Case Report: Remission of Chronic Idiopathic Myelofibrosis to Busulfan Treatment

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ABSTRACT: Three patients with chronic idiopathic myelofibrosis have responded to busulfan treatment with an excellent hematologic remission and reversal of myelofibrosis and myeloid metaplasia. Four months after busulfan therapy all three patients showed an improvement of hematocrit and hemoglobin and reduction of the number of leukoerythroblasts. Cellular bone marrow was re-established in two patients. A decrease of hepatomegaly and splenomegaly also occurred and was well correlated with the hematologic response. In one patient, when busulfan was discontinued for about 2 years after achieving an excellent remission, hematologic relapse was accompanied by increase of hepatomegaly and splenomegaly. When busulfan treatment was resumed, hematologic response and decrease of hepatomegaly and splenomegaly reoccurred. This observation has demonstrated the beneficial effect of busulfan in chronic idiopathic myelofibrosis; therefore, the role of busulfan in the management of this disease should be further investigated. KEY INDEXING TERMS: Myelofibrosis; Myeloid Metaplasia; Busulfan. [Am J Med Sci 1988; 295(5): 472–476.]

Chronic idiopathic myelofibrosis is a progressive myeloproliferative disorder characterized by anemia with severe poikilocytosis, leukoerythroblastosis, marked splenomegaly, and myeloid metaplasia. The disorder is almost always refractory to treatments and usually requires frequent blood transfusion because the major problem is anemia. In the management of anemia, various therapeutic approaches, including androgens, glucocorticosteroids, and splenectomy, also have been employed, but with little or no success.[1-12] Radiation therapy and chemotherapy have been used primarily in patients with massive splenomegaly to control symptoms related to organomegaly and splenic infarction.[13-15] However, these treatments generally are ineffective and offer little benefit, and there is no evidence that any of these treatments improves the quality of life or increases longevity of the patients.

We observed three patients with chronic idiopathic myelofibrosis with myeloid metaplasia, who showed an excellent clinical and hematologic remission to busulfan treatment. In this report, the effect of busulfan on their clinical course and hematologic parameters is presented, and the possible role of busulfan in the management of chronic idiopathic myelofibrosis is discussed.

Case Reports

Patient 1 (MG). A 63-year-old black man was admitted to the hospital with the chief complaint of progressive abdominal discomfort caused by massive splenomegaly and anemia of hemoglobin of 9.0 gm%. Five years previously, the patient was diagnosed as having chronic idiopathic myelofibrosis with myeloid metaplasia and had been treated with periodic blood transfusion to maintain the hemoglobin level at more than 9.0 gm%. Physical examination revealed both hepatomegaly and splenomegaly. The liver extended 12 cm below the right costal margin at the right midclavicular line and the spleen, 18 cm below the left costal margin at the left midclavicular line. Hemogram showed the nucleated blood cell count of 25,500/μL, hemoglobin 8.0 gm%, hematocrit 25.5%, and platelet count 472,000/μL. Differential nucleated blood cell count showed 35% segmented neutrophils, 27% bands, 5% lymphocytes, 1% eosinophils, 6% basophils, 11% metamyelocytes, 7% myelocytes, 2% promyelocytes, 2% blasts, and 4% nucleated red cells. Numerous poikilocytes and teardrop red cells were present on the blood smear. A bone marrow biopsy showed extensive myelofibrosis, and the diagnosis of chronic idiopathic myelofibrosis was established. Daily busulfan treatment was started, and the dosage was adjusted according to the white cell and platelet counts. As seen in Figure 1, an excellent clinical and hematologic remission was achieved within 3 months, with an improvement of the hemotocrit and decrease of hepatosplenomegaly. No further blood transfusion has been required.

Patient 2 (ES). A 72-year-old white woman was admitted to the hospital because of anemia and thrombocytosis. Past medical history was unremarkable. Physical examination revealed splenomegaly extending 3 cm below the left costal margin at the left midclavicular line. The liver was not palpable. Hemogram showed the

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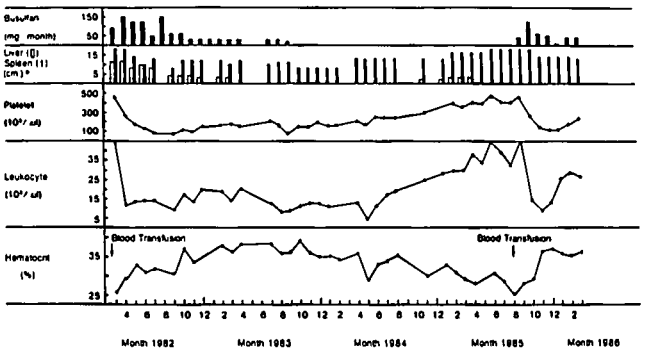

Figure 1. Clinical course of patient 1 from March 1982 to March 1986. Hematologic parameters are correlated with therapeutic trial of busulfan. Note improvement of the hematocrit and decrease of hepatosplenomegaly when treated with busulfan. When the drug was discontinued, the hematocrit decreased and splenomegaly increased. Retreatment with busulfan again increased the hematocrit. *Palpable size below the right (liver) or left (spleen) costal margin at the midclavicular line.

nucleated blood cell count of 10,300/μL, hemoglobin 10.2 gm%, hematocrit 29.6%, and platelet count 1,600,000/μL. Differential nucleated blood cell count showed 60% segmented neutrophils, 5% bands, 15% lymphocytes, 4% eosinophils, 2% blasts, 5% metamyelocytes, 5% myelocytes, and 4% nucleated red cells. Many poikilocytes and teardrop red cells were present on the blood smear. Following a bone marrow biopsy, the diagnosis of chronic idiopathic myelofibrosis was established. Daily dose of busulfan 12 mg was given for 6 days, and daily maintenance dose of between 2 and 6 mg, depending on the white cell and platelet counts, was initiated. The hematocrit improved markedly, and the spleen was no longer palpable below the costal margin 3 months after the initiation of busulfan. Blood transfusion has not been needed.

Patient 3 (RM). A 64-year-old white man was admitted to the hospital for an evaluation of anemia of 9.0 gm% and unexplained splenomegaly. About 1 year before this admission, splenomegaly and anemia were detected by a family physician, but the patient received no specific treatment or blood transfusions. Physical examination revealed hepatomegaly extending 4 cm below the right costal margin at the right midclavicular line and splenomegaly extending 16 cm below the left costal margin at the left midclavicular line. Hemogram showed the nucleated blood cell count of 21,000/μL, hemoglobin 8.8 gm%, hematocrit 28.0%, and platelet count 243,000/μL. Differential nucleated blood cell count showed 62% segmented neutrophils, 26% bands, 1% metamyelocytes, 2% myelocytes, 7% lymphocytes, 1% monocytes, and 1% nucleated red cells. Many poikilocytes and teardrop red cells were present on the blood smear. A bone marrow biopsy confirmed the diagnosis of chronic idiopathic myelofibrosis. An intermittent regimen of busulfan was started, with a daily dose of 14 mg for 4 days, and the drug has been continued at 4- to 5-week intervals. Within 4 months, hematologic improvement and a decrease of splenomegaly, as seen in Figure 2, occurred.

Methods

The complete blood count, including the platelet count, was obtained, and these tests were repeated at regular intervals. Blood smears were reviewed for both the degree of poikilocytosis of red cells and calculation of the percent of the sum of metamyelocytes, myelocytes, promyelocytes, blasts, and nucleated red cells in the differential nucleated blood cell count. The degree of poikilocytosis of red cells was graded as follows: 1+ for 5%–25% of poikilocytes, 2+ for 25%–50%, 3+ for 50%–75%, and 4+ for 75%–100%. These parameters were compared before and after remission to busulfan treatment.

The degree of hepatomegaly and splenomegaly was determined by physical examination at regular intervals. The palpable size of the liver and spleen was recorded by the centimeter (cm) below the right costal margin at the right midclavicular line and below the left costal margin at the left midclavicular line, respectively.

The biopsy specimens of the bone marrow were obtained before busulfan treatment, and the biopsy was repeated at multiple sites on several occasions when the patients' hematologic remission was achieved.

In patient 1, busulfan treatment, which lasted more than 1 year, brought on hematologic remission, but the drug was discontinued for about 2 years because of a modest thrombocytopenia. Evidence of relapse of myelofibrosis and myeloid metaplasia was documented (Figure 1). To confirm the initial response of myelofibrosis to busulfan, the drug was reinstituted, and the patient's clinical course and hematologic changes were observed.

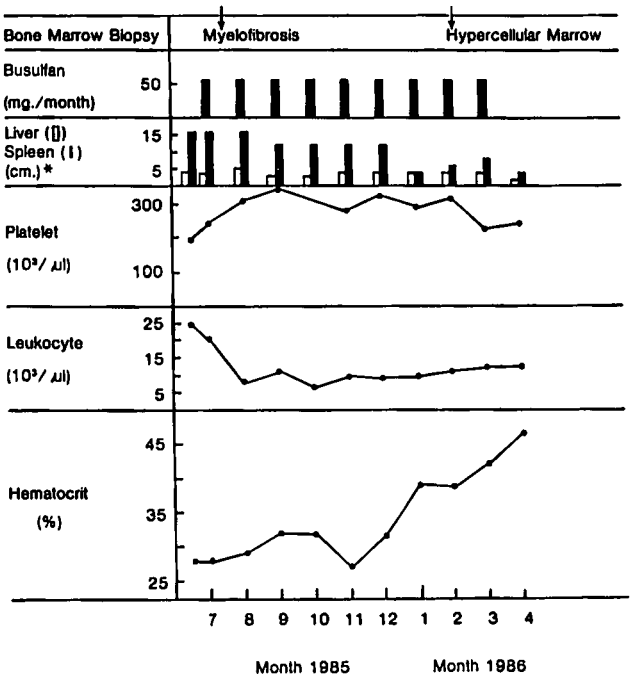

Figure 2. Clinical course of patient 3. Note normalization of hematocrit and reduction of splenomegaly after busulfan treatment. *Palpable size below the right (liver) or left (spleen) costal margin at the midclavicular line.

Results

Blood Counts and Morphology. In Table 1, hematologic parameters before busulfan treatment and after response to the drug are summarized. In all three patients, hematologic improvement occurred with increase or normalization of the hemoglobin and hematocrit. The differential nucleated blood cell count showed reduction or disappearance of leukoerythroblasts. Also, blood smears revealed a definite decrease of the number of poikilocytes and teardrop red cells.

Splenomegaly and Hepatomegaly. Hepatomegaly and splenomegaly were the indications for presence of active myeloid metaplasia, which also was supported by production of poikilocytes, teardrop red cells, and leukoerythroblasts. As shown in Table 1 and in Figures 1 and 2, following busulfan treatments, all three patients showed a marked regression of hepatomegaly and splenomegaly. This response also was accompanied by the improvement of subjective symptoms, such as abdominal pain and discomfort.

Bone Marrow. In all three patients, the aspiration showed no detectable marrow particles, and the biopsy showed extensive myelofibrosis. Following busulfan treatment, patient 1 revealed a modest reduction of myelofibrosis, and there has been emergence of some cellularity in serial bone marrow examinations. In patient 2, after 15 months of busulfan treatment, myelofibrosis reversed to an extremely hypercellular marrow (Figure 3). Also, in patient 3, gradual reversal of myelofibrosis to hypercellular marrow has been observed in serial bone marrow examinations.

Effect of Interruption of Busulfan Treatment. Patient 1 had an excellent hematologic remission with busulfan treatment. When the hematologic parameters improved and the hepatosplenomegaly decreased, the patient was maintained on low dose of busulfan for about 1½ years. Then, the drug was discontinued because of mild thrombocytopenia. Over the next 2 years, anemia, leukocytosis, and leukoerythroblastosis gradually worsened, and increase of hepatomegaly and splenomegaly was seen (Figure 1). Hematologic progression of chronic idiopathic myelofibrosis was diagnosed. When busulfan was resumed, gradual hematologic response was noted again, and a modest decrease of splenomegaly occurred. The patient is alive and well more than 10 years since his initial diagnosis, without blood transfusion requirement.

Discussion

Chronic idiopathic myelofibrosis, unlike other myeloproliferative disorders, such as polycythemia vera, chronic granulocytic leukemia, and primary thrombocythemia, still is regarded as a disease whose natural history cannot be altered by medical treatments for either a short-term or long-term benefit. Whether or not the patient is maintained on blood transfusion, most patients eventually succumb to progression of the disease and its complications, such as congestive heart failure, bleeding, debilitation and cachexia, and infection.[9,16] Transformation to acute leukemia occurs in about 5% of cases.[17,18]

Various treatments have been investigated. Some benefits have been claimed with high doses of androgens and glucocorticosteroids, mainly by increasing the levels of hemoglobin and hematocrit.[1-3,6,7,15] However, the benefit usually has been marginal and has

TABLE 1
Hematologic, Liver and Spleen Changes Following Busulfan Therapy

	Patient 1		Patient 2		Patient 3	
	Before Busulfan	While on Busulfan	Before Busulfan	While on Busulfan	Before Busulfan	While on Busulfan
Hemoglobin (gm %)	8.0	11.6	10.2	12.7	8.8	13.0
Hematocrit (%)	25.5	39.3	29.6	38.9	28.0	39.3
Nucleated blood cells (per μL)	25,500	11,000	10,300	4,000	21,000	9,800
Platelets (per μL)	472,000	138,000	1,600,000	556,000	243,000	297,000
Poikilocytes (degree)	3+	2+	2+	1+	2+	1+
Leukoerythroblastosis* (%)	26	17	16	0	4	0
Liver/spleent (cm)	12/18	0/8	0/3	0/0	4/16	2/4

* *Percent of the sum of metamyelocytes, myelocytes, promyelocytes, blasts, and nucleated red cells in the differential nucleated blood cell count.*

† *Palpable size of the liver below the right costal margin at the right midclavicular line or that of the spleen below the left costal margin at the left midclavicular line.*

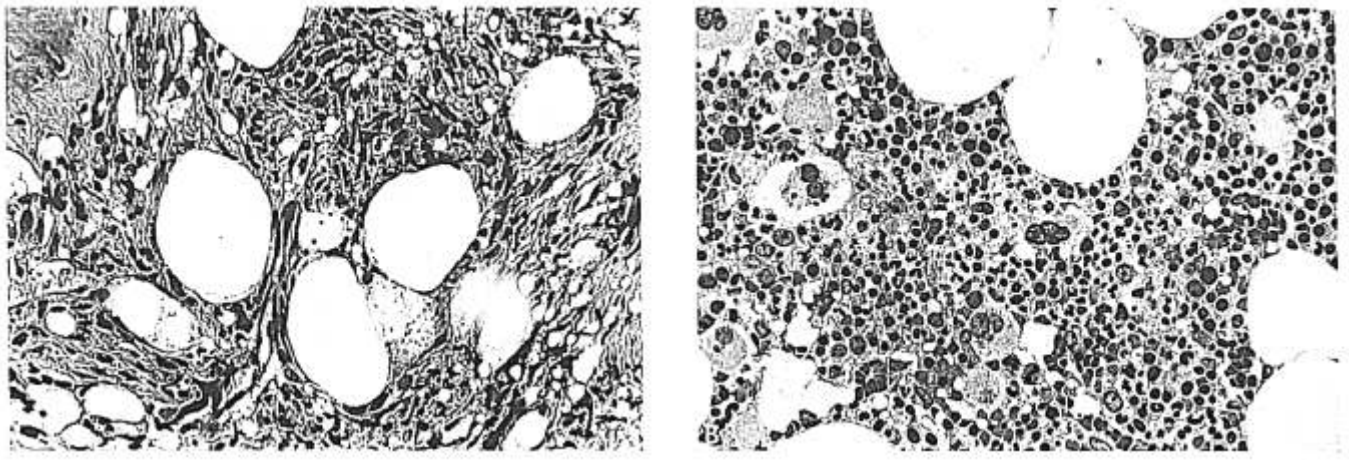

Figure 3. Bone marrow biopsy (A) before and (B) after remission following busulfan treatment in patient 2.

not been enough to improve the quality of life. Splenectomy has been advocated for painful spleen, hypersplenism, and portal hypertension.[9,11,16] The benefit of this approach has been questionable in most cases, and often the postoperative complications have been frequent. An analysis of reported cases in the literature shows a postoperative mortality rate of 25%.[9] In addition, the surgery does not seem to alter the overall clinical course of the surviving patients, and the patients die of the same causes as patients who have not had splenectomy.[19] The vitamin, 1,25 dihydroxyvitamin D_3, has been reported to be beneficial in some patients with myelofibrosis.[20] In our experience, the vitamin has not shown any benefit in a trial of 6 patients.[21] Recently, bone marrow transplantation was attempted in a few patients with acute myelofibrosis,[22-24] but it has not been advocated in chronic idiopathic myelofibrosis. Moreover, the high morbidity and mortality associated with such a procedure in an older age group of patients, assuming a matched donor is available, make the bone marrow transplant an unwise approach. Mechanical curettage of small amounts of fibrotic bone marrow from the iliac bones showed an increase of hemoglobin in one patient with primary myelofibrosis.[25]

In an extensive review of the literature, busulfan occasionally was mentioned as useful in the treatment of myelofibrosis with myeloid metaplasia.[14-16,26-28] Some benefits and, at times, considerable improvement, resulting in an increase of hemoglobin and decrease of splenomegaly, have been recorded in a few patients. Because of busulfan's potential additive suppressive effect on the diseased marrow, lower doses of the drug have been used in the treatment of myelofibrosis than have been used in treating chronic granulocytic leukemia and polycythemia vera. The lower doses may be inadequate, which could account for the failure of busulfan treatment.

In our three patients who received adequate doses of busulfan, an excellent remission was achieved. Not only did hematologic parameters, including the hemoglobin and hematocrit, improve, but reversal of myelofibrosis also was observed. Regression of splenomegaly, reduction of poikilocytes and teardrop red cells, and lessening of leukoerythroblastosis also were evidence of reversal of myeloid metaplasia. Quality of life has improved in all three patients. One patient seems to have an extended life since he is alive and well for more than 10 years after the diagnosis. In all three patients, blood transfusion has not been needed during busulfan treatment. In one patient, termination of busulfan treatment resulted in hematologic relapse. Second remission, which occurred after resumption of busulfan, supports that initial hematologic response was induced by the drug.

The mechanism of action of busulfan in myelofibrosis is uncertain. Since busulfan is an alkylating agent, the beneficial effect may have been derived from direct effect of the drug on proliferating hematopoietic cells. Busulfan has decreased the bone marrow granulopoietic pool at the expense of the erythropoietic one in a patient with myelofibrosis.[28] It would be interesting to study the effect of busulfan on bone marrow stem cells and fibroblasts from patients with myelofibrosis.

Although our observation suggests the beneficial effect of busulfan in the treatment of chronic idiopathic myelofibrosis, a judicious use of the drug is recommended since busulfan is a toxic drug that causes delayed marrow suppression. Special precaution is necessary for patients with thrombocytopenia. In the light of our experience, it seems to be appropriate to design a large scale controlled study with

busulfan and possibly other alkylating agents in the treatment of chronic idiopathic myelofibrosis.

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Erratum

In "The Athlete, Cocaine and Lactic Acidosis," which appeared in the December 1987 issue of *The American Journal of the Medical Sciences,* Len Bias's cause of death was printed incorrectly on page 413.

The sentence should read, "Len Bias, the University of Maryland's star basketball player, died from cocaine in June 1986."

We apologize for any inconvenience this may have caused.