

## HYDROXYUREA FOR PATIENTS WITH ESSENTIAL THROMBOCYTHEMIA AND A HIGH RISK OF THROMBOSIS

SERGIO CORTELAZZO, M.D., GUIDO FINAZZI, M.D., MARCO RUGGERI, M.D., OSCAR VESTRI, M.D.,  
MONICA GALLI, M.D., FRANCESCO RODEGHIERO, M.D., AND TIZIANO BARBUI, M.D.

**Abstract Background.** Abnormalities in the number and function of platelets may contribute to thromboembolic complications in patients with essential thrombocythemia. We assessed whether maintaining the platelet count below 600,000 per cubic millimeter with hydroxyurea reduces the incidence of thrombosis in patients with essential thrombocythemia and a high risk of thrombosis.

**Methods.** A total of 114 patients with essential thrombocythemia (77 women and 37 men; median age, 68 years; range, 40 to 85) and a median platelet count of 788,000 per cubic millimeter (range, 533,000 to 1,240,000 per cubic millimeter) were randomly assigned to receive hydroxyurea (56 patients) or no myelosuppressive therapy (58 patients). Ninety-seven (85 percent) were over 60 years old, and 52 (46 percent) had had thrombosis. The two groups were matched for age, sex,

and platelet count at randomization. Antiplatelet prophylaxis with aspirin or ticlopidine was not stopped. Follow-up lasted a median of 27 months in both groups.

**Results.** Two patients (3.6 percent) treated with hydroxyurea had thrombotic episodes (one stroke and one myocardial infarction), whereas 14 patients (24 percent) in the control group had thrombotic episodes (one stroke, five transient ischemic attacks, five peripheral arterial occlusions, one deep-vein thrombosis, and two cases of superficial thrombophlebitis). The difference (20.4 percentage points; 95 percent confidence interval, 8.5 to 32 percent) was statistically significant (chi-square with Yates' correction, 8.3; 1 df;  $P=0.003$ ).

**Conclusions.** Hydroxyurea is effective in preventing thrombosis in high-risk patients with essential thrombocythemia. (N Engl J Med 1995;332:1132-6.)

**E**SSENTIAL thrombocythemia is a myeloproliferative disease with a high incidence of thrombotic complications, especially cerebral, myocardial, and peripheral arterial thromboses; pulmonary embolism and deep-vein thrombosis are less frequent.<sup>1</sup> Thrombocytosis and abnormal platelet function may contribute to these complications, but there is no clear evidence that they do. Moreover, up to two thirds of patients with essential thrombocythemia are asymptomatic.<sup>2</sup> Thus, essential thrombocythemia is a clinically heterogeneous disorder in which the use of drugs to lower the platelet count or to inhibit platelet function is often problematic.

In a previous study we stratified patients with essential thrombocythemia according to risk factors for thrombosis. We found a high vascular-complication rate among patients older than 60 years and patients who had already had a thrombotic event.<sup>3</sup> Such patients could be candidates for treatment to reduce their platelet counts.

Physicians often use hydroxyurea for the initial treatment of essential thrombocythemia. This drug has a broad dose-response range, mild side effects, and theoretically little mutagenic risk. Discontinuation of the drug quickly reverses any unwanted myelosuppression.<sup>2</sup> Although hydroxyurea reduces the platelet count, there is no convincing evidence that it also decreases thrombotic episodes in patients with essential thrombocythemia. Indeed, no clear relation has been established in this disease between the absolute platelet count and the frequency of thrombosis.<sup>2,4</sup> Moreover, hydroxyurea, which does not permanently control the thrombocytosis, must be given indefinitely.<sup>5</sup> This arouses concern because of the leukemogenic potential of hydroxyurea<sup>6</sup> and clouds estimates of the drug's risk-benefit ratio.

We conducted a prospective, randomized trial to assess whether hydroxyurea, given to keep the platelet count below 600,000 per cubic millimeter, reduces the incidence of thrombosis in patients with essential thrombocythemia who are at high risk for thrombotic complications.

### METHODS

#### Characteristics of the Patients

In a cohort of 198 patients seen at our two institutions who were given a diagnosis of essential thrombocythemia according to previously reported criteria,<sup>3</sup> 114 patients (57.6 percent) were eligible for the present trial because they were more than 60 years of age (62 patients), had had a previous thrombosis (17 patients), or met both criteria (35 patients), and had a platelet count of 1,500,000 per cubic millimeter or less. The last criterion was based on the reported association between bleeding and very high platelet counts.<sup>1</sup> For this reason, we believed that patients with platelet counts above 1,500,000 per cubic millimeter required treatment and thus could not be randomly assigned to the untreated control group. The 114 patients enrolled in the study included 52 patients with newly diagnosed essential thrombocythemia and 62 with previously diagnosed disease (median time after diagnosis, 16 months; range, 2.5 to 42). In the latter group 54 patients (87 percent) were not receiving chemotherapy at the time of randomization (34 had never been treated and 20 had stopped taking busulfan or hydroxyurea at least six months before enrollment), whereas 8 (23 percent) were taking hydroxyurea at entry into the study.

#### Hemostatic and Coagulation Studies

Base-line bleeding-time and coagulation studies, including measurement of the activated partial-thromboplastin time, one-stage prothrombin time, thrombin time, and fibrinogen levels, were performed according to standard methods. They were normal in all but five patients, who had prolonged bleeding times (more than six minutes).

#### Treatments

Between April 1990 and August 1993, 56 patients were randomly assigned to hydroxyurea treatment and 58 patients were randomly assigned to the control group (no hydroxyurea treatment). The treated patients were seen every two weeks until the platelet count was below 600,000 per cubic millimeter, and at least every two months thereafter. The 58 control patients were seen every two months.

Informed consent was obtained from each patient. The starting dose of hydroxyurea (Oncocarbide; Simes, Vicenza, Italy) was 15 mg

From the Division of Hematology, Ospedali Riuniti di Bergamo, Bergamo (S.C., G.F., O.V., M.G., T.B.), and the Division of Hematology, Ospedale Civile S. Bortolo di Vicenza, Vicenza (M.R., F.R.) — both in Italy. Address reprint requests to Prof. Barbui at the Divisione di Ematologia, Ospedali Riuniti di Bergamo, Largo Barozzi 1, 24100 Bergamo, Italy.

per kilogram of body weight per day.<sup>7</sup> Thereafter, a maintenance dose of the drug was administered to maintain the platelet count below 600,000 per cubic millimeter without lowering the white-cell count below 4000 per cubic millimeter. The treatment goal of a platelet count of 600,000 per cubic millimeter was selected because our previous study<sup>3</sup> showed that patients with counts below that level had a relatively low rate of thrombotic complications. Fifty patients (44 percent) received aspirin (300 mg per day orally) and 29 (25 percent) ticlopidine (500 mg per day orally) as prophylaxis because of previous arterial thrombosis (51 patients) or to control ischemic symptoms (28 patients), such as acroparesthesias and burning toes or fingers, poorly localized atypical neurologic symptoms, blurred vision, or headache.<sup>2</sup> We did not withdraw antiplatelet drugs because of their potentially protective effect in patients with a history of a thrombotic event. The proportion of patients receiving antiplatelet prophylaxis was the same in the two groups (Table 1).

### Cardiovascular Risk Factors

Information concerning five major risk factors for vascular disease (hypertension, cigarette smoking, diabetes mellitus, hyperlipidemia, and previous thrombotic events), defined as previously reported,<sup>3</sup> was recorded with use of a standard questionnaire.

### Thrombosis

Arterial complications included transient ischemic attacks (an episode of focal cerebral ischemia that resolved within 24 hours), non-hemorrhagic cerebrovascular accidents (complete stroke) documented by computed tomography or nuclear magnetic resonance imaging, myocardial infarction, and digital microvascular ischemia.<sup>1</sup> Dysesthesias of the hands and feet and unexplained headache relieved by a single dose of aspirin were not counted in the analysis. Venous complications included deep-vein thrombosis of the peripheral vasculature, diagnosed by phlebography or Doppler ultrasound, and superficial phlebitis of the leg.

### Hemorrhage

We classified bleeding as major<sup>8</sup> if it required hospitalization or blood transfusion. All other episodes of bleeding were classified as minor (grade 1 to 2 according to World Health Organization criteria).<sup>9</sup>

### Statistical Analysis

The rates of thrombotic complications in the two groups of patients were compared by the chi-square test with Yates<sup>1</sup> correction; 95 percent confidence limits for the difference in the rates of thrombosis were calculated according to the method of Gardner and Altman.<sup>10</sup> The Kaplan-Meier method was used to construct curves for thrombosis-free survival.<sup>11</sup> The log-rank statistic was used to compare distributions.<sup>12</sup> The Cox proportional-hazards model<sup>13</sup> was used for multivariate analysis of possible predictors other than hydroxyurea treatment (e.g., age, sex, platelet count at randomization, cardiovascular risk factors, previous thrombosis, previous chemotherapy, newly diagnosed disease, and use of antiplatelet drugs). To adjust for covariates when evaluating hydroxyurea treatment, we kept the treatment in the model and applied backward regression to the other covariates.

## RESULTS

### Characteristics of the Patients

The main characteristics of the patients in the two groups were similar (Table 1). Both groups were followed for a median of 27 months (range in the hydroxyurea group, 2.5 to 42 months; range in the control group, 3.8 to 40 months). Eight percent of the patients (two women and seven men; median age, 78 years; range, 66 to 85) died of cardiac failure. Five were in the hydroxyurea group, and four were in the control group. No patient was lost to follow-up.

In all patients in the hydroxyurea group, treatment

Table 1. Base-Line Characteristics of 114 Patients with Essential Thrombocythemia.

CHARACTERISTIC	HYDROXYUREA GROUP (N = 56)	CONTROL GROUP (N = 58)
Age — yr		
Median	67	69
Range	40–82	50–85
Sex — F/M	33/23	44/14
Splenomegaly $\leq 3$ cm — no. (%)	6 (11)	8 (14)
Platelets — $\times 10^{-3}$ mm <sup>3</sup>		
Median	809	747
Range	533–1165	620–1240
Hemoglobin — g/liter		
Median	131	136
Range	111–164	100–160
White cells — $\times 10^{-3}$ mm <sup>3</sup>		
Median	8.8	9.0
Range	5.0–21.7	5.3–20.0
Bleeding time — min		
Median	4.0	4.3
Range	2.0–9.0	3.0–9.3
Newly diagnosed disease — no. (%)	23 (41)	29 (50)
Cigarette smoker — no. (%)	9 (16)	7 (12)
Other cardiovascular risk factors — no. (%)	17 (30)	22 (38)
Previous thrombosis — no. (%)	30 (54)	22 (38)
Previous chemotherapy — no. (%)	13 (23)	15 (26)
Antiplatelet prophylaxis — no. (%)	39 (70)	40 (69)

with the drug resulted in a decrease in the platelet count to below 600,000 per cubic millimeter (median count, 459,000 per cubic millimeter; range, 285,000 to 628,000 per cubic millimeter) after a median of 30 days (range, 16 to 60). The response continued with long-term therapy, and there was no need for frequent adjustments of the dose (Fig. 1). The immediate and late toxicity of the drug was negligible; there were no episodes of leukopenia (white-cell count less than 4000 per cubic millimeter) or thrombocytopenia. Neither rash nor symptoms of gastric irritation were seen.

In the control group, the platelet count ranged from 892,000 to 986,000 per cubic millimeter at six months (Fig. 1). No single platelet count exceeded 1,500,000 per cubic millimeter during follow-up. If such a count had been recorded, the patient would have been removed from the control group.

### Thrombosis

Sixteen patients (14 percent) had thrombotic complications (Table 2). One 76-year-old man and one 71-year-old woman in the hydroxyurea group (3.6 percent) had a cerebral or cardiac occlusive episode 9 and 10 months, respectively, after enrollment. The platelet counts at the time of the events were 490,000 and 632,000 per cubic millimeter, respectively. Fourteen controls (24 percent; median age, 65 years; range, 51 to 82.5) had a total of six cerebral episodes, five distal ischemic episodes, and three venous occlusive complications. Three were men, and 11 were women. These thromboses occurred a median of 11 months after enrollment (range, 3 to 24) at a time when the median platelet count was 900,000 per cubic millimeter (range, 700,000 to 1,394,000 per cubic millimeter). The differ-

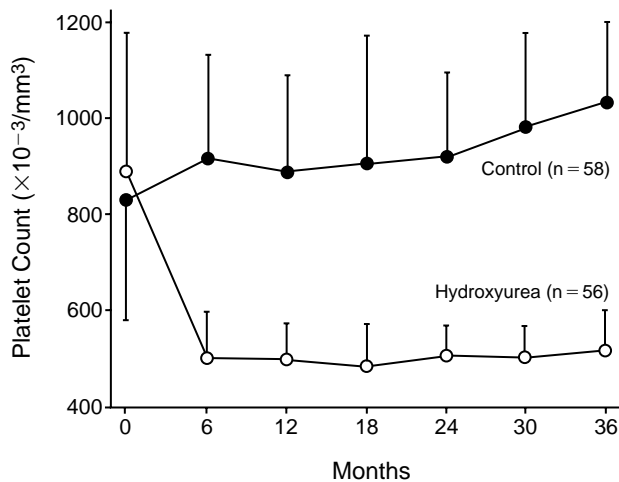


Figure 1. Mean ( $\pm$ SD) Platelet Counts of 114 Patients with Essential Thrombocythemia Treated with Hydroxyurea or Left Untreated.

ence in the rate of thrombotic complications between the hydroxyurea group and the control group (20.4 percentage points; 95 percent confidence interval, 8.5 to 32 percent) was significant (chi-square with Yates' correction, 8.3; 1 df;  $P=0.003$ ). Since the follow-up times differed among the patients, we analyzed thrombosis-free survival. The analysis revealed a significant difference in thrombosis-free survival between the hydroxyurea group and the control group (chi-square with Yates' correction, 10.35;  $P=0.005$ ) (Fig. 2).

Ten of 16 patients with thrombosis (62.5 percent) — 2 in the hydroxyurea group and 8 in the control group — had been taking aspirin ( $n=6$ ) or ticlopidine ( $n=4$ ) before thrombosis occurred, as compared with 69 of 98 asymptomatic patients (70 percent). Multivariate analysis did not reveal a significant effect of antiplatelet drugs on the outcome. Smoking status was the only variable other than hydroxyurea treatment associated with thrombosis (Table 3).

### Hemorrhage

Five patients (4.4 percent) — three taking aspirin and two taking ticlopidine — had bleeding episodes. One 60-year-old patient with a normal bleeding time at enrollment (bleeding time, 3.5 minutes) had minor gas-

trointestinal bleeding 11 months after starting treatment with hydroxyurea; the platelet count was 318,000 per cubic millimeter. The other four patients, who were in the control group (median age, 61 years; range, 61 to 82), had bleeding times ranging from 3.5 to 5 minutes at enrollment and had a total of three mild episodes of epistaxis and one minor gastrointestinal hemorrhage a median of 5 months (range, 3 to 15) after enrollment at a time when the median platelet count was 800,000 per cubic millimeter (range, 700,000 to 985,000 per cubic millimeter).

### DISCUSSION

This prospective, randomized trial demonstrates the usefulness of hydroxyurea in preventing thrombosis in high-risk patients with essential thrombocythemia. This myelosuppressive drug, which is not an alkylating agent, is in wide use for the treatment of essential thrombocythemia and other myeloproliferative disorders.<sup>5</sup> Its advantages include convenience, efficacy in reducing the platelet count, and low level of toxicity.<sup>2</sup> However, hydroxyurea must be taken continuously, and if it is inadvertently stopped an excessive rebound increase in the platelet count may occur.<sup>14</sup>

The ability of hydroxyurea to reduce the platelet count in patients with essential thrombocythemia is well established, but its efficacy in reducing the rate of thrombotic complications is not. Recently, Turlure et al.<sup>15</sup> reported their experience with hydroxyurea in 79 patients with essential thrombocythemia who had a high risk of thrombotic or hemorrhagic complications because they were older than 65 years, had platelet counts above 1,500,000 per cubic millimeter, or had had previous thrombotic, ischemic, or hemorrhagic episodes. Despite treatment with hydroxyurea, 16 percent of the patients had major ischemic episodes. However, the lack of an untreated control group hinders interpretation of this study.

In our study, 2 of the 56 patients treated with hydroxyurea had thrombotic episodes (stroke in a 71-year-old woman and myocardial infarction in a 76-year-old man) during the 27-month follow-up period. By contrast, there were 14 vascular occlusive events in the 58 untreated controls. In all patients randomly assigned to hydroxyurea treatment, the platelet count decreased below 600,000 per cubic millimeter within two to eight weeks and was maintained at this level with long-term treatment. Our results confirm a previous observation that patients with platelet counts below 600,000 per cubic millimeter have a reduced rate of thrombosis.<sup>3</sup>

As in previous studies of essential thrombocythemia,<sup>3,4</sup> the most frequent thrombotic complications in high-risk patients involved the central nervous system and peripheral and coronary arteries. Hemorrhagic complications occurred in only five patients (4.4 percent), and these patients were all taking aspirin or ticlopidine prophylactically, indicating once again that the main hemostatic problem in essential thrombocythemia is thrombosis, at least in patients with platelet counts below 1,500,000 per cubic millimeter.

This study was not designed to assess the role of

Table 2. Incidence of Thrombosis in 114 Patients with Essential Thrombocythemia.

TYPE OF THROMBOSIS	HYDROXYUREA GROUP	CONTROL GROUP
	(N=56)	(N=58)
	<i>no. (%)</i>	
Arterial	2 (100)	11 (79)
Transient ischemic attacks	0	5
Digital microvascular ischemia	0	5
Stroke	1	1
Myocardial infarction	1	0
Venous	0	3 (21)
Superficial thrombophlebitis	0	2
Ileofemoral venous thrombosis	0	1
Total (% of treatment group)	2 (3.6)	14 (24)*

\*There was a difference of 20.4 percentage points in the rate of thrombosis between the groups (95 percent confidence interval, 8.5 to 32 percent; chi-square with Yates' correction, 8.3; 1 df;  $P=0.003$ ).

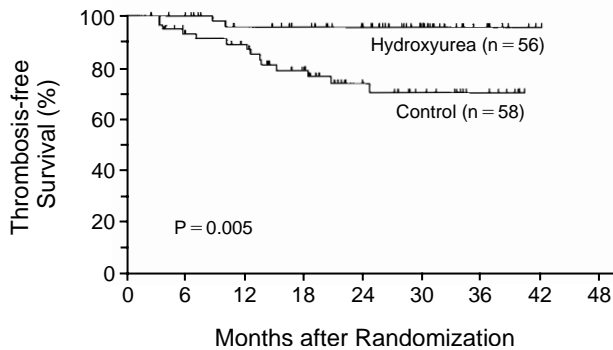


Figure 2. Probability of Thrombosis-free Survival in 114 Patients with Essential Thrombocythemia Treated with Hydroxyurea or Left Untreated.

The P value is for the difference between the two groups (by the log-rank test). The median follow-up was 27 months. Tick marks indicate surviving patients who were continuously free of thrombosis.

antiplatelet drugs in preventing vascular complications; many patients enrolled in this trial were already receiving antiplatelet treatment at the time of randomization. These potentially useful drugs were not stopped, but their clinical impact was retrospectively examined by multivariate analysis. We found no significant influence of antiplatelet drugs on the outcome.

In the group of 56 patients treated with hydroxyurea, the rate of thrombotic events was 3.6 percent. However, in our previous analysis of 200 patients with monoclonal gammopathies of undetermined importance followed for 40 months and matched with patients with essential thrombocythemia for age, sex, and cardiovascular risk factors, the rate of thrombotic events was 3 percent.<sup>3</sup>

Among the cardiovascular risk factors that we assessed, cigarette smoking was significantly associated with thrombosis, confirming a retrospective study<sup>16</sup> in which a high rate of thrombotic complications was found in patients with essential thrombocythemia who smoked. Nonetheless, because of the small numbers of events and of exposed patients (14 percent), we cannot draw firm conclusions about the role of cigarette smoking

as a risk factor for thrombosis in this group of patients.

A major concern about chemotherapy in the treatment of essential thrombocythemia is conversion to acute leukemia.<sup>6</sup> In our cohort of 114 patients with essential thrombocythemia who were followed for a maximum of 42 months, we did not observe any instance of malignant transformation. However, since this complication is generally seen only after long-term treatment, careful follow-up of hydroxyurea-treated patients is mandatory. Hydroxyurea treatment of essential thrombocythemia has been associated with a 6 percent rate of death from malignant conditions<sup>15</sup>; a similar rate of leukemic transformation (5.9 percent) was observed in a historical, nonconcurrent analysis of 51 patients with polycythemia vera treated with hydroxyurea for up to 389 weeks.<sup>17</sup> Both essential thrombocythemia and polycythemia vera may have an inherent tendency to leukemic transformation, which hydroxyurea treatment accelerates. It is not known whether hydroxyurea is leukemogenic in patients who do not have a myeloproliferative disease.

Murphy et al.<sup>18</sup> emphasized that therapy with alkylating agents increased the risk of acute leukemia in patients with essential thrombocythemia who were initially treated with hydroxyurea. Busulfan was a widely used alkylating agent<sup>3,19</sup> because of its ability to reduce the platelet count to below 400,000 per cubic millimeter. However, because of concerns about its leukemogenic effects, occasional prolonged myelosuppression, and pulmonary and gonadal toxicity, busulfan is no longer used as first-line therapy for essential thrombocythemia, particularly in patients younger than 60 years of age.

In conclusion, we found that hydroxyurea was effective not only in reducing the platelet count in patients with essential thrombocythemia but also in preventing thrombosis. However, particular care should be exercised in prescribing this drug to young patients because the risk of secondary leukemia is not known.

We are indebted to Dr. R. Marchiori and Dr. A.M. Marfisi (Centro di Ricerche Farmacologiche e Biomediche Consorzio Mario Negri Sud, Lanciano, Italy) and Dr. L. Naldi (Divisione di Dermatologia, Ospedali Riuniti, Bergamo, Italy) for statistical analysis of the data, and to Mrs. J. Baggott (Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy) for her help in revising the manuscript.

Table 3. Multivariate Analysis of Prognostic Factors for Thrombosis in 114 Patients with Essential Thrombocythemia.

VARIABLE	RELATIVE RISK (95% CONFIDENCE INTERVAL)	P VALUE
Hydroxyurea treatment	0.13 (0.03–0.58)	0.0072
Age	1.01 (0.95–1.07)	0.7625
Sex	1.10 (0.30–3.40)	0.8624
Platelet count at enrollment	0.999 (0.997–1.001)	0.4277
Newly diagnosed disease	0.82 (0.28–2.37)	0.7143
Cigarette smoker	4.57 (1.44–14.55)	0.0100
Diabetes*	—	—
Hypertension	1.87 (0.69–5.06)	0.2167
Hyperlipidemia	3.28 (0.42–25.83)	0.2583
Previous thrombosis	1.39 (0.51–3.73)	0.5175
Previous chemotherapy	2.15 (0.78–5.90)	0.1368
Current use of antiplatelet drugs	0.53 (0.19–1.49)	0.2311

\*Only three patients had diabetes, and all had thrombosis.

## REFERENCES

- Schafer AI. Essential thrombocythemia. *Prog Hemost Thromb* 1991;10:69-96.
- van Genderen PJJ, Michiels JJ. Primary thrombocythemia: diagnosis, clinical manifestations and management. *Ann Hematol* 1993;67:57-62.
- Cortelazzo S, Viero P, Finazzi G, D'Emilio A, Rodeghiero F, Barbui T. Incidence and risk factors for thrombotic complications in a historical cohort of 100 patients with essential thrombocythemia. *J Clin Oncol* 1990;8:556-62.
- Barbui T, Cortelazzo S, Viero P, Bassan R, Dini E, Semeraro N. Thrombohaemorrhagic complications in 101 cases of myeloproliferative disorders: relationship to platelet number and function. *Eur J Cancer Clin Oncol* 1983;19:1593-9.
- Lofvenberg E, Wahlin A. Management of polycythaemia vera, essential thrombocythaemia and myelofibrosis with hydroxyurea. *Eur J Haematol* 1988;41:375-81.
- Lofvenberg E, Nordenson I, Wahlin A. Cytogenetic abnormalities and leukemic transformation in hydroxyurea-treated patients with Philadelphia chromosome negative chronic myeloproliferative disease. *Cancer Genet Cytogenet* 1990;49:57-67.
- Murphy S, Hand H, Rosenthal D, Lazlo J. Essential thrombocythemia: an interim report from the Polycythemia Vera Study Group. *Semin Hematol* 1986;23:177-82.

8. Levine MN, Raskob G, Hirsh J. Hemorrhagic complications of long-term anticoagulant therapy. *Chest* 1986;89:16S-25S.
9. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981;47:207-14.
10. Gardner MJ, Altman DG. Confidence intervals rather than P values: estimation rather than hypothesis testing. *BMJ* 1986;292:746-50.
11. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457-81.
12. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 1959;22:719-48.
13. Cox DR. Regression models and life-tables. *J R Stat Soc [B]* 1972;34:187-220.
14. Pearson TC, Messinezy M. Polycythaemia and thrombocythaemia in the elderly. *Baillieres Clin Haematol* 1987;1:355-87.
15. Turlure P, Le Prise PY, Letortorec S, et al. Essential thrombocythemia (E.T.) clinical course and results of a multicenter prospective study. *Blood* 1993; 82:Suppl 1:1979. abstract.
16. Watson KV, Key N. Vascular complications of essential thrombocythaemia: a link to cardiovascular risk factors. *Br J Haematol* 1993;83:198-203.
17. Kaplan ME, Mack K, Goldberg JD, Donovan PB, Berk PD, Wasserman LR. Long-term management of polycythemia vera with hydroxyurea: a progress report. *Semin Hematol* 1986;23:167-71.
18. Murphy S, Peterson P, Iland HJ, Fruchtman S. Hydroxyurea and other myelosuppressive agents in the treatment of essential thrombocythemia: analysis of leukemogenic potential. *Thromb Haemost* 1993;69:564. abstract.
19. Van de Pette JEW, Prochazka AV, Pearson TC, Singh AK, Dickson ER, Wetherley-Mein G. Primary thrombocythaemia treated with busulphan. *Br J Haematol* 1986;62:229-37.

---

#### IMAGES IN CLINICAL MEDICINE

Images in Clinical Medicine, a weekly *Journal* feature, presents clinically important visual images, emphasizing those a doctor might encounter in an average day at the office, the emergency department, or the hospital. If you have an original unpublished, high-quality color or black-and-white photograph representing such a typical image that you would like considered for publication, send it with a descriptive legend to Kim Eagle, M.D., University of Michigan Medical Center, Division of Cardiology, 3910 Taubman Center, Box 0366, 1500 East Medical Center Drive, Ann Arbor, MI 48109. For details about the size and labeling of the photographs, the requirements for the legend, and authorship, please contact Dr. Eagle at 313-936-5275 (phone) or 313-936-5256 (fax), or the *New England Journal of Medicine* at [images@edit.nejm.org](mailto:images@edit.nejm.org) (e-mail).