Comparison of 6-Mercaptopurine and Busulfan in Chronic Granulocytic Leukemia

By the SOUTHEASTERN CANCER CHEMOTHERAPY COOPERATIVE STUDY GROUP

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SINCE the alkylating agent, busulfan (Myleran), was introduced by Had-dow and Timmis1 and Galton2 in 1953, it has generally been regarded as the treatment of choice for chronic myelocytic leukemia. There is evidence that the survival of patients treated with busulfan is longer than that of untreated patients and is at least as long as that of patients treated with radiophosphorus or x-radiation.3 Currently, it is the standard against which the effectiveness of any other agent must be measured. Regardless of the treatment given, patients with chronic myelocytic leukemia eventually become refractory to therapy, usually because of the development of a “blast crisis.” Busulfan does not prevent the occurrence of this terminal myeloblastic phase nor is it effective in controlling it.

Six-mercaptopurine, one of a series of antipurine drugs, was introduced by Burchenal et al. in 1953.4 It has been particularly useful for acute leukemia. It is one of the most effective drugs available for treatment of the blast phase of chronic myelocytic leukemia and has also been shown to be active in the earlier stages of this illness. At the Conference on 6-mercaptopurine in 1954, a large number of investigators reported their exploratory studies with this drug in myelocytic leukemia.5-10 Summation of their reports showed that of 46 trials in chronic myelocytic leukemia, favorable results were obtained in 35 (76 per cent). Of 50 trials in the blast phase of the disease, there were favorable results in 27 (54 per cent). Although long remissions were sometimes obtained in early chronic myelocytic leukemia, it was felt that remissions were usually too short for practical use. In the surge of enthusiasm for busulfan which occurred at this time, 6-MP found little favor in the treatment of this illness. Inasmuch as 6-MP is effective for the blast phase of this disease, it might possibly be preferable to other agents for the over-all management. Unless it has an effectiveness in the earlier phases of the illness which at

89
least approaches that of busulfan, it would not be practical to attempt long-
term management with it.

The study of purine derivatives continues to be an important area in the
development of chemotherapeutic agents for malignant diseases. Chronic
 granulocytic leukemia is especially suitable for assaying the anti-tumor activity
of these antimetabolites. 6-MP is the standard agent against which any
new compound in this series must be measured. Our group felt that a more
careful documentation of the effects of 6-MP in patients with chronic granulo-
cytic leukemia was in order and, in particular, a critical comparison of the
effectiveness of this drug with that of busulfan. The present study was de-
signed to attain these objectives.

**METHODS AND PROCEDURES**

The procedures followed were identical with those used in a previous group study by
the Southeastern Cancer Chemotherapy Cooperative Study Group which compared the
effectiveness of busulfan and chlorambucil in the short-term control of chronic granulocytic
leukemia. In brief they were the following.

Patients were admissible who had chronic granulocytic leukemia which was uncon-
trolled or in relapse whether or not previous treatment had been given and whether
or not there were overt symptoms or physical evidences of disease. Patients with more than
10 per cent myeloblasts in the blood or other evidence of acute myeloblastic exacerbation
were excluded.

**Administration of Drugs**

Patients were assigned to one or the other drug by a randomization method. Treat-
ment was initiated with a single daily dose of 6 mg. of busulfan or 3 mg. per Kg. of 6-MP.
After the first 2 weeks the dose was varied by thirds to achieve either 1) complete sup-
pression of physical and hematologic evidence of disease, or 2) depression of bone
marrow function as evidenced by peripheral blood counts to a degree indicating that
the maximum tolerable dose had been administered. The study was continued for 12
weeks before evaluation of the effect.

**Evaluation of Results**

Each completed case was reviewed by all investigators. As in the previous study, re-
sponses were classified as "excellent," "good," "fair," "questionable," or "no ef-
f ect." In brief, "fair" indicated 25 to 50 per cent improvement, "good" better than 50
per cent improvement and "excellent" the disappearance of symptoms, physical findings
and alterations in the blood counts attributable to the disease.

**Statistical Methods**

Responses were divided into two groups: "good" or better, and "fair" or worse. The
significance of the observed differences were tested by chi square using Yates correction of
continuity. The blood counts and hemoglobin concentrations were analyzed by dis-
criminatory analysis, which is equivalent to Hotelling's T². Before analysis, the blood
counts were transformed by logarithm (count plus 1). Hemoglobin levels were analyzed
without transformation.

We were interested in the degree of control of the manifestations of illness which was
achieved in 12 weeks, the rapidity with which this was brought about, and the ease with
which the improvement was maintained over this period, as well as in the over-all hemat-
ologic effects of the drugs.
COMPARISON OF 6-MP AND BUSULFAN IN CGL

RESULTS

Thirty-two patients were admitted to the present study. The patients were assigned to treatment at random in a proportion of two patients on 6-MP to one on busulfan for reasons that will be evident below. Twenty-two patients were begun on 6-MP. Only 15 satisfied fully protocol requirements for the full 12-week course. Ten patients were treated with busulfan, nine of whom completed the prescribed course.

Additional busulfan-treated controls were obtained from patients treated in the previous study ("Study I") in which busulfan and chlorambucil were compared utilizing a protocol identical to that of this study ("Study II"). In both studies the agents were chosen at random, and the investigators and protocols were identical. Analysis of the two busulfan-treated groups demonstrated that they were similar in terms of age, sex, duration and severity of the disease (see table 1). The differences in response were not significant by the chi square test (see table 2). Hematologic studies of the two groups were not statistically different either at the beginning or at the end of 12 weeks of treatment. We, therefore, combined both groups into a single busulfan-treated group for comparison with the 6-MP-treated group.

Table 1.—Summary of Clinical Data

<table>
<thead>
<tr>
<th></th>
<th>Myleran</th>
<th>Study I</th>
<th>Study II</th>
<th>6-MP</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>31</td>
<td>16</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Age (yrs.):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>47.7</td>
<td>51.4</td>
<td>47.3</td>
<td></td>
</tr>
<tr>
<td>median</td>
<td>47</td>
<td>48.5</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>range</td>
<td>17–79</td>
<td>37–77</td>
<td>28–77</td>
<td></td>
</tr>
<tr>
<td>Sex:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>9</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>female</td>
<td>22</td>
<td>13</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Duration of disease (mos.):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>11.6</td>
<td>51.1</td>
<td>26.3</td>
<td></td>
</tr>
<tr>
<td>median</td>
<td>10</td>
<td>16.5</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>range</td>
<td>0(?)-80</td>
<td>1–336†</td>
<td>0(?)-192†</td>
<td></td>
</tr>
<tr>
<td>Previous therapy:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>x-ray</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>chemotherapy</td>
<td>10</td>
<td>11</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>none</td>
<td>14</td>
<td>4</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

*One patient had received radium brick therapy.
†One woman had been followed at Duke Hospital for 28 years. If she is omitted: mean = 32.1, median = 16, range = 1–195. One woman at Emory University had been aware of a left upper quadrant mass for 16 years without other symptoms until 3 weeks before diagnosis. If she is omitted as well as the above: mean = 20.2, median = 15.5, range = 1–77.
‡The woman at Emory University who had had symptoms for 16 years was treated with 6-MP before being treated with Myleran. If she is omitted: mean = 14.5, median = 11, range = 0–50.
Table 2.—Summary of Therapeutic Responses

<table>
<thead>
<tr>
<th>Response</th>
<th>Busulfan</th>
<th>6-mercaptopurine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study I</td>
<td>Study II</td>
</tr>
<tr>
<td>Excellent</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Good</td>
<td>22</td>
<td>8</td>
</tr>
<tr>
<td>Fair</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Questionable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No change</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dead</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>31</td>
<td>16</td>
</tr>
</tbody>
</table>

Thirty-one patients were treated with busulfan in Study I. The results of 21 patients have been published previously. Treatment in 10 others was completed after the deadline for the previous analysis.

Six patients treated with busulfan in Study I were subsequently admitted to Study II. Three received busulfan again and three received 6-MP.

Seven of the patients who were treated with 6-MP in Study II were permitted to relapse after completing the study and were then treated with busulfan according to the same protocol in a "switchback" study. Two of these patients had previously received busulfan in Study I.

Thus, a total of 62 twelve-week courses of study were completed in 49 patients. A single study was made in 38, two studies in 9 and three studies in 2. Twenty-six of the 62 studies were made on patients who had not received treatment previously. The contribution of completed studies from individual institutions was as follows:

- University of Alabama ............... 1
- Duke University ..................... 4
- Emory University .................... 28
- University of Kansas ................ 3
- University of Mississippi .......... 5
- University of North Carolina ....... 8
- Medical College of Virginia ......... 4
- Washington University .............. 9

Total No. Completed Studies ........... 62

Data comparing age, sex, duration of disease and previous therapy of these patients is tabulated in table 1.

The evaluations of the therapeutic responses of the three groups at the end of 3 months are summarized in table 2. The differences in response to the two drugs as evaluated at the end of 12 weeks of treatment were highly significant. A response defined as "good" or better was obtained in 89 per cent of the patients treated with busulfan, but in only 33 per cent of the patients treated with 6-MP. One can predict with 95 per cent confidence that 77 to 95 per cent of patients with chronic granulocytic leukemia selected and treated as described will have a "good" or excellent" response to busulfan and that only 14 to 63 per cent of those treated with 6-MP will respond as well. The
Table 3.—Summary of Hematologic Effects of Busulfan and 6-mercaptopurine in Chronic Granulocytic Leukemia

<table>
<thead>
<tr>
<th>Week</th>
<th>Busulfan</th>
<th>6-mercaptopurine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Hemoglobin Gm. %</td>
<td>11.4</td>
<td>11.4</td>
</tr>
<tr>
<td>std. dev. (obs. scale)</td>
<td>2.2</td>
<td>1.9</td>
</tr>
<tr>
<td>Platelets x 10^-3</td>
<td>439.0</td>
<td>367.6</td>
</tr>
<tr>
<td>std. dev. (obs. scale)</td>
<td>471.4</td>
<td>401.7</td>
</tr>
<tr>
<td>std. dev. (log scale)</td>
<td>.31</td>
<td>.29</td>
</tr>
<tr>
<td>Total leucocytes x 10^-3</td>
<td>103.4</td>
<td>20.54</td>
</tr>
<tr>
<td>std. dev. (obs. scale)</td>
<td>139.2</td>
<td>76.17</td>
</tr>
<tr>
<td>std. dev. (log scale)</td>
<td>.39</td>
<td>.48</td>
</tr>
<tr>
<td>Immature granulocytes x 10^-3*</td>
<td>22.37</td>
<td>.90</td>
</tr>
<tr>
<td>std. dev. (obs. scale)</td>
<td>62.75</td>
<td>31.35</td>
</tr>
<tr>
<td>std. dev. (log scale)</td>
<td>.85</td>
<td>1.25</td>
</tr>
</tbody>
</table>

*Granulocytes less mature than band neutrophils.

difference in “good” or better responses between busulfan-treated patients in Study I and Study II was not significant.

The hematologic status of the two groups before therapy, at the end of 4 weeks and at the end of 12 weeks, is compared in Table 3 and in Figure 1. Before analysis, the blood counts were transformed by logarithm and plotted in terms of geometric mean (the antilogarithm of the average logarithm) on a logarithmic scale. The hemoglobin values were analyzed and plotted without transformation. The 95 per cent range is indicated for all values except those of immature granulocytes in which the range was so great as to be off scale.

A statistical analysis showed that the combined busulfan groups were not significantly different from the 6-MP groups at the beginning of the study. The groups treated with 6-MP and with busulfan were significantly different at 4 and at 12 weeks. The difference was accounted for chiefly by differences in hemoglobin concentration and number of platelets. The previous studies of this group demonstrated in patients with chronic granulocytic leukemia and chronic lymphocytic leukemia the exceptional susceptibility of platelets to busulfan. In chronic granulocytic leukemia, this effect of busulfan is often advantageous. The excessively high platelet counts exhibited by most patients with chronic granulocytic leukemia is usually brought to normal levels by busulfan. Table 3 and figure 1 illustrate the failure of 6-MP to provide adequate control of the high platelet count in this disease. There was often a rise in platelet count during the period of study.

Busulfan brought excessively high platelet counts to normal in 20 of 31 trials, producing thrombocytopenia in only two instances. Of four trials beginning with thrombocytopenia, the platelet level rose to normal in three. Platelet counts remained normal in all 10 trials which started at a normal level.
Fig. 1.—Hematologic effects of busulfan and 6-mercaptopurine in chronic granulocytic leukemia; mean values at start of therapy and at 4 and 12 weeks are plotted with the 95 per cent range indicated. Except for hemoglobin, the blood counts were transformed to logarithm prior to analysis and are plotted on a logarithmic scale.

6-MP brought an excessively high platelet count to normal in only four of nine trials. One trial beginning with thrombocytopenia ended with a normal platelet count. Platelet counts which were initially normal remained so in each of four instances. Although thrombocytopenia developed during treatment in two patients, the platelet count rapidly returned to normal and remained so.

In summary, the platelet count was high at the end of nine of 45 trials of busulfan and low in three. Following 6-MP the platelet count was excessively high in five of 14 trials and low in none. The mean platelet count at the end of treatment with 6-MP was more than twice that after treatment with busulfan.

Only three of 32 previously treated patients had a hemoglobin concentration below 10 Gm. per cent at the beginning of therapy, and all of these improved. In the previously untreated group, however, 15 of 26 patients were anemic to this degree. Two of nine patients treated with busulfan and one of six
treated with 6-MP failed to rise above 10 Gm. per cent within 12 weeks. It will be noted from figure 1, however, that on the average there was a rise of 1.4 Gm. per cent hemoglobin during the 12-week study in those patients treated with busulfan, but no change in the average hemoglobin in those patients treated with 6-MP.

The most interesting effects of the two drugs were those on the total leukocyte count and the immature leukocyte count. Busulfan produced a steady fall in both of these counts and normal or nearly normal levels were achieved within 12 weeks in most instances. Six-MP in the dosage used produced a more rapid drop in both of these measurements so that the status of these patients at the end of 4 weeks appeared to be better than that of the busulfan-treated group. After the initial rapid fall, however, there was often considerable fluctuation, making it very difficult to maintain full control. This is seen in the mean leukocyte count and also in the variance. At 12 weeks the variance of the immature white cell count for busulfan- and 6-MP-treated patients was 14.59 and 39.82 respectively and for the total white cell count the variance was 82.26 and 742.02. Both of these differences are statistically significant.

It may be possible to achieve smoother control of chronic granulocytic leukemia with 6-MP by performing blood counts and regulating the dose more often than once a week. In some of the patients in whom this was done, there was still a striking fluctuation of the total white count. Failure of recognition of this need for frequent adjustment of 6-MP dosage resulted in poorer responses in some of the patients treated early in the course of the investigation than might have been obtained. Management with busulfan was generally smooth and required less frequent adjustment of dosage.

Another indication of success of therapy is the reduction of the total leukocyte count to the level of 15,000 per cu. mm. or less at some time during the 12-week study period. This level was achieved in 39 of 46 trials of busulfan and in 12 of 14 trials of 6-MP. Once achieved, however, it was more likely to remain low for the duration of the study in busulfan-treated patients than in those treated with 6-MP.

In patients treated with 6-MP, the initial leukocyte count level seemed to influence very little the rapidity of response or the total dose required to achieve it. When busulfan was used, the rate of fall of the leukocytes was more predictable and the time and dosage required to achieve control was related to the initial leukocyte count, as has been documented by Haut et al.³ When the count was above 100,000 per cu. mm., 47 days and 204 mg. of busulfan were required for the average patient. Patients with leukocyte counts between 50,000 and 100,000 per cu. mm. required an average of 32 days and 178 mg., and those with counts below 50,000 per cu. mm. required an average of 26 days and 128 mg.

The changes in performance status, bone tenderness and spleen size were also analyzed (table 4). All of these improved with both drugs. While the end results appear to be better with busulfan, the differences are not significant.

Untoward effects with either agent were minimal. In only two patients in
Table 4.—Average Changes in Performance Status, Bone Tenderness and Size Spleen from Beginning to End of Treatment

<table>
<thead>
<tr>
<th></th>
<th>6-MP Beginning</th>
<th>6-MP End</th>
<th>Myleran Beginning</th>
<th>Myleran End</th>
</tr>
</thead>
<tbody>
<tr>
<td>Performance status</td>
<td>80</td>
<td>88</td>
<td>89</td>
<td>96</td>
</tr>
<tr>
<td>Number with bone tenderness</td>
<td>6 (29%)</td>
<td>4 (19%)</td>
<td>14 (31%)</td>
<td>7 (16%)</td>
</tr>
<tr>
<td>Spleen size (cm. below ribs)</td>
<td>4.3</td>
<td>2.7</td>
<td>4.1</td>
<td>1.4</td>
</tr>
</tbody>
</table>

None of these differences are significant.

Table 5.—Therapeutic Responses of Patients with Chronic Granulocytic Leukemia in Whom Sequential Trials of Busulfan and 6-mercaptopurine Were Made

<table>
<thead>
<tr>
<th>Sequence of Drug Trial</th>
<th>Patient</th>
<th>Busulfan</th>
<th>6-mercaptopurine</th>
<th>Busulfan</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>good</td>
<td>questionable</td>
<td>fair</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>good</td>
<td>questionable</td>
<td>good</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>good</td>
<td>good</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>good</td>
<td>questionable</td>
<td>fair</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>good</td>
<td>excellent</td>
<td>good</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>good</td>
<td>good</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>questionable</td>
<td>fair</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>fair</td>
<td>good</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>good</td>
<td>good</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>fair</td>
<td>excellent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>questionable</td>
<td>died*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Patient died in blast crisis after making an apparently favorable response to therapy during first 4 weeks.

each group was there a fall in platelet count to below normal levels. In both instances in which thrombocytopenia was produced by 6-MP, the count quickly returned to normal. Thrombocytopenia after busulfan is more persistent. In one patient treated with 6-MP, there was a transient slight fall in hemoglobin concentration.

As was previously noted, 11 patients completed more than one study. The results of these sequential or "switch-back" studies are tabulated in table 5. It is noted that when busulfan was given more than once, the response was the same to each course in two of five patients and varied by only one category in the other three. This relatively constant response to busulfan in repeated courses has been pointed out by Haut et al.º

In striking contrast, only one of the eight patients who received a course of treatment with each drug had a better response to 6-MP than to busulfan and only two responded as well. In two the response to busulfan was better than that of 6-MP by two categories. In patient number 11 the comparison is perhaps not quite fair, inasmuch as in the second course of treatment the patient was making an apparently favorable response to busulfan therapy during the first 4 weeks when a blast crisis developed and the patient died.

Sequential trials of several drugs in the same patient should provide a valid comparison of their relative effectiveness. The objections to such a thesis are that the disease may become more refractory to treatment with time or,
on the other hand, that the patient is usually sicker and has a higher leukocyte count and a larger spleen on the occasion of first treatment than he is permitted to develop before treatment of subsequent relapses. This may make him easier to treat in later studies. Inspection of table 5 would suggest that in our patients these objections were not applicable and that sequential trials in the same patient do indeed confirm the findings of randomized trials in different patients. In these 11 patients, responses of "good" or better were obtained in 10 of 16 trials of busulfan and in only 2 of 8 trials of 6-MP.

There were two characteristics in which 6-MP was superior to busulfan. It produced a more rapid fall in the total leukocyte count and in the immature granulocyte count than did busulfan and might be expected, therefore, to effect more rapid improvement at times in patients with very high counts. It did not induce thrombocytopenia as often and recovery was more rapid when this did occur. It might therefore be of value as an alternative treatment in patients with thrombocytopenia and in particular in patients who have had a prolonged thrombocytopenia after previous treatment with busulfan. In all other respects, busulfan was a more effective drug.

Shullenberger has reported a long-term study of the Southwestern Cancer Chemotherapy Study Group comparing the relative effectiveness of busulfan and 6-MP over a prolonged period of time.25 The data reported are of a different kind than those discussed in this paper and a comparison of the results of the two series is not possible. Shullenberger concluded that the degree of control of the measurable aspects of chronic granulocytic leukemia fluctuates less under busulfan therapy than under 6-MP but that this does not appear to be a significant difference since the spread between the effects of the two drugs on the various parameters was not wide. Neither drug seemed to prevent or delay blastic transformation of the leukemic process nor to significantly prolong survival. We wish to emphasize that the criteria by which the comparisons of the two drugs were made was quite different from ours. We believe that the criteria we used for over-all clinical effect were reasonable ones and our results indicate such a striking difference in the degree of improvement noted in individual patients over a reasonable period of time that we would not recommend the use of 6-MP for the routine treatment of this disease.

Summary and Conclusions

The relative effectiveness of 6-MP and busulfan for the achievement and maintenance of control of chronic granulocytic leukemia over a period of 12 weeks has been studied. In a randomized study, 15 patients received 6-MP and 9 busulfan. In addition, results of a similar study in which 31 patients were treated with busulfan were combined with the current study. Sequential studies in which patients received more than one course of study were made in 11 patients so that altogether 62 studies were completed in 49 patients.

6-MP produced "good" or "excellent" responses in only 5 (33 per cent) of 15 trials, whereas, 42 (89 per cent) of 47 trials using busulfan responded to this degree.
Busulfan is superior to 6-MP for the over-all control of chronic granulocytic leukemia during a 12-week course of study. Not only are the results obtainable with 6-MP inferior to those with busulfan, but 6-MP is also more difficult to use.

Busulfan in the dosage used reduces the granulocyte count somewhat more slowly than does 6-MP, but the effect is more prolonged. The escape of the granulocytes from depression by 6-MP is very rapid.

The reduction of platelet counts from abnormally high levels to normal is more effectively achieved with busulfan than with 6-MP since, in doses sufficient to reduce the granulocyte count, the latter drug is less likely to affect the level of platelet counts than is busulfan.

It may be possible to exploit these differences occasionally. If a patient becomes difficult to control with busulfan because of thrombocytopenia, 6-MP may offer control with greater safety. In patients whose marrow function is especially susceptible to depression with busulfan, 6-MP may offer the safety valve of a more rapid escape from overtreatment.

In general, 6-MP is not recommended for the routine management of chronic granulocytic leukemia prior to the development of the blast stage.

**Summario in Interlingua**

Esseva studiate le relative efficacia de 6-mercaptopurina e de busulfano in effectuar e mantener stabilisation de chronic leucemia granulocytic durante un periodo de 12 septimanas. In un studio aleatorisate, 15 patientes recipeva 6-mercaptopurina e 9 recipeva busulfano. In plus, le resultatos de un simile studio in que 31 patientes esseva tractate con busulfano esseva combine con le presente investigation. Studios sequential in que patientes recipeva plus que un curso esseva effectuate in 11 casos, de manera que un total de 62 studios esseva complete in 49 patientes.

6-Mercaptopurina produceva “bon” o “excellente” responsas in solmente 5 de 15 essayos (33 pro cento), durante que 42 de 47 essayos con busulfano (89 pro cento) resultava in ille mesme grado de responsa in le uso de busulfano.

Busulfano es superior a 6-mercaptopurina in le stabilisation general de chronic leucemia granulocytic durante un curso de studio de 12 septimanas. E non solmente es le resultatos obtenible con 6-mercaptopurina inferior a illos obtenite con busulfano, 6-mercaptopurina es etiam plus difficile a usar.

In le dosages usate in le presente studio, busulfano reduce le numeration granulocytic un pauco plus lenetemente que 6-mercaptopurina, sed le effecto de busulfano es plus prolongate. Le escappamento del granulocytos ab le effecto deprimitori de 6-mercaptopurina es multo rapide.

Le reduction del numeration del plachettas ab anormalmente alte nivellos usque al norma esseva effectuate plus efficacemente con busulfano que con 6-mercaptopurina, proque—in doses sufficiente a reducer le numeration granulocytic—6-mercaptopurina suifre de un plus basse probabilitate de afficer le nivellos del plachettas que busulfano.

Occasionalmente il va sin dubita esser possibile exploitar iste differentias.
COMPARISON OF 6-MP AND BUSULFAN IN CML

Si, per esempio, un paziente è difficile a stabilizzar con busulfano a causa di trombocitoopenia, 6-mercaptopurina offre forse un più salve medio di stabilisation. In paziente in qui la funzione medullare è specialmente susceipitibile a essere deprimite per busulfano, 6-mercaptopurina offre possibilmente un solution gratias a più rapido escappamento ab excessos therapeutic associato con illo.

A generalmente parlar, 6-mercaptopurina non è recommandate pro l'trattamento routinari de chronic leucemia granulocytic ante le disveloppamento del stadio blastic.

REFERENCES

19. Wilson, S. J.: The clinical and hemato-


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Comparison of 6-Mercaptopurine and Busulfan in Chronic Granulocytic Leukemia

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