Busulfan in the Treatment of Chronic Myelocytic Leukemia. The Effect of Long Term Intermittent Therapy


Busulfan is a palliative agent for the treatment of chronic myelocytic leukemia. The initial course of treatment generally results in amelioration of the symptoms and signs of leukemia; undesirable side effects occur infrequently. After the initial response, which is often readily achieved by any one of a number of palliatives, the value of busulfan in comparison to other agents can be adduced by examining the total period of time over which the beneficial effect of busulfan can be repeatedly achieved, the frequency and nature of side effects after protracted use of the compound, the frequency with which the late, acute myeloblastic phase occurs and, eventually, the longevity of the treated patients. In this report, more than seven years of experience with intermittent courses of busulfan are examined to appraise the long-term effects of the drug.

Material and Methods

Thirty unselected patients with chronic myelocytic leukemia, who began treatment with busulfan between November, 1952 and July, 1958 are reported here. Observations on these patients up to February 1, 1960 are included. The known duration of leukemia in these patients up to February 1, 1960, ranged up to 85 months. The patient with the longest survival is still alive. The initial data on some of these patients were reported earlier.

The diagnosis of chronic myelocytic leukemia was established by the criteria outlined elsewhere. Myelofibrosis was excluded by clinical and hematological considerations, surgical, Vim-Silverman needle or aspiration biopsy of the bone marrow, as indicated, as well as by roentgenographic study of the bones.

Half of the patients were males. Except for one child of seven years, the patients' ages at the time of the first evidence of disease ranged from 23 to 72 years; half were younger than 48 years.

In all, 114 courses of busulfan were prescribed. Individuals received from one to twelve courses of intermittent treatment over periods up to 84 months. All 30 patients received at least one course of busulfan; 23 received two or more courses; eight received six or more
courses. One patient received 12 courses over a period of six years. Prior to busulfan treatment, six of the 30 patients had received other therapy, including radioactive phosphorus, x-ray, urethane, colcemide, triethylene melamine, nitrogen mustard, and whole blood transfusions.

The methods for determining the numbers of leukocytes and erythrocytes, the volume of packed red cells (VPRC), and the cyanmethemoglobin technic for determining concentration of hemoglobin are described elsewhere. The Brecher-Cronkite method was used in counting platelets; the normal value by this method is 250,000 per cu. mm. with 95 per cent confidence limits of 140,000 to 440,000 per cu. mm.

**METHOD OF TREATMENT**

Consideration was given to the degree of anemia, leukocytosis, splenomegaly, hepatomegaly, sternal tenderness, general malaise and weight loss in judging the need for treatment. Effects of treatment were measured by the changes in these signs and symptoms.

In most cases, four or six milligrams of busulfan were given orally as a single dose each morning during the period of treatment. Generally, this dose was equivalent to between 60 and 85 micrograms per kilogram per day, with the extreme values of 46 micrograms per kilogram of body weight per day in an 88 kilogram man and 229 micrograms per kilogram per day in a 20 kilogram child.

Except for our earliest experience with the drug, once busulfan was prescribed, it was continued until the leukocyte value fell to 10,000 per cu. mm. or less. Treatment was then interrupted until the leukocyte value rose to 50,000 per cu. mm. or more. Occasionally, treatment was resumed when the leukocyte value was lower, to spare a patient the inconvenience of an additional clinic visit, entailing another lengthy trip in one or two weeks.

Fifty per cent of the initial treatment courses were 69 days or less in duration; 80 per cent were three months or less. Of subsequent courses of treatment, half were 42 days or less, and 80 per cent were 70 days or less in duration.

While receiving therapy the patients were examined and the leukocyte count, differential count, platelet count and VPRC were determined at one to three week intervals. The same examinations were performed at two week to three month intervals during the periods of remission.

The remission was measured from the day treatment was stopped to the day therapy was resumed because of signs of relapse. Unless the leukocyte value was less than 25,000 per cu. mm. and the differential count and clinical findings were improved when busulfan was stopped, a remission was not considered to have been obtained. In most instances, the "remission" corresponded to the time elapsed, without therapy, before the leukocyte value again rose to 50,000 per cu. mm.

**RESULTS**

Our findings after the initial courses of treatment are in agreement with those of other authors. The changes resulting from subsequent courses of treatment are compared here with the well defined response to the initial treatment.

**Symptoms**

**Initial course:** Improvement in appetite and sense of well-being were the first changes to be noted. In most cases this coincided with the initial decrease in the leukocyte value but occurred before changes in organ size or in volume of packed red cells were evident.

**Later courses:** The qualitative response was unchanged, but a less rapid response was apparent after a number of courses were prescribed. In some patients, symptoms had not recurred even though further treatment was needed.
**Physical Signs**

*Spleen: Initial course:* The spleen was palpable in 27 of the 30 patients prior to the first course of treatment with busulfan. It varied in size from just palpable up to one which filled the entire left side of the abdomen and extended to the right iliac crest. In most patients during the first course of busulfan, the spleen began to decrease in size after two to three weeks of treatment and continued to decrease for three to eight weeks after treatment was stopped. After the first course of treatment (fig. 1) the spleen was not palpable in 15 patients. In most of the remaining cases the spleen decreased at least 50 per cent in size.

*Later courses:* The spleen frequently enlarged somewhat during the interval without treatment. With succeeding courses of therapy splenomegaly was again reduced (fig. 1). The over-all effect after repeated courses, was, in the main, progressive reduction in splenomegaly. In three patients, including the one with the largest spleen, splenomegaly persisted after the first course but disappeared after the second or third course of busulfan. When the spleen failed to decrease at least 50 per cent in size after a course of busulfan it was usually a sign of poor prognosis and heralded the intervention of the acute, myeloblastic phase of chronic myelocytic leukemia.

*Sternal Tenderness* was observed in all but three cases and decreased at about the same time and rate as did the splenomegaly. It usually disappeared completely after each course of treatment and then recurred with each relapse in a similar fashion for both first and later courses. When the acute phase of chronic myelocytic leukemia appeared, bone tenderness did not improve after treatment with busulfan.

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**Fig. 1.—The changes in splenomegaly with successive courses of busulfan. Each dot represents a single patient; solid dots before, and open dots after treatment.**
LYMPHADENOPATHY: Enlargement of the superficial lymph nodes up to two cm. in diameter, was present in five of the 30 patients at the time they were first seen. The adenopathy was usually unaffected by busulfan therapy even in those patients who otherwise responded well to several consecutive courses.

Six of the 22 deceased patients had superficial lymph nodes two to four cm. in diameter at the time of death. An additional three patients who did not have superficial adenopathy were found to have enlarged deep thoracic and abdominal nodes at autopsy. All nine of these patients with adenopathy had entered the acute phase of chronic myelocytic leukemia.

LABORATORY DATA

Leukocytes: The leukocyte value at the time a course of treatment was begun ranged between the extremes of 30,000 per cu. mm. and 1,000,000 per cu. mm. It usually fell below the initial value within two weeks, but in some this fall did not occur until after three weeks of therapy. The weekly reduction in the leukocyte value was usually great at first and diminished as the number of leukocytes approached normal, even though the dose of busulfan was unchanged. The decline in the number of leukocytes followed an exponential function, as was previously reported. This was found to be equally true for initial and later courses. The instances in which the leukocytes failed to respond to busulfan are discussed in the section on drug-resistant disease.

The duration of busulfan treatment necessary to reduce a given leukocyte value to normal was found to be an exponential function of the number of leukocytes per cu. mm. at the time therapy was begun. This can be illustrated by the linear fall of the number of leukocytes plotted against time on semi-logarithmic graph paper. It was previously suggested that for the initial course of treatment the rate of response (i.e., the slope of such a graph) is related to the dose of busulfan per unit of body weight. For the present experience this correlation coefficient was $r = 0.65$; for the previously reported experience it was $r = 0.84$. We found no correlation at all between the rate of response of the leukocytes and the daily dose of busulfan when the latter was calculated per unit of body surface area.

The rate of response of the leukocytes following repeated courses of treatment in the same individual was not constant from one course to the next (fig. 2). However, neither did a continuing trend toward diminishing or increasing rapidity of response occur. Instead, the rate of response varied about a mean value.

Volume of Packed Red Cells: First course: In the majority of the patients there was a substantial increase in the volume of packed red cells (VPRC); anemia, when present, was relieved (fig. 3). Only one anemic patient failed to show an increase in VPRC; in this instance chronic infection was present. In the remaining cases the VPRC increased by 10 to 30 per cent of the pre-treatment value, the greatest increases occurring in the most anemic individuals.

An increase in VPRC was seen by the end of the second week in half of the anemic patients and by the end of the third week in all of them. Characteristically, the VPRC rose rapidly from the second to the sixth week of therapy, increasing more slowly thereafter. Frequently, it continued to rise after busulfan...
was discontinued and reached a maximum during the ensuing period of remission.

Second and later courses of treatment: The same general type of response occurred in later courses. For the most part, prior to retreatment there was only slight anemia, if any at all, since the first course was associated with relief of anemia and significant anemia rarely returned before the leukocyte count reached 50,000 per cu. mm. In most instances changes were of a smaller magnitude than during the first course. The rise of the VPRC usually occurred in the fourth to sixth week of therapy but sometimes the initial VPRC was not surpassed for two or three months. In some cases, the post-treatment VPRC after fourth and later courses (fig. 4) did not achieve the maximum values attained after the first or second course. However, a VPRC as low as that present prior to the first treatment was seen only in those courses of treatment terminating with the death of the patient in the acute, myeloblastic phase.

Platelets: First Course: Thrombocytosis was present initially in two-thirds of our cases. After the first course of busulfan, most patients had a normal or elevated platelet count; however, four became thrombocytopenic. Three of four cases with thrombocytopenia before treatment had normal numbers of platelets afterwards.
Similar findings were observed after the second and third courses of treatment.

*Fourth and later courses* were examined apart from the others for evidence of cumulative toxicity depressing platelets. This was not found. In the main, the platelet changes were similar to those observed in earlier courses except that a rise to normal from thrombocytopenic levels did not occur.

Among 114 courses of therapy, busulfan was started in the presence of thrombocytopenia on 11 occasions in five patients. Three of these 11 courses
were subsequently stopped because of the thrombocytopenia, when the patient was otherwise responding well, to avoid any possibility of increasing the risk of hemorrhage. In seven instances the clinical and hematological response to busulfan was good, whether or not thrombocytopenia was relieved. The response was incomplete in one patient who developed the acute phase of leukemia.

Fourteen of the 16 patients who had thrombocytopenia at sometime, exhibited hemorrhagic phenomena. In order of frequency of occurrence the latter included the following: purpura; cerebral, gastrointestinal and retinal hemorrhage; and hemothorax. Purpura occurred in the presence of platelet values as high as 116,000 per cu. mm. Cerebral vascular accidents occurred with platelet values as high as 109,000 per cu. mm.

Other Effects:

Generalized skin hyperpigmentation, amenorrhea, mild transient gynecomastia, and an instance of agranulocytic angina after a single dose of four milligrams at least three months after the last previous treatment with busulfan have been reported previously.

Very few of our patients have noted undesirable side effects. Two of our patients experienced recurrent nausea with occasional vomiting and one had chronic diarrhea until the busulfan was taken in divided doses. Two patients developed generalized hyperpigmentation of the skin. One of these, because he was partially resistant to the drug (see below), took eight milligrams of busulfan daily for as long as eight months. During the last three months of this time he had generalized hyperpigmentation, excessive dryness and fragility of the skin, complete anhydrosis, almost complete epilation, marked dryness of the oral mucous membranes, atrophy of the papillae of the tongue, a marked distaste for salt and sweets, cheilosis and impotence. Most of these changes were aggravated when busulfan treatment was supplanted by colcemide but they disappeared later when colcemide was replaced by 6-mercaptopurine.

Resistance to Busulfan

First course of busulfan: Only one patient, a 49 year old white female who was referred because she had ceased to respond satisfactorily to x-ray after 3½ years of therapy, failed to respond well to the first course of busulfan. After busulfan, she showed a brief partial response to colcemide but then entered the acute phase and died.

Subsequent courses: Another patient responded well to the first course of busulfan but became partially resistant during the second. Although the patient took eight milligrams of busulfan daily for more than eight months, the leukocyte value failed to decrease below about 33,000 per cu. mm. However, the leukocyte value rose abruptly to about 240,000 per cu. mm. when chemotherapy was stopped. In addition, six patients who had previously responded well to 2, 2, 4, 5, 6 and 7 courses of busulfan, respectively, became completely resistant when they developed the acute phase of chronic myelocytic leukemia.
Remissions

Under the plan of therapy employed, busulfan was discontinued when the leukocytes fell to a satisfactory level. After a period without therapy, the leukocytes increased in number again. The duration of remission after the initial course of treatment in 30 patients is shown in figure 5.

Three factors were evaluated with reference to the duration of remissions: (1) the leukocyte value at the time busulfan was discontinued; (2) the number of preceding courses of busulfan; (3) the duration of disease at the time therapy was prescribed. These are considered separately.

(1) Final leukocyte value: The duration of remissions after 92 initial and subsequent courses of treatment in all 30 patients were grouped according to the leukocyte value at the time busulfan was discontinued (table 1). The remaining courses of treatment could not be included because of inadequate data.

The longest remissions were achieved when the number of leukocytes was reduced to 10,000 or less per cu. mm., before therapy was stopped. When the leukocyte count was not reduced to this extent, remissions were shorter. This is also illustrated by the sequential changes in the leukocyte values following the conclusion of the first course of treatment (fig. 6) in the 26 patients for whom these data are available. The patients fall into three distinct groups:

![Figure 5](image)

**Fig. 5.—**The duration of remission after the initial course of busulfan in all 30 patients. Each column represents a single patient.
Table 1.—Duration of Remission According to Leukocyte Value at the End of a Course of Busulfan

<table>
<thead>
<tr>
<th>Group</th>
<th>Final WBC</th>
<th>No. of Patients</th>
<th>Number of Remissions</th>
<th>Number of Remissions Continuing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 months or more</td>
</tr>
<tr>
<td>A</td>
<td>10,000/cu.mm. or less</td>
<td>20</td>
<td>61</td>
<td>52</td>
</tr>
<tr>
<td>B</td>
<td>&gt;10,000/cu.mm. to 12,000/cu.mm.</td>
<td>15</td>
<td>15</td>
<td>9</td>
</tr>
<tr>
<td>C</td>
<td>&gt;12,000/cu.mm. to 25,000/cu.mm.</td>
<td>10</td>
<td>16</td>
<td>7</td>
</tr>
</tbody>
</table>

**Group I:** Unusually long remissions: These three patients either took the drug longer than advised or received a larger than customary daily dose of busulfan. After achieving the usual beneficial effects of treatment they experienced a period of pancytopenia from which they later recovered. The remission which followed ranged from 11 to 26 months in duration.

**Group II:** Moderately long remissions: Twelve additional patients enjoyed remissions longer than six months in duration. Two had transient, mild leukopenia (WBC 4,250 and 4,400 per cu. mm.); none had significant toxicity. All but two of these patients received busulfan until the leukocyte value was less than 11,000 per cu. mm. In these two the final leukocyte values were 14,850 and 18,000 per cu. mm.

Fig. 6.—The sequential changes in the blood leukocyte count following the termination of the initial course of busulfan. Each line represents one patient.
Group III: Short remissions: In eight of these 11 cases the leukocyte value returned to 50,000 per cu. mm. or higher in less than 45 days. In only one instance was the leukocyte value less than 10,000 per cu. mm. at the time busulfan was stopped, whereas in the others the values ranged up to 23,000 per cu. mm.

(2) The number of courses of busulfan: After the first and second courses of busulfan, final leukocyte values of 10,000 per cu. mm. and less were associated with long remissions in almost all patients. However, after fifth and later courses of treatment, similar final values were followed by both long and short remissions.

The duration of remissions after first and fifth or later courses of treatment with busulfan are compared in figure 7. Only courses with final leukocyte values of 10,000 per cu. mm. or less are considered. It was found that 85 per cent of the remissions were six months or longer and 39 per cent were 12 months or longer following the first treatment with busulfan. After fifth or later courses of busulfan only 19 per cent were six months or longer; none were as long as 12 months.

(3) Duration of disease: The duration of chronic myelocytic leukemia prior to the initiation of a course of therapy does not appear to be the factor governing the duration of remissions after busulfan treatment (fig. 8). The occurrence of complete and long remissions in patients who receive their first course of busulfan after a few years of other therapy is additional evidence which speaks some independence between these factors.

In general, it can be said that there was a strong likelihood of producing a long remission if the leukocyte value was below 10,000 per cu. mm. before
Patients with C.M.L. less than 20 years old were compared with those presumed to have had leukemia for one year or less.

Fig. 8.—The relation of the duration of chronic myelocytic leukemia to the length of remission after busulfan treatment, without regard for the number of preceding courses of busulfan. Patients with chronic myelocytic leukemia known for more than three years at the time a course of therapy was begun are compared with those presumed to have had leukemia for one year or less.

Busulfan was stopped; this effect was not observed in some instances after multiple courses of treatment. In fact, for any course of therapy, unless the number of leukocytes was reduced to 10,000 per cu. mm., or less, before busulfan was stopped, long remissions were most uncommon.

Deaths

Twenty-two patients (73 per cent of the group) have died. Nine had developed the acute phase of chronic myelocytic leukemia within a few months preceding their demise. In an additional six patients, the evidence was less complete, but that which was available was consistent with the development of the acute phase, as described later. Of the remaining seven deaths, the circumstances were rheumatic heart disease with congestive heart failure; mesenteric thrombosis; following gastrectomy for a gastric ulcer; cerebral hemorrhage (three patients); and, in one patient, death was unexpected and ascribed to intracranial bleeding following a head injury.

Longevity

Eight of the 30 patients were alive on February 1, 1960, having survived from 20 to 85 months after the first appearance of symptoms attributed to chronic myelocytic leukemia.

For the 22 deceased patients, the total duration of disease ranged from 10 to 85 months. Survival after the first course of busulfan ranged up to 83 months.

Evaluation of the survival of busulfan treated patients can be approximated from our data. Nearly three-fourths of the group have died; however, six of the 22 deceased patients received other treatment prior to busulfan. Of the
eight living patients, four have yet to reach the median survival of the untreated group reported by Minot in 1924. With these limitations in mind we may make some estimates (table 2) by using the log-probability technic employed by Tivey and Osgood and by comparison with data of others.

Our 30 busulfan treated patients, including those still living and those already dead, appear to have lived longer (median survival 42 months) (fig. 9) than Minot's untreated controls (median, 31 months). The median survival of our group is at least as long as that of comparable groups treated by radioactive phosphorus or x-ray (median 32 to 41.5 months) excepting Osgood's combined myelocytic and lymphocytic leukemia group (table 2). Data on a larger number of patients treated only with busulfan would be necessary for a more definitive evaluation of the effect of this drug on longevity of patients with chronic myelocytic leukemia.

**DISCUSSION**

Busulfan has been found to retain most of its beneficial effects through as many as 12 courses of treatment over periods up to six years. There is a tendency for improvement to begin later after repeated courses, and for remissions to be shorter. Nevertheless, it should be noted that most of the patients were less sick, less anemic, and had less splenomegaly and less leukocytosis during most of the later courses of therapy than they had had prior to the initial treatment.

**Remissions:** Interrupted courses of therapy were designed to treat the patients as the individual situations required it, with the object of withholding busulfan when the patient could fare well without it. Continuing the daily treatment with 4 or 6 milligrams of busulfan until the leukocytes are reduced

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of Cases</th>
<th>Treatment</th>
<th>Median Survival, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minot</td>
<td>52</td>
<td>supportive</td>
<td>31</td>
</tr>
<tr>
<td>Tivey</td>
<td>1090</td>
<td>x-ray, radioactive phosphorus</td>
<td>32</td>
</tr>
<tr>
<td>Reinhard</td>
<td>118a</td>
<td>radioactive phosphorus</td>
<td>32</td>
</tr>
<tr>
<td>Tivey</td>
<td>&lt;330</td>
<td>radioactive phosphorus</td>
<td>37</td>
</tr>
<tr>
<td>Osgood</td>
<td>61f</td>
<td>spray x-ray, or</td>
<td>41.5</td>
</tr>
<tr>
<td>Osgood</td>
<td>100§</td>
<td>spray x-ray, or</td>
<td>38</td>
</tr>
<tr>
<td>This series</td>
<td>30</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Six of these patients were alive at the time of the report. An additional 170 patients with chronic myelocytic leukemia seen at the same clinic in the same period as the study group could not be included by Reinhard.

†Six of these patients were alive at the last report.

‡Thirty-eight of the group treated by Osgood's titrated radiation technic.

§All patients were treated by Osgood's technic. Chronic lymphocytic as well as chronic myelocytic leukemia are included. Both types were reported to have statistically indistinguishable survival.

||Eight patients still living.

†Six patients treated with other agents before busulfan.
SURVIVAL IN CHRONIC MYELOCYTIC LEUKEMIA

Fig. 9.—Comparison of survival of patients in this report with those reported by Minot in 1924.10 Points represent original data. The lines are transcribed from log-probability plots of the data.

to 10,000 per cu. mm., or less, appears to be an important part of the program of intermittent treatment. Unless this goal is achieved, there is little likelihood of a long continuing remission once busulfan therapy has been stopped. Furthermore, we noted especially long remissions in three patients who were treated beyond the usual end point and therefore experienced leukopenia and then temporary pancytopenia. Nine other instances of long remissions following pancytopenia have been reported in the literature (table 3). Such cases suggest that treatment to be most successful should be continued to the verge of producing leukopenia or pancytopenia. Unfortunately, the risks entailed cause one to hesitate to continue therapy to this extent. The doses we have employed exert a gradual effect and make it feasible to continue treatment and approach this end point without entailing undue risk.

The shortening of remissions after later courses of treatment in some patients, decreases the interval the patient may remain without therapy. The occurrence of a relapse within a month or two despite optimal treatment with reduction of the leukocyte value to less than 10,000 per cu. mm., could be construed as sufficient reason for a trial of continuous therapy at an appropriately reduced dose rate. This decision should not be made hastily since in an occasional patient, a single short remission was followed by a longer remission after a subsequent course of treatment.

Thrombocytopenia: Thrombocytopenia was noted at some time during the course of the disease in 16 of the 30 patients. The prognosis depended upon the circumstances surrounding its appearance. A good response to busulfan
Table 3.—Duration of Remission in Chronic Myelocytic Leukemia: after Busulfan-Induced Pancytopenia

<table>
<thead>
<tr>
<th>Item</th>
<th>Author</th>
<th>Author's Case No.</th>
<th>Total Dose mg.</th>
<th>Days of Treatment</th>
<th>Duration of Remission after Pancytopenia (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Galton</td>
<td>5</td>
<td>300</td>
<td>16</td>
<td>48</td>
</tr>
<tr>
<td>2</td>
<td>Videbaek</td>
<td>8</td>
<td>404</td>
<td>58</td>
<td>15*</td>
</tr>
<tr>
<td>3</td>
<td>Miesch</td>
<td>1</td>
<td>?</td>
<td>?</td>
<td>15*</td>
</tr>
<tr>
<td>4</td>
<td>Miesch</td>
<td>2</td>
<td>?</td>
<td>?</td>
<td>5*</td>
</tr>
<tr>
<td>5</td>
<td>Miesch</td>
<td>3</td>
<td>?</td>
<td>?</td>
<td>“long remission”</td>
</tr>
<tr>
<td>6</td>
<td>Greig</td>
<td>13</td>
<td>360</td>
<td>45</td>
<td>12</td>
</tr>
<tr>
<td>7</td>
<td>Turesson</td>
<td>–</td>
<td>?</td>
<td>?</td>
<td>18</td>
</tr>
<tr>
<td>8</td>
<td>Unugar</td>
<td>1</td>
<td>670</td>
<td>150</td>
<td>19</td>
</tr>
<tr>
<td>9</td>
<td>Hayhoe</td>
<td>2</td>
<td>470</td>
<td>134</td>
<td>18</td>
</tr>
<tr>
<td>10</td>
<td>Present report</td>
<td>7</td>
<td>430</td>
<td>91</td>
<td>11</td>
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<tr>
<td>11</td>
<td>Present report</td>
<td>28</td>
<td>300</td>
<td>75</td>
<td>18</td>
</tr>
<tr>
<td>12</td>
<td>Present report</td>
<td>22</td>
<td>772</td>
<td>193</td>
<td>24</td>
</tr>
</tbody>
</table>

*Signifies patient was still in remission at the time of the report.

Treatment was not precluded by virtue of this complication alone. When thrombocytopenia was part of a pancytopenia attributable to a high daily dose of busulfan or to an excessively long period of therapy, the outlook was good once the drug was stopped. Two patients with evidence of disease for less than a year had thrombocytopenia prior to any therapy. They survived an additional five years and two years eight months, respectively, under busulfan treatment.

By contrast, when thrombocytopenia appeared in a previously treated patient in whom there were no other signs which one might attribute to drug toxicity, or when thrombocytopenia occurred in a patient after three or more years of known chronic myelocytic leukemia, the prognosis was poor. These patients soon developed other features characteristic of the acute phase and died 1½ to 8 months later. In 10 such cases the median survival was three months after the appearance of thrombocytopenia.

"Acute Phase": The sensitivity of the blood granulocytes to the suppressive action of busulfan during successive periods of therapy was not progressively diminished by repeated and protracted use of busulfan. When the leukocytes did become resistant, however, the change was usually abrupt and marked. This almost always coincided with a change in the morphological pattern of the blood so that, in contrast to the usual findings of chronic myelocytic leukemia, myeloblasts and/or promyelocytes comprised at least 20 per cent of the leukocytes.

We have considered this morphological change to be part of the syndrome of the "acute phase" of chronic myelocytic leukemia. Other features which resembled acute myeloblastic leukemia were: progression of anemia, thrombocytopenia, splenomegaly and lymphadenopathy; an increasing percentage of myeloblasts and promyelocytes in the blood and bone marrow, until they eventually predominated; and, an increase in the marrow M:E ratio even if leukocytosis was absent in the blood. Auer bodies were observed in one of the 15 cases undergoing this transformation. None of these features was re-
busulfan. Colcemide and 6-mercaptopurine produced only temporary benefit in some and had no effect in other cases. In the four instances in which it was prescribed, x-ray therapy directed to the spleen was ineffective in controlling these signs and symptoms of the acute myeloblastic phase.

At least nine and probably 15 of the 22 deceased patients developed the acute phase of chronic myelocytic leukemia. One might question whether this represents merely the natural history of the disease; or whether this number indicates a greater frequency than occurs in the untreated disease, although no more so than that associated with radiation therapy; or whether there is an increased occurrence of the acute phase as the consequence of busulfan treatment. These questions cannot be resolved readily.

We were able to find 15 reports in the literature providing information on the occurrence of the acute phase in groups of patients treated with busulfan, totaling more than 300 cases (table 4). On the other hand, very little documentation could be found with regard to the occurrence of the acute phase in untreated patients and in those treated only with x-ray or radioactive phosphorus (table 4), although the impression is given by several authors that this event is not uncommon.

In the aggregate, over 500 cases are represented by this compendium. Nevertheless, only a few generalizations can be drawn. Certain limitations of the raw data preclude the application of statistical tests. About 60 per cent of the busulfan treated group listed in table 4 were still living while only about 5 per cent of those not receiving busulfan were alive. Furthermore, the latter group is dominated by the experience of one author, while the busulfan tabulation is not dominated by a single experience. Lastly, in many reports the exact criteria defining the "acute phase" were not stated. Although it is likely that there was considerable uniformity, it seems probable that some authors included cases in this classification that others would exclude, and vice versa. It is of interest that the experience of Reinhard with radioactive phosphorus records the lowest group rate.

What significance one may attach to these figures is uncertain. When the records are closed on a greater proportion of the busulfan treated cases, the figures may be different. At this time, perhaps the most that one can conclude is that, of patients with chronic myelocytic leukemia, about half (range, 35–68 per cent) will develop the acute myeloblastic phase, whether they are un-

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**Table 4.—Incidence of the Myeloblastic Phase**

<table>
<thead>
<tr>
<th>Mode of Therapy</th>
<th>No. of Cases</th>
<th>Total No.</th>
<th>%</th>
<th>Myeloblastic phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>None⁴⁹</td>
<td>27</td>
<td>27</td>
<td>100</td>
<td>16</td>
</tr>
<tr>
<td>Busulfan</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present Report</td>
<td>30</td>
<td>22</td>
<td>73</td>
<td>15</td>
</tr>
<tr>
<td>Busulfan</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>386</td>
<td>153</td>
<td>42</td>
<td>88</td>
</tr>
<tr>
<td>X-ray + p³² 12.1⁵⁴</td>
<td>61</td>
<td>55</td>
<td>90</td>
<td>31</td>
</tr>
<tr>
<td>p³² 14</td>
<td>118</td>
<td>112</td>
<td>95</td>
<td>39</td>
</tr>
</tbody>
</table>

*References: (1,7–9,16,18,20–28).*
treated or receive irradiation or busulfan. No certain advantage or disadvantage can be ascribed to any one of these agents in this regard. It may be added that, even if termination in the acute myeloblastic phase were to prove to be more frequent in busulfan treated cases than in those treated by other means, it appears that longevity is probably at least as great and possibly greater in the former than in patients treated by other means.

Resistence to busulfan: Three types of resistance were seen. First, busulfan was ineffective when the acute phase of chronic myelocytic leukemia appeared. Regardless of therapy with this or other agents, these patients died shortly thereafter, as already noted.

Secondly, in a few patients, partial resistance was noted. In two such cases, there was only partial reduction of leukocytosis, and anemia and splenomegaly were not improved. A continuing though partial effect of the drug was apparent, for when busulfan was discontinued there was a prompt sevenfold rise in the leukocyte value and a dramatic recrudescence of other manifestations of the disease. This has also been observed by Till.4

Finally, the shortening of remissions after successive courses of busulfan may also be interpreted as evidence of drug resistance. The recurrence of leukocytosis is probably attributable to cells derived from the residual mitotic pool of granulocytes in the marrow. When this pool is obliterated by excessive treatment, marked and sometimes permanent granulocytopenia ensues. When it is little affected by therapy, recurrence of leukocytosis is prompt. One might speculate that the mitotic pool of granulocytes in the bone marrow is less affected by later courses of busulfan than by the initial exposure, thus resulting in shorter remissions after repeated treatment even though the number of circulating leukocytes may be reduced to normal.

Summary

1. The observations made during the administration of 114 courses of busulfan to 30 patients over a period of seven years are recorded. The responses to initial courses of therapy corresponded with those reported previously. With repeated courses of therapy, subjective improvement, the decline in the number of leukocytes, decrease of anemia and the subsidence of physical signs of the disease were as satisfactory as during the first course but tended to appear later. Patients were ambulatory and most were symptomatically and objectively improved during and after repeated courses as compared to their status beforehand.

2. Remissions were longest when the leukocyte values were 10,000 per cu. mm., or less, at the time busulfan was discontinued. Among such patients, remissions of six months or longer were seen in 85 per cent after the initial course of busulfan but in only 19 per cent after fifth or later courses.

3. Evidence of partial resistance to busulfan was seen in some cases after multiple courses of treatment. Complete resistance occurred in 15 patients upon development of the acute, myeloblastic phase of chronic myelocytic leukemia. When busulfan failed, 6-mercaptopurine and colcemide were temporarily of value; x-ray was not of benefit. After the onset of the acute phase, the median
survival was three months. This mode of termination is probably no more frequent (50 per cent of cases) since the advent of busulfan therapy than before.

4. If anemia was not relieved, or a large spleen was not reduced 50 per cent in size following a course of therapy, the prognosis was poor and the acute phase imminent.

5. Thrombocytopenia in early, untreated cases was not necessarily a bad sign, nor was the use of busulfan precluded because of it. However, when thrombocytopenia appeared in a previously treated patient, without other evidence indicating busulfan toxicity, or when it occurred in a patient with three or more years of known disease, it usually presaged the development of the terminal acute phase.

6. Side effects of busulfan were significant in only one patient; this man received 8 milligrams daily, double the usual dose, for eight months and developed glossitis, anhydrosis and alopecia totalis. The major hazard in the use of the drug was the occurrence of pancytopenia. This could be related to excessive dosage.

7. Morbidity was clearly decreased. Longevity (median 42 months) was greater than in Minot’s untreated cases (median 31 months) and at least as great as that achieved by treatment with radioactive phosphorus and x-ray (median 32–41 months). Repeated courses of busulfan are considered to offer an effective and practical palliative form of therapy for chronic myelocytic leukemia, up to the time of appearance of the terminal acute myeloblastic phase.

**Summario in Interlingua**

1. Es registrate le observationes facite durante le administration de 114 cursos de busulfan a 30 patientes durante un periodo de septe annos. Le responsas a cursos de therapia initial correspondeva a illos previemente reportate. In cursos de therapia repetite, le melioration subjective, le declino in le numero del leucocytos, le reduction del anemia, e le subsidentia del signos physic del morbo eseva tanto satisfactori como in cursos initial sed tendeva a manifestar se plus tardivemente. Le patientes eseva ambulatori, e le majoritate de illes se trovava symptomatically e objectivemente meliorate durante e post cursos de repetita in comparation con lor stato anterior.

2. Le duration del remissiones eseva maximal quando le numeration de leucocytos eseva 10.000 per mm³ o minus al tempore quando le administration de busulfan eseva arrestate. Inter le patientes de iste categoria, remissiones de sex menses de duration o plus eseva obtenite in 85 pro cento del casos post le curso initial de busulfan sed in solmente 19 pro cento del casos post le quinte o ancora plus avantiate curso.

3. Signos de resistentia partial contra busulfan eseva notate in certe casos post multiple cursos de tractamento. Un resistentia complete occurreva in 15 patientes post le disveloppamento del acute phase myeloblastic de chronic leucemia myelocytic. Quando busulfan falleva, 6-mercaptopurina e colcemida eseva temporarimente de valor. Radios X non eseva benefic. Post le declara-
tion del phase acute, le supervivencia median esseva tres menses. Il es probable que iste modo de termination—characteristic de 50 pro cento del casos—non ha devenite plus frequente deposito le advento del therapia a busulfan.

4. In casos in que le anemia non esseva alleviate o in que un allargate splen non se reduciva in dimension per 50 pro cento post le curso de tractamento, le prognose esseva paucio favorabile e le phase acute esseva imminente.

5. Thrombocytopenia in precoce, non tractate casos non esseva necessariamente un signo pessimistic, e su presentia in tal casos non prohibiva le uso de busulfan. Tamen, quando thrombocytopenia appareva in un previemente tractate patiente in qui nulle altere signos de toxicitate per busulfan esseva presente o quando illo occurra in un patiente con tres o quatro annos de documentate morbiditate, illo esseva usualmente sequite per le disveloppamento del acute phase terminal.

6. Le adverse effectos lateral de busulfan esseva significative in solmente un del patientes. Iste esseva un homine qui recipeva 8 milligrammas per die—i.e. duo vices le dose usual—durante octo menses. Ille disveloppava glossitis, anhydrosis, e alopecia total. Le risco principal in le uso del droga esseva le occurrentia de pancytopenia. Isto poteva esser relationated a excessos de dosage.

7. Morbiditate esseva claramente reducite. Le supervivencia—de un duration median de 42 menses—esseva plus longe que in le non tractate casos de Minot (31 menses) e al minus equal a illo obtenite per therapia a phosphoro radiactive e radios X (32 a 41 menses). Es opinate que repetitive cursos de busulfan offere un efficace e practic forma de therapia palliative in chronic leucemia myelocytic, usque al tempore del apparition del acute phase myeloblastic terminal.

REFERENCES

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BUSULFAN TREATMENT OF CHRONIC MYELOCYTIC LEUKEMIA

19


The frequent occurrence of histamine-resistant achyia in myeloblastic, and particularly lymphatic leukemia was stressed. The discussion concerns the meaning of this finding in terms of the humoral theory of the origin of leukemia. When histamine-resistant achyia is found it is necessary to include in the differential diagnosis not only carcinoma of the stomach and pernicious anemia, but also leukemia.—L. D.
Busulfan in the Treatment of Chronic Myelocytic Leukemia. The Effect of Long Term Intermittent Therapy

A. HAUT, W. S. ABBOTT, M. M. WINTROBE and G. E. CARTWRIGHT