%) achieved major HI and 11 (18%) achieved minor HI (Table IV). Stratifying patients by International Prognostic Score System (IPSS) into risk groups indicated that most HI responders were patients with low or intermediate-1 risk MDS (Table V).

Response rate and cytogenetic response. Four patients (6.7% of the ITT group or 9.5% of the EP) exhibited complete remission (CR) or partial remission (PR). From the cytogenetic point of view, only one patient (1.7% of the ITT group or 2.4% of EP) had a major response and one patient (1.7% of the ITT group or 2.4% of EP) a minor response (Table VI).

Table II. *Disease evaluation of patients with myelodysplastic syndrome (MDS) at baseline.*

Baseline characteristic		Total (N=60)
Duration of MDS (days)	Mean (SD)	132.87±385.78
	Median (IQR)	14.0±28.0
	Min-Max	0-2343
Type of MDS	RA	24 (40.0%)
	RARS	3 (5.0%)
	RAEB	33 (55.0%)
Hematological criteria	Pre-transfusion Hb ≤10 g/dl	55 (91.7%)
	Pre-transfusion platelets ≤50,000/mm^3	22 (36.7%)
	Absolute neutrophils ≤1,000/mm^3	25 (41.7%)
ECOG performance at screening visit	Grade 0	44 (73.3%)
	Grade 1	16 (26.7%)
	Grade 2	0 (0.0%)
	Grade 3	0 (0.0%)
	Grade 4	0 (0.0%)

SD: Standard deviation; IQR: interquartile range; RA: refractory anemia; RARS: RA with ringed sideroblasts; RAEB: refractory anemia with excess blasts; ECOG: Eastern Cooperative Oncology Group.

Cytokine changes. The effect of thalidomide on the concentration of several cytokines, and on angiogenic and growth factors including TNF-α, IFN- γ, IL-6, VEGF, and bFGF were measured. The net change between week 12, the last study treatment visit, and the baseline of the investigated cytokines are listed in Table VII. Net reduced levels of TNF-α, VEGF and bFGF cytokine were observed in the peripheral blood of patients treated with thalidomide. Similarly, reductions of VEGF and bFGF were also noted in the bone marrow.

Adverse events. Adverse events (AEs) were measured using The Coding Symbols for a Thesaurus of Adverse Reaction Terms (15). A total of 910 AEs were reported, out of which 58.0% were grade 1, followed by 25.5%, 12.6%, 3.3%, and 0.2% of grade 2, 3, 4, and grade 5 AEs, respectively. Out of the 910 AEs reported, 189 (20.8%) were marked as being treatment related. The most frequent reported treatment-related AEs occurring in the ITT population was constipation (85.0%), followed by leukopenia (50.0%) and dizziness (41.7%). Table VIII summarizes adverse events with an incidence greater than 30%.

Table III. *Thalidomide treatment duration and the mean daily dose.*

		Total (N=60)
Treatment duration (days)	Mean (SD)	105.73±69.22
	Min-Max	2.00-222.00
Mean daily dose[1] (mg/day)	Mean (SD)	204.52±84.13
	Min-Max	74.6-373.21

SD: Standard deviation; [1]mean daily dose=dose actually taken (mg)/duration of exposure (day).

Table IV. *Hematological improvement in the ITT population.*

Hematological improvement (HI)	Response	N (%)
HI-E (N=55)	Major	4 (7.3%)
	Minor	8 (14.5%)
HI-P (N=22)	Major	1 (4.5%)
	Minor	6 (27.3%)
HI-N (N=25)	Major	2 (8%)
	Minor	0 (0%)
Total (N=60)	Major	6 (10%)
	Minor	11 (18.3%)

HI-E: Erythroid response; HI-P: platelet response; HI-N: neutrophil response.

Discussion

Thalidomide has demonstrated anti-inflammatory, immunomodulatory, and antiangiogenic effects *in vitro* (16, 17). Thalidomide disturbs angiogenesis mediated by bFGF and VEGF, inhibits TNF-α gene activation by reducing nuclear factor kappa-light-chain-enhancer of activated B cells binding, and reduces IL-6 secretion (18-21). These antiangiogenic, immunomodulatory, and growth-suppressive effects form the rationale for investigating thalidomide in the treatment of various types of malignancy. The heterogeneous biological effects of thalidomide on hematopoiesis have supported its use in the treatment of MDS (8-14).

This single-arm, non-comparative, multicenter, and open label phase II clinical trial aimed to examine the efficacy of thalidomide in patients with MDS in Taiwan. The primary endpoint of the trial was HI which included HI-E, HI-P, and HI-N. Administration of thalidomide, increasing from 100 mg

Table V. *Hematological improvement (HI) in the intent to treat (ITT) group and evaluable population (EP) by International Prognostic Score System (IPSS) scores.*

	IPSS				
ITT	Low	Intermediate-1	Intermediate-2	High	Total
N	14	30	15	1	60
HI response					
N	7	10	0	0	17
%	50%	33%	0	0	28%
EP	Low	Intermediate-1	Intermediate-2	High	Total
N	9	25	8	0	42
HI response					
N	7	10	0	0	17
%	78%	40%	0	0	40%

Table VI. *Treatment and cytogenetic response.*

	Treatment response		
	Category	N (%)	95% CI
ITT	Response	4 (6.7)	1.8%-16.2%
	No response	56 (93.3)	
	Total	60 (100)	
EP	Response	4 (9.5)	2.7%-22.6%
	No response	38 (90.5)	
	Total	42 (100)	
	Cytogenetic response		
	Category	N (%)	
ITT	Major response	1 (1.7)	
	Minor response	1 (1.7)	
	No response	58 (96.7)	
	Total	60 (100)	
EP	Major response	1 (2.4)	
	Minor response	1 (2.4)	
	No response	40 (95.2)	
	Total	42 (100)	

ITT: Intent to treat; EP: evaluable population; CI: confidence interval.

per day to no more than 400 mg per day over 12 weeks, resulted in HI in 28% of patients in the ITT analysis and in 40% in the EP. As indicated by HI, thalidomide provided more effective results for patients with MDS with a low to intermediate-1 IPSS score. These treatment response results obtained from patients with MDS in Taiwan fall within previous findings by other groups (11, 22, 23).

The secondary endpoints of the study were to determine the response to and toxicity of thalidomide in these patients.

Table VII. *Net change from baseline to the end of treatment of concentrations of the investigated cytokines.*

Cytokine		Peripheral blood (pg/ml)	Bone marrow (pg/ml)
TNF-α	Mean (SD)	–0.07±4.09	0.81±5.59
	Min-Max	–11.40-6.00	–13.60-7.90
IFN-γ	Mean (SD)	2.38±5.76	5.43±13.99
	Min-Max	0.00-22.30	–7.30-54.30
IL-6	Mean (SD)	0.44±7.94	3.48±12.04
	Min-Max	–14.17-16.06	–21.09-27.36
VEGF	Mean (SD)	–60.17±294.85	–6.48±196.77
	Min-Max	–966.80-438.40	–487.10-395.80
bFGF	Mean (SD)	–0.13±17.81	–15.65±58.43
	Min-Max	–47.30-55.63	–148.03-158.22

TNF-α: Tumor necrosis factors alpha; IFN-γ: interferon gamma; IL-6: interleukin-6; VEGF: vascular endothelial growth factor; bFGF: basic fibroblast growth factor.

Table VIII. *Adverse events with incidence greater than 30% in 60 patients with myelodysplastic syndrome.*

Condition	N (%)
Constipation	51 (85%)
Asthenia	20 (33.3%)
Hypocalcemia	18 (30%)
Dizziness	25 (41.7%)
Somnolence	23 (38.3%)
Dyspnea	21 (35%)
Leukopenia	30 (50%)
Thrombocytopenia	20 (33.3%)
Rash	23 (38.3%)

The response rate that indicated the proportion of patients having CR or PR was 6.7% in the ITT population and 9.5% in the EP. Only two patients exhibited a cytogenetic response to thalidomide treatment. The second aim of our study also included monitoring of the impact of thalidomide on several factors implicated in angiogenesis and immunomodulation in patients with MDS. Levels of TNF-α, VEGF and bFGF were reduced in the peripheral blood and reduction of VEGF and bFGF were noted in the bone marrow of patients. Given the wide ranges in the levels of these cytokines in this small sample, the correlation between these changes and the clinical benefit from treatment with thalidomide could not be established in this study.

In general, the safety profile of thalidomide in this study was within what we expected from the studied regimen and correlated with what has been reported previously (11, 22, 23). In the absence of serious side-effects, a low thalidomide dose of 100 mg/day, with an increase, if tolerated, to 400 mg, may produce favorable responses in patients with MDS.

In summary, this clinical study showed that thalidomide was efficacious and improved hematopoiesis in at least a subset of patients with MDS. Patients with a low to intermediate-1 IPSS score were most likely to respond. Future clinical studies should be designed in order to confirm the angiogenic and immunomodulatory properties of thalidomide in larger sample sizes and to examine the efficacy of combining thalidomide with other therapies to further improve treatment response.

Declaration of interests

The Authors have declared that no competing interest exists.

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