Pipobroman Therapy of Polycythemia Vera

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Between 1971 and 1981, 74 patients with polycythemia vera were treated with pipobroman using a high-dose induction, low-dose maintenance regimen. Complete remission was achieved in 51 of 54 previously untreated patients (94.4%) and in 17 of 20 patients (85%) previously treated with radioactive phosphorus (32 p) and busulfan. The earliest modifications were noted on day 16, and on the average, blood counts were normal by day 45. Thirty percent of the patients relapsed, the mean duration of the remission being 17.5 mo. Following recurrence pipobroman was consistently effective in the same doses but the mean duration of the next remissions was 10 mo. Transient leukopenia and thrombocytopenia occurred in 8% and 7% of patients, respectively, during initial phase, and anemia was noted in 3 patients. Macrocyesis was noted in 20% of patients during maintenance phase. Three cases of acute leukemia and 3 cases of osteomyelosclerosis were recorded, all occurring in patients who had previously received 32 p and/or busulfan. No hematologic malignancies were seen among patients treated with pipobroman alone; follow-up exceeded 6 yr for 20 patients and the median follow-up period was 3.6 yr. Pipobroman appears safer than other alkylating agents; it is as effective as 32 p and works more quickly. Longer follow-up will be required to evaluate the drug’s oncogenic potential, which is still not known.

PHLEBOTOMY, radioactive phosphorus, and cytotoxic drugs are the modalities that have been used to treat patients with polycythemia vera.

Phlebotomy rapidly reduces blood volume, but in the long-term, it does not prevent the onset of thromboembolic complications and achieves a shorter median survival than the other forms of therapy.1

The introduction of radioactive phosphorus profoundly modified the prognosis of the disease. The median survival was extended to over 10 yr, and cardiovascular complications were reduced by half as compared to patients treated by irradiation. It appears very likely, however, that radioactive phosphorus promotes hematologic malignant transformation that accounts for between 30% and 40% of deaths.1,8

Cytotoxic drugs have generally been employed in combination with radioactive phosphorus to permit less frequent administration of the latter or to treat recurrences occurring after increasingly shorter remission periods. The effect of cytotoxic drugs alone has not been extensively studied.5,9,11 The most effective drugs are the alkylating agents busulfan, chlorambucil, and melphalan, but these drugs are associated with a number of untoward effects. Furthermore, the oncogenic potential of long-term treatment with chlorambucil15 and melphalan16 is now starting to be recognized.

In view of the shortcomings of standard forms of therapy, we undertook an evaluation of pipobroman, a piperazine derivative, advocated for the treatment of polycythemia vera since 1962.12 However, this drug has not been tested in long-term studies with the exception of a recent series reported by Bernard et al.13 In this article, we present the results of a protocol initiated in, and followed up since 1971, which consists of induction and systematic maintenance therapy with pipobroman.

MATERIALS AND METHODS

Seventy-four patients with polycythemia vera were treated by pipobroman between 1971 and 1981. There were 49 male and 25 female patients.

The diagnostic criteria required for the diagnosis of polycythemia vera were: a hematocrit above 55% in men and 52% in women; a total red blood cell volume exceeding 36 ml/kg in men and 32 ml/kg in women; and at least two of the following: splenomegaly, a white blood cell count exceeding 12 × 10^3/liter in the absence of infection, a platelet count above 400 × 10^3/liter, panhyperplasia with diminished fat vacuolation on bone marrow aspirates, and exclusion of a respiratory or tumor origin of polycythemia.

All patients studied had active disease. Volume Packed Red Cells (VPRC) was above 60% in 51 patients (69%), between 56% and 60% in 15 patients (20%), and between 52% and 56% in 8 patients (11%). White blood cell counts (WBC) were above 12 × 10^3/liter in 37 patients (50%) and above 8 × 10^3/liter in 24 patients (32%). Platelets were above 400 × 10^3/liter in 39 patients (53%) and above 300 × 10^3/liter in 21 patients (31%). A mild splenomegaly was palpable in 35 patients (47%) and a large spleen in 3 patients. Phlebotomy was performed before the start of pipobroman when polycythemia was badly tolerated in 24 patients. In these cases, the VPRC after phlebotomy was used as initial data to determine the potency of pipobroman. Fifty-four patients had received no prior treatment (group I). Among the 20 previously treated patients (group II), 15 had received 32 p, either alone or combined with busulfan, and the other 5 had been treated only with busulfan and phlebotomy.

The treatment was administered in two phases. In the initial phase, the daily dose was 75 mg of pipobroman. Ten of the first patients, however, received only 50 mg/day. This dose was main-
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tained until the hematocrit dropped to 52% in men and 50% in women. Dosage was then reduced to 50 mg/day until the hematocrit was below 48% in men and 46% in women. The blood count was controlled every 2 wk during this phase. If there was no significant decrease in the hematocrit (i.e., 3 units) after 1 mo of treatment, the dose was raised to 100 mg/day for 2 wk. If despite this dosage increase there was still no result, the treatment was considered a failure.

The maintenance phase was begun as soon as the hematocrit had returned to normal. Pipobroman was administered in a unit dose of 25 mg at variable intervals (once a day to once a week), adequate dosage being 75 mg/wk on the average after an adaptation period lasting 2 mo. Blood counts were performed monthly during the first 2 mo and every 4 mo thereafter. Patients included in the protocol were selected solely on the basis of the possibility of regular follow-up. The results were classified into the following categories. (1) Complete remission was defined as disappearance of all clinical signs and return to a normal count: hematocrit <48% in men and <46% in women, WBC <10 x 10^9/liter, platelets <400 x 10^9/liter. (2) Partial remission was defined by the persistence of either splenomegaly or a hematocrit between 48% and 55% in men and 46%-52% in women. (3) Treatment failures were defined by the absence of any response.

RESULTS

The overall results for the two groups of patients are shown in Table 1. Group I: Among the 54 patients who received pipobroman as first-line therapy, 51 achieved a complete remission (94.4%), with the 3 remaining patients achieving a partial remission. Group II: In the 20 previously treated patients, a complete remission was observed in 17 cases (85%), a partial remission in 2 cases, and in 1 case treatment with pipobroman was a failure.

In patients who received only 50 mg of pipobroman daily, the mean duration of the initial treatment phase was 62 days as compared to 46 days for patients who initially received 75 mg/day.

A notable decrease in hematocrit values, (i.e., 3 units) was recorded after 16 days of treatment on the average.

As a rule, the number of white blood cells and platelets was also reduced. The decrease in platelet numbers paralleled the declining hematocrit. The platelet count dropped below 400 x 10^9/liter in all patients after a mean interval of 56 days. In 7 patients (8%), the number of platelets dropped below 100 x 10^9/liter, and in 2 cases treatment was temporarily discontinued.

White blood cells diminished more slowly than the hematocrit, and it took around 20 wk for the WBC count to return to normal. Leukopenia below 3 x 10^9 WBC/liter was observed in 6 cases. Thrombocytopenia and leukopenia were transient and were rapidly reversed.

Three cases of anemia (hemoglobin 10 g/dl) were recorded during the induction phase, but hemoglobin returned to normal levels within a few weeks. In one of these cases, severe bone marrow sideroblastosis prompted discontinuation of pipobroman as a precautionary measure, and the patient was treated by phlebotomy. Macrocytosis was observed in 20% of patients during maintenance treatment.

Pipobroman induced few adverse effects. In one patient treatment was discontinued because of a skin rash. Three patients had diarrhea, requiring withdrawal of treatment in two cases. Neither hair loss nor amenorrhea was observed.

Course

Patients have been followed for up to 10 yr after beginning of the treatment with pipobroman. The median follow-up period was 3.6 yr for group I and 4.9 yr for group II. The follow-up period exceeded 6 yr for 20 patients of group I.

Six deaths were recorded in the two groups (74 patients) during the period covered by this study. Two of these deaths resulted from vascular accidents that occurred 3.5 and 6 yr after the diagnosis of polycythemia vera. The other 4 deaths were due to hematologic malignancies.

Despite the maintenance treatment, adjusted according to hematocrit fluctuations, recurrences did occur. Recurrence was defined as an elevation of the hematocrit to 55% or above in men, 52% or above in women.

Of the 68 group I and II patients who achieved a complete remission, 19 (30%) had at least one recurrence. The mean duration of the first remission in these patients was 17.5 mo. Resumption of treatment with the initial doses again produced a complete remission in all patients.

Sixteen patients had a recurrence more than one occasion. The mean duration of the next remissions was 10 mo. On each subsequent occasion, the disease remained just as responsive to pipobroman. In two patients the duration of remission between the third and fourth recurrences was shorter than 6 mo, and pipobroman was discontinued for this reason.

Hematologic Malignancies

Seven hematologic malignancies were observed, including 3 cases of acute leukemia, 3 cases of osteo-

<table>
<thead>
<tr>
<th>Table 1. Results of Initial Treatment With Pipobroman</th>
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<tbody>
<tr>
<td>Result</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Complete remission</td>
</tr>
<tr>
<td>Partial remission</td>
</tr>
<tr>
<td>Treatment failure</td>
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<tr>
<td>Total</td>
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myelosclerosis (Table 2), and 1 chronic granulocytic leukemia (Table 2).

The three cases of acute myeloblastic leukemia supervened in patients treated with 32 p (mean dose 12 mCi) before pipobroman. Two of these three patients had also received busulfan for 3 and 7 yr, respectively.

The mean interval between the diagnosis of polycythemia vera and that of acute leukemia was 13 yr. The mean interval between the first administration of 32 p and onset of leukemia was 7 yr. These 3 patients were treated with pipobroman for an average of 3 yr.

The three patients who developed osteomyelosclerosis were all treated with 32 p prior to receiving pipobroman (mean dose 18.6 mCi). One patient had also received busulfan for 4 yr. The mean interval between the diagnosis of polycythemia vera and that of osteomyelosclerosis was 6.8 yr. The mean interval between the first administration of 32 p and the diagnosis of osteomyelosclerosis was 6.8 yr. The mean duration of treatment with pipobroman prior to the onset of the malignancy was 3.2 yr. One of these patients died of a lung infection.

One case of chronic granulocytic leukemia was diagnosed on the basis of a characteristic blood picture and the presence of the Ph1 chromosome anomaly 3 yr after polycythemia vera was first recognized. A cytogetic study had not been performed at that time. This patient was treated with pipobroman alone.

### DISCUSSION

Pipobroman is a piperazine derivative first shown to possess antitumor properties in 1960. It is a neutral amide derivative of nitrogen mustard (NH2) containing a part of the piperazine ring. Its mechanism of action is of the alkylating type; it inhibits the activity of DNA polymerase and RNA polymerase and reduces the incorporation of pyrimidine nucleotides into DNA and RNA.

In animals, the drug produces a number of chromosome changes. Its effects are more marked on differentiated cells than on pluripotent stem cells.

Pipobroman exerts clear-cut antitumor effects in animal models, but clinical trials in human solid tumors and hematologic malignancies have been disappointing. However, definite efficacy has been observed in myeloproliferative syndromes, notably in polycythemia vera.

Our results confirm the efficacy of pipobroman in the treatment of polycythemia vera, regardless of whether it is administered as first-line therapy or following radioactive phosphorus or other alkylating agents. The complete remission rate recorded in our study (94%) is comparable to that reported in other series of the literature.

Pipobroman acts quickly, an effect being noticeable at the beginning of the third week of treatment, on the average, with a dose of 75 mg/day. This dosage appeared to us to be adequate. The blood picture returned to normal after 46 days of treatment on the average, this interval being similar to that observed in other series and shorter than that reported by Bernard et al. (78 days).

The maintenance treatment advocated in the early studies is easily adjustable during the 2 mo that follow the remission, and a control every 4 mo thereafter suffices to ensure adequate dosage and absence of toxicity. The mean duration of remission (17.5 mo) is consistent with previous reports.

As reported in earlier studies, we observed only very moderate clinical and hematologic toxicity. The cases of moderate cytopenia observed in this study were always transient. The very rare cases of bone marrow aplasia reported were always associated with excessive dosage or inadequate patient follow-up.

Thus, we observed one case of a patient from this study who was lost to follow-up for 6 mo and who kept taking 75 mg/day for this entire period. None of the usual side effects of alkylating agents were noted.

In light of these data, pipobroman appears to occupy a privileged position among the alkylating agents used to treat polycythemia vera. The complete remission rate obtained with pipobroman is comparable to that achieved with other drugs: 86% for busulfan, 90% for chlorambucil and melphalan, 75% for hydroxyurea.

The time required to achieve a complete remission is shorter with pipobroman: 1.5 mo, on the average, as compared to 2.6 mo for melphalan and 3.9 mo for chlorambucil. Pipobroman also produces less hematologic toxicity, with leukopenia in 7%–8% of cases versus 20% on the average with melphalan and chlo-

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**Table 2. Features of Malignant Hematologic Transformation (6 Cases)**

<table>
<thead>
<tr>
<th>Treatment with 32 p (mCi)</th>
<th>Treatment with busulfan (duration in months)</th>
<th>Treatment with pipobroman (duration in months)</th>
<th>Time to onset (yr)</th>
<th>Course</th>
<th>Dead</th>
<th>Alive</th>
<th>Dead</th>
<th>Alive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Leukemia Case 1</td>
<td>6</td>
<td>10</td>
<td>6</td>
<td>Dead</td>
<td></td>
<td></td>
<td>Dead</td>
<td></td>
</tr>
<tr>
<td>Acute Leukemia Case 2</td>
<td>12</td>
<td>24</td>
<td>4.5</td>
<td>Dead</td>
<td>6</td>
<td></td>
<td>Dead</td>
<td></td>
</tr>
<tr>
<td>Acute Leukemia Case 3</td>
<td>18</td>
<td>84</td>
<td>30</td>
<td>Dead</td>
<td></td>
<td></td>
<td>Dead</td>
<td></td>
</tr>
<tr>
<td>Osteomyelosclerosis Case 1</td>
<td>30</td>
<td>60</td>
<td>13</td>
<td>Alive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteomyelosclerosis Case 2</td>
<td>14</td>
<td>36</td>
<td>4.5</td>
<td>Alive</td>
<td></td>
<td></td>
<td>Dead</td>
<td></td>
</tr>
<tr>
<td>Osteomyelosclerosis Case 3</td>
<td>12</td>
<td>18</td>
<td>3</td>
<td>Alive</td>
<td></td>
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<td>Alive</td>
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</tbody>
</table>
chlorambucil. In addition, other side effects were less frequent with pipobroman: 4.5% versus 18%.2

Comparison with 32 p revealed that both modalities produced an identical complete remission rate (93%).3 but that the remissions were achieved sooner with pipobroman.

The requirement for maintenance treatment must be taken into account for comparative assessment of remission durations. The mean remission of 17.5 mo was similar to that of busulfan, exceeded that of chlorambucil (10 mo) and melphalan (13 mo), and was less than that achieved with 32 p (25 mo) for which therapy was not maintained.2,17

The search for new forms of therapy in polycythemia vera is justified by the known risk of supervening hematologic malignancies, probably heightened by the use of 32 p which is otherwise effective, easy to use, and associated with little toxicity. The reported incidence of acute leukemia in patients treated with 32 p ranges form 4% to 19%,1,3,20,22 that of splenic myeloid metaplasia from 2.5% to 25%.1,3,31 The mean interval between the first administration of 32 p and diagnosis of acute leukemia ranges from 6 to 11.7 yr in different series and from 6 to 13 yr for splenic myeloid metaplasia.

The oncogenic potential of some alkylating agents is now also beginning to emerge.

Long term treatment of polycythemia vera with chlorambucil increases dramatically the risk of acute leukemia3 as well as in nonhematologic disorders.6 It also appears highly likely that prolonged administration of melphalan for cancer is associated with an increased risk of acute leukemia,4 but little is known about its potential for inducing acute leukemia in patients with polycythemia vera.23 No cases of acute leukemia were observed among the 54 patients treated with pipobroman alone, but only 20 of these patients have been followed for more than 6 yr.

CONCLUSION

The results obtained with pipobroman encourages us to pursue the study of this drug. Pipobroman is an active and relatively atoxic agent if treatment is administered in accordance with certain rules and properly controlled. It is equally active when administered as first-line therapy, following other treatment modalities, or for recurrence. Toxicity is clearly lower than with other alkylating agents. Among the latter, chlorambucil and melphalan have definite oncogenic properties and should no longer be used to treat patients with polycythemia vera.

The position of pipobroman with regard to that of 32 p awaits clarification. This will be possible only after the drug has been used for longer periods, permitting assessment of its oncogenic potential.

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REFERENCES


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