Treatment of Polycythemia Vera: The Use of Hydroxyurea and Pipobroman in 292 Patients Under the Age of 65 Years

By Yves Najean and Jean-Didier Rain for the French Polycythemia Study Group

Nonradioimmunoe tic drugs, hydroxyurea (HU) and pipobroman (Pi), were administered to relatively young subjects with polycythemia vera (PV) in an attempt to decrease the leukomogenic risk observed in patients treated with $^{32}$P. Clinical safety, hematological efficacy, risk of carcinoma or leukemia, and frequency of progression to myelofibrosis have not yet been defined in long-term studies, and no comparative studies of HU and Pi have been conducted. Since 1980, 292 patients with PV diagnosed before the age of 65 years were randomized to receive treatment with HU (25 mg/kg/d, followed by low-dose maintenance) or Pi (1.2 mg/kg/d, followed by low-dose maintenance). Patients were followed until death or until May 1997. Drug tolerance was often poor; leg ulcers and buccal aphthous ulcers (with HU) and gastric pain and diarrhea (with Pi) sometimes required treatment change, mainly in the HU arm. Hematological stability, especially in terms of platelet count, was very often insufficient with HU (45% of cases), but the risk of thrombo-embolic event was similar in both arms. Actuarial survival was similar in the two arms and shorter than that of the reference population. The risk of leukemia was approximately 10% at the 13th year, with no significant difference between the two arms. The risk of carcinoma (when excluding the skin cancers) was similar in both groups. There was a high risk of progression to myelofibrosis in the patients treated by HU, which was significantly higher than with Pi.

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The usual methods of estimation of actuarial survival and actuarial risk of complications were used. However, to accurately analyze the clinical results, we took into account treatment changes or discontinuations decided by the consultant hematologist or by the physician in charge because of toxicity or insufficient efficacy (23 cases because of clinical toxicity, 23 cases because of...
insufficient efficiency, 6 cases decided by the physician without objective reasons, 3 cases switched to $^{32}$P because of neuro-psychiatric reasons). A protocol must accept the physician’s right to personal initiative, even if it interferes with the statistical analysis of the results.\textsuperscript{13} Actuarial survival was thus calculated according to the “intention to treat,” and also to the “main treatment received.” As complications may be related to the true treatment received, these data are only presented here according to the main treatment received (“main treatment”). Because of a difference in the mean follow-up between the two arms, the risk of death or complication was calculated in reference to the expected risk (log-rank test), and the difference between the two arms was assessed by the chi-squared test. The mean life expectancy and cancer risk of the French population\textsuperscript{14} and international populations\textsuperscript{15} were used as reference.

RESULTS

Clinical tolerance of the drugs used. In contrast with $^{32}$P radiotherapy, which is nearly always perfectly well tolerated,\textsuperscript{4} continuous chemotherapy can induce clinical adverse effects ranging from merely bothersome to sometimes requiring a change of treatment. Table 2 indicates the frequency of these complications in cases followed for at least 2 years. The main toxicity of Pi was gastrointestinal and was sufficiently severe to warrant a change of treatment in 8 cases; these gastrointestinal disorders generally occurred early, during the initial phase of treatment, when relatively high doses of the drugs were used. In contrast, the toxicity of HU was essentially limited to cutaneous disorders (acne), buccal disorders (aphthous ulcers), and especially leg ulcers, which healed only when HU treatment was stopped; these complications appeared generally late (5 years or more after initiation of treatment) and they constituted a frequent reason for change of treatment. Interestingly, leg ulcers generally resolved when HU was replaced by Pi.

Hematological efficacy and toxicity. Complete remission (ie, normal counts of the three myeloid lines) was obtained at the proposed doses in all but 5 cases (3 initial failures of Pi, 2 of HU). Several cases of severe thrombocytopenia (less than 50.10\textsuperscript{9}/L) were observed during induction treatment (2 cases with Pi, 5 cases with HU) or during the first months following introduction of maintenance treatment (5 cases with Pi, 5 cases with HU). These drug-induced thrombocytopenias or pancytopenias were observed in the oldest patients, and resolved spontaneously in a few weeks, or months.

In contrast, maintenance therapy was frequently ineffective. Table 3 indicates that long-term platelet control (lower than 400.10\textsuperscript{9}/L) was obtained much less often with HU than with Pi ($P < .01$). In these cases it may be difficult to increase the maintenance dose when the platelet count is high and hemoglobin low. Erythrocyte maintenance (hematocrit [Hct] lower than 50\%) was ensured in 86\% of cases, but once again with an advantage of Pi over HU ($P = .11$). In case of insufficient efficacy or progressive resistance, drug escalation or eventually drug switching to the other arm was.
used (Table 3). Treatment changes for hematological reasons were significantly more frequent in the HU arm than in the Pi arm \( (P = .025) \). Cross-resistance between the drugs was observed in half the cases. \(^{32}\)P was only used in the oldest cases or in patients with failure of both drugs.

Erythrocyte macrocytosis (>100 fL, generally 115 to 130 fL) was observed in all the cases treated by HU, but not in those treated by Pi. No significant increase of fetal hemoglobin was noted in the HU arm (observed values always less than 3%).

**Survival.** The actuarial survival in the two groups was determined according to the ‘intention to treat’ and to the ‘main treatment’ received. Life expectancy at the 14th year was about 70% in the two arms, whatever the type of analysis used (Fig 1A and B). Comparison of expected and observed deaths did not reveal any significant difference between the two groups (log-rank test, \( P > .3 \); Wilcoxon test, \( P > .20 \)).

The mean life expectancy of a sex- and age-matched population in France is 26.5 years, \(^{14}\) which would lead to a 14-year survival of 83.7% (significantly higher than that observed in the PV series presented here). However, the very long-term survival still remains unknown.

**Risk of vascular complications.** Despite the relatively young mean age and absence of serious vascular history in 89% of the cases, 6 patients died from vascular accident and 34 patients developed a nonfatal serious vascular thrombotic event (venous [16 cases] or arterial [24 cases]).

The risk is slightly higher in the HU arm in the first 8 years, but not significantly (log-rank test, \( P = .16 \)); at the 14th year it is similar in the both arms (Fig 2). At the time of the vascular event, the platelet count was normal in 10 out of 14 cases in the Pi arm, but in only 13 of 26 cases in the HU arm. However, the difference is not statistically significant (chi-squared, \( P = .16 \)).

**Risk of leukemia.** Thirteen cases of leukemia (9 acute myelogenous leukemias [including 4 cases after myelofibrosis] and 4 myelodysplastic syndromes [refractory anemia with excess of blasts]) were observed. All of these cases died within 1 year after diagnosis, including the 4 refractory anemia with excess of blasts (RAEB) (two of them after evolution to acute myeloid leukemia [AML], another after inefficient chemotherapy, one from intercurrent femoral fracture). In comparison with the \(^{32}\)P-treated patients of our other trial,\(^4\) neither chronic lymphocytic leukemia nor multiple myeloma was observed, probably owing to the younger age of these chemotherapy-treated cases.

The actuarial risk of leukemia as indicated in Fig 3 is about 10% at the 13th year with no difference in the two groups (log-rank test and Wilcoxon’s test, \( P > .30 \)). However, a longer delay of follow-up is necessary because of the late occurrence of this complication, as shown on Fig 3. The time of occurrence of the observed cases did not differ from that observed in the \(^{32}\)P-treated patients.\(^4\)

**Risk of cancer.** Sixteen patients developed a carcinoma. The actuarial cancer risk is shown in Fig 4. The incidence at the 14th year was approximately 15%, ie, a risk of 1.1% per year, which is only slightly greater than the frequency expected for this age group (0.8% per year according to French statistics).\(^{14}\) The type of cancer observed is shown in Table 4. The figures are too small to allow comparison with the relative frequency in France or in the world.\(^{14,15}\) Two cases of nonasbestos-related mesothelioma, a rare tumor, not previously reported to be associated with chemotherapy alone,\(^16,17\) should be noted because two other cases were also observed in the group of patients treated with \(^{32}\)P. Four cases of cutaneous cancer (basal-cell or epidermoid carcinomas) are observed in the HU arm against only one in the Pi arm.

**Risk of progression to a spent phase or to myelofibrosis with myeloid splenomegaly.** A total of 26 cases were observed in the HU arm, with only 3 cases in the Pi group: 8 cases presented with spent phase associated with increasing splenomegaly, anemia caused by excess of plasma volume, reticulinc myelofibrosis, and \(^{111}\)In-transferrin splenic uptake without decreased bone marrow uptake;\(^{18}\) 18 cases had a huge splenomegaly, collagen myelofibrosis, and low uptake of \(^{111}\)In-transferrin in the bone-marrow.\(^{19}\) The statistical difference is highly significant between the two arms (Fig 5), even when taking into account the shorter follow-up of the Pi-treated patients (log-rank test, \( P = .03 \); Wilcoxon’s test, \( P = .01 \)). Seven patients from among these cases have now died (4 of them from acute leukemia). The surviving cases have been followed for 1 to 9 years after the diagnosis of myelofibrosis (mean 2.9 years), so that one could expect in the next few years an adverse influence of this complication on the survival curve of patients treated with HU. The frequency (40% at the 16th year) and the early onset (as soon as the 4th year) are greater in HU-treated cases than in patients treated with \(^{32}\)P,\(^4\) but only slightly different from

### Table 3. Control of the Red Cell and Platelet Cell Lines on HU and Pi (in Patients Followed More Than 2 Years)

<table>
<thead>
<tr>
<th></th>
<th>HU (on 133 cases)</th>
<th>Pi (on 108 cases)</th>
<th>Escalation</th>
<th>Further Change of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Red cell line</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efficient control (Ht &lt; 50%)</td>
<td>109 cases (82%)</td>
<td>97 cases (90%)</td>
<td>HU 20 cases</td>
<td>6 cases</td>
</tr>
<tr>
<td>Insufficient control</td>
<td>24 cases (18%)</td>
<td>11 cases (10%)</td>
<td>Pi 8 cases</td>
<td>3 cases</td>
</tr>
<tr>
<td>(Ht increasing toward 50%)</td>
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<tr>
<td>Efficient control (&lt;400.10^9/L)</td>
<td>75 cases (55%)</td>
<td>84 cases (78%)</td>
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<tr>
<td><strong>Platelet line</strong></td>
<td></td>
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<tr>
<td><strong>(in patients with initial platelet excess)</strong></td>
<td></td>
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</tr>
<tr>
<td>Platelet count stable between 400 and 600.10^9/L</td>
<td>43 cases (32%)</td>
<td>19 cases (17%)</td>
<td>HU 32 cases</td>
<td>4 cases</td>
</tr>
<tr>
<td>Platelet count increasing beyond 600.10^9/L</td>
<td>15 cases (13%)</td>
<td>5 cases (5%)</td>
<td>Pi 15 cases</td>
<td>8 cases</td>
</tr>
</tbody>
</table>
CHEMOTHERAPY OF POLYCYTHEMIA VERA

Fig 1. (A) Actuarial survival of the patients treated by HU or Pi ("intention to treat" analysis). (B) Actuarial survival of the patients treated by HU or Pi, taking into account any switch of therapy ("main treatment" analysis). ( ), HU; ( ), Pi.

Though doses higher than those generally used for maintenance of $^{32}$P-induced remissions were used, the efficacy of maintenance therapy was often insufficient, particularly for controlling the platelet count. Despite dose escalation, the platelet count permanently exceeded 400.10^9/L in 22% of cases treated with Pi and in 45% of cases treated with HU. This insufficient efficacy was responsible for a significant number of treatment changes, namely in HU patients. However, dose escalation is often impossible because of a low
inhibits DNA repair,\textsuperscript{28,29} is not supported by our results. A similar risk of leukemia is also observed in the HU-treated thrombocytthemas.\textsuperscript{30} Though no case of leukemia has been published in patients treated with HU for psoriasis or sickle-cell anemia, the follow-up of these studies is still short,\textsuperscript{31-33} and it is possible that the leukemogenic potential is observed only in preleukemic myeloproliferative syndromes, as it was also suggested for \textsuperscript{32P}.\textsuperscript{34}

The slight excess of carcinomas observed in the chemotherapy-treated PV patients still requires a longer follow-up. A slight, but still not significant, excess of skin cancers occurred in the HU arm and also in the HU-maintained patients of the \textsuperscript{32P-treated group.}\textsuperscript{35} Similar data have been previously reported.\textsuperscript{35}

A striking finding of the present study is the considerable relative risk of myelofibrosis observed in the patients treated with HU, a risk that is significantly higher than that observed in the Pi-treated cases. In line with the suggestion that myelofibrosis develops in response to secretion of fibrogenic cytokines, especially platelet-derived growth factor, in a persistently hyperplastic bone marrow,\textsuperscript{36-38} HU was less effective than Pi in controlling the platelet count. The bone marrow hematocrit value. As in other series\textsuperscript{24,25} no statistically significant correlation between the vascular risk and the platelet count was observed even if a better maintenance of the platelet count in the Pi arm seems to be associated with a slightly lower risk of vascular events, at least in the first 6 to 8 years.

These young subjects have a long life expectancy. The length of this study’s follow-up, at least for the Pi arm, is still not sufficient to precisely calculate the median survival,\textsuperscript{26} but in both groups mortality did exceed that expected for a matched control population. The high occurrence of late-occurring myelofibrosis in patients treated with HU raises concern about an excess of late mortality in this group of cases.

An important point concerns the risk of leukemia, approximating 10% at the 13th year. This number is not significantly different from that observed in \textsuperscript{32P-treated patients.}\textsuperscript{3} However, the number of cases followed at very long term is still too low to allow precise evaluation of the risk at long term. No significant difference was observed between the HU- and the Pi-treated cases (log-rank test) despite the fact that Pi is an alkylating and mutagenic agent in vitro.\textsuperscript{27} The suggestion that HU is not leukemogenic, which seems unlikely as it

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig2.png}
\caption{Thrombo-embolic events (lethal or not) observed according to the main treatment received, including recurrent events occurring in the same patient (actuarial analysis). ( ), HU; ( ), Pi.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig3.png}
\caption{Actuarial risk of leukemia, according to the main treatment received. ( ), HU; ( ), Pi.}
\end{figure}
years was 19 years. Fourteen patients died from leukemia, myelodysplasia, or lymphoma between 3.5 and 18 years after starting treatment (actuarial incidence of 11.3% at the 12th year). Only 4 cases of progression to myelofibrosis were observed (between 3 and 14 years after the diagnosis). The second unpublished series, by F. Bauters and P. Fenaux, includes 37 cases under the age of 65 years who were treated for 2 to 10 years. This investigation reports good hematologi-
cal efficacy, low mortality at the present time (4 deaths from vascular accident), absence of leukemia, and only one case of progression to myelofibrosis. However, these two studies cannot be combined with our results for comparative analysis of Pi versus HU because of the absence of randomization and the fact that the inclusion and follow-up criteria were not similar to those adopted in our protocol. However, these two series are in line with our findings concerning the risks and advantages of Pi.

As emphasized by Fayers, statistical analysis implies not only a sufficient number of cases but also a sufficient number of events (deaths, complications) to be analyzed. Despite the large number of cases included in this protocol, the number of events is probably still too small to allow these conclusions to be considered as final. However, several relevant points can be made:

1. The safety of the two drugs is less satisfactory than what was generally considered. Fortunately, the complications are not the same for the two drugs, allowing an effective switch.
2. HU ensures less effective hematological control than Pi, especially regarding platelets.
3. An actuarial leukemia rate of 10% at the 13th year was observed that is similar to that observed with $^{32}$P alone. Thus, the expected advantage of chemotherapy over radiotherapy has not been confirmed.
4. The rate of progression to myelofibrosis with HU was considerable and was much higher than that observed with myelosuppression by $^{32}$P or Pi.

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We are indebted to Roberte Beaune, Marthe De Rosa, and Mickael Le Bail for their secretarial assistance, and to Dr Salaun and Pr Chomienne for the linguistic review of our manuscript. Seventy-four consultants in hematology or in internal medicine departments evaluated and followed the patients included in the present protocol. We mention here only those who contributed for more than 5 cases to the present study: Drs Allard (Meaux); Belanger and Varet (Paris-Necker); Brahimi (Troyes); Brouet, Fermant, Mariette, and Marullo (Paris-Saint-Louis); Casassus (Aubervilliers); Castaigne and Gruyer (Versailles); Dupuy (Paris-Lariboisière); Gabreau (Auxerre); Gandhour (Rennes); Goguel (Boulogne); Grange (Paris-Bichat); Lejeune (Bundy); Lenoble and Echard (Monterfert); and Rousselot and Witte (Chartres). We also acknowledge the private physicians of our patients, who followed them and informed us of clinical events. Finally, we acknowledge Professors J.F. Bernard and P. Boivin (Chartres). We also acknowledge the private physicians of our acute leukemia. J Clin Oncol 2:558, 1984

We mention here only those who contributed for more than 5 cases of polycythemia vera: Hypersplenism in the absence of myeloid metaplasia and a critical evaluation of its relationship with the Polycythaemia Vera Study Group. Br J Haematol 86:233, 1994

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