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Practice guidelines for the therapy of essential thrombocythemia. A statement from the Italian Society of Hematology, the Italian Society of Experimental Hematology and the Italian Group for Bone Marrow Transplantation

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A B S T R A C T

Background and Objectives. The Italian Society of Hematology (SIE) and the two affiliated Societies (SIES and GITMO) commissioned a project to develop guidelines for the therapy of essential thrombocythemia (ET) using evidence-based knowledge and consensus formation techniques.

Design and Methods. Key questions on the optimal management of ET patients were formulated by an Advisory Council (AC) and approved by an Expert Panel (EP) composed of 7 senior hematologists. The AC systematically reviewed the published literature from 1980 to August 2002, and articles were graded according to their internal validity and quality. Using the Delphi technique, the EP was asked to answer the key questions according to the available evidence. From September 2002 to March 2003, four Consensus Conferences were held in accordance with the Nominal Group Technique with the goal of solving residual disagreement on recommendations.

Results. The EP provided recommendations on when to start platelet-lowering therapy, the most appropriate platelet-lowering agent, the use of anti-platelet therapy, and the management of women in childbearing age and of pregnant women.

Interpretation and Conclusions. By using evidence and consensus, recommendations for the treatment of key problems in ET have been issued. Statements are graded according to the strength of the supporting evidence and uncertainty is explicitly declared.

Key words: essential thrombocythemia, practice guidelines, recommendations, consensus.

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Essential thrombocythemia (ET) is the chronic myeloproliferative disorder (CMD) with the most favorable outcome. In large cohort studies, ET patients showed equal or slightly shorter survival than an age- and sex-matched healthy population.[1-5] Major causes of death were disease-related, thrombotic or hemorrhagic complications or malignant progression due both to the natural history of the disease and, possibly, to the use of chemotherapeutic agents. This clearly identifies the need to prevent both thrombo-hemorrhagic events and leukemic transformation.

Perceiving the need for rigorous, consistent, and feasible recommendations to facilitate decisions concerning the management of patients with ET, the Italian Society of Haematology (SIE) and the two affiliated Societies (SIES and GITMO) commissioned the development of guidelines for the treatment of ET. An Expert Panel (EP) and an Advisory Committee (AC) developed guidelines through a systematic process that involved the assessment of evidence and the use of consensus techniques.

Design and Methods

The development of the guidelines was a multistep process, as outlined in a previous paper.[6] In summary, a 3-member Advisory Council (AC) composed of a hematologist, a statistician and a clinical epidemiologist, was constituted in June 2002. An Expert Panel (EP) composed of seven physicians active in both patient care and clinical research, was selected by the AC. Panel bias was minimized by eliminating from consideration strong advocates for or against one specific therapy. Each panelist provided a

statement attesting the lack of financial conflicts of interest in being a panel member and gave a pledge of objectivity before final appointment (meeting) and acceptance of the position.

The AC decided to shape the guidelines around a list of key clinical questions. Question topics were chosen by a prioritization process according to the burden of illness, availability of evidence, perceived variation in practice, potential to affect treatment decisions, and resource utilization.

Systematic review of evidence

The AC and an expert librarian systematically retrieved literature in four categories: original papers, reviews and educational reports, abstracts of conference proceedings, and ongoing trials. Indexed papers and reviews were identified through a computerized search of the available bibliographic databases: MEDLINE, PubMed, CANCERLIT, Cochrane Library, and EMBASE. The first search was performed on 31st August 2002; however, relevant papers published up to 31st May 2003 were subsequently searched. Articles published in letter format were excluded. The *related articles* function of PubMed was used to identify additional citations. Conference proceedings were retrieved manually. The following proceedings were examined: American Society of Haematology, 2000 and 2001; European Haematology Association, 2001 and 2002; American Society of Clinical Oncology, 1999-2002. A specific bibliographic database was built by importing PubMed records into a Reference Manager 8.0 archive (*ET database*). Ongoing or finished, but yet unpublished trials registered at the NCI web site which included patients with ET were selected and then protocol descriptions were downloaded. All the ET database papers were classified according to the key question they addressed.

Two members of the AC filled in a form for each relevant paper. The form included a full description of the enrolled population, design of the study, outcomes and outcome predictors. A final judgment as to the quality of the evidence was agreed upon by the two reviewers, according to the statements of the Scottish Intercollegiate Guidelines Network (SIGN).[7] Briefly, randomized studies, systematic reviews or meta-analyses were graded 1; longitudinal studies were graded 2, and case series 3. Lastly, each clinical question was provided with a table of evidence that synthesized the pertinent literature. Translated evidence, that is evidence obtained in populations other than those with ET but which could be extrapolated to ET patients, was not fully reviewed, but extrapolations were made by the panelists as appropriate.

Consensus phase

The panelists formulated proper recommendations for each assigned question following a review of the available scientific studies. In the absence of evidence-based studies, the panelists offered recommendations based on their own experience. Subsequently, each panelist scored his/her agreement with the statements made by other panelists (score from 1 to 9) and provided suggestions for rephrasing.

To reach a consensus on those statements for which there was disagreement during the first-round postal phase, the EP was convened and four consensus conferences were held in Bologna, Italy, from September 2002 to March 2003. The 7 panelists, assisted by the AC, attended these meetings. The nominal group technique was used to solve residual disagreements on each selected item. Participants were first asked to comment in a round-robin fashion on their pre-meeting votes, and then a new vote was taken. If 80% consensus on the statement was not achieved, the choices were discussed and a second vote was taken. If 80% consensus was still not attained, the issue was declared undecidable and no further attempt to reach a majority decision was made. When consensus was not reached, minority opinions were recorded. The recommendations were ranked according to the supporting level of evidence. Grade A recommendations were supported by level 1 studies, grade B by level 2 studies, grade C by level 3 studies and grade D by expert judgment, according to the SIGN classification method.[7]

Diffusion and implementation

The AC and the EP agreed on the diffusion plan for these guidelines. A full report will be submitted to the National Clearinghouse that holds the largest repository of guidelines. Scientific societies, as well as the European Agency for the Evaluation of Medical Products (EMEA) and SIGN will be provided with a full report of the guidelines. The recommendations will be fully explorable through an interactive query at the official site of Haematologica (*http://www.haematologica.org*).

These guidelines are intended to expire in 2005. An update by a consensus meeting is planned for the first half of 2006.

Results

Deciding about platelet-lowering therapy

The AC reviewed the literature aimed at defining the natural history of ET in terms of life expectancy, incidence, and determinants of thrombotic and hemorrhagic events.

Survival. Five cohort studies compared overall survival in ET patients with that of the general population (level 2).[1-5] Four of them demonstrated a shorter life expectancy among patients with ET than among age- and sex-matched controls. The standardized relative risk of death in an Italian population was 4.17 (CI, 1.6-8.6).3 However, when the analysis was restricted to female patients aged younger than 50 years, overall survival was similar to that of an age- and sex-matched control population.[8]

Incidence of major thrombotic and hemorrhagic complications. The incidence of thrombotic and hemorrhagic complications was investigated in overall 1850 patients with ET enrolled into 21 retrospective cohort studies (level 2-3). In the only study that also evaluated a control population (level 2),[9] the overall risk of thrombotic episodes was 6.6%/patient-year in a historical cohort of 100 patients with ET versus 1.2%/patient-year in 200 patients with a benign monoclonal gammopathy of undetermined significance. The incidence rate of major hemorrhagic complications in ET patients was 0.33%/patient-year.

In the reviewed cohort studies, the frequency of thrombosis and hemorrhage at diagnosis ranged from 9% to 84%, and from 3.9% to 63%, respectively. After diagnosis, reported cumulative rates for subsequent thromboses and hemorrhages ranged from 7% to 17% and 8% to 14%, respectively. However, the studies reported widely heterogeneous patient populations, used different definitions of major and minor vascular events, and were conducted in different clinical settings (hematology departments, internal medicine units, vascular units, thrombosis units), introducing substantial risks of selection and referral biases.

Age, previous history of thrombotic events and a long duration of thrombocytosis were identified as major risk factors for thrombosis by the only controlled study.[9] Age above 60 and a history of major ischemic events were also risk factors for atherothrombotic complications in a large uncontrolled study of 148 ET patients.[10]

The incidence of major thrombotic or hemorrhagic events in patients below 60 years of age, with no history of thrombotic or hemorrhagic events and a platelet count lower than $1,500\times10^9$/L was addressed by a prospective, controlled study.[11] After a median follow-up of 4.1 years, 5 out of 65 patients had had thrombotic episodes (7.69%) *versus* 4 out of 65 age-and sex-matched controls (6.15%): the incidence of thrombosis in patients and controls (1.91%/patient-year and 1.5%/patient-year, respectively) was not statistically different ($p = 0.36$).

Prospectively followed, non-controlled cohorts of patients with low-risk disease were also reported by two hematology institutions in France and Italy.[12] Patients left untreated were followed-up and vascular episodes were registered. In the French series (20 cases), the median age was 40 (range 7-64), the median platelet count was 909×10^9/L (range 600-1470) and the observation period was 6.7 years. Major vascular events were recorded in 4 cases (20%) and minor ischemic events in 3 (15%). No hemorrhages were reported. The rate of major and total thrombotic complications was 3%/patient-year and 5.1%/patient-year, respectively. In the Italian series (40 cases), the median age was 37 (range 4-55), the median platelet count was 808×10^9/L (range $600-1350\times10^9$/L) and the observation period was 4.3 years. Seven patients had thrombotic complications (17.5%). The rate of vascular occlusion was 4.1% every patient/year.

Two studies reported hemostatic complications in young patients with ET.[8,13] In 74 young women (median age 35, range 18-48), in the absence of a history of thrombosis and regardless of the platelet count, the risk of recurrent thrombosis was 1.2% every patient-year.[8] In 28 patients (mean age 30.8 years) with no history of thrombosis or hemorrhage followed for a median time of 4-6 years (10 on aspirin), only one patient had a portal thrombosis after unadvised discontinuation of aspirin, and no other patient developed major thrombosis.[13]

The incidence of thrombotic events in high-risk patients was studied in a randomized trial in 114 patients who were above the age of 60 or had had a previous thrombosis, or met both criteria.[14] Fitfy-six were randomly assigned to treatment with hydroxyurea (HU) and 58 were assigned to the control group. The goal of therapy was to lower the platelet count to below 600×10^9/L. Anti-aggregating drugs were allowed. During a median follow up of 27 months, two thromboses were recorded in the HU-treated group (3.6%, 1.6%/patient-year) versus 14 in the control group (24%, 10.7%/patient-year) ($p = 0.003$).

Determinants of thrombo-hemorrhagic events. The AC performed a systematic review in order to assess the predictive value of thrombophilic factors in the development of thrombosis in patients with ET. Two papers reported prospective studies of series of patients with ET and compared the allele frequencies of thrombophilic genotypes (prothrombin 20210 mutation and factor V Leiden mutation, 43 patients,[15] and MTHFR mutation, prothrombin 20210, and factor V Leiden mutation, 42 patients)[16] in cases with thrombotic complications with those without the complications. No significant correlation was found between clotting factor polymorphisms and thrombo-hemorrhagic complications. In a retrospective analysis of 304 patients with polycythemia vera or ET a higher rate of venous thromboembolism (16%) was observed in patients with a factor V Leiden mutation than in asymptomatic patients (3%, $p = 0.003$).[17] In two cross-sectional studies the

prevalence of anti-phospholipid antibodies (APA) in ET patients was compared to that in *normal* or *elderly* controls (>50 years).[18,19] There was a significantly higher rate of anticardiolipin IgM and anti β2-glycoprotein I IgM antibodies in the patients with ET. Thrombosis occurred in 10 out of 20 patients with APA and in 12 out of 48 without APA ($p = 0.04$, relative risk 2.0, 95% CI 1.03-3.86).[18]

A retrospective observational study evaluated the frequency of natural anticoagulant deficiencies (antithrombin III, protein C, protein S) in patients with ET.[20] A higher frequency was found in ET patients with thrombosis (20/46), whereas in patients without thrombosis the frequency was 2/35. Only for protein C was there a significant reduction of natural anticoagulant activity with respect to that in controls (without myeloproliferative disease and no thrombosis).

Two studies (level 2) investigated the correlation between hyperhomocysteinemia and thrombosis in 50 patients with chronic myeloproliferative disorders (10 with ET),[21] and in 182 patients with polycythemia vera or ET (83 with ET),[22] respectively. Even though mild to moderate hyperhomocysteinemia occurred in a large number of patients with ET, no correlation between hyperhomocysteinemia and thrombosis was found.

Cardiovascular risk factors. The primary goal of 3 retrospective cohort studies[10,23,24] was to assess the predictive value of vascular risk factors (smoking, diabetes mellitus, arterial hypertension, hypercholesterolemia) in 148, 132 and 46 ET patients, respectively. In two studies,[10,23] 52% and 48% of the patients, respectively, had vascular risk factors at the time of diagnosis. Arterial hypertension and hypercholesterolemia were associated with an increased risk of developing major vascular complications. The presence of one or more vascular risk factors increased the risk of arterial thrombotic complications, and male gender and smoking proved to be independent risk factors for arterial thrombotic complications.[23] Vascular risk factors, especially smoking, more than doubled the risk of complications.[24]

In 6 other cohort studies, which were not primarily aimed at studying the factors predictive of thrombotic complications, cardiovascular risk factors did not predict the occurrence of thrombosis (level 2).[2,4,20,25-27]

Clonal hematopoiesis. Evidence for clonal hematopoiesis as a risk factor for thrombosis in ET was derived from 3 cohort studies.[28-30] In all of them clonality was assessed by the X chromosome inactivation pattern. Shih *et al.*[28] studied a cohort of 54 females with ET and showed by multivariate logistic analysis that the odds ratio for thrombosis was 6.87 in patients with clonal vs polyclonal hematopoiesis. Harrison *et al.*[29] studied 46 females with a diagnosis of ET according to the Polycythemia Vera Study Group (PVSG) criteria. Monoclonal myelopoiesis could be shown definitively in only 10 patients, and patients with polyclonal hematopoiesis were less likely to have experienced thrombotic events than patients with clonal hematopoiesis ($p = 0.039$). Clonal analysis of hematopoiesis was also performed in 40 females with a median age of 40.5 years (range from 20 to 64) and a median platelet count of 700×10^9/L (range from 220 to 1300×10^9/L).[30] Clonal hematopoiesis was found in 17 (42.5%) patients. Thrombotic episodes were significantly more frequent in the group with monoclonal hematopoiesis ($p = 0.04$).

Platelet count. A cohort study of 56 patients with ET aimed at determining the lowest platelet count that was associated with thrombotic and hemorrhagic manifestations,[31] reported severe complications at platelet counts lower than 600×10^9/L in 22% of the patients.

In a review of 200 consecutive published cases of ET,[32] the degree of thrombocytosis influenced the nature of the hemostatic complication: in general, arterial thrombotic complications occurred at lower platelet counts than did hemorrhagic complications. Recurrent bleeding from mucous membranes or the digestive tract was reported more frequently in patients with a platelet count over $1{,}000\times10^9$/L.

An inverse relationship could be established between the platelet count and the presence of large von Willebrand factor (VWF) multimers in plasma of 36 patients with ET and 26 patients with reactive thrombocytosis.[33] Normalization of the platelet count was accompanied by restoration of a normal plasma VWF multimeric distribution.

Recommendations

Framing the decision to start a platelet-lowering treatment

The Panel agreed on a definition of major thrombotic events that included stroke, transient ischemic attack, myocardial infarction, angina pectoris, peripheral arterial thrombosis, retinal artery occlusion, deep venous thrombosis and pulmonary embolism.

Microcirculatory events were defined as vascular headaches, dizziness, visual disturbances, burning pain sensation in the palms of the hands and soles of the feet, distal paresthesia and acrocyanosis.

Familial thrombophilia was defined as carrying a thrombophilic risk factor associated with a thrombotic event in at least one family member carrying the risk factor.

Before deciding whether to start platelet-lowering treatment, patients should be questioned regarding their history of thrombotic or hemorrhagic events (grade B), the presence of cardiovascular risk factors, i.e. smoking, hypertension, hypercholesterolemia or diabetes melli-

tus (grade B), and symptoms of microcirculatory disturbances (grade B).

A questionnaire-guided history of hemorrhagic or thrombotic events is recommended (grade D).

Only those patients with a familial or personal history of thrombosis should be screened for thrombophilia, namely factor V Leiden mutation, prothrombin 20210 mutation, lupus anticoagulant, antiphospholipid antibodies (grade C), antithrombin III, protein C, protein S, and homocysteinemia (grade D).

Candidates for platelet-lowering treatment (Figure 1)

The platelet count needs to be reduced by platelet-lowering treatment in patients who are above the age of 60 years, have a history of major thrombosis or major bleeding, or have a platelet count over 1500×10^9/L (grade A).

Patients who are between the ages of 40 to 60 years are also candidates for platelet-lowering treatment if their platelet count is over 1000×10^9/L and they have a cardiovascular risk factor (i.e. smoking, arterial hypertension, hypercholesterolemia or diabetes mellitus) or familial thrombophilia (grade D).

Patients who are younger than 40 years of age are also candidates for platelet-lowering treatment if they have a co-morbid condition that greatly increases their thrombotic risk (homocystinuria, familial dominant hypercholesterolemia) (gradeD).

Patients who suffer from severe microcirculatory symptoms, despite anti-platelet therapy, are also candidates for platelet-lowering treatment (grade D).

The EP could not reach a consensus on a recommendation for platelet-lowering treatment in patients between 40 to 60 years of age, with a platelet count lower than 1000×10^9/L, without a personal history of major thrombotic or hemorrhagic events, but with a cardiovascular risk factor or familial thrombophilia.

Target of therapy and monitoring

The target platelet count in patients treated with platelet-lowering therapy is 400×10^9/L. This target is highly recommended for patients with a history of a major thrombotic event (grade D).

A platelet count of 600×10^9/L may be an appropriate target for those patients with a high risk of toxicity, i.e. patients who require higher than standard drug doses (grade D). Those patients who do not receive platelet-lowering treatment need to be examined every 3-4 months during the first year after the diagnosis and

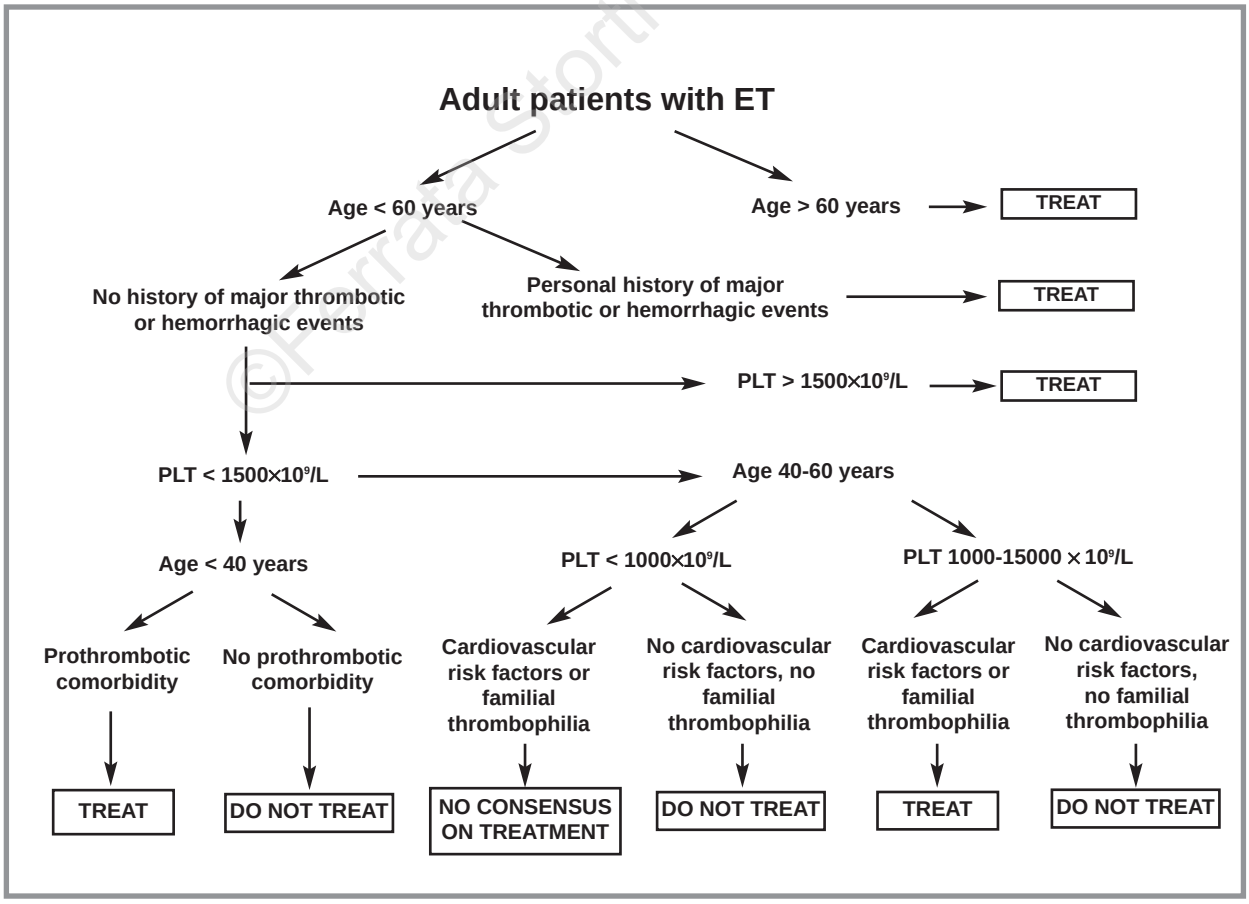

Figure 1. Algorithm for the decision to start platelet-lowering treatment in adult patients with ET.

every 6 months thereafter. Periodic monitoring should include complete blood count with differential, physical examination of the spleen, a search for signs and symptoms of thromboembolic and hemorrhagic events, enquiry concerning drug utilization (i.e. antiplatelet-drugs, estro-progestins) and reassessment of cardiovascular risk factors (grade D).

Deciding which platelet-lowering agent

The AC reviewed the literature addressing the efficacy, side effects and mutagenic potential of platelet-lowering agents, i.e. hydroxyurea, interferon, pipobroman, anagrelide, ^{32}phosphorus and other alkylating agents.

Hydroxyurea: Since 1980, hydroxyurea has been the agent of choice for the treatment of thrombocytosis and erythrocytosis due to ET and polycythemia vera. It is a non-alkylating, non-specific myelosuppressive agent that induces dose-related cytoreduction of all myelogenous lineages. Its mechanism of action is inhibition of DNA synthesis by blocking the activity of the enzyme ribonucleoside reductase.

Regarding HU efficacy in controlling the platelet count in ET patients, the AC considered 1 randomized trial and 3 cohort studies. In the prospective, randomized trial,[14] 56 patients were assigned randomly to HU treatment, and 58 patients were assigned to the control group. The starting dose of HU was 15 mg/kg of body weight; therafter a maintenance dose of the drug was administered to maintain the platelet count below 600×10^9/L without lowering the white blood cell count below 4×10^9/L. Both groups were followed for a median of 27 months. All the patients assigned to HU had a decrease in the platelet count below 600×10^9/L after a median of 30 days (range 16 days to 60 days). This response persisted throughout the whole treatment period and there was no need for frequent adjustments of the dose. In the control group, the platelet count at six months ranged from 892 to 986×10^9/L.

In the 3 non-controlled cohort studies,[34-36] the starting dose of HU was 30 mg/kg of body weight per day, followed by reduction of the dose to 15 mg/kg of body weight. A complete or good partial response at 6 months was achieved in 91% of the patients. This meant a reduction of the platelet level to less than 500×10^9/L within 8 weeks in 80% of the patients. After a median follow-up of 8 years (range 5 years to 14 years), no patient had had to stop taking the drug because of intolerance or adverse effects.[34]

Concerning the efficacy of HU in reducing the rate of thrombotic events, the AC considered one randomized trial[14] and one cohort study,[34] both of which investigated high-risk patients. During the follow-up period, thrombotic episodes occurred in 2 patients randomized to HU treatment (3.6%) versus 14 (24%) in the control group. This difference was statistically significant. After a more prolonged period of observation of the same two cohorts of patients (median follow-up of 73 months),[37] the antithrombotic efficacy of HU was confirmed: 5 patients receiving HU developed major or minor thrombotic complications (1.5%/patient-year), compared with 26 patients in the untreated group (7.4%/patient-year). In the cohort of 25 ET patients younger than 50 years who were treated because of a high thrombotic risk, one case (4%) of transient ischemic attack was recorded, but no major thrombosis or severe bleeding was recorded.[34]

To date there are no randomized studies powered to assess the relative risk of malignant transformation in HU-treated patients. The AC provided the EP with a systematic review of transformation rates of ET, which indicated that ET has an inherent tendency to evolve into acute leukemia, even in absence of specific therapy.[38,39] Thus, studies that enrolled patients in need of therapy automatically selected patients with more active disease, and thus, with a higher propensity to malignant transformation. Furthermore, leukemic transformation occurs after a lead-time of several years. A review of the literature from 1981 to 1994 identified a total of 40 ET cases which transformed into acute leukemia after a mean time from presentation of 6.5 years.[39] Consequently, only long-term studies are appropriate to assess this issue, despite a possible bias inherent in the higher rate of treatment in patients with long-standing disease.

The AC analyzed 1 randomized trial,[37] and 5 case series with long follow-up in which the occurrence rates of secondary malignancies were analyzed according to treatment.[34,40-43] In the randomized trial,[37] none of the 20 never-treated patients developed neoplasia vs. 3 of the 77 patients given HU only (3.9%; p = NS), and 5 of the 15 patients given busulphan plus HU (33%; p <0. 0001). This shows that the sequential use of busulphan and HU significantly increases the risk of second malignancies.

A French study followed 357 patients for a median of eight years,[40] and found that the rate of leukemic transformation was significantly higher in patients treated sequentially with HU followed by alkylating agents, suggesting that HU sensitizes myelogenous tissue and potentiates the leukemogenicity of other agents (level 2).

An Italian series of 25 ET young patients treated with HU showed no case of leukemic or neoplastic transformation after a median follow-up of 8 years (range 5-14 years).[34] Similarly, no leukemic transformation was reported in 110 patients treated for a long time solely with HU (level 2).[41] In contrast, a multicenter prospective study showed that HU treatment was associated with a 6% rate of death from malignant conditions;[42]

and in a retrospective study in which 23 patients were followed for 104 months[43] the risk of leukemic transformation was higher in patients treated with HU than in those untreated or treated with pipobroman only (17.3% vs 3.77%).

It should be stated that the above studies from France[40] and Italy,[43] revealed a high frequency of 17p chromosomal deletions in patients with acutely transformed disease who were treated with HU. The majority of these patients also had p53 mutations and a specific type of dysgranulopoiesis (17p- syndrome). The AC considered, as translated evidence, two papers which documented that 17p deletions also occur in other hematologic disorders, including both *de novo* and treatment-related cases of acute myeloid leukemia and myelodyplastic syndromes. Moreover, further analysis of the French data revealed a stronger association of 17p- with advanced age than with HU treatment.[44]

The AC considered, as translated evidence, papers dealing with HU therapy for non-malignant disorders (eg. sickle cell anemia and cyanotic congenital disease):[45] there is a single case report of leukemia in a patient with sickle-cell anemia after 6 years of therapy with HU out of thousands of patients treated.[46] The AC, however, stressed the fact that these patients did not have a clonal myeloproliferative disorder.

The risk of transformation to myelofibrosis with myeloid metaplasia (MMM) seems to be nearly null in the first years after the diagnosis, but increases thereafter. Level 2 studies consistently supported the estimation of a nearly constant transformation risk of about 0.9% per year.[47-50] The incidence rate of MMM was lower in younger patients.[13,40,49] No study examined the predictors of MMM transformation.

The risk of congenital anomalies among infants of women treated with HU during pregnancy may be substantial, since HU inhibits DNA synthesis. However, no epidemiological study has been reported. In 15 infants born to women who were treated with hydroxyurea at conception and/or during pregnancy,[51-59] no malformations were observed, and only one stillbirth was reported in a woman with eclampsia.

Regarding the overall survival of ET patients treated with HU, the AC considered one randomized trial conducted in high risk patients.[14,37] In the long-term outcome analysis (median follow-up 73 months, range 3-94), 46 out of 54 patients (85%) originally randomized to HU were alive, compared with 49 of 58 patients (84%) in the control group (p = NS).

Interferon-α (IFN-α): Recombinant IFN-α is a cytokine able to inhibit, by a direct and dose-dependent mechanism, the *in vitro* growth of multipotent hematopoietic progenitor cells (CFU-GEMM) and megakaryocytic forming units (CFU-Meg). Furthermore, the biological characteristics of IFN-α make it devoid of leukemogenic risk. The AC identified 27 clinical studies related to the use of IFN-α in ET. Fifteen studies included only patients with ET, while 12 studies also included patients with other CMD and thrombocytosis. A preliminary report of a multicenter, randomized (IFN-α vs HU) trial was excluded from the analysis because it lacked minimally required information.[60] Using the SIGN scale, 9 of the studies selected for the analysis had an evidence level 2 and the others level 3. No randomized controlled trial, systematic review, or meta-analysis has been found.

Overall, 292 ET patients were reported, 22.2% of them having been pretreated with chemotherapy. The mean platelet count was below $1,000\times10^9$/L in 14.3%, between 1,000 and $1,500\times10^9$/L in 66.7%, and above $1,500\times10^9$/L in 19% of the studies. There was a wide dispersion in the age of the enrolled patients (mean age between 39 and 66 years).

The weekly starting dose of IFN-α ranged between 6 MU to 70 MU, the most used being 21 MU (10 studies): the dose was not adjusted for body weight in any of the studies except one. After an induction period ranging from 2 to 12 weeks, the dose was adjusted to maintain the response (3 MU to 42 MU/week): the maintenance period ranged between 3 and 96 weeks. In a dose-finding study, hematologic response was maintained with 3 MU/week of IFN-α in 15% of the patients, with 9 MU/week in 64% and with 21 MU/week in 24%.

All of the studies reported the efficacy of IFN-α in reducing platelet count and the incidence of side effects. Data on clinical findings (splenomegaly) were reported in 6 studies and on symptoms in 4 studies. Using the original response criteria of each study, the overall response rate was 84.6%, while 15.4% of the patients were primarily resistant to the treatment and achieved no response. Complete normalization of the platelet count was obtained in 54.3% of the patients. A positive correlation was found between the initial platelet count and the cumulative dose administered until achievement of a complete response[60] or the time required to achieve the response.[62,63] Discontinuation of IFN-α led to a progressive increase in the platelet count; however, 8 cases have been described of prolonged remissions continuing for 3 to 19 months after discontinuation of the drug.[64-67]

A reduction of splenomegaly, when present, was reported in 66% of the patients, and one study reported the complete disappearance of splenomegaly in 17% of cases.[67] A positive effect on clinical symptoms was found, with their complete disappearence when platelet counts were normalized.[61,62,64,66,67]

At the beginning of INF-α treatment, side effects (mainly flu-like syndrome) occurred in virtually all patients, but thereafter they generally subsided, requiring drug discontinuation in only 16.5% of patients. No

deaths related to IFN-α treatment were reported.

A preliminary report at the 2001 Meeting of the American Society of Hematology addressed the issue of cost-effectiveness of the main therapeutic options for ET (HU, anagrelide, IFN-α), showing that IFN-α was not a cost-effective option in the clinical scenarios analyzed.[68]

Three further studies used other types of IFN in this setting: Abegg-Werter *et al.*[69] used IFN-γ (0.5 mg thrice weekly for three months) in 6 patients, obtaining a moderate decrease of the platelet count in each of them. However, none achieved complete normalization, and severe side effects were observed in all. Merup *et al.*[70] used human leukocyte IFN (3MU five times a week) in one patient with ET no longer responsive to recombinant IFN-α because of the appearance of anti-IFN antibodies. Gugliotta *et al.*[71] described the effectiveness of pegylated IFN-a (starting dose of 25 mg/week) in 90 patients with ET: after 1 year of treatment, 77% had a hematologic response (67% on an intention to treat basis), without substantial toxicity.

Anagrelide. Anagrelide is an oral imidazo-quinazoline compound that has been shown to reduce elevated platelet counts in patients affected by ET and related CMD. It appears to act in the post-mitotic phase of megakaryocytes development, by inhibiting megakaryocyte maturation. As an oral treatment the Food and Drug Administration currently approves anagrelide for ET and for thrombocytosis associated with polycythemia vera.

The AC identified 7 clinical studies related to the use of anagrelide in ET: 4 studies included only patients with ET,[72-75] while 3 other studies included also patients with other CMD and thrombocytosis.[76-78] Since the response was stratified according to diagnosis, all these studies were included in the analysis. The study by Laguna *et al.*[75] was excluded from the analysis because it lacked minimal required information (drug dosage, duration of treatment). Further reports, dealing with pediatric patients and long-term follow-up, were identified, and the results are reported separately.

No randomized controlled trial, systematic review or meta-analysis was found. All the studies used PVSG diagnostic criteria. There was a wide dispersion in the age of the enrolled patients (mean age between 33 years and 60 years). Overall, 442 ET patients were included in these studies; 82% of them had undergone some form of cytoreductive treatment. Mean platelet counts were below $1{,}000\times10^9$/L in 50% of the studies, having been influenced by previous treatment. Two studies provided no definition of hematologic response;[75,78] one study defined only one grade of response,[77] while 3 studies distinguished between complete and partial response.[72-74]

The daily starting dose of anagrelide ranged between 1 and 4 mg (higher doses were used only in the first, dose-finding report).[76] After the induction period, the dose was changed in relation to the platelet count. The most commonly used approach was to begin treatment at 0.5 mg *q.i.d*, and to adjust the dose weekly, by increases of 0.5 mg per day, until the treatment goal was achieved.[73,77]

All the selected studies reported data on anagrelide effectiveness in reducing platelet count and on the drug's toxicity. Seventy-six percent of the patients evaluable for response came from the Anagrelide Study Group report.[77] Using the original response criteria of each study, the overall response rate was 93%, while 7.3% of the patients (27/367 patients) were primarily resistant to the treatment. Platelet reduction was frequently observed within one week of treatment, while time to complete response ranged from 15 to 25 days (longer times were, however, observed). Sixty-three out of 441 (14.3%) of the patients stopped the treatment because of side effects (mainly headache, tachycardia, fluid retention, gastrointestinal intolerance).

Two reports regarding long-term follow-up were identified.[79,80] In 1997, Petitt *et al.*[79] reported ongoing results of the Anagrelide Study Group multicenter study, regarding 942 CMD patients treated for a minimum of 4 years. The response rate with the ET group (546 patients) was 73%. The most common adverse events (reported as a percentage in the entire CMD population) were headache (27%), palpitations (26%), diarrhea (20%), and fluid retention (22%); 13% of the patients stopped the treatment because of side effects.

Two reports dealing with young patients were identified.[80,81] In the first one,[80] the population included 35 consecutive patients younger than the age of 50 who were selected from a retrospective series of patients with ET followed at the Mayo Clinic, and who started anagrelide therapy before 1992. There were no restrictions regarding thrombosis risk profile. The median age of the group was 38 years (range, 17 to 48): 20% of the cases had a history of thrombosis, 26% had a history of hemorrhages, and 55% of vasomotor manifestations. Twenty-four patients (69%) had previously been treated with either HU or busulfan. The median platelet count at the start of therapy was $1{,}075\times10^9$/L. The median duration of therapy was 10.8 years (range, 7 to 15.5). Seven patients (20%) experienced a total of 10 episodes of thrombosis over the duration of the study (cerebrovascular event, transient ischemic attack, deep vein thrombosis, superficial thrombophlebitis). Four major thrombotic episodes occurred despite platelet counts of 400 to 600×10^9/L. Only two of the 7 patients with thrombotic events had a history of thrombosis. Thus, the overall incidence of thrombosis was 5/35 (14.2%). Hemorrhagic events occurred in 7 out of 35 patients (20%) and platelet counts during the bleeding episodes ranged from 400×10^9/L to 924×10^9/L. Anemia was the only new

side effect that emerged after long-term therapy. Eight patients (24%) experienced a more than 3 g/dL decrease in hemoglobin level.

Anagrelide is contraindicated in pregnancy because of its ability to cross the placenta and uncertainty about its teratogenic potential. So far, no case of leukemic transformation has been reported in ET patients treated exclusively with anagrelide.

Pipobroman. Pipobroman has a chemical structure similar to alkylating agents and has been used, mainly in European countries, for the treatment of polycythemia vera and ET. The AC identified 6 studies related to the use of pipobroman in ET. Three of them were cohort studies from the same institution, reporting short-term results on 24 ET patients,[82] long-term follow-up of 118 high-risk ET patients[83] and leukemic evolution in 106 high-risk ET patients.[43] Another Italian institution reported a cohort study of 21 patients,[84] which was subsequently updated.[85] The daily starting dose of pipobroman ranged between 0.8 and 1 mg/kg; after a mean induction period shorter than 60 days, a maintenance dose (0.3-0.6 mg/kg/day) was identified. According to the original response criteria, the overall response rate was 95.4%, while 4.6% of the patients (9/192 patients) were primarily resistant to the treatment and achieved no form of response.[85] The median time to remission was 7-10 weeks (range 2-20). After a median follow-up of 10 years (range 1-22), hematologic remission was maintained in 85% of patients (47% complete and 38% partial), while in the remaining 15% of patients, the platelet count ranged between 600 and 800×10^9/L. Eleven percent of the patients (13/118) had thrombotic episodes during the follow-up period (fatal in 6 patients), which is a cumulative risk of 7%, 14% and 18% at 5, 10 and 15 years, respectively.[83] A direct correlation of the thrombotic risk with age, but not with platelet count, was found. Acute leukemia occurred in 3 patients (2.5%), corresponding to a cumulative risk of 0%, 3% and 6% at 5, 10 and 15 years, respectively.

Busulfan. Busulfan is an alkylating agent that has been used most commonly in the past for chronic myeloid leukemia. The AC identified two studies, involving a total of 52 ET patients, who were treated with busulfan alone.[86,87] In the first study,[86] clinical results were restricted to 24 patients followed for at least 4 years: 76% of them achieved a controlled phase, defined as a platelet count below 400×10^9/L for at least 1 year off therapy. The median duration of the controlled phase was 164 weeks (range 59-720) and the median dose of busulfan required to achieve this control was 589 mg. In the second study,[87] 15 patients were treated, and a clinical and hematological response was obtained in all of them. No cases of acute leukemia were reported in either study, however both had a follow-up shorter than 6 years. No study was found which specifically adressed the efficacy of busulfan on thrombotic events. One study was identified in which symptomatic patients, i.e. with microvascular circulation disturbances, atypical transient ischemic attacks or acute coronary syndrome, were treated with one course of busulfan and aspirin.[88] All 20 patients achieved a complete remission of ET (platelet count lower than 350×10^9/L) and their symptoms disappeared. At complete remission, treatment with busulfan and aspirin was discontinued until symptoms returned. Remission of ET (platelet count lower than 400×10^9/L) induced by busulfan lasted from 3 to more than 9 years.

Regarding the transformation potential of busulfan, no study was found that measured the trasformation rate of ET in patients treated with busulfan only. Finazzi *et al.*[37] reported the long-term outcome of 114 ET patients included in a randomized controlled trial (HU versus no myelosuppression): in the subgroup of patients included in the HU arm who had been pretreated with busulfan they found a high incidence of secondary malignancies (5/15).

Melphalan. In 1982 the PVSG reported the preliminary results (12 months of follow-up) of two randomized trials, comparing melphalan versus ^{32}phosphorus in ET patients.[89] Of 13 patients treated with melphalan and with valuable responses, 11 had a complete response, without significant toxicity. Gris *et al.*[90] reported the case of an ET patient who developed acute leukemia after melphalan therapy. A paper published in 1985 by de Pauw *et al.*[91] was excluded from the review analysis because it included thrombocytosis secondary to infection, anemia and splenectomy and did not provide subgroup analyses.

Radioactive phosphorus (^{32}P). In the 1970s the PVSG conducted two randomized studies (PVSG04, PVSG10), in which 31 ET patients were randomized to receive ^{32}P or melphalan.[92] In PVSG10, patients younger than the age of 40 were excluded and higher ^{32}P doses were administered. At 3 months, the complete remission rate was 17% in PVSG04 and 63% in PVSG10 (versus 67% and 100% in the melphalan arm, respectively). At 12 months the complete remission rate was 50% in PVSG04 and 63% in PVSG10 (versus 50% and 71% in the melphalan arm, respectively). Long-term results were reported in 1997: out of 55 patients originally randomized, 21 were switched to HU. In 4 of the remaining 34 patients, there was leukemic evolution; while leukemia occurred in 5/7 patients initially treated with HU and switched to ^{32}P.

The other reports were non-controlled studies. Wagner *et al.*[93] reported on 8 patients with treatment durations of 2-15 years. Three of the 8 patients required chemotherapy after multiple doses of ^{32}P, and one developed acute leukemia. Randi *et al.*[94] reported on 230 patients with CMD (16 ET) treated with ^{32}P. No patient

reported hematologic complications, including acute leukemia evolution. Two studies, describing 625 patients with CMD (polycythemia vera and ET),[95,96] without any subgroup analysis reported that 50% of patients achieved a normal blood count.[95] However, 29 out of 345 (8.4%) developed acute leukemia within 2-15 years from the start of ^{32}P treatment.

Recommendations

Platelet-lowering therapy in patients younger than 40 with no childbearing potential

For patients younger than 40 years, who are candidates for platelet-lowering therapy, either male or female with no childbearing potential, the first-line therapy should be interferon or anagrelide (grade D).

On giving this recommendation, the Panel agreed on using a cautionary principle against the use of hydroxyurea in very young subjects, even in the absence of strong evidence about the risk of malignant transformation due to the drug. The Panel agreed on recommmending that the use of anagrelide should be controlled and administered within clinical trials or a registry that tracks responses and adverse effects (see also Appendix). In the case of side effects that impair a patient's quality of life or, if there is a high toxicity risk (i.e. requirement of higher than standard doses) with the use of interferon and anagrelide, the recommended alternative therapy is hydroxyurea (grade D).

Patients treated with hydroxyurea should be informed that an increased risk of leukemia with long-term use of the drug cannot be excluded.

Platelet-lowering therapy in patients aged 40 to 60 with no childbearing potential

Patients aged 40-60 years who are candidates for platelet-lowering therapy, male or female with no childbearing potential, who have a history of a major thrombotic event, should receive first-line platelet-lowering therapy with hydroxyurea (grade A).

Without a history of a major thrombotic event, these patients should receive first-line platelet-lowering therapy with interferon or anagrelide (grade D). The same treatment considerations made for younger patients hold for anagrelide therapy in this age group.

Platelet-lowering therapy in females with childbearing potential

Females with childbearing potential who are candidates for platelet-lowering therapy should receive interferon as the first-line therapy (grade D). In the presence of therapy side effects that impair a patient's quality of life or if there is a high toxicity risk (i.e. requirement of higher than standard doses), the patient should receive anagrelide, reserving hydroxyurea as a possible alternative therapy (grade D).

Patients on anagrelide or hydroxyurea should be advised to stop taking the drug in the presence of menstrual delay, until the result of a pregnancy test is available (grade D).

Platelet-lowering therapy in patients aged older than 60

Hydroxyurea should be the first-line treatment for those patients who start platelet-lowering therapy at the age of 60 to 70 years (grade A). In the presence of therapy side effects that impair a patient's quality of life, or if there is a high toxicity risk (i.e. requirement of higher than standard doses), busulfan or pipobroman should be the second-line therapy (grade D).

Hydroxyurea, busulfan or pipobroman should be the first-line platelet-lowering therapy in patients older than the age of 70, according to the treatment Center's experience (grade D). Those patients aged over 60 years who are successfully receiving platelet-lowering therapy with interferon or anagrelide, should continue that treatment (grade D).

An accurate drug dosing and monitoring strategy is recommended (Table 1).

Anti-platelet and anti-thrombotic therapy

In ET, platelets are primarily involved in the etiology of thrombotic occlusions of the acral microvasculature. Platelet activation, persistently elevated levels of thromboxane A2, and endothelial cell damage are essential factors in the etiology and formation of platelet-rich thrombi in erythromelalgic areas. Antiplatelet therapy is used with the rationale of controlling platelet function, thus preventing platelet-mediated microvascular circulatory disturbances in ET.

The AC reviewed the literature on drugs used as antiplatelet agents in ET patients.

Aspirin: Aspirin plays a well-established role in preventing arterial thrombosis in the general population.[97] The AC could not find appropriate prospective studies aimed at evaluating the antithrombotic efficacy of aspirin in ET; only retrospective studies were available. The AC considered one review reporting prompt relief from neurologic and visual symptoms in 17 ET cases in response to low-dose aspirin.[98] In addition, the AC considered 2 retrospective studies on the efficacy of aspirin on microvascular thrombotic symptoms: the studies reported a good efficacy (80-90%) of aspirin alone on the incidence of microvascular thrombotic symptoms.[4,99]

Concerning the efficacy of anti-platelet treatment in preventing major thrombotic events, the AC considered a retrospective analysis of a large cohort of 195 consecutive patients diagnosed according to PVSG criteria and followed-up for a median of 6.34 years.[100] No significant difference in the mean thrombosis-free survival

Table 1. Strategy for drug dosing and monitoring for the most commonly used platelet-lowering agents.

Hydroxyurea

The starting dose of HU is 15-20 mg/Kg/day until response is obtained. Thereafter, a maintenance dose must be administered to keep the platelet count at response levels without affecting hemoglobin and WBC count values. Complete hemogram and platelet count should be recorded every two weeks during the first 2 months, then every month, and, in steady state in responding patients, every 3 months.

α-Interferon

α-IFN is contraindicated in patients with thyroid and/or mental disorders: for this reason an accurate evaluation of thyroid function and inquiry of previous or present mental disorders in candidate patients are recommended. α-IFN should be administered at the dose of 3MU daily until a response is reached, then, maintenance therapy is adjusted to the lowest weekly doses which control the platelet number at response level. Platelet count and complete hemogram must be recorded every week during the first month of therapy, every two weeks during the second month, then every month and, in steady state in responding patients, every 3-4-months.

Peg-IFN is probably equivalent to α-IFN, however, these recommendations are intended solely for the α-IFN, since no specific recommendations regarding Peg-IFN can be provided at present.

Anagrelide

Accurate monitoring of cardiac function (with ECG and echocardiography) before and during treatment with anagrelide is advisable. Anagrelide is contraindicated in patients with grade 4 (WHO) cardiovascular disease and caution must be exercised in patients with documented coronary ischemia. Anagrelide should be administered at the starting dose of 0.5 mg every 12 hours for seven days. Subsequently, the daily dose should be increased by 0.5 mg/day every week, until the response is obtained. Daily dosages exceeding 3.5-4 mg are not advisable, due to the risk of side effects. In responding patients, maintenance therapy, with daily doses very close to those used to achieve response (about 2-2.5 mg), is always required to keep the platelet count at response levels. Platelet count and complete hemogram should be recorded every week during the first month of therapy, every two weeks during the second month, then every month and, in steady state responding patients, every 3-4 months.

time was observed in the different treatments groups (aspirin alone, aspirin plus myelosuppressive drugs, myelosuppressive drugs alone or no therapy). In patients with a previous major thrombotic event, myelosuppressive drugs reduced re-thrombosis in a more efficient way than did aspirin alone (2.7% vs 25%), but were associated with a higher rate of bleeds (16% vs 4%). In asymptomatic patients receiving myelosuppressive drugs associated with aspirin, the rate of thrombosis was lower (5%) than in those receiving aspirin alone (7.2%) or only myelosuppressive drugs (17%). However, the comparisons were never adjusted for risk level and other prognostic factors.

Jensen *et al.*[4] found, in 96 consecutive patients, that thrombotic or microvascular complications were incurred by 21% of aspirin-treated patients vs 45% of the patients who had never received aspirin. Furthermore, 11 of the 14 observed thrombotic complications occurred after aspirin had been discontinued or before aspirin had been begun. Thus, most of the events occurred while the patients were off-aspirin. Conversely, only 4 out of 51 patients who took aspirin for the entire follow-up had thrombotic complications (p <0.001). The efficacy of aspirin used in association with cytoreductive therapy on reducing thrombotic risk was consistently observed.[31,88,99,100] However, no adjustment was made either *a priori* or *a posteriori* (multivariate analysis) to control for the propensity to treat with an association therapy.

The doses of aspirin used in the different studies varied from 40 mg to 500 mg per day. Low-dose aspirin was effective in relieving symptoms, even when the platelet count remained high. The optimal effective dose of aspirin for long-term prophylaxis of microvascular circulatory disturbances is unknown: a dose of 100 mg is generally recommended, but some studies indicate that daily doses of 40-50 mg may be effective for the primary and secondary prevention of platelet-dependent vascular complications in ET patients.[99,101,102]

The long-term use of aspirin at about 300 mg per day for primary/secondary cardiovascular prevention in the general population increases the risk of bleeding by 1.8% per year,[103] which is nearly double the baseline risk. From one-half to one-third of ET patients who had bleeding were reported to have been on aspirin therapy at the time of bleeding. The baseline risk of bleeding in untreated patients with platelet counts between 600-1,000$\times 10^9$/L is similar to that of the general population (1.6% per year),[99] but it is increased by more than 7% during aspirin treatment, with a risk ratio ranging from 3.7 to 4.5. This may be due to the additive effects of platelet dysfunction and antiplatelet therapy.[99,100] Most of the hemorrhagic events were reported in patients with platelet counts over 1,000$\times 10^9$/L.[99,104]

The two most frequent sites of major bleeding are the gastrointestinal tract and the central nervous system: 34% of the patients with gastrointestinal bleeds were receiving aspirin in a 444-patient cohort,[105] while all the three patients with hemorrhagic cerebrovascular events were taking aspirin.

Ticlopidine and clopidrogrel. Ruggeri *et al.*[106] compared

ticlopidine with aspirin for the management of patients with CMD and thrombocytosis and found no advantage from the use of ticlopidine on the principal outcomes. Erythromelalgia and other microcirculatory disturbances proved to be refractory to ticlopidine. The AC did not find any study dealing with the use of clopidrogrel in ET.

Indomethacin and dipyridamole. Indomethacin and dipyridamole, with or without aspirin, are reported treatments for ET patients, but their outcomes have never been analyzed.

As translated evidence, the Sixth American College of Chest Physicians Consensus Conference on Antithrombotic Therapy[107] was presented and taken as the basis in order to shape the most appropriate anti-platelet therapy in ET patients for primary and secondary prevention.

Recommmendations

Framing the decision for anti-platelet therapy

Tests to study hemostasis are not indicated to decide whether to start anti-platelet therapy (grade D).

Candidates for anti-platelet therapy

Anti-platelet therapy is recommended in patients with microcirculatory symptoms, provided that no absolute contraindication to anti-platelet therapy is present (grade B). Anti-platelet therapy is also recommended in patients with a recent major arterial vascular event (ischemic stroke, transient ischemic attack, peripheral arterial occlusion, myocardial infarction, unstable angina) or for whom there is clinical or laboratory evidence of coronary artery disease, provided that no previous clinically significant bleeding has occurred (grade B).

In patients with extreme thrombocytosis (platelet count greater than $1{,}500\times10^9$/L) and an indication for anti-platelet therapy, platelet-lowering therapy should be started promptly in order to control the platelet count rapidly (grade D).

The EP could not reach a consensus concerning the use of anti-platelet therapy in patients over 40 years of age who had one or more cardiovascular risk factors (cigarette smoking, arterial hypertension, diabetes mellitus, hypercholesterolemia).

The recommended anti-platelet therapy

The appropriate anti-platelet therapy is aspirin: plain, enteric-coated or buffered aspirin can be used (grade B). As long as the indication for anti-platelet therapy holds, aspirin should be administered at the dose of 75-100 mg qd, during or after a meal. Concurrent administration of proton pump inhibitors is advised in patients with gastric symptoms (grade D).

Clopidogrel should be reserved to patients who have major contraindications to aspirin therapy (aspirin intolerance or allergy, documented gastritis or peptic ulcer). Clopidogrel should be administered at the daily dose of 75 mg (grade D).

Management of patients under anti-platelet therapy

Anti-platelet therapy should be interrupted promptly in the case of clinically significant bleeding while on treatment (grade D).

Anti-platelet therapy should also be withheld at least one week before elective surgery in interventions involving a high-risk of bleeding or in which even minor bleeding could result in life-threatening complications, such as neurosurgery, or requiring heparin prophylaxis (grade D).

Anti-platelet therapy should be interrupted 3-5 days before starting elective anticoagulation with heparin or thrombin inhibitors and on the first day of oral anticoagulation. However, anticoagulation can be started even in patients who are still taking anti-platelet therapy, when anti-thrombotic treatment is mandatory and urgent (i.e. myocardial infarction, ischemic stroke, percutaneous coronary interventions) (grade D).

Aspirin should be restarted 24 hours after stopping heparin prophylaxis, while clopidogrel should be started 3-5 days before stopping heparin (grade D).

Prescription or self-administration of non-steroidal anti-inflammatory drugs in association with anti-platelet therapy should be strictly avoided (grade D).

No specific monitoring is advised during anti-platelet therapy, apart from clinical surveillance of adverse events such as bleeding, especially gastrointestinal (grade D).

Treatment of thrombotic events

Patients with ET who have a major arterial or venous thrombotic event should receive standard therapy (grade D).

Pregnancy

Pregnancy often occurs in ET patients since females in childbearing age comprise quite a large proportion of the ET population. The AC pooled outcome data from 461 pregnancies reported by retrospective and prospective cohort studies analyzed for the natural history of the disease, or relevant for the outcome.[108-110]

Among the pooled cases, the mean age at pregnancy was 29 years with a mean platelet count at the beginning of the pregnancy of $1{,}000\times10^9$/L. During the second trimester, platelet count reached a nadir value of 599×10^9/L indicating an average spontaneous decline of 350×10^9/L to 400×10^9/L in platelet count.[110] Overall, 204 of the 461 pregnancies had an unsuccessful outcome (44%), which is about three-fold higher than in

the general population. The median duration of gestation was 38 weeks due to abortions and pre-term deliveries. Cesarean section was necessary in 15% of the patients. Placental infarctions were reported in 18 cases: these were often responsible for intrauterine fetal growth retardation (11 cases). Abruptio placentae was reported in 9 cases (3.6%), a rate which is higher than in the general population (1%) (RR =3.6). Pre-eclampsia was reported in 5 cases (1.9%), which is equal to that among the general population (1.7%). Post-partum thrombotic episodes were reported in 13 patients (venous thrombosis, pulmonary embolism, sagittal sinus thrombosis, transient ischemic attack, Budd-Chiari syndrome), occurring in 5.2% of the pregnancies. This rate is higher than in the overall poulation of pregnant women.[109] Overall, no specific therapy for ET was given in 122/251 (48%) of the pregnancies; IFN was used in 19 cases; low molecular weight heparin (pre/post-partum) in 26; and aspirin therapy at dosages ranging from 75 mg to 500 mg per day, was administered in 106 pregnancies (42%). In 11 patients, aspirin was prescribed in combination with dipyridamole. Eight patients received platelet apheresis, 3 HU, 1 busulphan, and 2 radioactive phosphorus. There were 13 minor or major, pre or post-partum bleeding events. Seventy-nine out of 106 (74%) patients treated with aspirin during pregnancy had successful pregnancies, while only 80/145 (55%) of the patients not receiving aspirin had successful pregnancies. The average platelet count (maximal or at beginning of pregnancy) in patients with successful pregnancies was $1{,}010\times10^9$/L, while it was 977×10^9/L among those with an unsuccessful outcome: thus, the platelet count did not predict pregnancy outcome. A first pregnancy was unsuccessful in 35% of the cases, and subsequent pregnancies were unsuccessful in 37%. The rate of successful pregnancies was significantly lower in patients who had previous abortions (48% failure rate); but those on aspirin had a failure rate of 36% (like the overall pooled population with ET).

The EP concluded that no direct evidence of the efficacy of aspirin overall in pregnant ET women (or subgroups) is available, but it seems possible that aspirin increases the rate of successful pregnancies.

Recommendations

Platelet-lowering therapy in pregnancy

Pregnant women are candidates for platelet-lowering therapy when there is a history of major thrombosis, or of major bleeding, or when the platelet count is greater than $1{,}000\times10^9$/L, or when familial thrombophilia or cardiovascular risk factors are documented (grade D).

Pregnant women who are candidates for platelet-lowering therapy should receive interferon (grade B).

Anti-platelet therapy in pregnancy

Thrombophilia tests are not necessary to decide whether specific anti-platelet prophylaxis is appropriate for pregnant women with ET, except in those with a previous history of major thrombosis or a previous pregnancy failure (grade D).

Anti-platelet therapy is recommended for pregnant women with a history of microvascular symptoms or with a previous pregnancy (at least one event) (grade D).

Prophylaxis and therapy of thrombosis during pregnancy

All pregnant women with a previous thrombosis should receive low molecular weight heparin at prophylactic doses during the third trimester. Oral anticoagulation therapy with warfarin should be continued for 6 weeks in the puerperium: longer periods are recommended for those patients with familial thrombophilia (grade D).

Women with a thrombotic episode (peripheral, placental) during pregnancy should receive low molecular weight heparin at therapeutic doses, and oral anticoagulant therapy (PT INR 2-3) for at least 6 weeks in the puerperium. Longer periods are recommended for patients with familial thrombophilia (grade D).

Discussion

The present paper provides recommendations for the management of key clinical problems in ET patients. In the search of evidence, 438 papers were retrieved from 1980 to 2002 in a systematic manner. The design, number of patients, outcome analysis, and factors confounding the studies were analyzed and the supporting evidence was graded according to explicit criteria for quality and strength.[7] The result of the systematic literature review was that scientific evidence did not cover all the important key questions in the management of the disease. Meta-analyses or large randomized clinical trials, i.e. the best techniques to compare specific therapies, were lacking in ET because the disease is uncommon and efficacy end-points occur late in the history of the disease. Thus, a large amount of evidence was derived from non-controlled, non-randomized studies, in which selection and time-to-treatment biases precluded definite conclusions on the efficacy of therapies. Expert panel consensus was required to complete the guidelines.

According to a strict methodology for eliciting the experts' consensus, the Panel provided recommendations for the following questions in the treatment of patients with ET: when to start platelet-lowering therapies, which agent to use in different age groups and risk categories, when to treat with anti-platelet agents, how

to manage pregnant patients. Sufficient level 1 evidence was available only to formulate three grade A recommendations. This finding reflects experience in most hematology-oncology disorders. As a matter of fact, currently, practice guidelines can be based on high-quality scientific evidence only for decisions in newly diagnosed patients with the most common hematologic disorders. However, treatment of rare disorders without curable therapies continues to be based on clinical skill and experience. This is reflected in our guidelines in which many of the recommendations are based on expert judgements' consensus.

The results of these guidelines suggest that the critical determinants for planning platelet-lowering therapy in patients with ET are the disease-associated risk of thrombosis, the patient's age and the non-ET-associated risks of thrombosis (such as congenital or familial thrombophilia or individual cardiovascular risks) (Figure 1). The EP agreed on the importance of stratifying patients into different risk groups for major thrombotic or hemorrhagic events. In high-risk patients, i.e patients older than 60 years of age, a previous thrombotic or hemorrhagic event, or a platelet count higher than $1,500\times10^9$/L, platelet-lowering therapy was considered to be mandatory. Also intermediate risk patients, i.e. patients between 40 to 60 years, with a platelet count greater than $1,000\times10^9$/L and personal non-ET-associated cardiovascular risks of thrombosis (diabetes mellitus, arterial hypertension, smoking and hypercholesterolemia) or familial thrombophilia associated with a thrombotic event in the family, were judged worthy of platelet-lowering treatment. Low-risk patients, i.e. patients between 40 to 60 years of age, a moderately high platelet count (lower than $1,000\times10^9$/L), without a personal history of major thrombotic or hemorrhagic events, but with cardiovascular risk factors or familial thrombophilia associated with thrombotic events in the family, were considered as possible candidates for platelet-lowering treatment. However, the EP did not reach a consensus on the necessity of treating such patients. Part of the panel judged the risk of side effects of the available drugs or their risk of inducing secondary malignancies greater than their beneficial effect on the thrombotic tendency of the patients.

Three drugs were considered to be appropriate options as first line treatment for patients with disease requiring platelet-lowering therapy: hydroxyurea, interferon, and anagrelide. Relevant literature documented the efficacy of all of these as platelet lowering-agents. However, strong evidence of efficacy on the reduction of the risk of thrombosis was mostly lacking. A randomized controlled trial comparing the major thrombotic and hemorrhagic events in treated and untreated patients was available only for hydroxyurea.[14,37] This piece of evidence was considered strongly by the EP which recommended hydroxyurea as first line therapy in patients older than 40 years of age, without childbearing potential and a previous thrombotic event, and in all patients over 60 years old. In contrast, in patients younger than 40 years, a precautionary attitude was chosen, and the non-mutagenic drugs, like interferon or anagrelide, were recommended. The recommmenation was, however, consensus based, and a controlled use of anagrelide was suggested as a way to track side-effects and adverse events related to its use.

Uncertainty was also explicity expressed in the recommendations for the use of anti-platelet therapy. While aspirin use was strongly recommended in patients with microcirculatory disturbances and for secondary prophylaxis in patients who have had prior major thrombotic events, the EP withheld from pronouncing on its use for primary prophylaxis of thrombotic events in ET patients. The lack of dedicated, well-designed controlled trials prompted the members of the Panel to weigh the drug's inherent risk of causing hemorrhages against the disease's risk of causing thrombosis. Thus, the EP could not reach a consensus on recommending the use of anti-platelet therapy in ET patients who had not experienced a previous cardiovascular event, even in the presence of one or more cardiovascular risk factors (cigarette smoking, arterial hypertension, diabetes mellitus, hypercholesterolemia).

These guidelines cannot be compared with other recommendations for therapy of ET issued with the same methodology. Only author-derived suggestions for the treatment of ET are available, most of which are derived from a partial review of the literature or from recently or personally published evidence. It is believed that the therapeutic recommendations set forth in these guidelines may be modified by additional clinical trials that will be concluded in the next years. The present guidelines should, therefore, be replaced by the end of 2006.

Addendum

Literature review up to 31 October 2003

Since the present guidelines were based on a systematic review of literature published up to March 2003, an analysis of data published since that date up to 31 October 2003 was performed before publication of the paper. We found 3 new studies dealing with therapy of ET.

A multi-institutional, phase II trial of IFN^{111} in patients with CMD was aimed at investigating the response rate and response durability, and assessing toxicities. Initially, patients were started on IFN at a dose of 5 MU/m^2 per day as a subcutaneous injection. After the first 16 patients had been treated, the starting dose of IFN was reduced to 2 MU/m^2 per day because of unexpected toxicities. IFN demonstrated different levels of efficacy and

toxicity in each of the CMD studied. The overall response rate achieved in ET was 88.2% (n = 17 patients; 1 complete response and 14 partial responses). In another study, the feasibility and safety of imatinib mesylate and anagrelide combination therapy were investigated in patients with CMD with persistent thrombocythemia.[112] Of 22 patients, 2 had ET. The combination therapy with imatinib mesylate and anagrelide was feasible and tolerable. No responses were noted in patients with ET.

In a pilot study of PEG-IFN2b,[113] ET patients were required to have either thrombo-hemorrhagic signs and/or symptoms if previously untreated; persistence of thrombo-hemorrhagic signs and/or symptoms if receiving anagrelide, IFN-α, or hydroxyurea; or intolerance to anagrelide, IFN-α, or hydroxyurea. The initial PEG-IFN2b dose was from 1.5 to 4.5 μg/kg per week subcutaneously with subsequent dose adjustments as indicated by response and adverse events. Eleven patients (nine females, median age 54 years, range 26-69 years) were treated. PEG-IFN2b rapidly controlled platelet counts and resolved symptoms in all patients. The median duration of PEG-IFN2b therapy on-study was 9 months (range 4-17 months). No patient had signs or symptoms of thrombosis or hemorrhage while on study. After 2 months of therapy, 10 patients (91%) were in complete remission, and 11 (100%) after 4 months. One patient discontinued therapy at 4 months because of persistent grade 3 fatigue and a second at 5 months because of anxiety and depression.

Eighty-three patients with various CMD were analyzed for the occurrence of acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) during treatment with HU alone or HU following treatment with busulfan.[114] In the HU-treated group (n = 58) 7 patients developed AML and 5 patients MDS. Five of the 12 patients had been treated with HU alone, and 4 patients had received both HU and busulfan. In the non-HU-treated group (n = 25), 1 patient developed acute myeloid leukemia. The incidence of AML and MDS was approximately 14% when HU was used alone. The incidence was markedly increased to about 30% when HU was preceded by treatment with busulfan. The AC graded this as translated evidence of grade 3 because of the biases inherent to the retrospective design of the study and derived from not having stratified patients according to disease type and severity.

At the 2nd International Congress on Myeloproliferative Diseases and Myelodysplastic Syndromes held in New York from 16th to 18th of October 2003, Dr. T.A. Green reported the notice that the PT-1 trial was precociously closed in September 2003 by the Data Monitoring Committee. PT-1 was a Medical Research Council randomized trial to compare HU plus aspirin versus anagrelide plus aspirin in high-risk ET. The study objectives were to determine whether anagrelide is as effective as HU in reducing elevated platelet counts in high-risk patients and to assess whether treatment modality alters the risk of leukemic and myelofibrotic transformations in high and intermediate risk patients. Patients were randomized to one of two treatment arms: aspirin 75 mg daily plus HU 0.5-1.0 g daily; or aspirin 75 mg daily plus anagrelide given at a starting dose of 0.5 mg twice daily which could be increased by 0.5 mg per day every one to two weeks to a maximum dose of 10mg per day (average 2-2.5 mg daily). The trial was stopped because the incidence of hemorrhagic events in patients receving anagrelide and aspirin was higher than that in patients receiving HU plus aspirin. No published report of these preliminary results is available.

The strength of evidence was in no case enough to question the validity of the recommendations of these guidelines. However, the study on the incidence of MDS and AML transformation after HU,[115] although of low grade evidence, supports the cautionary principle used in not indicating HU for young patients needing platelet-lowering therapy. The notice of the early discontinuation of the PT-1 trial strengthens the necessity for a controlled use of anagrelide and that patients receiving anagrelide should be enrolled within clinical trials or a registry that tracks responses and adverse effects. Moreover, the result of the trial raise a cautionary note on the association between anagrelide and aspirin, a possible therapy resulting from these guidelines. This issue will be a matter of discussion in the next revision of these guidelines when the full results of the trial will be available.

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