Busulfan Therapy in Myeloid Metaplasia

By NOBORU OISHI, SCOTT N. SWISHER AND STANLEY B. TROUP

BUSULFAN* (1,4-dimethanesulphonyloxybutane) is a radiomimetic agent which appears to inhibit cellular metabolism through its ability to alkylate nucleoproteins.1-3 Cells undergoing division seem particularly susceptible to the action of busulfan. Since it was synthesized by Haddow and Timmis,4 busulfan has been successfully used in the treatment of chronic myelocytic leukemia.5,6 Elson11 demonstrated that, in contrast to another alkylating agent, chlorambucil,7 busulfan affects chiefly myeloid and erythroid cells, with very little effect on lymphoid cells.

More recently, busulfan has been used in the treatment of polycythemia vera. Wald et al.12 reported giving busulfan to 5 such patients, some of whom received multiple courses of treatment with this drug. The average dose that produced full remission of the polycythemia was 29.4 mg. per week, and ranged from 22 to 40 mg. per week. The total dose in 6 of the 9 courses of therapy ranged from 236 to 408 mg. of the drug. Remissions occurred after 7 of the 9 courses and were characterized by improvement in both clinical states and laboratory findings. In the two instances of incomplete remission, clinical improvement occurred and white blood cells and platelets decreased in number, but there was no significant change in the red blood cell values. Louis13 reported the treatment of 18 polycythemic patients with busulfan for periods ranging from 4 to 76 weeks, with a mean duration of therapy of 38 weeks. The doses administered varied from 2 to 10 mg. daily, with a mean of 3 mg. daily, or 21 mg. per week. The leukocyte counts and hematocrits of Louis's patients were lowered in all instances. Six patients had palpably enlarged spleens; in 5 patients, spleen size decreased; in 1 patient, the spleen became impalpable.

This report describes the results of busulfan therapy in 7 patients with myeloid metaplasia of the spleen and liver.

Patients and Methods

The seven patients reported in this study have been followed in the Hematology Clinics of the University of Rochester Medical Center for periods up to eight years. Patient ages ranged from 42 to 73 years, and five of the seven were females.

During the period of this study, routine laboratory determinations, using standard procedures, consisted of hematocrit determination, leukocyte count and critical analysis of stained peripheral blood smears. Hemoglobin concentration, red blood cell count, reticulocyte count using the New Methylene Blue method,14 bone marrow aspiration, leukocyte alkaline phosphatase activity and other determinations were obtained at intervals. Direct smears and smears of the concentrated myeloid-erythroid layer were prepared from all

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*Myleran (Burroughs-Wellcome and Co.).

†Leukeran (Burroughs-Wellcome and Co.).
marrow samples. Leukocyte alkaline phosphatase activity was determined by the histochemical method in use in this laboratory as described by Brodell and Swisher. Normal values of leukocyte alkaline phosphatase index range between 80 and 185.

The leukocyte alkaline phosphatase activity is usually elevated in the blood of patients with myeloid metaplasia. Mitus et al. in their studies of the leukocyte alkaline phosphatase activity in various myeloproliferative syndromes found that cases of myeloid metaplasia fell into two distinct groups: (1) those with higher than normal enzyme activity (16 cases), and (2) those with low normal or lower than normal activity (7 cases). Similar findings have been observed in this laboratory. In 6 of the 7 patients reported in the present study, the leukocyte alkaline phosphatase activity was higher than normal, ranging from 195 to 387 units. The one patient (C. R.) with lower than normal activity of this enzyme had an 11 year history of splenomegaly with a benign clinical course.

The blood smears of all seven patients reflected changes consistent with myeloid metaplasia. Marked variation in size and shape of erythrocytes was evident; nucleated red blood cells were seen in all blood smears, as were immature myeloid elements. Platelet numbers varied, but abnormally large platelets and megakaryocyte fragments were found in the blood smears of all patients.

For purposes of this report, the patients were classified as follows: (1) post-polycythemic myeloid metaplasia; and, (2) myeloid metaplasia with "primary" osteomyelosclerosis or myelofibrosis.

Five of the 7 patients had well documented polycythemia vera in the past. During the course of time, they had developed progressive splenomegaly and changes in the peripheral blood smear consistent with myeloid metaplasia. These patients have been classified as post-polycythemic myeloid metaplasia. The remaining two patients had consistently hypocellular bone marrow, as determined by examining aspirated specimens, splenomegaly and leuko-erythroblastic changes in the peripheral blood. These two patients have been considered to have myeloid metaplasia with "primary" osteomyelosclerosis or myelofibrosis. Surgical bone marrow biopsy was not performed on either patient, but bone survey films of one of these two patients displayed changes compatible with diffuse osteomyelosclerosis.

Busulfan was administered in divided daily doses in 4 of the cases. In the remaining 3 cases, the drug was administered in a single daily dose while fasting, usually one-half hour before breakfast. The patients were seen at intervals of 10 to 14 days during the administration of the drug. Busulfan treatment was discontinued after substantial clinical improvement occurred or when leukopenia or thrombocytopenia developed.

**RESULTS**

Treatment of the patients with busulfan usually was instituted when they developed symptoms related to progressive or massive splenomegaly or symptoms of hypermetabolism; the latter usually were characterized by heat intolerance, easy fatigability and weight loss despite an adequate or increased appetite. All patients treated noted distinct improvement of clinical status with amelioration of symptoms and reduction of spleen size.

The total dose of busulfan for each course of treatment ranged between 212 and 290 mg. over periods of from 30 to 111 days in five of the patients. Patient W. L. had continuous therapy for 114 days, by which time he had received a total dose of 866 mg. Table 1 summarizes the total drug dose and duration of therapy in the seven patients.

Busulfan therapy was discontinued in patients M. S., C. A. and C. R. following the development of leukopenia. While receiving busulfan, mild thrombocytopenia developed in most of the patients; platelets were more severely reduced in those patients who also developed leukopenia simultaneously. Leuko-erythroblastic changes in the peripheral blood diminished, and in some
patients, normoblastemia and immature myeloid elements virtually disappeared. Table 2 is an abstract of hematologic data from these patients during the course of treatment.

All patients experienced significant reduction of spleen size during treatment, and further reduction occurred for a few weeks after discontinuance of therapy in most patients. Except in patient C. A., the patients' hematocrits remained stationary or increased during busulfan therapy. In patients W. L. and M. M., phlebotomies became necessary because of continued rise in hematocrit and re-establishment of a polycythemic state during therapy. In patient B. R., the hematocrit rose slowly during therapy and phlebotomy was deemed necessary one month after therapy.

Patient M. S. had a short-term response to splenic irradiation. Two months after the course of x-ray treatment to the spleen was completed, busulfan was administered because of increasing abdominal fullness, heat intolerance and fatigue. The drug was discontinued after 47 days of therapy and a total dose of 168 mg. because of leukopenia and moderate thrombocytopenia. The patient had obtained moderate relief of abdominal discomfort and symptoms of hypermetabolism. During the next 18 months, increasing splenomegaly recurred without reappearance of symptoms. Patient C. R. noted improvement of her symptoms of heat intolerance and left upper abdominal discomfort after busulfan therapy was instituted. For four months following discontinuance of therapy, she remained in apparent good health. The spleen then enlarged but was still measurably smaller than before busulfan was administered. The leukocyte count remained at low normal levels.

Patient M. M. showed striking reduction of spleen size and although the leukocyte count remained mildly elevated, it decreased substantially compared to pretreatment levels. Patient C. A. developed mild leukopenia during treatment which persisted for over six months after busulfan treatment was discontinued. Although the spleen enlarged minimally after stopping treatment with busulfan, no recurrence of abdominal discomfort, heat intolerance, weight loss or fatigue was noted.

Patient B. R. had substantial reduction of total leukocyte count and spleen size following busulfan therapy. The symptoms of hypermetabolism also were
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*Splenic and hepatic measurements were obtained in the midclavicular line below the costal margin.
†These determinations were obtained before beginning splenic x-ray therapy.
completely relieved. Because of the appearance of distinct polycythemia (30 days after discontinuance of busulfan therapy), 5 mc. of P₃₂ were given two and one-half months later. Forty-two days after P₃₂ therapy the hematocrit, leukocyte count and spleen size had decreased further.

Patient A. J. had two courses of busulfan therapy. There was significant clinical improvement and reduction of spleen size after each course. During the 12 months following the second course of treatment, the spleen again began to enlarge slowly. His weight was constant and no recurrence of night sweats or gastrointestinal discomfort was noted. The leukocyte count remained at low normal levels following therapy.

Patient W. L. entered with symptoms of acute intermittent intestinal obstruction, while upright, probably secondary to the remarkable degree of splenic enlargement. During more than three months of continuous busulfan therapy, in 6 to 8 mg. daily doses, the spleen size decreased markedly. Figure 1 shows this change. The patient's serum uric acid fell from a pre-treatment level of 11.0 mg. to 6.4 mg./100 ml. He had been known to have polycythemia vera for eight years; during this period he had frequent bouts of back pain accompanied by microscopic hematuria, presumably due to urate calculi. During periods of uncontrolled hematopoietic proliferation, the symptoms of back pain frequently recurred. He has had no recurrence of symptoms during the period since busulfan was administered until the time of this report.

DISCUSSION

The natural history of myeloid metaplasia has been well reviewed by other authors. In all of the patients reported here, the duration of the illness with relatively benign course, the marked splenomegaly and lesser hepatomegaly.

Fig. 1A (at left).—Patient W. L., 2/2/59, before busulfan therapy.
Fig. 1B (at right).—Patient W. L., 5/25/59, after completion of busulfan therapy; total dose given, 866 mg.
ly, and the leuko-erythroblastic changes in the peripheral blood, including abnormally large platelet forms and megakaryocyte fragments, are typical of the clinical picture of myeloid metaplasia.

Myeloid metaplasia of the spleen frequently presents a difficult therapeutic problem. The large spleen is physically often very distressing to the patient. Splenic infarction may occur and simulate an acute surgical condition. Furthermore, some patients present evidence of an excessive rate of red blood cell destruction, probably related in some way to the massively enlarged spleen. Thus, severe anemia may develop because of inadequate hematopoiesis to compensate for the shortened red cell life span. The development of symptoms related to hypermetabolism is well known in myeloid metaplasia but is frequently not appreciated as a major clinical problem. The heat intolerance, weakness and weight loss may be uncomfortable and worrisome to the patient. Progressive weight loss, inanition and death may ensue. Various therapeutic measures have been employed to cope with these problems; among these are x-ray therapy directed to the spleen, splenectomy, corticosteroids, and recently, testosterone.29

X-ray therapy to the spleen in patients with myeloid metaplasia has occasionally yielded satisfactory results.20,32 Hickling32 described beneficial results in five of seven patients so treated. He correlated the beneficial results of x-ray with the presence of leukocytosis and myeloid immaturity in the peripheral blood. Korst et al.25 reported that five of their 23 patients with myeloid metaplasia had x-ray treatment to the spleen. Their patients experienced decreases in leukocyte count and some relief of symptoms, but no improvement of anemia or apparent change in the course of the disease. Splenic irradiation has proven to be ineffective therapy in some patients with myeloid metaplasia and actually harmful to other patients with this syndrome.33-34 Although the spleen may decrease in size temporarily, anemia may become quite severe.

Four patients in this report previously received splenic x-ray therapy. All patients experienced reduction in splenic size, but in three of the four patients improvement lasted less than three months. The fourth patient was free of symptoms for 23 months after splenic irradiation. One patient who was retreated failed to respond to the x-ray therapy.

The role of splenectomy in patients with myeloid metaplasia has been in dispute for many years. In the past, splenectomy has been considered contraindicated.35-37 More recently splenectomy has been performed in some patients, with relief of such complications as excessive hemolysis or bleeding due chiefly to thrombocytopenia.25,38-41 Splenectomy occasionally has been followed by a striking increase in white blood cells and platelets in the peripheral blood.38 Progressive hepatomegaly has also been described in patients with myeloid metaplasia following splenectomy.28,42,43

Korst et al.25 reported no significant response in two patients with myeloid metaplasia treated with busulfan. Dameshek and co-workers,44 however, have observed that the use of busulfan resulted in significant reduction in spleen size in their patients with this disorder. They reported that four of eight patients experienced marked reduction of spleen size following this treatment.
The leukocyte counts were also lowered significantly and there was either no change or improvement in red blood cell counts.

The initial doses of busulfan in our patients ranged between 6 and 10 mg, daily in seven of the eight courses of treatment. Because of the occurrence of significant leukopenia and thrombocytopenia, the drug was discontinued in three patients. It seems likely that the dose of busulfan given to patients with myeloid metaplasia should be less than that usually given to patients with chronic myelocytic leukemia. Very careful follow-up of the patients during the period of treatment is imperative.

The results obtained in our patients suggest that busulfan should be considered in the treatment of myeloid metaplasia when such patients develop massive splenomegaly and/or symptoms of hypermetabolism. All of our patients were benefited to some degree by this drug. Although the experience thus far reported is too small to permit firm conclusions, it appears that in some patients busulfan therapy has resulted in more prolonged benefit than has splenic irradiation.

The present experience and previous reports suggest that busulfan provides an additional useful therapeutic method for dealing with the complex clinical problems associated with this disorder.

**Summary**

1. Seven patients with myeloid metaplasia, massive splenomegaly and hypermetabolism were treated with busulfan in eight courses of therapy. In each instance, reduction in spleen size and improvement of symptoms occurred.

2. The total dose of busulfan in five of the cases ranged between 212 and 290 mg. Three of the patients developed leukopenia of moderate degree necessitating discontinuance of drug therapy.

3. It would appear that initial and maintenance doses of busulfan should be lower in patients with myeloid metaplasia than the doses customarily used in the treatment of patients with chronic myelocytic leukemia.

**Summario in Interlingua**

1. Septe patientes con metaplasia myeloide, splenomegalia massive, e hypermetabolismo eseva tractate con octo cursos de busulfano (1,4-dimethanesulphonyloxybutano). In omne casos, reduction del dimensiones del splen e melioration del symptomata occurreva.

2. Le dosage total de busulfano in cinque del casos variava inter 212 e 290 mg. Tres del patientes disveloppava moderate grados de leucopenia que rendeva necessari le interruption del therapia a busulfano.

3. Il pare que le doses initial e le dosage de mantenentia de busulfano deberea esser plus basse in patientes con metaplasia myeloide que lo que es costumarimente usate in le tractamento de patientes con chronic leucemia myelocytic.

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Busulfan Therapy in Myeloid Metaplasia

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