Single agent bevacizumab for myelofibrosis: results of the Myeloproliferative Disorders Research Consortium Trial

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ABSTRACT

The myeloproliferative neoplasm, myelofibrosis, is a morbid and frequently fatal illness encompassing primary myelofibrosis, and end-stage essential thrombocythemia and polycythemia. Bevacizumab (15 mg/kg intravenous (i.v.) every 21 days) was tested in a phase II international trial conducted by the Myeloproliferative Disorders Research Consortium. Thirteen patients were enrolled in the first stage of this 2-stage trial. Among the 11 patients who received therapy, only 3 received more than 4 cycles of therapy; none of the patients achieved an objective response. Furthermore, significant toxicity, not directly related to the vascular or gastrointestinal events typically associated with the anti-VEGF monoclonal antibody preparation in other disease states, was observed. Lack of objective responses coupled with toxicity led to the decision to terminate the study early. If future studies incorporate bevacizumab in combination therapy for myelofibrosis, more modest doses should be considered. *(clinicaltrials.gov Identifier 00667277)*.

Introduction

Myelofibrosis (MF) is a chronic myeloproliferative neoplasm (MPN) that leads to significant anemia and other profound cytopenias, extramedullary hematopoiesis, significant constitutional symptoms, hepato-splenomegaly, and transformation to acute leukemia. MF can either present *de novo* as primary myelofibrosis (PM) or progress from an antecedent MPN (i.e. post-polycythemia vera myelofibrosis (post-PV MF) or post-essential thrombocythemia myelofibrosis (post-ET MF).[1] No medical therapy has yet demonstrated efficacy for altering the natural history of MF. Interest in angiogenesis inhibition as a therapeutic goal in MF is derived from: 1) palliative benefit observed with angiogenesis inhibitors such as thalidomide, lenalidomide, pomalidomide;[2] and 2) the observation that MF is associated with the development of an increased marrow microvessel density[3] due to the release of growth factors such as vascular endothelial growth factor (VEGF) from cells belonging to the malignant clone. The Myeloproliferative Proliferative Disorders Research Consortium (MPD-RC), therefore, conducted a 2-stage multicenter phase II trial of the VEGF inhibitor bevacizumab in patients with MF.

Methods

Patients

Symptomatic, relapsed/refractory and intermediate-/high-risk[4] MF patients (both PM and post ET/PV MF) were eligible. No minimal levels of hematologic parameters were required at study entry since thrombocytopenia was not expected as a toxic event with bevacizumab. However, patients with either recent vascular events or surgery were not eligible because of the known association between bevacizumab and hemorrhagic events.[5] The trial was reviewed and approved at Mount Sinai Institutional Review Board (IRB) as well as individual participating member IRBs.

Therapy

Patients received bevacizumab as a single agent at a dose of 15 mg/kg intravenously on Day 1 of a 21-day cycle for 4 cycles. This standard single agent dosing schedule was chosen based on the safety profile in other indications. Patients were evaluated for response after cycles 4 and 8. Non-responders were to be removed from study after cycle 8; patients who responded could receive as many as 17 cycles. No dose modifications were built into the protocol; a threshold effect of dose was expected to be required for efficacy, and toxicities were best handled by dose delay or withdrawal from the trial.

Statistical analysis

This trial was designed as a 2-stage phase II Simon design to test the null hypothesis that the response rate (complete and major best response by 6 months) was 10% or under *versus* the alternative hypothesis that this response rate was 30% or over at an α level of 0.05 (actual level is 0.044) with 80% power. With 14 patients enrolled in the first stage of this multicenter trial, if 2 or fewer patients were observed to have a complete or major response by 24 weeks, the drug was to be rejected for further study. If there were 3 or more responses in the first 14 patients, the trial was to continue to accrue up to 29 patients. An interim analysis was to be conducted six months after the enrolment of the first 14 eligible patients (calculations from PASS

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2005, NCSS, J Hintze, Kaysville, UT, USA). All patients who received at least one dose of bevacizumab have been included in the intent-to-treat analysis for efficacy and safety.

Results and Discussion

Table 1 provides a summary of patients' characteristics at study entry. Thirteen patients (10 males: 77%) were enrolled in this study between May 2008 and March 2009. Of these, 8 had PMF (62%), 3 post-ET MF, and 2 post-PV MF. Median age was 71 years, typical for the disease. Median hemoglobin concentrations were 9.2 g/dL (range 3.0-10.7); 5 of these 13 patients were erythrocyte-transfusion dependent at trial entry. Six of the 12 patients (50%) had an MF-associated molecular mutation (5 JAK2-V617F, one MPL-515). All patients were either intermediate (Int 1 n=2, Int 2 n=3) or high risk (n=8) by the Dynamic International Prognostic Scoring System for myelofibrosis.[4]

Table 2 summarizes the outcomes of the 13 patients who entered the study. Eleven of these 13 patients were eligible for response assessment. Two patients withdrew consent prior to initiation of therapy. These 11 patients received a total of 40 cycles of bevacizumab. Five of these 11 patients (46%) received 4 or more cycles. Three of these 5 continued with the second phase of therapy (cycles 5-8) for "stable disease"; one of these 3 patients completed the 8th cycle and stopped due to a lack of response. No patient had an objective response according to either EUNMET[6] or IWG-MRT[7] response criteria. Reasons for termination of therapy are shown in Table 3. These included: toxicity (n=5), disease progression (n=1), withdrawal from study (n=4: decision by investigators or patients due to suboptimal tolerance or desire for alternative therapy).

At the interim analysis of the 13 enrolled patients (of whom 11 were evaluable), there were no observed clinical responses and it was concluded that it was unlikely that responses in the next 3 evaluable patents would be observed. The External MPD-RC Data Safety Monitoring Board reviewed these results in November 2010, and agreed that the study should be terminated due to lack of response activity in the setting of an unacceptable toxicity profile at the completion of the first stage.

Seven patients (54%) experienced one or more moderate to severe adverse events that were attributed to bevacizumab therapy (*Online Supplementary Table S1*). Serious adverse events classified as probably related to therapy included abnormalities in liver function tests (n=2), myelosuppression (n=2), pain (n=2), infection (n=2), diarrhea (n=1), heart failure (n=1), and other (n=3). One death occurred due to congestive heart failure shortly after initiation of bevacizumab therapy; the event was judged to be likely related to the administration of the drug although a history of heart disease was present. Despite concerns at trial entry, no hemorrhagic or thrombotic events were observed. In addition, no episodes of gastrointestinal perforation or obstruction were observed (events which have occurred in solid tumor patients on bevacizumab therapy).[5]

Bevacizumab is currently approved for use by the US Food and Drug Administration (FDA) in combination with appropriate chemotherapy or interferon-alpha for metastatic colorectal cancer, non-squamous cell lung cancer, breast cancer and renal cell carcinoma in doses ranging from 5 to 15 mg/kg every two to three weeks. The only current use of single agent bevacizumab is for the treatment of patients with glioblastoma multiforme. The dose chosen for this trial was in the range used for the treatment of solid tumor patients (i.e. 15 mg/kg i.v. every 3 weeks). The explanation as to why bevacizumab was so poorly tolerated in this patient population remains unknown. Of note, the occurrence of hemorrhage or gastrointestinal perforation leading to termination of bevacizumab therapy in solid tumor studies was not observed in this study. The major reason here for bevacizumab cessation was physician and/or patient choice owing to an

Table 1. Baseline characteristic of patients enrolled in the MPD-RC phase II single agent trial of bevacizumab in myelofibrosis (N=13).

Characteristic	Number of patients (n=13)	Percent of patients (100%)
Diagnosis		
PMF	8	62
Post ET MF	3	23
Post PV MF	2	15
Gender		
Male	10	77
Female	3	23
DIPSS MF risk class		
High	8	62
Intermediate 1	2	15
Intermediate 2	3	23
Mutation status Jak2V16F		
Mutated	6	46
Wild type	6	46
Unknown	1	8
	Mean (SD)	Median (range)
Spleen size(cm BLCM)	9.1 (9.33)	5.0 (0–24.0)
HGB (g/dL)	8.8 (2.1)	9.2 (3.0–10.7)
Plts (x 10^9/L)	215 (124)	257 (200–411)
WBC (x 10^9/L)	22.5 (23.5)	16.7 (2.0–77.5)
Age (years)	69.6 (11.0)	72 (49–85)

cm BLCM (cm the spleen edge is palpated below left costal margin in mid clavicular line) MF Type: PMF (primary myelofibrosis), Post ET MF (post essential thrombocythemia myelofibrosis), Post PV MF (post polycythemia vera myelofibrosis). DIPSS: Dynamic International Prognostic Scoring System for MF.[3]

Table 2. Patient outcomes for myelofibrosis patients treated on single agent bevacizumab (n=13).

Reason for therapy discontinuation	Number of patients (n=13)	Percent of patients (100%)
Physician decision	6	46
Patient refusal	5	38
Death	1	8
End of study	1	8
	Mean (SD)	Median (range)
Number of cycles	3.1 (2.6)	2 (0-8)
Time on study (weeks)	11.1 (8.5)	10.6 (0.0-25.3)

increase in constitutional symptoms such as fatigue.[8] Unfortunately, this study antedated the development and validation of the Myelofibrosis Symptom Assessment Form (MF-SAF: an instrument for reporting patient outcomes for PM patients),[9] therefore no serial quantification of symptom change was possible.

The experience from this trial indicates that at the doses employed bevacizumab is not well tolerated in patients with MF. The mechanistic reasons for the poor level of tolerance remain unclear; perhaps future studies with anti-angiogenesis inhibitors in MF could analyze changes in the detrimental cytokine milieu in the disease[10] as a possible explanation. However, we have no data to allow us to conclude whether bevacizumab at an alternate dose and schedule would be better tolerated and would permit a longer duration of therapy. In addition, since the benefits of bevacizumab are more frequently observed when used in combination with other agents, we cannot assume whether a similar strategy will be helpful in MF patients.

In general, although the inhibitors of JAK2 have led to a reduction in splenomegaly, disease-associated symptoms,[11,12] and even survival, medical therapy still offers opportunities for deeper responses for MF patients. Immunomodulatory drugs (IMID) have primarily improved PM-associated cytopenias, without any improvement in marrow histology.[13] Interferon has re-surfaced as a therapy for MPNs and pegylated interferon alpha-2a has led to molecular remissions of the $JAK2^{V617F}$ allele burden[14] and change in marrow architecture in some patients with early forms of PMF.[15] Although the findings of this trial do little to stimulate any enthusiasm on our part for further MF trials with bevacizumab, perhaps a more modest dosing strategy of bevacizumab in combination with a JAK2 inhibitor, IMID, or even interferon will be tolerable and effective. In conclusion, bevacizumab at the standard dose and schedule was poorly tolerated in patients with MF.

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Authorship and Disclosures

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References

1. Vardiman JW, Thiele J, Arber DA, Brunning RD, Borowitz MJ, Porwit A, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. Blood. 2009;114(5):937-51.
2. Thapaliya P, Tefferi A, Pardanani A, Steensma DP, Camoriano J, Wu W, et al. International working group for myelofibrosis research and treatment response assessment and long-term follow-up of 50 myelofibrosis patients treated with thalidomide-prednisone based regimens. Am J Hematol. 2011;86(1):96-8.
3. Mesa RA, Hanson CA, Rajkumar SV, Schroeder G, Tefferi A. Evaluation and clinical correlations of bone marrow angiogenesis in myelofibrosis with myeloid metaplasia. Blood. 2000;96(10):3374-80.
4. Passamonti F, Cervantes F, Vannucchi AM, Morra E, Rumi E, Pereira A, et al. A dynamic prognostic model to predict survival in primary myelofibrosis: a study by the IWG-MRT (International Working Group for Myeloproliferative Neoplasms Research and Treatment). Blood.115(9):1703-8.
5. Bevacizumab package leaflet. Available from: www.medicine.org
6. Barosi G, Bordessoule D, Briere J, Cervantes F, Demory JL, Dupriez B, et al. Response criteria for myelofibrosis with myeloid metaplasia: results of an initiative of the European myelofibrosis network (EUMNET). Blood. 2005;106(8):2849-53.
7. Tefferi A, Barosi G, Mesa RA, Cervantes F, Deeg HJ, Reilly JT, et al. International Working Group (IWG) consensus criteria for treatment response in myelofibrosis with myeloid metaplasia, for the IWG for Myelofibrosis Research and Treatment (IWG-MRT). Blood. 2006;108(5):1497-503.
8. Mesa RA, Niblack J, Wadleigh M, Verstovsek S, Camoriano J, Barnes S, et al. The burden of fatigue and quality of life in myeloproliferative disorders (MPDs): an international internet-based survey of 1179 MPD patients. Cancer. 2007;109(1):68-76.
9. Mesa RA, Schwager S, Radia D, Cheville A, Hussein K, Niblack J, et al. The Myelofibrosis Symptom Assessment Form (MFSAF): an evidence-based brief inventory to measure quality of life and symptomatic response to treatment in myelofibrosis. Leuk Res. 2009;33(9):1199-203.
10. Pardanani A, Finke C, Abdelrahman RA, Lasho TL, Tefferi A. Associations and prognostic interactions between circulating levels of hepcidin, ferritin and inflammatory cytokines in primary myelofibrosis. Am J Hematol. 2013;88(4):312-6.
11. Verstovsek S, Mesa RA, Gotlib J, Levy RS, Gupta V, DiPersio JF, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. N Engl J Med. 2012;366 (9):799-807.
12. Harrison C, Kiladjian JJ, Al-Ali HK, Gisslinger H, Waltzman R, Stalbovskaya V, et al. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. N Engl J Med. 2012;366(9):787-98.
13. Thapaliya P, Tefferi A, Pardanani A, Steensma DP, Camoriano J, Wu W, et al. International working group for myelofibrosis research and treatment response assessment and long-term follow-up of 50 myelofibrosis patients treated with thalidomide-prednisone based regimens. Am J Hematol. 2011;86(1):96-8.
14. Kiladjian JJ, Cassinat B, Chevret S, Turlure P, Cambier N, Roussel M, et al. Pegylated interferon-alfa-2a induces complete hematologic and molecular responses with low toxicity in polycythemia vera. Blood. 2008;112(8): 3065-72.
15. Silver RT, Vandris K, Goldman JJ. Recombinant interferon-alpha may retard progression of early primary myelofibrosis: a preliminary report. Blood. 2011;117(24): 6669-72.