

Safety and efficacy of thalidomide in patients with myelofibrosis with myeloid metaplasia

GIOVANNI BAROSI,¹ ALBERTO GROSSI,² BENEDETTO COMOTTI,³ PELLEGRINO MUSTO,⁴ GABRIELLA GAMBA⁵ AND MONIA MARCHETTI⁵ ¹Laboratory of Medical Informatics, IRCCS Policlinico S. Matteo, Pavià, ²Division of Haematology, Policlinico Careggi, Florence, ³Haematology and Oncology Unit, Policlinico S. Pietro, Ponte San Pietro, Bergamo, ⁴IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, Foggia, and ⁵Department of Internal Medicine and Clinical Oncology, IRCCS Policlinico S. Matteo, Pavia, Italy

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Summary. We administered the anti-angiogenic drug thalidomide to 21 patients (12 men) with myelofibrosis with myeloid metaplasia (MMM), who were not responsive to standard treatment. Patients received thalidomide at an escalating dose from 100 to 400 mg/d. Administration of the drug was discontinued before the planned 6 months of treatment in 19 patients (90.5%), mainly because of somnolence and/or fatigue, neurological symptoms or neutropenia. Of the 13 evaluable patients (who received more than 30 d of therapy), anaemia improved in three out of seven (43%) who were treated because of anaemia; thrombocytopenia improved in two out of three (66.6%) who were treated because of thrombocytopenia; splenomegaly was reduced in four (30.8%). Undesired increases in white blood cell and platelet

counts were observed in three (23.1%) and five (38.5%) patients respectively. A severity score, indexed on haematological and clinical parameters, improved in two patients (15.4%), but worsened in five (38.5%). In conclusion, standard-dose thalidomide in MMM patients is burdened with a high rate of side-effects, which prevent prolonged treatment. Because the drug is effective in improving anaemia and thrombocytopenia and in reducing splenomegaly, low-dose therapy warrants evaluation. The unexpected observation of leucocytosis and thrombocytosis suggests biological studies and better criteria for selection of patients for treatment.

Keywords: myelofibrosis with myeloid metaplasia, thalidomide, CD34⁺ cells, somnolence, low-dose thalidomide.

Myelofibrosis with myeloid metaplasia (MMM) is a chronic myeloproliferative disorder characterized by native bone marrow fibrosis and extramedullary haematopoiesis (Barosi, 1999). At present, ablation of the abnormal haemopoietic clone with high-dose chemotherapy followed by allogeneic stem cell transplantation provides the only chance of achieving a cure in MMM (Guardiola *et al.*, 1999). Traditional treatments with androgens to sustain erythropoiesis, and cytostatics to slow down the progression of splenomegaly and splenectomy, in selected cases, provide poor control of disease progression. Therefore, the disease is burdened with high morbidity and mortality, and alternative effective approaches are warranted.

In recent years, there has been a renewed interest in thalidomide, a drug with anti-angiogenic and immunological effects (D'Amato *et al.*, 1994; Hales, 1999). The potential therapeutic applications span a wide spectrum of diseases,

including infectious, autoimmune and dermatological diseases (Anderson, 2000). Moreover, an anti-tumour effect has been documented in advanced tumours (Fine *et al.*, 2000) and refractory multiple myeloma (Singhal *et al.*, 1999; Yakoub-Agha *et al.*, 2000).

As for MMM, a prognostically detrimental increase in bone marrow microvessel density has been demonstrated (Lundberg *et al.*, 2000; Mesa *et al.*, 2000) and a pilot study with thalidomide has been reported (Thomas *et al.*, 1999). In that preliminary communication, the drug decreased the transfusion need, improved cytopenias and decreased the need for cytoreductive agents in some of the patients. However, toxicity (mainly fatigue, constipation and rash) occurred in the majority of the treated cases.

We report the results in terms of feasibility and objective responses of thalidomide in patients with MMM who had proved refractory to standard therapy.

PATIENTS AND METHODS

Patients. Between January 1999 and November 2000, 21

Correspondence: Dott. Giovanni Barosi, Laboratorio di Informatica Medica, IRCCS Policlinico S. Matteo, 27100 Pavia, Italy. E-mail: barosig@smatteo.pv.it

patients from four Italian centres were treated with oral thalidomide under a compassionate-use protocol. There were 12 men with a median age of 66.5 years (range 41–81 years). An individual administrative authorization was obtained for each patient before starting thalidomide treatment, and all patients gave a written informed consent.

Patients had received at least 6 months of conventional therapy (hydroxyurea for splenomegaly, androgens, danazol or corticosteroids for anaemia) and had documentation of non-response. They had a stable disease during the previous 3 months.

Each patient had a definite diagnosis of MMM (17 primary and 4 post-polycythaemia vera) according to the Italian Consensus Conference Criteria for the Diagnosis of MMM (Barosi *et al.*, 1999). Three patients had a disease classifiable as 'high risk' and 14 as 'intermediate risk' according to the classification of Dupriez *et al.* (1996), based on haemoglobin (Hb) level and white blood cell (WBC) count. High-risk patients presented with Hb < 10 g/dl (or transfusion dependent) and WBC < $4 \times 10^9/l$ or $> 30 \times 10^9/l$. Intermediate-risk patients presented with Hb < 10 g/dl or WBC < $4 \times 10^9/l$ or $> 30 \times 10^9/l$. Four patients had a low-risk disease, i.e. they presented with

Hb > 10 g/dl and WBC between $4 \times 10^9/l$ and $30 \times 10^9/l$. They were treated because they had either splenomegaly extending more than 10 cm from the costal margin or a platelet count < $150 \times 10^9/l$.

Median time from the diagnosis was 60 months (range 9–216 months). Eight patients were receiving a stable dose of hydroxyurea (500 or 1000 mg/d) for splenomegaly, one was receiving 600 mg/d of Danazol for anaemia and four other patients were on regular blood transfusion regimens. The demographic and baseline characteristics are summarized in Table I.

Treatment modalities. Thalidomide was supplied in 100 mg capsules (Grünenthal GmbH, Stolberg, Germany) and administered at bedtime. Patients were planned to be treated for 6 months in a dose-escalating schedule of 100 mg/d \times 1 month, 200 mg/d for a further month, 400 mg/d for a further month and then at the maximum tolerated dose. If at the end of study period a response was achieved, patients were to be allowed to continue the treatment. Thalidomide was administered in addition to the patients' concurrent therapies: patients being treated with stable doses of androgens, corticosteroids or cytostatics at the beginning of the trial were allowed to continue these

Table I. Demographic and baseline characteristics of 21 patients with MMM at the time of starting with thalidomide therapy.

| Characteristics | Median (range) | Value | No patients (%) |
|--|----------------|--------------------|-----------------|
| Age (years) | 66.5 (41–81) | < 50 | 3 (14.3) |
| Sex | | Male | 12 (57.1) |
| Haemoglobin g/dl | 9.3 (5.6–13.8) | < 10 | 12 (57.1) |
| | | ≥ 10 , < 12 | 5 (23.8) |
| | | ≥ 12 | 4 (19.1) |
| White blood cell count, $\times 10^9/l$ | 10.0 (1.14–87) | < 4 | 5 (23.8) |
| | | ≥ 4 , < 30 | 14 (66.6) |
| | | > 30 | 2 (9.6) |
| Circulating immature myeloid cells, % | 8.0 (0–47) | = 0 | 3 (14.3) |
| Circulating blasts, % | 0.5 (0–3) | = 0 | 9 (42.8) |
| Circulating erythroblasts, % | 2.0 (0–86) | = 0 | 7 (33.3) |
| Platelet count, $\times 10^9/l$ | 243 (5.0–857) | < 150 | 7 (33.3) |
| | | ≥ 150 , < 500 | 11 (52.4) |
| | | > 500 | 3 (14.3) |
| Spleen size, cm below left costal margin | 13.5 (0–22) | = 0 | 1 (4.8) |
| | | > 0, ≤ 10 | 8 (38.1) |
| | | > 10 | 12 (57.1) |
| Liver size, cm below right costal margin | 4.0 (2–11) | = 0 | 0 (0) |
| | | > 0, ≤ 10 | 16 (76.2) |
| | | > 10 | 5 (23.8) |
| Time from diagnosis to treatment, months | 60 (9–216) | | |
| Dupriez score* | 1 (0–2) | 0 | 4 (19.1) |
| | | 1 | 14 (66.6) |
| | | 2 | 3 (14.3) |
| 'Severity' score** | 4 (1–6) | < 2 | 1 (4.8) |
| | | ≥ 2 , < 4 | 7 (33.3) |
| | | ≥ 4 | 13 (61.9) |

*A Dupriez score (Dupriez *et al.*, 1996) of 0 (low risk) was assigned for Hb > 10 g/dl and WBC between $4 \times 10^9/l$ and $30 \times 10^9/l$; a score of 1 (intermediate risk) for either Hb < 10 g/dl or WBC > $30 \times 10^9/l$ or < $4 \times 10^9/l$; and a score of 2 (high risk) if both the Hb and WBC were in the aberrant ranges.

**The 'severity' score is the sum of severity points derived from the values of Hb, WBC, platelet count and spleen volume (see text).

medications at the same dose during the first month. Patients entering the second month of therapy could taper associated drugs if there was a response. Patients requiring additional intervention or increased doses of concurrent therapy were considered to have failed treatment.

Patients could voluntarily withdraw from the study at any time. Medication adherence was determined by pill count at each visit.

Examinations. Baseline assessment included physical examination and medical history, complete blood count, peripheral blood smear examination and serum lactic dehydrogenase (LDH) level. WBC was corrected for the number of circulating erythroblasts. Blasts were defined as undifferentiated cells with an immature nucleolated nucleus and basophilic cytoplasm with or without azurophilic granules. Patients were also studied for spleen and liver measurement. The size of the organs was assessed using ultrasonography by measuring the length from the splenic tip to the costal margin in centimetres. Blood examinations were repeated every month or at the end of the study. Spleen and liver measurement was repeated at the end of the study or at the time of drug discontinuation.

To analyse the change in myeloproliferation, CD34⁺ cell number in peripheral blood from two patients was assayed at regular intervals over the whole period of thalidomide treatment. Cells were counted and their phenotype determined using flow cytometry analysis. Cells were incubated with CD45 and CD34 antibodies, and each fluorescence analysis included a double negative isotype control (Becton Dickinson Immunocytometry Systems, San Jose, CA, USA). The analysis was completed using the cell gating guidelines recommended by the International Society of Hematotherapy and Graft Engineering (ISHAGE) (Keeney *et al*, 1998).

Response analysis. Response analysis was performed at the reference date of 1 December 2000. Patients who had received thalidomide for less than 30 d were excluded from the analysis. Response was evaluated after 1, 3 and 6 months of therapy. Because there was no accepted definition of disease progression, we evaluated a 'severity' score by indexing leucocytosis, thrombocytosis and splenomegaly (myeloproliferation index), and anaemia, leucopenia and thrombocytopenia (myelodepletion index). Three grades for splenomegaly, or hepatomegaly in splenectomized patients (0 = non-palpable, 1 = 10 cm or less below the costal margin, 2 = more than 10 cm below the costal margin); two grades for leucocytosis (0 = WBC < 15 × 10⁹/l; 1 = WBC ≥ 15 × 10⁹/l); and two grades for thrombocytosis (0 = platelet count < 500 × 10⁹/l, 1 = ≥ 500 × 10⁹/l), made the myeloproliferation index to range from 0 to 4. Three grades for anaemia (0 = Hb > 12 g/dl, 1 = from 10 to 12 g/dl, 2 = < 10 g/dl or under transfusion); two grades for leucopenia (0 = WBC > 4 × 10⁹/l, 1 = WBC ≤ 4 × 10⁹/l); and two grades for thrombocytopenia (0 = platelet count between > 150 × 10⁹/l, 1 = platelet count equal or lower than 150 × 10⁹/l) made the myelodepletion index range from 0 to 4. The overall 'severity' score ranged from 0 to 6.

A response was defined as a decrease in at least 1 point in the severity score; patients with no reduction or increase in

the score were considered to have had no response to thalidomide.

RESULTS

Tolerance of treatment

At the reference date, the median follow-up from the start of thalidomide treatment was 31 d (range, 2–267 d); two patients were on treatment at d 110 and d 267. Eight patients doubled the initial dose at the end of the first month of treatment and one patient took the 400 mg/d dose at the end of the second month. Adverse events were reported by 19 of 21 (90.5%) treated patients. Table II shows all adverse events reported throughout the study. Somnolence and constipation were the most common events. Administration of the drug was discontinued before 1 month of treatment in eight patients (38.1%) and from 1 to 3 months in another eight patients (76.2% cumulative). The drug was discontinued before the planned 6 months of treatment in 19 out of 21 patients (90.5%) (Fig. 1). Eleven patients discontinued treatment because of somnolence, asthenia or confusion, four because of depression, two because of neurological symptoms and two because of neutropenia. All patients refused to re-institute the drug at lower doses.

Response to treatment

Of the 13 evaluable patients (who received more than 30 d of therapy), anaemia improved (Hb increase of more than 1 g/dl or transfusion need decreased) in three (23.1%). However, by considering only patients who were treated because of anaemia (Hb < 10 g/dl), three out of seven responded (43%), and in one case the response was of major clinical importance as the need for two red cell units per week was abolished. Of the three patients who were treated because of thrombocytopenia (platelet count < 150 × 10⁹/l), two (66.6%) responded (increase in platelet count > 150 × 10⁹/l), with an increased platelet count of 347 × 10⁹/l and 69 × 10⁹/l respectively. Splenomegaly decreased (> 1 cm) in four patients (30.8%), with a reduction ranging from 1.5 to 4 cm. In four out of the five patients (80%) with a WBC > 15 × 10⁹/l, the count decreased from a median value of 33.7 × 10⁹/l (range 15.4–88.7 × 10⁹/l) to 12.2 × 10⁹/l (range 7.8–20.3 × 10⁹/l). In all four of

Table II. Observed side-effects of thalidomide.

| | Number of patients (%) |
|--|------------------------|
| Somnolence and/or fatigue and/or confusion | 11 (52.4) |
| Constipation | 10 (47.6) |
| Dizziness | 6 (28.6) |
| Mood changes or depression | 4 (19.0) |
| Cramp or tremors | 2 (9.5) |
| Nausea and vomiting | 1 (4.76) |
| Peripheral neuropathy | 1 (4.76) |
| Neutrophil count < 1 × 10 ⁹ /l | 2 (9.5) |

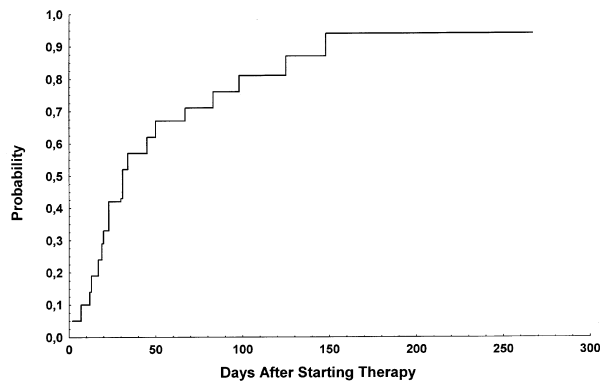


Fig 1. Duration of treatment. The graph shows the probability of discontinuing thalidomide treatment. Nineteen out of 21 patients discontinued the drug before the planned 6 months of therapy.

these patients, a reduction in spleen volume was also evidenced. In summary, 8 out of 13 patients (61.5%) had at least one parameter of response attained. The effective dose was 100 mg/d in five and 200 mg in three patients.

Untoward haematological effects

An undesired increase in WBC was observed in 3 out of 13 evaluable cases [from a median of $10.6 \times 10^9/l$ (range $8.4\text{--}14.7 \times 10^9/l$) to $23.9 \times 10^9/l$ (range $13.1\text{--}26.8 \times 10^9/l$)]. An undesired increase in platelet count was observed in five patients [from a median of $264 \times 10^9/l$ (range $113\text{--}366 \times 10^9/l$) to $462 \times 10^9/l$ (range $420\text{--}610 \times 10^9/l$)]. The platelet count returned to baseline after cessation of therapy in four patients who stopped treatment. Only one patient had both WBC and platelet count increased, and in all patients the counts started increasing after d 30 of therapy. Four of these patients had a concomitant increase in LDH [from a median of 967 mU/ml (range 297 mU/ml to 2109 mU/ml) to 2497 U/l (range 2120 U/l to 3453 U/l)]. In two of these patients, the consecutive CD34⁺ cell count in peripheral blood was assayed during therapy. An increase from $127 \times 10^6/l$ and $247 \times 10^6/l$ to a value of $448 \times 10^6/l$ and $411 \times 10^6/l$, respectively, was evidenced with the increase starting at the first month of therapy.

Of the seven patients with an increased cell count, two were on stable doses of hydroxyurea: in one patient, the drug was augmented at the ninth week of treatment for a concomitant increase in spleen volume.

Global assessment of response

By measuring the severity score, two of the evaluable patients (15.4%) responded (the score reduced from 5 to 3 and from 5 to 4). The improvement of the score in the first patient was as a result of a decrease in the myeloproliferative index and in the second to a decrease in both the myeloproliferative and myelodepletive index. Five of the 13 evaluable patients (38.5%) had a worsening score (1 point in four and 2 points in one patient). In three of these patients, this was caused by

worsening of the myeloproliferative index and, in two patients, to worsening of the myelodepletive index.

DISCUSSION

We used thalidomide in MMM patients with the main aim of taking advantage of its anti-angiogenic effect, thus improving the microenvironment and haematopoietic cell maturation in the bone marrow and extramedullary sites. From the experience with thalidomide in other inflammatory and malignant diseases, we used thalidomide at the starting dose of 100 mg. At this dose, 38.1% of the patients discontinued the drug before 30 d of treatment and 76.2% before 3 months. Overall, the drug discontinuation rate was 90.5% before the end of the 6 months of planned therapy. This is quite similar to the discontinuation rate (92%) reported recently in patients treated with thalidomide for chronic graft-versus-host disease (Koc *et al*, 2000), but lower than reported in most other studies (Singhal *et al*, 1999; Yakoub-Agha *et al*, 2000). However, we observed somnolence and fatigue in 52.4%, constipation in 47% and neurological side-effects in 4% of the patients, which are in the range of values reported in the literature. Owing to the open design of the study and the nature of a compassionate-use protocol, the patients were aware of taking a drug possibly charged with side-effects and, particularly, with neurological toxicity. As a matter of fact, with the exception of two cases in which a severe neutropenia induced the physician in charge to stop the drug, patients themselves requested to stop treatment because of side-effects. It is possible that patients enrolled in previously published studies had considerably more encouragement and support than we gave to sustain compliance with a regimen of thalidomide at even higher doses.

In this study, the response to treatment was evaluable in only 13 (62%) of the patients. In eight of them (61.5%), some response was evidenced as improvement in anaemia, correction of thrombocytopenia, reduction in leucocytosis and/or reduction in spleen volume. However, when these effects were measured using a 'severity' score that accounted for major changes in haematological and clinical parameters, only two patients (15.4%) had a score reduction and were classified as responders.

An unexpected and undesired increase in WBC and/or platelet count, associated with increased serum LDH levels, occurred in seven patients. Such changes caused the 'severity' score to increase by 1–2 points (out of 6) in five of these patients. This result confirms an observation reported recently by Tefferi & Elliott (2000) of drug-related steep increases in platelet and leucocyte counts in three patients with MMM. In our study, the increase in peripheral cell count was moderate and not associated with disease complications. In only one patient, who extended treatment because of a beneficial effect on anaemia, were changes associated with an increase in spleen volume. In contrast, Tefferi & Elliott (2000) documented a rise in platelet count up to more than $1000 \times 10^9/l$ and the development of pericardial effusion secondary to extramedullary haematopoiesis in one

patient. The mechanism of this detrimental activity of thalidomide remains to be determined. However, in two of our patients we were able to document a steep rise in the number of circulating CD34⁺ cells that paralleled the increase in the circulating mature cells. Circulating CD34⁺ cells are constitutively elevated in MMM and their number reflects the myeloproliferative characteristic of the disease (Barosi et al, 2000). This leads to the conclusion that thalidomide may act by inducing myeloproliferation in MMM. This is also surprising considering that in other patients we documented a reduction in the number of WBC, and changes in both the myeloproliferative and myelodepletive indexes. The immunosuppressive and anti-inflammatory action of thalidomide, which inhibits the production of tumour necrosis factor α (TNF- α) (Klaushner et al, 1996), and a possible direct antiproliferative action of the drug on tumour cells, as documented in myeloma cells (Hideshima et al, 2000), could explain these different effects.

In conclusion, the results of this study show that standard-dose thalidomide treatment in MMM is burdened with a high number of side-effects that limit its long-term use. However, the drug acts by both improving and worsening the clinical and haematological picture of the disease. The possible myeloproliferative effect of thalidomide requires biological studies in order to better understand the mechanism of action of the substance and for better targeting of the therapy. Prospective trials are required to delineate the role of this drug in MMM, and also to document whether low-dose treatment may be effective and well tolerated. The reported experience with low-dose treatment in neoplastic and non-neoplastic diseases suggests that a dose of 50 mg/d as a starting dose may be both effective and well tolerated (Larkin, 1999; Vasiliauskas et al, 1999; Kyriakis et al, 2000).

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