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Thrombosis-free survival and life expectancy in 187 consecutive patients with essential thrombocythemia

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Abstract A total of 187 consecutive patients with essential thrombocythemia (ET) were diagnosed and followed by our Hematology Department in the period October 1980–November 1994. The overall follow-up was 773 patient-years. Thrombosis-free survival and overall survival were calculated for the whole cohort; the same parameters were then calculated after arbitrary division of the cohort into two groups, according to the median age at diagnosis (55 years). Fifty percent of the patients had at least one thrombotic episode within 9 years after diagnosis. The thrombosis-free survival curves calculated for patients younger or older than 55 years at diagnosis were comparable. About 85% of the patients were alive 10 years after diagnosis. The survival curves for patients younger and older than 55 years at diagnosis were not significantly different in the observation period, and the observed mortality (seven patients) among patients younger than 55 years at diagnosis was significantly higher than expected (1.68 cases). The relative risk of death was four times greater (SMR = 4.17, 95% C.I. 1.6–8.6, $p < 0.01$) than for healthy, age-matched people living in the same area. Age at diagnosis, smoking, sex, hypercholesterolemia, peak number of platelets, hypertension, and diabetes were not significant prognostic cardiovascular risk factors in our cohort. In conclusion, our data show that ET has to be considered a serious disease that significantly decreases both quality of life (expected life without thrombosis) and life expectancy for younger patients.

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Introduction

Essential thrombocythemia (ET) is a chronic myeloproliferative disease (MPD) characterized by a clonal proliferation of megakaryocytes and an elevated platelet count ($>0.6 \times 10^6/mm^3$). ET is one of the less rare variants of MPD in adults [1–4]. Thrombotic and hemorrhagic events are typical and frequent complications in these patients [1, 5–10]. Thrombotic episodes have been reported to be more frequent than hemorrhagic: moreover, thromboses are a frequent cause of permanent disability and sometimes lethal. A very high platelet count is a risk factor for bleeding [11–15], while a previous thrombotic episode [8, 16], age >60 years, and long persistence of thrombocytosis [8] have been described as risk factors for thrombosis [17]. Overall survival among ET patients has been evaluated in very few studies; the results show that the life expectancy of these patients is not significantly different from that of healthy, age-matched subjects [4, 5, 11]. Thus ET is generally considered a slowly evolving disease, not influencing life expectancy and rarely progressing to other, more serious, oncohematological forms [18, 19].

Our clinical experience appeared to contradict published reports concerning the frequency of thrombotic events and death of these patients. In fact, we often observed thrombotic complications in ET patients, including younger ones, either at diagnosis or during follow-up; sometimes these events caused invalidity or were lethal. This prompted us to seek a better understanding of the clinical course of these patients. The aim of this work was to evaluate thrombosis-free survival and overall survival in our cohort of 187 consecutively diagnosed ET patients. Moreover, age at diagnosis, smoking, sex, hypercholesterolemia, peak number of platelets, hypertension, and diabetes were also evaluated as a prognostic factors of cardiovascular risk.

Patients and methods

Patients

A total of 187 consecutive ET patients (121 women, 66 men), diagnosed according to the Polycythemia Vera Study Group (PVSG) criteria [1], were followed from October 1980 to November 1994. Diagnoses made prior to 1986 ($n=15$) were later confirmed according to PVSG criteria. The median age at diagnosis was 55 years. Complete blood cell counts and physical examinations were performed every 2–3 months or more frequently, according to the clinical status. At diagnosis, 66 patients had platelet counts between 0.6 and 0.8×10^6/mm^3, 48 between 0.8 and 1×10^6/mm^3, 73 more than 1×10^6/mm^3, and the maximum number of platelets was 3×10^6/mm^3. All patients with thrombotic episodes were given chemotherapy with the intention to reduce the platelet count to below 0.6×10^6/mm^3. Each patient with more than 1×10^6/mm^3 platelets was treated with chemotherapy or interferon with the intention to lower the platelet count below 0.6×10^6/mm^3. In all, 85% of our patients were treated with antiaggregants (aspirin, ficlopidine, indobufene, dipyridamole). No antiplatelet drug was given to patients who had hemorrhagic episodes. Cytogenetic examinations carried out at diagnosis in 130 patients (69.5%) showed chromosomal abnormalities in 13 (10%): they were aspecific, including various mosaicisms and deletions. Thrombotic episodes were objectively documented. Deep venous thrombosis was diagnosed by venography or ultrasonography; thrombosis in intracerebral vessels by computed tomography scanning, magnetic resonance, or angiography; retinal vein thrombosis by ophthalmological examination; peripheral or mesenteric-artery thrombosis by arteriography or thrombectomy during surgery. The diagnosis of acute myocardial infarction required an acute clinical presentation with typical electrocardiographic features and elevated creatine-kinase MB fraction [20]. For the diagnosis of cerebral transient ischemic attack (TIA), neurological symptoms or signs lasting less than 24 h in patients who met the criteria for the classification of cerebrovascular disease of the National Institute of Neurological Disorders and Stroke [21] were required. Patients with deep venous thrombosis were treated first with heparin and then with oral anticoagulants. Patients with acute myocardial infarction, stroke, or TIA were treated with platelet antiaggregants indefinitely. Particular attention was paid to evaluating previous thrombotic episodes and additional risk factors for thrombosis: blood pressure >140/90, smoking more than ten cigarettes daily, diabetes mellitus, and hypercholesterolemia (defined by a fasting serum total cholesterol concentration >200 mg/dl). All data were stored in a data base. Patients who did not come in for more than 6 months were contacted by phone. Data were analyzed as a whole and then with the cohort divided into two groups according to the median age at diagnosis: younger or older than 55 years.

Statistical analysis

Continuous data were compared using the *t*-test and category data using the chi-square test. The Kaplan-Meier actuarial method was used to calculate probabilities of survival. The following end points were analyzed: overall survival, with failure defined as one death for any cause; thrombosis-free survival, with failure defined as an ascertained thrombotic episode. Thrombotic episodes occurring within 6 months before diagnosis were considered ET related in the absence of another clinical cause. Data for surviving or thrombosis-free surviving patients were checked at the date of the last follow-up visit. The log-rank statistic was used to compare distributions. To identify independent predictors of thrombosis-free survival, Cox multiple regression analysis was used. The coefficients were estimated on the basis of maximum likelihood criteria, and their significance was evaluated with the Wald test. Two-sided alpha levels less than or equal to 0.05 were considered to indicate statistical significance. These analyses were performed with the Statistical Analysis Software. The expected number of deaths used for computation of the Standardized Mortality Ratio (SMR) was based on age-specific rates measured in Piedmont in the period 1980–1984.

Results

General characteristics of the patients are summarized in Table 1.

Thrombosis-free survival and hemorrhagic complications

Fifty percent of the patients had one (or more) thrombotic episode within 9 years from diagnosis. No significant difference in thrombosis-free survival was observed between patients younger and those older than 55 years at diagnosis (Fig. 1). Characteristics of thrombohemorrhagic episodes are summarized in Table 2.

Table 1 General characteristics of 187 ET patients

	n	%
Sex (F/M)	121/66	–
Median age at diagnosis (years)	55	–
Overall follow-up (patient-years)	773	–
Mean follow-up (months, ±s.d.)	49.2±37.2	–
Antiplatelet treatment	159	85
Anticoagulant treatment	8	4
Cytoreductive treatment	131	70
Busulphan	23	18[a]
Hydroxyurea	80	61[a]
Pipobroman	1	0.5[a]
Interferon	27	20[a]
Drop-out	8	4,5

[a] Percentage of each treatment with respect to all treatments

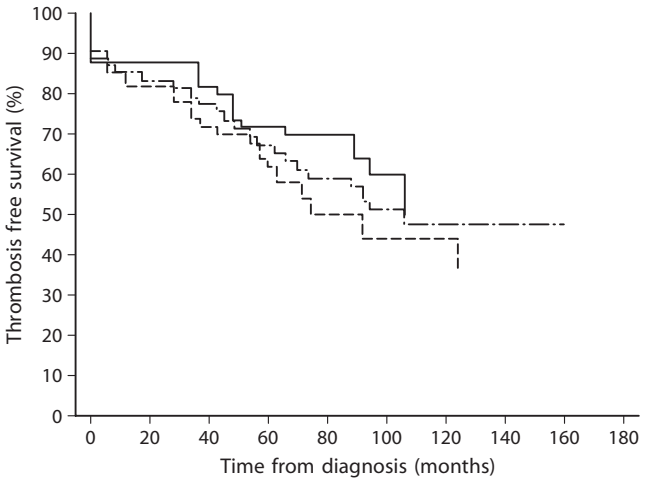

Fig. 1 Thrombosis-free survival curves plotted according to age at diagnosis in 187 consecutively diagnosed ET patients. *Thin line* represents overall thrombosis-free survival, *boldface* and *broken lines* represent patients younger and older than 55 years, respectively, at diagnosis ($p=$n.s.)

Table 2 Thrombotic events and bleeding episodes in 187 ET patients

Event/episode	*n*
Thrombotic events	82
Arterial	62
Transient ischemic attacks	25
Stroke	15
Myocardial infarction	12
Peripheral	10
Venous	20
Deep-vein thrombosis	8
Abdominal vein thrombosis	10
Cerebral sinuses	2
Bleedings	7
Gastrointestinal	4
Cerebral	1
Large ecchymoses	2

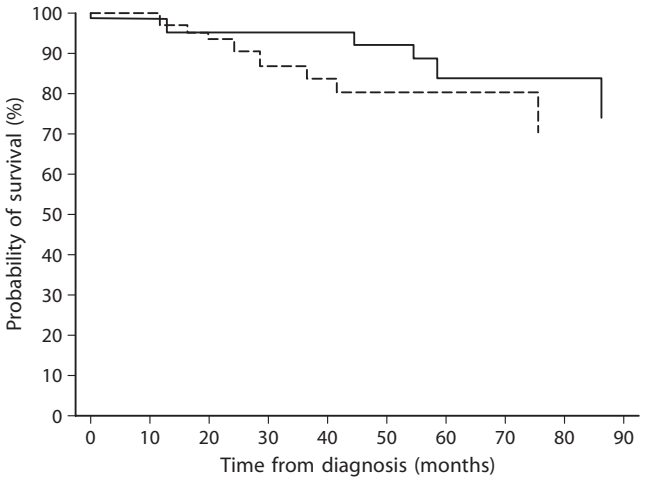

Fig. 2 Overall survival curves plotted according to age at diagnosis in 187 consecutively diagnosed ET patients; *solid* and *broken lines* represent patients younger and older than 55 years, respectively, at diagnosis (p = n.s.)

Thrombotic complications are much more frequent than hemorrhagic (thrombosis versus bleeding ratio is 11.7:1); arterial thrombotic events are more frequent than venous (arterial vs venous ratio is 3.1:1). The majority of arterial complications are thromboses of the cerebrovascular region (64% of all arterial events). The majority of venous thromboses are located in unusual sites: 60% of all venous thromboses are in cerebral venous sinuses and abdominal veins. At the time of the thrombotic event, 53 ET patients had a platelet count between 0.6 and $0.8 \times 10^6/mm^3$, 20 had between 0.8 and $1 \times 10^6/mm^3$, and nine had more than $1 \times 10^6/mm^3$. Fifty-eight percent of the patients were taking antiaggregant drugs at the time of the thrombotic complication; 29% were receiving chemotherapy. Seven major hemorrhagic complications were observed during follow-up, but neither deaths nor permanent disabilities were observed after these complications. Age at diagnosis, sex, smoking, hypercholesterolemia, peak number of platelets, hypertension, and diabetes were not significant prognostic factors of cardiovascular risk.

Overall survival

Approximately 85% of the patients were still alive 10 years after diagnosis (Fig. 2). During the follow-up period 15 deaths were registered: seven patients younger and eight older than 55 years at diagnosis. Four patients died after an arterial thrombotic complication, three events were defined as "sudden deaths", two patients died after progression to acute leukemia, one died of lung cancer, one of acute respiratory failure, one of heart failure, one of liver cirrhosis, and two of unknown causes; no death was secondary to bleeding complication. The survival curves of patients younger or older than 55 years at diagnosis were not significantly different. The observed mortality (seven patients) was significantly higher than expected (1.68 cases) in the younger patient group. The calculated relative risk of death was four times greater (SMR = 4.17, 95% C.I. 1.6–8.6; $p < 0.01$) than for healthy, age-matched people living in the same area (Piedmont). Insertion of cytogenetic examination as an additional covariate did not change the hazard ratio: there was no difference in survival between the two groups with or without chromosomal aberrations at diagnosis.

Discussion

Essential thrombocythemia has generally been described as the most benign variant of the MPDs, the survival of these patients being not significantly different from that of healthy, age-matched people [4, 5, 11, 13, 22]. This view led hematologists to an usually conservative treatment of ET patients. Only few studies of large cohorts are available [4] concerning survival, and the results show no significant difference from an age- and sex-matched healthy population. Our data, obtained in a large cohort and compared with those on age-matched healthy people living in the same area, are in apparent contrast with data from previous studies. Our results demonstrate that thrombotic episodes are much more frequent than hemorrhagic episodes, despite the employment of conventional therapeutic strategies (antiaggregant agents in association, or not, with cytoreductive therapy). In fact, half of our patients had at least one thrombotic episode within 9 years from diagnosis. These episodes occurred when platelet counts were increased (mainly between 0.6 and $0.8 \times 10^6/mm^3$). In patients younger and older than 55 years at diagnosis the observed thrombosis-free survival was comparable; therefore, age alone is not a critical risk factor for thrombosis in this cohort. We also found that patients aged less than 55 years at diagnosis have a significantly shorter life expectancy than healthy, age-matched, people. Consequently, ET itself has to be

considered to carry a significant risk of death for younger patients (SMR = 4.1). In this view, ET is a serious disease that significantly decreases both life expectancy and thrombosis-free survival, particularly for younger patients, and different therapeutic approaches are needed [8, 10, 11, 19, 23–25]. The difference between our data and those from previous studies could be due, at least in part, to the fact that ET patients came to our Thrombosis Unit for observation mainly if they had thrombotic complications; this could represent an unexpected selection bias. The high incidence of thrombotic episodes and microcirculatory disturbances makes it necessary to discuss the role of antiaggregant drugs and of cytoreductive treatments for ET patients. Only 58% of our patients were under antiaggregant treatment at the time of the thrombotic event, and our data suggest that antiaggregation must be used as primary prevention for all patients, independent of the platelet number, with the exception of those who have major bleeding complications. Some preliminary studies have revealed a normal life expectancy and thrombosis-free survival among aspirin-treated ET patients [11, 24], but further prospective, randomized studies are needed to better clarify which drug (and at what dose) and the better benefit/risk profile, are needed. Platelet number itself could play a role in favoring thrombotic complications; even if a direct correlation between platelet number and thrombotic events does not exist, at the time of the thrombotic event all patients had more than $0.6 \times 10^6/mm^3$. Starting from this outcome, a critical issue seems to be the threshold of cytoreduction: it should be important to lower the platelet count to obtain value under $0.6 \times 10^6/mm^3$. Some consensus exists for cytoreduction in ET patients with platelet count in excess of $1.5 \times 10^6/mm^3$ [26], history of major thrombosis or bleeding, bleeding elicited by aspirin, progression of low-risk to high-risk ET during follow-up, and signs of progression of the MPD such as splenomegaly, myelofibrosis, or leukocytosis [10, 11, 24, 27, 28], and a recent study has shown that chemotherapy (hydroxyurea) reduces thrombotic complications in selected high-risk patients [23]. Another unsolved question is which cytoreductive therapy in ET has the best risk/benefit ratio. The problem of hydroxyurea is its possible leukemogenic potential [29]; alpha-interferon and anagrelide [30] must be considered as alternative drugs, particularly in younger patients. IFN has well-known adverse side effects, partially limiting its long-term use [31]. Anagrelide is not free from side effects, and it is not currently available in every country [25, 32]. Nevertheless, these two drugs could be a good choice for treating ET patients younger than 60 years who need cytoreduction, making it possible to avoid the potential mutagenic effect of conventional chemotherapy.

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