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Acute leukaemia after hydroxyurea therapy in polycythaemia vera and allied disorders: Prospective study of efficacy and leukaemogenicity with therapeutic implications

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Abstract: Fifty consecutive patients, 30 of whom had polycythaemia vera (PV), 10 essential thrombocythaemia (ET), and 10 myelofibrosis (MF), entered a long-term prospective study of hydroxyurea (HU) therapy. The indication for treatment was mainly thrombocytosis or symptomatic splenomegaly. Control of erythrocytosis and thrombocytosis was achieved in 70% of the patients. Continuous maintenance treatment was required. In 15% of responding patients with thrombocytosis, unexpected rises of the platelet count occurred during maintenance therapy. Severe thrombo-embolic events occurred in 6 patients. The size of the spleen decreased in all patients who did not develop thrombocytopenia and could absorb adequate HU doses. Acute leukaemia (AL) was diagnosed in 9 patients and a myelodysplastic syndrome in one. Seven of them had been treated with HU alone. Among the patients with PV and ET, 6 developed AL and 4 of them were treated with HU alone (3 PV and 1 ET), giving an incidence of 10.5%. In previously untreated patients with initially normal karyotypes (n = 19), chromosome abnormalities developed during HU therapy in 7 (37%). Our results indicate that HU should be regarded as leukaemogenic, at least when used for treatment of PV and allied diseases. Since myelosuppressive treatment of PV does not prolong survival, the use of HU should be restricted to patients in whom the treatment indication outweighs the risk of leukaemia induction.

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Introduction

Polycythaemia vera (PV), essential thrombocythaemia (ET) and myelofibrosis with myeloid metaplasia (MF) are related entities within the Ph-negative chronic myeloproliferative syndromes. The aim of therapy in these disorders is to treat or prevent symptoms and to prolong complication-free life, using either phlebotomy to remove the end products of the erythrocytic proliferation, or ^{32}P or cytostatic drugs to suppress the growth of all cell types at both medullary and extramedullary sites (1).

Transition into acute leukaemia (AL) is a rare event when PV is treated with phlebotomy alone, but the risk is significantly enhanced when ^{32}P or alkylating agents are used (2, 3, 4). For active myelosuppression the non-alkylating agent hydroxyurea (HU), supposed to be non-mutagenic, has therefore been recommended (5). This drug has mainly been used for treatment of chronic myelogenous leukaemia, but in recent years also in trials of PV and ET (6, 7, 8). The Polycythemia Vera Study Group (PVSG) published two reports of their experience with the drug (9, 10).

We report the findings in a prospective study of HU-treated patients with PV and allied myeloproliferative disorders, started in 1976, with special regard to HU efficacy and the development of cytogenetic abnormalities and acute leukaemia.

Material and methods

The study comprised 50 consecutive patients with chronic Ph-negative myeloproliferative disorders, in whom an indication for myelosuppressive treatment was present.

PV

Thirty patients with a mean age of 61 (range 33 to 76) yr were diagnosed according to the PVSG criteria (11). In 15 of them HU therapy was started within 1 yr from the diagnosis. In 21 patients no other myelosuppressive therapy had been given, while 9 patients previously had obtained alkylating agents or ^{32}P.

The indications for treatment were: in 18 patients thrombocytosis (mean platelet count $1.239 \times 10^9/l$), 8 symptomatic splenomegaly, and in 4 that the patient could not follow a phlebotomy regimen.

ET

Ten patients with a mean age of 60 (range 34 to 82) yr were diagnosed according to the PVSG criteria (12). The mean initial platelet count was $1.380 \times 10^9/l$. In 8 patients HU was started within a few months after diagnosis. Only 1 patient had prior ^{32}P treatment.

MF

Ten patients with a mean age of 66 (range 49 to 77) yr all had $\geq 30\%$ collagen fibrosis in the bone marrow, splenomegaly and a leukoerythroblastic peripheral blood picture (13). Three patients had a previously confirmed diagnosis of PV and 2 more might have had the disease. Three patients received other prior myelosuppressive treatment. The indications for treatment were: in 3 patients thrombocytosis and in the others space-restricting splenomegaly.

Cytogenetic examination

Chromosomes from aspirated bone marrow were prepared with conventional techniques, either directly or after short-term culture. The chromosomes were stained for G- and Q-bands (14, 15). Karyotyping was done in accordance with the ISCN (16).

Treatment

HU (Hydrea®, Squibb) during the 1st wk was administered in two divided doses of usually 30 mg/kg/d. From d 8 the dose was reduced by 50% and subsequently adjusted to the blood counts. During maintenance HU was given in a dose of 0.5 to 1.5 g/d.

Results

Thrombopoiesis and erythropoiesis were controlled with HU in about 70% of PV AND ET patients. During the induction treatment the reduction of the platelet count was rapid. After 2 wk of treatment the mean platelet count dropped to 28% in PV and 44% in ET of its respective pretreatment value. However, with the HU doses used in this study, a marked thrombocytopenia developed in 30% of the PV patients, rapidly followed by a rebound thrombocytosis after drug withdrawal (Fig. 1). Lowering of the 1st week's loading dose diminished appreciably the occurrence of the thrombocytopenic events. Two PV patients with thrombocytosis showed a high sensitivity to even small doses of the drug, and alternated between thrombocytopenic purpura and rebound thrombocytosis after drug withdrawal. In 15% of the responding PV and ET patients with thrombocytosis,

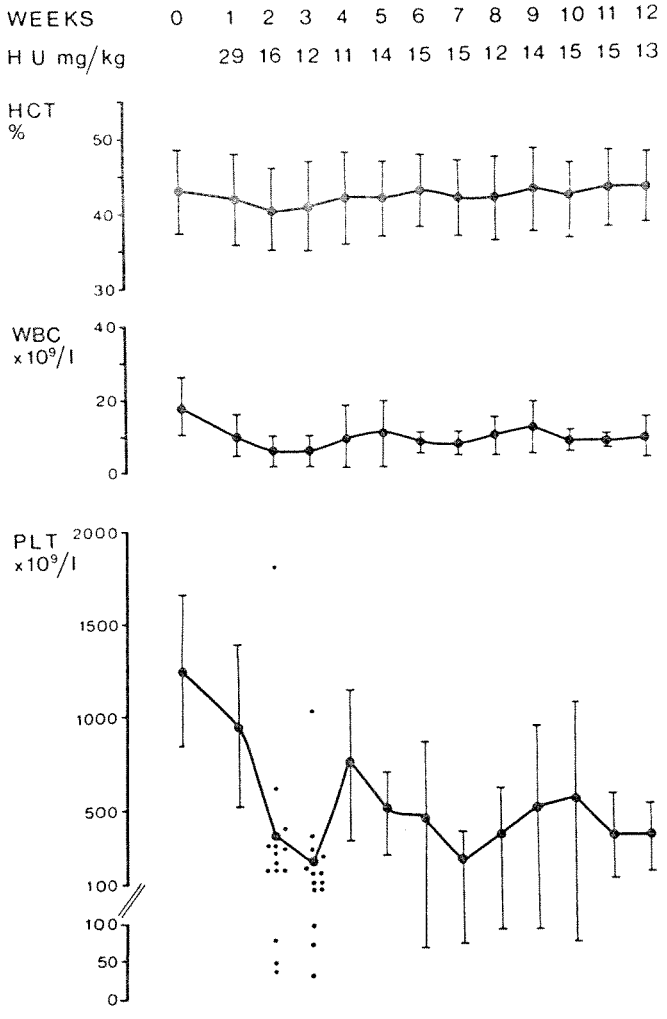

Fig. 1. The blood counts (mean ± 1 SD) during the first 12 weeks of hydroxyurea (HU) treatment of 18 polycythaemia vera patients with thrombocytosis. Thrombocytopenia followed by rebound thrombocytosis occurred in 30% of the patients during the 2nd and 3rd weeks of therapy.

unexpected rises of the platelet count to $> 600 \times 10^9$/l occurred during maintenance therapy.

Unmaintained relapse

In PV patients with thrombocytosis who developed thrombocytopenia during induction therapy, withdrawal of HU caused rebound thrombocytosis within a mean of 12 d (Fig. 1). After 1 yr of maintenance therapy HU withdrawal in PV and ET caused a relapse of thrombocytosis after a mean of 40 and 37 d, respectively.

Effect on splenomegaly and on bone marrow fibrosis

Nine PV and 5 MF patients with enlarged spleens and a normal or high platelet count responded promptly to HU therapy with a decrease of the spleen size by 50 to 70% and disappearance of symptoms. Among them were 4 patients with very large spleens. However, in another 10 patients with huge spleens the effect was not satisfactory, due to the development of thrombocytopenia.

In 1 patient with a post-PV myelofibrosis, HU treatment induced a rapid decrease of the spleen and reversal of the fibrotic bone marrow to a hypercellular one, as seen in active PV. In 3 further patients with pronounced myelofibrosis, who have been treated with HU because of post-splenectomy thrombocytosis, a reversal or reduction of fibrosis and reappearance of a hypercellular marrow was observed.

Clinical outcome

Twenty of the initial 50 patients are still followed. Their median observation time from the start of HU therapy is more than 10 yr and all patients were followed for a minimum of 5 yr. Thromboembolic complications occurred in 6 patients and were the cause of death in 4 of them. All thromboembolic events were associated with high platelet counts. They occurred in 3 patients while they were on continuous HU therapy, and in 3 patients after HU withdrawal because of thrombocytopenia and subsequent rebound thrombocytosis. Thirty patients died: 10 of them from AL, 2 from cancer, 6 from cardiovascular disease, 4 from thrombosis and lung emboli, 6 from the myeloproliferative disease, and 2 from other causes not related to the basic disease.

Acute leukaemia

In the total of 50 patients, 9 developed AL and 1 a myelodysplastic syndrome (MDS), giving an overall incidence of leukaemic disorders of 20%. Three of them received alkylating agents or ^{32}P in addition to HU. The other 7 patients with AL that developed among the remaining 47 patients (3 with PV, 1 with ET and 3 with MF), however, have been treated with HU alone, giving an overall incidence for this drug of 14.9% (7/47).

Among the 40 patients with PV and ET, 6 developed leukaemia. Two of them received alkylating agents before HU. In the remaining 38 patients, the 4 patients who developed AL (3 with PV and 1 with ET) have been treated with HU alone, giving an incidence of leukaemia for these entities of 10.5% (4/38). It may also be mentioned that the PV patient who developed MDS (Table 1, no. 22) was previously treated with melphalan for 7 months, while HU was his only treatment during the last 45 months before the development of MDS and death. In the 10 patients with MF, 4 developed AL and 3 of them were treated with HU alone.

We attempted to classify the leukaemias according to the FAB criteria (17) (Table 1). The leukaemia in 3 cases was considered as type M 1, in 5 as M 2,

Table 1. Clinical data of 10 patients with chronic myeloproliferative disorders and development of acute leukaemia (AL) after hydroxyurea (HU) therapy

				HU therapy before AL			
Pat. no.	Age at diagnosis (years)	Diagnosis	Prior myelosuppression	Months	Amount (g)	FAB class	Time from diagnos. to AL (years)
4	73	PV	None	111	3160	M2	9.5
7	50	PV	None	21[1]	76	M1	3.3
19	55	PV	None	94	3380	M2	9.3
39	53	ET	None	42	513	M2	3.5
44	49	MF	None	19	709	M2	3.5
45	54	MF	None	5	115	M2	10.7
46	63	MF	None	29	489	M1	4.0
22	58	PV	Melphalan	45	1595	MDS	7.4
9	61	PV	Melphalan	18	579	M6	4.8
50	41	MF	^{32}P	18	628	M1	28.0

Abbreviations: AL = acute leukaemia, ET = essential thrombocythaemia, FAB = French-American-British Cooperative Group, HU = hydroxyurea, MF = myelofibrosis, PV = polycythaemia vera.

[1] Patient 7 was treated with HU for only 3 months, followed by a stable phase of 18 months, before AL was diagnosed.

in 1 as M 6, and in 1 as MDS. In 3 of the 10 AL cases (2 with PV, 1 with MF; all treated with HU alone), the blastic transformation of the bone marrow was only partial (14 to 20% blasts), but the proportion of myeloblasts in the peripheral blood was high (40 to 50%) at a high WBC count (28 to 200×10^9/l). In one of the latter patients a massive myeloblastic infiltration was also found in a huge spleen.

In the 7 patients with AL who were treated with HU alone, the mean time from the start of HU treatment to the manifestation of leukaemia was 43 months. In the 4 patients with PV and ET who were treated with HU alone, the median time for occurrence of AL was 68 months after the start of HU treatment. The time from diagnosis of the myeloproliferative disorder to the development of AL for the individual patients is given in Table 1.

Cytogenetic results

A total of 97 cytogenetic examinations were performed in 30 patients (PV 19, ET 6, MF 5). In 28 of them at least one examination was done before the start of HU therapy; the remaining 2 patients had a normal karyotype in a later study. The median cytogenetic follow-up time from diagnosis was 71 (range 19 to 343) months, and from start of HU therapy 48 (range 5 to 80) months.

Development of chromosome abnormalities during HU therapy in previously untreated patients with initially normal karyotype

Eleven patients with PV, 5 with ET and 3 with MF had an initially normal karyotype. Four PV patients (36%), 1 ET patient and 2 MF patients developed clonal abnormalities after a mean HU treatment time of 40 (range 11 to 74) months. In 3 of the 4 PV patients the abnormal clone(s) appeared during the chronic phase; the 4th patient was still cytogenetically normal at the time of AL diagnosis, but later during the leukaemia multiple abnormalities occurred. The ET patient and one of the MF patients also developed abnormalities during the chronic phase. The 2 MF patient became abnormal first after the AL diagnosis.

Previously treated patients.

Three out of 6 previously treated patients (PV 2, MF 1) were cytogenetically normal at the start of the HU therapy, but developed abnormalities later during the course, after a mean of 32 months from the start of therapy.

Chromosome abnormalities were present at least during some part of the course in 16 of the 30 examined patients (53%). In all 7 patients who were examined after the diagnosis of AL, abnormalities were demonstrated.

Type of abnormalities

The most commonly affected chromosomes were No. 1 (4 patients), No. 9 (4), No. 12 (4) and No. 13 (5). Complete or partial trisomy for 1q was present in 2 (or possibly 3) patients. Monosomy 5 or a 5q-deletion was observed in 3 patients, in 2 of them first after the development of AL, but in the 3rd patient already during chronic phase. A 13q- deletion appeared in 2 patients (1 MF, the other PV). In the latter patient the clone diminished during HU therapy. A 20q- deletion was noted in 2 patients, 1 with PV and 1 with MF.

Discussion

Our findings confirm that HU is an effective and well-tolerated drug for the control of erythrocytosis, thrombocytosis and splenomegaly in patients with PV and allied myeloproliferative disorders. However, the rapid reversal of bone marrow suppression on drug withdrawal is a major disadvantage of HU therapy since it implies a need for continuous drug administration during the long course of the disease. In patients with thrombocytosis who inadvertently stop therapy, a dangerous rebound rise of the platelet count may occur. Another disadvantage is the appearance of unpredictable rises of the platelet count during maintenance therapy, which occurred in 15% of our responding patients. These rises were in some instances associated with thrombosis and emboli. In this respect busulfan and ^{32}P are safer and easier to manage, since they may induce long intervals of remission with stable blood counts during which no treatment is necessary.

A definite disadvantage with ^{32}P and alkylating agents, however, is that they are well established leukaemogenic drugs (2, 4). HU acts through mechanisms other than those of alkylating drugs, mainly by inhibiting the enzyme ribonucleotide reductase, which has a rate-limiting role in the regulation of DNA synthesis (18). Thus, the place of HU in the management of PV and allied disorders will essentially depend on whether HU can be proven to be less leukaemogenic than the other agents in use.

In the present investigation 50 HU-treated patients were prospectively followed long-term. For the 20 patients still alive, the median observation time is more than 10 yr, and the minimum is 5 yr. During this period AL developed in 10 of the 50 patients. Seven of them (PV 3, ET 1, MF 3) had no myelosuppression other than HU (Table 1). Among the 40 patients with PV and ET, 2 developed AL after treatment with both alkylating agents and HU,

while in the remaining 38 patients, 4 developed AL after treatment with HU alone, giving for the latter an incidence of 10.5%. This is comparable to figures (13.5 and 10.2%, respectively) given in two large series of PV patients treated with alkylating agents and ^{32}P (19, 20). In the 10 MF patients, 4 developed AL and 3 of them have been treated with HU alone.

In 5 of the 7 patients with AL who were treated with HU alone, the leukaemia manifested itself within 42 months from the start of therapy, and in 4 within 4 yr from diagnosis. This is in accordance with the AL time-elapse pattern seen in chlorambucil-treated patients, but differs from that found after ^{32}P treatment, where 60% of the ALs occur in the 6th to 10th yr of study (19). The leukaemic transformation in the bone marrow was only partial in 2 patients with AL who had a diagnosis of PV, and in 1 who had MF. This conforms with the observations made by Najean et al. (20). In Table 2, we summarize the hitherto published cases of AL developing after HU-only treatment of myeloproliferative diseases, as well as the findings in the present series. It is remarkable that in the series by Löfvenberg et al. (21), 3 of 32 cases of ET treated with HU alone developed AL (9%), although the natural occurrence of AL in ET it said to be rare (22). It seems obvious that the incidence of AL in HU-treated patients is higher than can be expected in patients treated with phlebotomy alone, which in the PVSG study was 1.5% (5). It is to be anticipated that, with longer observation time in ongoing HU series, more cases of AL will appear in the literature. The available information is not so complete, however, that an estimation can be made as to whether the risk after HU therapy is similar or less marked than after alkylating agents or ^{32}P.

Thirty patients of the present series could be followed with repeated cytogenetic examinations. Seven of 19 patients who were treated with HU alone and initially had a normal karyotype developed clonal chromosome abnormalities after the initiation of HU treatment (37%). Among the PV patients, 36% developed clonal abnormalities after HU was given. These figures are in good accordance with those we previously reported in PV patients treated with alkylating agents (23). In a study from the Mayo clinic (24), chromosome abnormalities were observed in 5 of 6 patients with PV treated with HU alone. The pattern of cytogenetic abnormalities observed in our HU-treated patients was similar to the findings after alkylating agent and/or ^{32}P therapy that we have previously analyzed in detail in a larger series of patients (23), and in accordance with reports from other centres (24, 25, 26). Chromosome abnormalities considered typical for secondary leukaemia, i.e. -5/5q- and -7/7q- (27, 28), were present in 4 of our patients.

Table 2. Cases reported in the literature of acute leukaemia in patients with polycythaemia vera (PV), essential thrombocythaemia (ET) and myelofibrosis (MF), treated with hydroxyurea alone

	PV	ET	MF
Kaplan et al. 1986 (10)	3/51[1]		
West 1987 (6)	2/100		
Najean et al. 1988 (20)	1		
Groupe Français de Cytogénetique Hématologique 1988 (29)	2	1	3
Löfvenberg et al. 1990 (21)		3/32	
Nand et al. 1990 (30)	1/8		
Anker-Lugtenburg & Sizoo 1990 (31)		1	
Holcombe et al. 1991 (32)	1		
Present series see text	3/28	1/10	3/9

[1] Denotes no. of cases with acute leukaemia/no. of cases studied.

The randomized PVSG study (protocol 01) has not only shown that the incidence of AL was significantly higher in the chlorambucil and ^{32}P arms and low in the phlebotomy arm, but also – which is of utmost interest – that the overall survival was significantly longer in the phlebotomy arm than in the two myelosuppressive arms (5, 33). On the other hand, the incidence of fatal thrombotic events was significantly higher in the phlebotomy arm, but only during the initial 3 to 4 yr of study. There was, however, no difference in survival during the same period of time. In order to decrease the number of thrombotic events during the early years of active disease, the PVSG suggested that PV patients should, during this period, be treated with HU, which was supposed to be a non-leukaemogenic drug (5, 10). Our study, as well as other reports (Table 2), indicate that HU is leukaemogenic, and that most of the ALs occur just during the first 4 yr of HU therapy. Furthermore, there is no good documentation that HU protects so well against thromboembolic events. In the present study there were 6 cases of severe thromboembolic events, and in a study by Fenaux et al. (33) 14 of 72 HU-treated patients experienced major thrombotic events. It seems to us therefore unjustifiable to treat all PV patients with HU for prophylaxis of thrombosis, if no special indication for it is present. In the present study the indication for HU therapy was marked thrombocythaemia, space-encroaching splenomegaly, or unfeasibility of a phlebotomy regimen. Generally, however, it would rather be advisable to cope with the increased risk of thrombosis during the first years of treatment by a closer supervision of the patient, by more gradual lowering of the haematocrit level, or by the use of the technique of isovolemic erythrocyte apheresis, recommended by Kaboth et al. (35), and perhaps cautious anticoagulation therapy in selected cases.

Since myelosuppressive treatment does not prolong survival and all agents in use for myelosuppression, including HU, carry the risk of inducing AL, we are of the opinion that phlebotomy should be the basic treatment for PV. Indications for drug therapy should be scrutinized in both PV and allied disorders with the general guideline that myelosuppressive treatment should be reserved for patients in whom the treatment indication outweighs the risk of inducing leukaemia.

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