OBJECTIVE: To present the results of a long-term analysis of 2 sequential phase 2 trials of thalidomide (alone or in combination) for palliation of myelofibrosis with myeloid metaplasia (MMM).

PATIENTS AND METHODS: We analyzed (March 1999 to August 2003) initial and long-term outcomes from 36 patients with symptomatic MMM who had enrolled in either our thalidomide single-agent trial (n=15) or our trial of low-dose thalidomide (50 mg/d) combined with prednisone (n=21).

RESULTS: Among the 36 study patients, 20 (56%) showed some improvement in their clinical course. Response rates for specific end points included improvements in anemia (15 of 36 [42%]), thrombocytopenia (10 of 13 [77%]), or splenomegaly (5 of 30 [17%]). The combination of low-dose thalidomide and prednisone, as opposed to single-agent thalidomide, was better tolerated and more efficacious. After a median follow-up of 25 months (range, 20-56 months), 10 of 36 patients (28%) showed an ongoing response, including 8 patients in whom protocol treatment has been discontinued for a median of 21 months (range, 16-31 months). Durable treatment responses were documented for only anemia and thrombocytopenia. Treatment response was not affected by the baseline status of bone marrow fibrosis, angiogenesis, osteosclerosis, cytogenetics, or circulating myeloid progenitor (CD34) cell count. Unusual drug effects, all reversible, included leukocytosis (8 patients) and/or thrombocytosis (6 patients).

CONCLUSIONS: Thalidomide (alone or combined with prednisone) is an effective first-line treatment of symptomatic anemia or thrombocytopenia in MMM. Thalidomide-based therapy has the potential to produce durable responses in MMM-associated cytopenias, even after discontinuation of the drug.


AMM = agnogenic myeloid metaplasia; IL = interleukin; MDS = myelodysplastic syndrome; MMM = myelofibrosis with myeloid metaplasia; TNF = tumor necrosis factor

Myelofibrosis with myeloid metaplasia (MMM) is a clonal stem cell disease that currently is classified with polycythemia vera and essential thrombocythemia as a chronic myeloproliferative disorder.1 Clinically, the disease is characterized by progressive anemia, marked splenomegaly, profound constitutional symptoms, cachexia, and risk of transformation into acute leukemia. These clinical features are accompanied by peripheral blood leukoerythroblastosis, intense bone marrow stromal reaction (collagen fibrosis, osteosclerosis, neoangiogenesis), and extramedullary hematopoiesis. Median overall survival of approximately 5 years2 has not been affected by conventional drug therapy. Furthermore, conventional therapy often is associated with suboptimal alleviation of anemia, splenomegaly, and thrombocytopenia. Splenectomy is a viable option for symptomatic splenomegaly that is unresponsive to cytoreductive agents3 and is preferred over treatment with splenic irradiation.4 The latter treatment is effectively applied for control of nonhepatosplenic extramedullary hematopoiesis.5 Although allogeneic hematopoietic stem cell transplantation is a potentially curative treatment option for MMM, its widespread use is limited by the substantial risk of transplant-related mortality and morbidity, especially in view of the advanced age of most of these patients.6

Thalidomide, a sedative-hypnotic drug with antiangiogenic7 and cytokine inhibitory8 properties, has shown therapeutic activity in a spectrum of hematologic malignancies including multiple myeloma9,10 and myelodysplastic syndrome (MDS).11 The presence of florid bone marrow angiogenesis in MMM12 encouraged the development of several small pilot studies that evaluated the therapeutic value of thalidomide for MMM, used either alone13-19 or in combination with other drugs.20,21 Although these studies have uniformly suggested drug activity to alleviate anemia, thrombocytopenia, and splenomegaly, few data exist on the long-term outcomes of thalidomide-responsive patients with MMM.

PATIENTS AND METHODS

Our article presents the results of a combined long-term analysis (March 1999 to August 2003) of 2 independent thalidomide-based treatment trials for MMM; preliminary short-term results from these 2 trials have been published previously.17,20 Both trials and the current study have been reviewed and approved by the Mayo Foundation Institutional Review Board. Diagnosis was according to conventional criteria.1 Patients with all 3 subtypes of MMM, including agnogenic myeloid metaplasia (AMM), post-polycythemic myeloid metaplasia, and post–thrombocythemic myeloid metaplasia, were eligible for the study. All study patients underwent pretreatment physical exami-
nation, baseline laboratory assessment of serum chemistries and circulating hematologic peripheral blood cell counts and serum chemistries, and bone marrow examination using cytogenetic and fluorescence in situ hybridization (FISH) studies to exclude occult cases of t(9;22) (ie, BCR/ABL positive) chronic myeloid leukemia and MDS, both of which may present occasionally with intramedullary fibrosis.

**Drug Administration**

Thalidomide was administered by rigorously adhering to the STEPS (System for Thalidomide Education and Prescribing Safety; Celgene Corp, Warren, NJ) program (www.celgene.com/steps/index.htm) for thalidomide safety. For patients who participated in the first of 2 treatment trials (n=15), oral thalidomide was initiated at a dosage of 200 mg/d with the intention to escalate the dosage to 1000 mg/d if tolerated. Drug toxicity limited the maximal dosage administered in that trial to 400 mg/d. Patients who participated in the second treatment trial (n=21) received a combination of low-dose thalidomide (50 mg/d) and a tapering dosage of prednisone (0.5 mg/kg for 1 month; 0.25 mg/kg for the second month; 0.125 mg/kg for the third month). Patients who responded after 3 months of combination therapy were treated for an additional 3 months with single-agent low-dose thalidomide (50 mg/d).

**Evaluation of Response**

A response in anemia, defined as either an increase in hemoglobin concentration of 2 g/dL or higher or a 50% or greater reduction in red blood cell transfusion requirement, was assessed only in those patients with a baseline hemoglobin value lower than 10 g/dL. Similarly, a response in thrombocytopenia was assessed only in those patients with a baseline platelet count lower than 100 × 10^9/L and was defined as a 50% or greater increase in platelet count with a minimum count of 30 × 10^9/L. A response in splenomegaly was defined as a 50% or greater reduction in palpable splenomegaly as measured by the maximum right-angle distance from the left costal margin. Improvements in anemia, thrombocytopenia, or splenomegaly had to be sustained for at least 4 weeks to be considered a positive response.

Baseline assessments of bone marrow histology (reticulin fibrosis, osteosclerosis, angiogenesis) and marrow karyotype were performed in all patients. Conventional methods were used to grade bone marrow fibrosis and osteosclerosis. Specialized tests included assessment of pretreatment and posttreatment bone marrow microvessel density (using CD34 immunohistochemistry on marrow vessels and semiquantitative light microscopic estimation), urinary markers of angiogenesis (basic fibroblast growth factor, vascular endothelial growth factor, thrombospondin 1), peripheral blood myeloid progenitor (CD34+ cell count, and nuclear scan (technetium Tc 99m sulfur colloid) assessment of extramedullary hematopoiesis. Toxicity was assessed by the National Cancer Institute Common Toxicity Criteria (version 2.0).

**Accrual of Follow-up Data and Statistics**

Complete and current follow-up information was obtained for all patients from both clinical trials. Specifically, information on survival, treatment institution in addition to or other than thalidomide, red blood cell transfusion history, and most recent complete blood cell count were obtained in each instance. Median survival after initiation of thalidomide therapy was defined as the interval from the first date of protocol treatment to either death or last contact. The Kaplan-Meier method was used to estimate survival distributions. A log-rank test was used to assess whether survival differed between responders and nonresponders to thalidomide therapy. For response rates, 95% confidence intervals were calculated.

**Results**

The entire study population consisted of 36 patients (24 men) (median age, 65 years; range, 41-79 years) with MMM (28 patients with AMM, 3 with post–polycythemic myeloid metaplasia, 5 with post–thrombocytemic myeloid metaplasia). The study included 15 patients from the chronologically first treatment protocol who used single-agent thalidomide and another 21 patients from the subsequent treatment protocol who used the combination of low-dose thalidomide and prednisone. The median time from diagnosis to protocol treatment was 36 months (range, 2-180 months). At the time of protocol treatment, 10 patients (28%) were high risk, 18 (50%) were intermediate risk, and 8 (22%) were low risk according to the Lille MMM prognostic scoring system (stratifies prognostic risk in MMM patients [into low, intermediate, and high] by the presence of anemia [hemoglobin, <10 g/dL] and/or a markedly abnormal leukocyte count [<4 × 10^9/L or >30 × 10^9/L]). Treatment was indicated in all patients because of clinically important anemia (hemoglobin, <10 g/dL; 27 patients) and/or symptomatic organomegaly (22 patients). Fifteen patients (42%) were red blood cell transfusion–dependent, and 22 patients (61%) had a platelet count lower than 100 × 10^9/L. Circulating blasts were present in 14 patients (39%). No patients had undergone splenectomy previously, and the spleen was palpable at a median of 12 cm (range, 0-26 cm) below the left costal margin.

**Initial Responses**

Of the 36 study patients, 20 (56%) had a response in anemia, thrombocytopenia, and/or splenomegaly (Table 1).
Among the 27 patients with symptomatic anemia (hemoglobin, <10 g/dL), 16 (59%) responded, including 8 who were red blood cell transfusion–dependent. Of 15 red blood cell transfusion–dependent patients, 5 (33%) became transfusion independent. Similarly, all 13 patients with a platelet count lower than 100 × 10^9/L (<50 × 10^9/L in 9 patients) had an increase in their platelet count, which was more than 50% of the baseline value in 10 patients (77%). The response in splenomegaly was not as impressive. Among 32 patients with palpable splenomegaly at treatment registration, only 5 (16%) experienced more than a 40% decrease in the maximum distance of palpable spleen edge from the left costal margin (Table 2). Among all study patients, the attainment of treatment response was not significantly correlated with the pretreatment status of bone marrow fibrosis, osteosclerosis, cytogenetics, or angiogenesis. Furthermore, these bone marrow histological parameters were not significantly affected by treatment in clinically responding patients (Table 3). A systematic measurement of pretreatment and posttreatment blood CD34 count and urinary levels of angiogenic markers, a blood lymphocyte subset analysis, and a radiographic (technetium Tc 99m sulfur colloid) estimation of extramedullary hematopoiesis were performed during the second treatment trial that used combination thalidomide and prednisone therapy. These parameters neither influenced nor accompanied treatment response (data not shown).

Thalidomide use was discontinued before completion of scheduled therapy in 10 patients (28%) because of drug toxicities (Table 1). The reasons for subsequent drug discontinuation after trial completion among responders are shown in Table 2. In the first treatment trial, which used single-agent thalidomide therapy, 9 (60%) of the 15 patients were unable to tolerate drug dosages of 200 mg/d or higher. In some of these patients, reduction of the thalidomide dosage to 50 mg/d was associated with better drug tolerance and continued efficacy. In contrast, all but 1 of the 21 patients in the second treatment trial (low-dose thalidomide plus prednisone) were able to complete the first 3 months of treatment. The addition of corticosteroids to thalidomide therapy in the combination trial resulted in only minor and reversible toxicities of hyperglycemia and insomnia. The median duration of treatment among nonresponders was 2.7 months (range, 0.5–8.7 months), whereas all treatment responses occurred during the first 3 months after drug initiation. Unusual drug effects, all reversible, included marked leukocytosis (8 patients), thrombocytosis (6 patients), substantial increase in blood CD34 count (5 patients), and deep venous thrombosis (1 patient).
THALIDOMIDE AND MYELOFIBROSIS WITH MYELOID METAPLASIA

### TABLE 2. Short-term and Long-term Effects of Thalidomide Therapy in 20 Responding Patients With MMM*

<table>
<thead>
<tr>
<th>Patient No./ age† (y)/ sex</th>
<th>MDM type</th>
<th>Maint dose</th>
<th>Thalidomide effects, short-term</th>
<th>Responses</th>
<th>Thalidomide effects, long-term</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hb Start</td>
<td>Max</td>
<td>PLT Start</td>
</tr>
<tr>
<td>1/74/M AMM</td>
<td>400</td>
<td>3 U</td>
<td>3 U</td>
<td>40</td>
<td>93</td>
</tr>
<tr>
<td>2/88/M AMM</td>
<td>200</td>
<td>10.2</td>
<td>10</td>
<td>83</td>
<td>179</td>
</tr>
<tr>
<td>3/56/F AMM</td>
<td>150</td>
<td>4 U</td>
<td>4 U</td>
<td>38</td>
<td>62</td>
</tr>
<tr>
<td>4/67/F AMM</td>
<td>50</td>
<td>4 U</td>
<td>9.2</td>
<td>144</td>
<td>142</td>
</tr>
<tr>
<td>5/41/F AMM</td>
<td>50</td>
<td>7.9</td>
<td>11.1</td>
<td>105</td>
<td>147</td>
</tr>
<tr>
<td>14/65/F AMM</td>
<td>200</td>
<td>9.5</td>
<td>9.9</td>
<td>41</td>
<td>93</td>
</tr>
<tr>
<td>17/55/M PPMM</td>
<td>50‡</td>
<td>12.9</td>
<td>15.2</td>
<td>303</td>
<td>477</td>
</tr>
<tr>
<td>18/78/M AMM</td>
<td>50‡</td>
<td>8.4</td>
<td>11.3</td>
<td>154</td>
<td>389</td>
</tr>
<tr>
<td>19/55/M AMM</td>
<td>50‡</td>
<td>4 U</td>
<td>10.8</td>
<td>127</td>
<td>214</td>
</tr>
<tr>
<td>20/73/F AMM</td>
<td>50‡</td>
<td>7.9</td>
<td>13</td>
<td>95</td>
<td>228</td>
</tr>
<tr>
<td>22/74/M AMM</td>
<td>50‡</td>
<td>2 U</td>
<td>9.8</td>
<td>448</td>
<td>890</td>
</tr>
<tr>
<td>25/73/F AMM</td>
<td>50‡</td>
<td>9.8</td>
<td>11.5</td>
<td>38</td>
<td>79</td>
</tr>
<tr>
<td>26/66/F PPMM</td>
<td>50‡</td>
<td>10.9</td>
<td>13</td>
<td>186</td>
<td>391</td>
</tr>
<tr>
<td>27/69/M AMM</td>
<td>50‡</td>
<td>2 U</td>
<td>10.4</td>
<td>32</td>
<td>96</td>
</tr>
<tr>
<td>28/74/M AMM</td>
<td>50‡</td>
<td>3 U 1 U</td>
<td>57 101</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td>29/46/M AMM</td>
<td>50‡</td>
<td>9.0</td>
<td>10.6</td>
<td>275</td>
<td>540</td>
</tr>
<tr>
<td>30/49/M MFM</td>
<td>50‡</td>
<td>8.3</td>
<td>11</td>
<td>192</td>
<td>390</td>
</tr>
<tr>
<td>31/66/F AMM</td>
<td>50‡</td>
<td>4 U 11.2</td>
<td>74 192</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>32/62/M AMM</td>
<td>50‡</td>
<td>3 U 1 U</td>
<td>162 316</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>36/73/F PTMM</td>
<td>50‡</td>
<td>3 U 1 U</td>
<td>23 44</td>
<td>6</td>
<td>5</td>
</tr>
</tbody>
</table>

*Bold entries = patients with unmaintained responses after thalidomide. AMM = agnogenic myeloid metaplasia; Choice = patient’s choice (not from toxicity or progression); F/U = follow-up (months); 
Hb = hemoglobin (g/dL) (units/month listed if patient was red blood cell transfusion–dependent); Maint = maintenance; Max = maximum; Min = minimum; MMM = myelofibrosis with myeloid metaplasia; PLT = platelet count (×10⁹/L); PPMM = post–polycythemic myeloid metaplasia; Prog = progression; PTMM = post–thrombocythemic myeloid metaplasia; Rx = treatment (months); Spleen = spleen size (cm below the left costal margin by palpation); WBC = white blood cell count (×10⁹/L).

†Age at registration.
‡Also undergoing 3-month prednisone taper.

LONG-TERM OUTCOMES

The median follow-up from the initiation of thalidomide-based therapy is now 25 months (range, 20-56 months). Twenty-two patients (61%) are still living, whereas 14 have died of disease-related complications. The median survival of patients who responded to treatment has not yet been reached (6 deaths), whereas it was 2.4 years in the nonresponding patients (8 deaths) (difference not significant). Among the 20 patients who responded to treatment, 7 continued receiving thalidomide after completing the planned 6 months of protocol therapy. The median duration of therapy in these 7 patients was 13.1 months (range, 7.6-28.5 months). Two patients are currently receiving low-dose (50 mg/d) thalidomide (for 23.4 and 28.5 months) with evidence of continued response and no evidence of long-term toxicity (Table 2). Reasons for discontinuing thalidomide (at trial completion or after) are outlined in Table 2. Patients who chose to discontinue thalidomide while responding (14 of 20, 70%) did so for various reasons, including expense (initial reimbursement issues subsequently resolved), mild toxicities, or a desire of the patient or physician to assess stability after discontinuing treatment.

Analysis of the entire study population discloses 8 patients (22%) who have remained in continued remission for a median of 21 months (range, 16-31 months) after discontinuation of thalidomide-based protocol therapy. Of note, these patients received no other MMM-directed therapy in the interim, and the reasons for drug discontinuation are listed in Table 2. In addition to these 8 patients, 2 others have remained in remission at 19 and 25 months while receiving maintenance therapy with low-dose thalidomide (50 mg/d). Therefore, the overall long-term response rate for thalidomide-based drug therapy in MMM in the current study was 28% (10 patients). Of note, all but 1 of the long-term treatment responders were diagnosed as having AMM. Durable treatment responses were seen for anemia and thrombocytopenia but not for splenomegaly (Table 2).

DISCUSSION

The short-term experience with thalidomide-based drug therapy for MMM has been reported previously, and studies that involved 10 or more patients have shown a response rate of 20% to 62% in anemia, 25% to 80% in
thrombocytopenia, and 7% to 30% in splenomegaly.14,15,17-19 The variable response rates reflect differences in patient selection and in definitions of response. In this article, we describe both the short-term and long-term treatment experiences in 2 sequential trials that used thalidomide to treat MMM-associated symptomatic anemia or splenomegaly. The results indicate that thalidomide definitely has therapeutic activity in MMM and strongly suggest that the addition of prednisone to low doses of thalidomide (50 mg/d) improves drug tolerance and may improve the efficacy of thalidomide in overcoming ineffective hematopoiesis. Also, long-term analysis of the data reveals that approximately 28% of patients with MMM, many with intermediate-risk or high-risk Lille criteria,24 experience a durable response, in anemia and thrombocytopenia, to thalidomide-based therapy. Patients who responded initially continued to respond, even after discontinuation of the drug. We make no assumption that the natural history of the disease is affected by thalidomide therapy. However, we believe that quality of life is improved in responding patients as a result of decreased transfusion requirement and decreased anemia-related adverse effects.

We underscore that the current study was not designed to compare single-agent thalidomide therapy with combined low-dose thalidomide and prednisone therapy. However, in agreement with preliminary observations from other investigators, our data strongly suggest that low-dose thalidomide, especially in combination with prednisone, might be as effective and yet less toxic for treatment of MMM. Obviously, these encouraging preliminary data need to be validated in a controlled study. The combination of corticosteroids and thalidomide has been touted to be superior to thalidomide alone for treatment of multiple myeloma.25,26 However, in contrast to the experience in multiple myeloma,27 thalidomide treatment benefit in MMM might not be dose dependent, and a lasting effect may persist even after the drug is discontinued. The latter observation is the most intriguing aspect of our research and is not easily explained.

Despite this encouraging treatment experience, the mechanism of action of thalidomide in MMM is an enigma. Remember that MMM is a clonal stem cell disease that is accompanied by a cytokine-mediated bone marrow stromal reaction (collagen fibrosis, osteosclerosis, angiogenesis) and ineffective hematopoiesis.1 Both angiogenesis12 and tumor necrosis factor α (TNF-α) have been implicated in the pathogenesis of MMM, and the latter may be particularly detrimental to effective erythropoiesis in both MMM28 and MDS.29 Therefore, it is tempting to attribute the observed effects of thalidomide to its antiangiogenic and anti–TNF-α properties.7,8 In this regard, the demonstrated activity of thalidomide in MDS30 and the recent evidence of antidisease activity by etanercept, a soluble TNF-α receptor antagonist, in MMM31 support a mechanism of drug action that is linked to TNF-α. However, regarding angiogenesis, our study showed no favorable effect of thalidomide on angiogenesis evaluated by both assessment of bone marrow microvessel density and measurement of urinary concentrations of angiogenic cytokines. Similarly, Grossi et al16 found no correlation between treatment response to thalidomide in MMM and the levels of several angiogenic cytokines (vascular endothelial growth factor and its receptor or transforming growth factor β). Obviously, continued assessment of bone marrow angiogenesis in long-term treatment responders is necessary to validate these preliminary impressions of an angiogenesis-independent mechanism of action.

Alternatively, thalidomide may facilitate effective hematopoiesis (thus accounting for an improvement in anemia and thrombocytopenia) through its immunomodulatory properties. Thalidomide costimulates T-lymphocyte proliferation,31 inducing Th2 cytokine (interleukin [IL] 4 and IL-5) but not Th1 cytokine (interferon γ) production32; IL-4 synergizes with stem cell factor and other cytokines to enhance effective hematopoiesis,33,34 whereas both interferon γ and TNF-α produce the opposite effect, possibly by promoting programmed cell death.35 Therefore, drug-
induced phenotypic shift in T-lymphocyte subsets might conceivably contribute to the observed clinical benefit, especially in light of the observation that MMM may display a quantitatively altered lymphocyte population with an increase in cytotoxic T cells (CD3+/CD56+). Furthermore, similar cytokine-mediated mechanisms also may be responsible for the occasional occurrence of disseminated extramedullary hematopoiesis as well as potentially detrimental drug-induced myeloproliferation seen in thalidomide-treated patients with MMM. Nevertheless, a more systematic study is required before accepting or refuting any of these possible drug mechanisms of action.

Thrombosis has been identified as an important adverse effect of thalidomide-based drug therapy in multiple myeloma, especially when the drug has been combined with either chemotherapy or corticosteroids. Because thrombosis is a well-established disease-associated risk in chronic myeloproliferative diseases, the patients in our study were closely monitored for this complication, and fortunately only 1 case of deep venous thrombosis was documented. Therefore, we currently are not inclined to use prophylactic anticoagulant therapy during treatment of MMM with thalidomide. This and other thalidomide-associated drug adverse effects might be effectively addressed in the future by the development of thalidomide analogues that are more potent and yet less toxic than the parent drug. One of these agents, CC-5013, has shown notable activity in the treatment of both multiple myeloma and MDS. Pilot trials with this agent in MMM are planned to begin soon at our institution and elsewhere.

**CONCLUSIONS**

Thalidomide used alone or in combination with prednisone may be considered an effective first-line treatment of symptomatic anemia or thrombocytopenia in MMM. Thalidomide-based therapy has the potential to produce du-
rable responses in MMM-associated cytopenias, even after thalidomide is discontinued.

We acknowledge the Celgene Corporation (Warren, NJ) for providing thalidomide and financial support for the administration costs of both clinical trials.

REFERENCES