Leukemia in Polycythemia Vera

Relationship to Splenic Myeloid Metaplasia and Therapeutic Radiation Dose


Berkeley, California

SUMMARY

Since the initial use of $^{32}$PO$_4$ in our clinic in 1939 for the treatment of polycythemia vera we have followed to termination 181 cases of the disease treated with $^{32}$P or $^{32}$P and X ray. Of these patients 45 of 181 (25%) developed significant splenic myeloid metaplasia, and 26 of 181 (14%) developed an acute myelogenous leukemia-like state. Sixteen patients had both "acute leukemia" and significant splenic myelopoiesis or myeloid metaplasia (that is, 16 of 45 or 36% of all cases with myeloid metaplasia developed "acute leukemia"), and 10 patients had only "acute leukemia" but no significant splenic myeloid metaplasia (that is, 10 out of 136 or 7% of all patients without myeloid metaplasia developed acute leukemia).

Patients who failed to develop myeloid metaplasia or acute leukemia, or both, were older at the time of onset and diagnosis than those with these developments and did not survive as long. The survival of patients who developed acute leukemia was not significantly different from patients who died with significant myeloid metaplasia alone.

The largest values of overall radiation exposure (both $^{32}$P and X ray) times time at risk were received by patients dying with splenic myeloid metaplasia alone.

The overall incidence of acute leukemia in this series of patients with polycythemia vera is 20 to 40 times greater than that expected for a population of "normal human subjects" exposed to similar radiation doses and times at risk.

These data are consistent with the hypotheses [1] that development of significant splenic myeloid metaplasia and acute leukemia-like states are part of the evolutionary history of polycythemia vera; [2] that myeloid metaplasia usually precedes the appearance of acute leukemia; and [3] that the incidence of acute leukemia in our patients treated with $^{32}$P may be primarily a result of prolonged survival rather than radiation dose.

S ubsequent to our first use of $^{32}$PO$_4$ for polycythemia vera in 1939 it has become apparent that this agent reduces morbidity and results in significant prolongation of life over that of patients treated without myelosuppressive therapy (1, 2). Although the therapeutic benefits of $^{32}$P in polycythemia vera remain unchallenged, the high incidence of acute leukemia-like states appearing late in the course of this disease has continuously raised the question of its possible radiation induction (3, 4). That radiation may increase the incidence of leukemia has been known for some time (5, 6) and was well appreciated by us when we first began using radioactive isotopes in human disease over 30 years ago (7-9). However, the lack of evidence that most patients could be controlled with venesection alone and the benefits attendant upon the management of polycythemia vera patients with $^{32}$P justified the possible risks of such therapy.

Since radiation effects generally show some radiation dose-dependency, we correlated radiation dose with presence of acute leukemia at death in this series of 181 polycythemia vera patients who had died at the time of initiation of this study.

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MATERIALS AND METHODS

In most cases studied, therapy and long-term follow-up were performed in association with the referring physician. Complete records were kept of all pertinent medical information throughout the patient's life. The decision as to what hematologic complication the patient had was made on the basis of both the patient's course and the findings at postmortem examination.

Before 1949 the diagnosis of polycythemia vera had been made on the basis of a sustained elevation of the red cell count in excess of 7 million cells/mm$^3$ without apparent cause and an associated elevated white cell count and splenomegaly. After 1949 all patients were diagnosed as having polycythemia vera on the basis of an increased circulating red cell volume (exceeding 34 ml/kg body weight), a normal arterial oxygen saturation, and, again, exclusion of those showing a cause for a secondary polycythemia. The red cell volume was determined by using $^{32}$P phosphate labeling of autologous red cells (10). Tumors associated with secondary erythrocytosis were excluded on the basis of complete medical evaluation (exclusion of renal disease, and so forth) during clinic visits, subsequent long-term follow-up of the patient's course, and findings including postmortem examination. In each case one or more of the following findings were present: an enlarged spleen, persistent thrombocytosis (in excess of 400,000/mm$^3$ by direct method), or leukocytosis (white blood cells (WBC) in excess of 10,000/mm$^3$).

Significant splenomegaly (spleen tip extending more than 3 cm beneath the costal margin), leukocytosis, and characteristic changes in red blood cells (RBC), WBC, and platelet morphology were noted before death in each case of significant splenic myeloid metaplasia (for example, anisopoikilocytosis, teardrop-shaped RBC, normoblasts, giant platelets, immature granulocytes in peripheral blood). The presence of significant splenic myeloid metaplasia was confirmed at the time of postmortem examination on the basis of histologic findings of myelopoiesis with megakaryocytes clearly identifiable in the spleen. In recent years we attempted to distinguish this state from chronic myelogenous leukemia by performance of leukocyte alkaline phosphatase and chromosome studies. In those cases with myeloid metaplasia, where the determinations were performed, leukocyte alkaline phosphatase was either normal or elevated, and the Philadelphia chromosome was absent. All cases in this category were placed within the “death with significant splenic myeloid metaplasia” group. Acute myelogenous leukemia with myeloid metaplasia was the term applied to those cases with leukocytosis and preceding significant splenic myeloid metaplasia with terminal findings of more than 20% blast cells in the circulating blood. Patients in this category usually had generalized infiltration of tissues by blast cells at postmortem examination. Generally, in these cases the peripheral blood contained a spectrum of cells at various levels of differentiation, from the mature granulocyte to the myeloblast.

Acute myelogenous leukemia without metaplasia was the term applied to those patients without preceding significant splenic myeloid metaplasia who suddenly demonstrated variable numbers of myeloblasts in the peripheral blood without evidence of differentiation of these cells to more mature elements. Examination of bone marrow in such patients generally showed a preponderance of myeloblasts.

In the series reported here of 181 patients with polycythemia vera followed to death $^{32}$P was the sole radiation modality used in 125 cases. In the remaining cases both X ray and $^{32}$P were used in therapy. (In all cases venesection was used as supplemental therapy.) In 12 of this latter group accurate measurement of X-ray dose was not available, and these cases were not used in analysis of radiation dose administered. Millicuries $^{32}$P was converted to “equivalent R” exposure by use of the figure suggested by Osgood (11) of 15R/mc. (This figure is higher than that used by us previously (1)). When X ray was used in therapy, the maximum radiation dose received by a myelopoietic area (bone or spleen) was taken as the “equivalent R” exposure for the entire body. Thus, values for radiation exposure in “equivalent R” represent maximum values. The product millicurie $^{32}$P or “equivalent R” times months at risk was obtained by multiplying millicuries or “equivalent R” times the time in months between administration and death for each radiation exposure and summing all such values for each patient.

Values were calculated for the mean and the standard error of the mean for each parameter. The probability that the value obtained for a given parameter in comparisons between groups of patients would be higher or lower by chance alone ($P$ values) was determined using routine statistical techniques utilizing tables of Student's $t$ distribution.
RESULTS

Table 1 presents a comparison of the age at onset and the duration of disease between groups of patients with polycythemia vera treated with $^{82}$P and other radiation modalities. Clinically, the patients were separated into two major groups composed of those patients who had and had not demonstrated evidence of significant splenic myeloid metaplasia. Under each of these major headings the patients were further subdivided into those who were judged to have developed a terminal acute leukemia-like state and those who did not show evidence of such a development.

Of the patients listed in Table 1, 45 of 181 patients (25%) developed significant splenic myeloid metaplasia, and 26 of 181 (14%) developed an acute myelogenous leukemia-like state. Sixteen patients had both “acute leukemia” and significant splenic myeloid metaplasia (that is, 16 of 45 patients or 36% of all patients with myeloid metaplasia developed “acute leukemia”), and 10 patients had only “acute leukemia” but no significant splenic myeloid metaplasia (that is, 10 of 136 or 7% of all cases without myeloid metaplasia developed “acute leukemia”).

Patients who developed significant splenic myeloid metaplasia or acute leukemia before death were found to be younger at both the age of onset and diagnosis and to survive longer than patients who developed neither myeloid metaplasia nor acute leukemia (uncomplicated group). (See Table 4 for results of test of significance between groups.) In other words, those patients who failed to develop significant splenic myeloid metaplasia or acute leukemia before death were older at the time of onset and diagnosis and failed to live as long after onset of their disease as those patients who did have these developments.

Among the group of patients who developed significant splenic metaplasia before death, there was no significant difference in terms of onset and duration of disease between those who developed acute leukemia-like states (acute leukemia with myeloid metaplasia group) and those who died without the development.

Table 2 presents results summarizing the total dose for polycythemia vera patients treated with $^{82}$P as the only source of radiation used in therapy. The dose is given as cumulative millicuries of $^{82}$P and also the sum of the product of millicuries of $^{82}$P administered times months at risk (time in months from $^{82}$P administration to death). The largest doses, expressed either as total millicuries administered or as the product of millicuries times months at risk, were received by patients who developed signifi-
TABLE 2. Radiation Dose for Deceased Polycythemia Vera Patients Treated with \(^{32}\)P Radiation Alone

<table>
<thead>
<tr>
<th>Lack of Significant Splenic Myeloid Metaplasia Before Death</th>
<th>Significant Splenic Myeloid Metaplasia (MM) Before Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Leukemia (Uncomplicated) (N = 92)</td>
<td>No Leukemia (MM) (N = 17)</td>
</tr>
<tr>
<td>Terminal Acute Leukemia (AL) (N = 8)</td>
<td>Terminal Acute Leukemia (ALw/MM) (N = 6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total Dose, mc</th>
<th>Duration to death from start of (^{32})P, yr</th>
<th>Total millicurie-months</th>
</tr>
</thead>
<tbody>
<tr>
<td>25.4 ± 2.5</td>
<td>7.9 ± 0.5</td>
<td>1,942 ± 244</td>
</tr>
<tr>
<td>29.0 ± 5.0</td>
<td>13.2 ± 1.8</td>
<td>3,098 ± 624</td>
</tr>
<tr>
<td>40.3 ± 4.8</td>
<td>10.4 ± 1.4</td>
<td>3,788 ± 717</td>
</tr>
<tr>
<td>26.4 ± 6.1</td>
<td>7.4 ± 2.0</td>
<td>1,726 ± 744</td>
</tr>
</tbody>
</table>

* For each category values for the mean and standard error of the mean are given; millicurie-months was determined in each case as the sum of the products of each dose of \(^{32}\)P (millicuries) times months from administration to death.

Significant splenic myeloid metaplasia but who did not show signs of acute leukemia (myeloid metaplasia group). The three other groups (uncomplicated, acute leukemia, and acute leukemia with myeloid metaplasia) had comparable total doses of \(^{32}\)P expressed as millicuries. The patients who died with acute leukemia but without significant splenic myeloid metaplasia (acute leukemia group) survived longer from the start of \(^{32}\)P therapy and correspondingly had a larger value of "dose risk" expressed as millicuries-months than did the uncomplicated and acute leukemia with myeloid metaplasia groups.

Similar findings are noted when all patients treated with either \(^{32}\)P alone or \(^{32}\)P and X ray are considered (Table 3). In this tabulation both groups of patients who developed splenic myeloid metaplasia (myeloid metaplasia and acute leukemia with myeloid metaplasia) received larger doses than those patients who failed to develop splenic myeloid metaplasia. Within each major category (presence versus absence of significant splenic myeloid metaplasia) there was no significant difference in radiation dose between those patients developing acute leukemia and those not developing it. Table 4 shows tests of significance.

The relationship between cumulative death (plotted as percent dead on the ordinate) and time after diagnosis (plotted in years on the abscissa) is shown in Figure 1 for patients dying of all causes and for patients in this group who died with acute leukemia.

TABLE 3. Radiation Dose for Deceased Polycythemia Vera Patients Treated with \(^{32}\)P and Other Radiation Modalities

<table>
<thead>
<tr>
<th>Lack of Significant Splenic Myeloid Metaplasia Before Death</th>
<th>Significant Splenic Myeloid Metaplasia (MM) Before Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Leukemia (Uncomplicated) (N = 114)</td>
<td>No Leukemia (MM) (N = 29)</td>
</tr>
<tr>
<td>Terminal Acute Leukemia (AL) (N = 10)</td>
<td>Terminal Acute Leukemia (ALw/MM) (N = 16)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total Dose, R</th>
<th>Total R-months</th>
</tr>
</thead>
<tbody>
<tr>
<td>545 ± 73</td>
<td>36,882 ± 4,616</td>
</tr>
<tr>
<td>468 ± 68</td>
<td>39,418 ± 8,761</td>
</tr>
<tr>
<td>1,027 ± 235</td>
<td>70,255 ± 16,309</td>
</tr>
<tr>
<td>1,386 ± 419</td>
<td>58,987 ± 17,191</td>
</tr>
</tbody>
</table>

* For each category values for the mean and standard error of the mean are given. The values for R-months were determined assuming each millicurie of \(^{32}\)P is equivalent to 15 R (9).
leukemia. The curves for both groups are roughly sigmoidal in shape.

In addition to the patients whose data are summarized above, we have followed a series of 15 patients with polycythemia vera who, usually, because of the relative benignity of their disease were managed either with phlebotomy alone (8 cases) or with phlebotomy and alkylating agents (7 cases). The median survival from diagnosis to the present for this group is 5 years. Two patients in this group have died so far, both showing significant splenic myeloid metaplasia at postmortem examination. Of the 13 patients who are still living and being followed, 1 who had been controlled with 2 to 4 venesections per year for 21 years, now has significant splenic myeloid metaplasia; another patient, who had been treated with 2 to 6 phlebotomies per year for 4½ years, has recently developed acute myeloblastic leukemia.

**DISCUSSION**

In many patients with polycythemia vera the condition can be viewed as a progressive process in which the initial increase in the rate of erythropoiesis is followed by progressive reduction in red cell survival, incompletely compensated for by increase in the rate of red cell production (12). During the course of this process the erythropoietic
bone marrow extends from its normal central location (in vertebral bodies, pelvic, and proximal femori and humeri), down the shaft of the long bones and into the distal extremities in association with progressive loss of such marrow from the central marrow cavities (13). At variable times during this course, extramedullary erythropoiesis may appear, first in the spleen and then in the liver (2, 12). Comparable changes appear to be occurring in the white cell series. The number of white cells appearing in the circulation generally increases as the disease progresses (12) in association with a variable increase in their degree of “immaturity.”

During the course of this process, a sudden change in the number or state of differentiation of circulating white blood cells is often described as a “leukemic” transformation. Whether or not such “leukemic” transformations in the course of polycythemia vera are causally identical to clinically similar leukemias occurring without the prior presence of polycythemia vera remains open to conjecture. Certainly the leukocytosis and splenomegally occurring in polycythemia vera patients with myeloid metaplasia simulating chronic myelogenous leukemia (CML) appear to differ from that seen in classical chronic myelogenous leukemia. In the former the Philadelphia chromosome is generally absent, and the leukocyte alkaline phosphatase is normal or elevated. Future techniques might demonstrate similar differences between the acute leukemia-like syndromes developing in polycythemia vera and the more classical forms of acute leukemia.

In order to analyze the effect of radiation dose on the incidence of acute leukemia in polycythemia vera it is important to define groups comparable with respect to age at onset, diagnosis, duration, and course but differing only in regard to radiation dose and presence or absence of acute leukemia. Ideally, we would wish to pair patients in terms of comparable myelokinetics, but, unfortunately, the only readily defined “signposts” in the evolution of cell kinetics in polycythemia vera are the development of significant splenic myeloid metaplasia and the development of acute leukemia (2). Therefore, we have classified our patients into groups dependent on the presence or absence of significant splenic myeloid metaplasia or acute leukemia. The findings that patients who died without development of these hematologic complications were older at onset and diagnosis and lived for a shorter time interval than those who did develop myeloid metaplasia or acute leukemia suggest that development of either is part of the natural history of polycythemia vera and that had these individuals who died without these “complications” survived sufficiently long with their disease many of them would have developed such complications. Furthermore, our results suggest that the usual hematologic progression in this disease involves development of significant myeloid metaplasia before the appearance of an acute leukemia-like syndrome as evidenced by the high incidence of significant splenic myeloid metaplasia in the patients with acute leukemia.
Presently available data indicate that in man the probability rate for development of leukemia is 1 to 2 per million exposed population per roentgen per year averaged over the time period of 1 to 15 years after radiation exposure (14). The subjects in such previous studies were not considered at risk during the first year after radiation exposure. In the present series the average exposure dose times the total months at risk subsequent to a given dose of radiation was 44,852 R-months for all groups studied. This is equivalent to 3,738 R-years. Multiplying this radiation exposure by 1 to 2 times $10^{-6}$ per R per year yields an expected incidence of leukemia from radiation exposure alone in the present series of approximately 0.37% to 0.74% as opposed to 14% actually observed. One should note that in the present series the patient was considered to be at risk from leukemia immediately after a given radiation exposure, and, thus, this calculated incidence of radiation-induced leukemia for our patients would be expected to be a high estimate. Since the observed incidence of acute leukemia in this series of polycythemia vera patients treated with radiation was roughly 20 to 40 times that expected other non-polycythemic groups within the population exposed to ionizing radiation, one must conclude either that the appearance of acute leukemia-like states in patients with polycythemia vera is relatively independent of radiation dose or that patients with polycythemia vera are more highly susceptible to radiation-induced acute leukemia-like states than other members of the population. (Similar findings have been previously reported by Osgood (15). If the latter findings were the case then one would anticipate that those patients dying with an acute leukemia-like state would have larger values of the product, radiation dose times months at risk, than comparable patients who failed to develop an acute leukemia-like state. In this series such was not the case. Indeed, the group that received the highest radiation dose was that in which patients developed significant splenic myeloid metaplasia before death but failed to develop acute leukemia. These patients also had the longest survival from onset or diagnosis than any of the remaining three groups.

Excellent results have been achieved using radioactive phosphorus in the treatment of polycythemia vera; the life expectancy is extended to nearly normal, and, furthermore, we do not see the high frequency of hemorrhage and of thrombotic episodes that are often observed when this disease is not adequately controlled (2, 16, 17). As for the question of a possible increase in the incidence of acute leukemia in patients treated with $^{32}$P, our findings suggest that this may be primarily

* For a group homogeneous with respect to survival time and susceptibility of acute leukemia development from radiation exposure but differing with respect to radiation dose, let: $D_i$ equal the value of “equivalent R” exposure times time at risk defining the $i^{th}$ group; $N_i$ equal the number of subjects in the $i^{th}$ group; $P$ equal the fractional probability of acute leukemia development per equivalent R exposure per unit time at risk. Average radiation exposure times time at risk ($R$) for all patients in the group is equal to equation 1 as follows:

$$\frac{\sum N_i D_i}{\sum N_i}$$

Average radiation exposure times time at risk for patients in groups not developing acute leukemia is equal to equation 2 as follows:

$$\frac{\sum N_i D_i - P \sum N_i D_i^p}{\sum N_i - P \sum N_i D_i}$$

It is clear the first term in the numerator and the first term in the denominator in equation 2 are identical to the numerator and denominator, respectively, in equation 1. Since $D_i$ has integer values greater than 1, it is also clear that $\sum N_i D_i^p > \sum N_i D_i$. Thus, equation 2 yields values smaller than equation 1. Consequently, the average radiation exposure times time at risk for patients failing to develop acute leukemia must be lower than the values obtained for the entire group. (Note that this simplified argument applies only when development of acute leukemia does not influence survival as is the case in the present study in comparing patients having myeloid metaplasia with those having acute leukemia and myeloid metaplasia.)
a result of prolonged survival rather than of radiation dose. It would help if we knew the incidence of acute leukemia among patients who have not been treated with ionizing radiation, but at the present time this is really not known. Until recently, with the advent of chemotherapeutic agents most patients with polycythemia vera have been treated with roentgen radiation or $^{32}$P, and, consequently, there are relatively few reports in the literature concerning large series of patients who had not been treated with some type of radiation.

In our clinic we have a group of 15 patients who because of the relative benignity of their disease were treated without the use of ionizing radiation, and it is noteworthy that in this small group followed for a median period of 5 years after therapy, one patient who was treated only with phlebotomy developed an acute myeloblastic leukemia. Halnan and Russell’s study (18) in 1965 compared survival and causes of death of an irradiated group (107 patients treated with X ray and radiophosphorus) and a nonirradiated group (117 patients treated without radiotherapy), and they found no cases of acute leukemia in either group. They had used data from Perkins, Israels, and Wilkinson (4) for their nonirradiated group, and in the latter’s paper one patient with polycythemia vera treated with venesection alone died of Di Guglielmo’s disease (acute erythroblastic leukemia). We have found six additional cases cited in the literature in which patients with polycythemia vera who had not received any radiation therapy developed an acute leukemia. Rosenthal and Bassen (19) reported a case of erythroleukemia in which there was active erythroblastic and leukoblastic involvement of the bone marrow before radiation therapy; Dameshek cited 2 such cases—1 among his own series of 50 patients and another that occurred among 100 patients treated at the Mayo Clinic (20); Williams and Mendel (21) reported a case of polycythemia vera terminating with myeloblastic leukemia, the patient having been treated only with venesection and low iron diet; Reinhard (22) reported 1 patient with polycythemia vera who had not received radiation therapy of any sort who died of acute myelocytic leukemia; and Modan and Lilienfeld (3) reported the development of acute leukemia in a patient with polycythemia vera after phlebotomy and myleran therapy.

In addition to these cases already cited in the literature, we have heard in discussions with and in letters from other physicians interested in this problem, of several unreported cases of acute leukemia developing in patients treated with myleran and alkaran. Apparently, these isolated cases do not get into the literature. The incidence of this complication after various forms of therapy, including the various chemotherapeutic agents, venesections, and $^{32}$P, is now being studied at the national level (National Institutes of Health Polycythemia Vera Study Group), but several years will be required to get the answer as to whether the incidence of acute leukemia and the prolongation of life with the use of chemotherapeutic agents, or venesections, or both, will be similar to those observed with the use of ionizing radiation. Until such knowledge is available we continue to recommend that benign cases of polycythemia vera should be treated with venesection alone and that, when it is necessary to use $^{32}$P or chemotherapy in combination with venesection in order to control the disease adequately and prevent the occurrence of complications such as hemorrhage or thromboses, then the dosage of $^{32}$P or of the chemotherapeutic agent should be kept as low as possible.

REFERENCES

2. Wasserman, L. R.: Polycythemia vera—its course and treatment: relation to myeloid meta-


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