Evidence-based Series 6-9 EDUCATION AND INFORMATION 2013

A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

The Management of Malignant Thrombocytosis in Philadelphia Chromosome-Negative Myeloproliferative Disease

J. H. Matthews, C.A. Smith, J. Herst, D. Lee, K. Imrie, and the Hematology Disease Site Group

Report Date: January 15, 2008

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Evidence-based Series (EBS) 6-9, consists of three sections:

- Section 1: Guideline Recommendations
- Section 2: Evidentiary Base
- Section 3: EBS Development Methods and External Review Process

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EBS 6-9 Education and Information

Evidence-based Series #6-9: Section 1

The Management of Malignant Thrombocytosis in Philadelphia Chromosome-Negative Myeloproliferative Disease: Guideline Recommendations

J. H. Matthews, C.A. Smith, J. Herst, D. Lee, K. Imrie, and the Hematology Disease Site Group

A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)
Developed by the Hematology Disease Site Group (DSG)

Report Date: January 15, 2008

QUESTIONS
This evidence summary was developed to provide information to aid clinicians in the management of patients with essential thrombocythemia (ET) and polycythemia vera (PV). The following questions were addressed:

1. Is there a definable subgroup of patients who are at a high risk of either thrombosis or bleeding?
2. Does controlling the platelet count with cytoreductive agents improve clinical outcomes such as overall survival, major and minor thrombosis, hemorrhage, and the development of myelofibrosis?
3. Does cytoreductive therapy produce additional transformation to acute leukemia (AL)?
4. What effect does aspirin therapy have on the occurrence of thrombosis or hemorrhage?

TARGET POPULATION
Patients with Philadelphia chromosome-negative myeloproliferative diseases, specifically ET or PV.

RECOMMENDATIONS
• All ET and PV patients with thrombocytosis should be managed with low-dose aspirin. Special precautions should be taken in the case of patients with greater bleeding risk or allergies (see “Qualifying Statements” for additional information).
• Management without cytoreductive therapy is a reasonable option for asymptomatic patients.
• Cytoreductive therapy should be considered as an option for patients with thrombocytosis who have thrombosis. Hydroxyurea is the preferred agent and should be administered to maintain a platelet count of less than $600 \times 10^9/L$ (see “Qualifying Statements” for additional information).

• If treatment with hydroxyurea is not appropriate, then either interferon or anagrelide are options. Physicians who choose anagrelide to reduce the risk of arterial thrombosis should be aware that there are data suggesting that it is inferior to hydroxyurea, and its efficacy in comparison to no cytoreductive therapy has not been established. Other than reducing the platelet count, interferon is of unknown efficacy.

QUALIFYING STATEMENTS
• Hydroxyurea should be regarded as a possible leukemogen in patients with myeloproliferative disease.

• The European Collaboration on Low-dose Aspirin in Polycythemia Vera (ECLAP) 2003 study used a 100 mg dose of aspirin. However, only an 81 mg pill is available in Canada for use in adults, and the Hematology DSG regards this as a reasonable dosage.

• In the randomized studies, target platelet counts of both <600 and <400 $x 10^9/L$ were shown to be safe and effective.

KEY EVIDENCE
• Evidence from one randomized controlled trial (RCT) showed low-dose aspirin (100 mg/day) reduces the risk of thrombosis (relative risk [RR]=0.4, $p<0.05$) in patients with PV treated with cytoreductive therapy. A non-randomized cohort study found a similar, though not statistically significant, effect (RR=0.6). Direct evidence for ET is limited.

• Data from a number of retrospective studies show that initial symptoms may be an important predictor of subsequent thrombosis. They do not show that age, platelet count, or vascular risk factors can define a group of high-risk patients needing cytoreductive therapy.

• There is strong evidence showing hydroxyurea reduces the incidence of total arterial thrombosis in ET when compared with anagrelide (4.2% versus [vs.] 9.1%, $p<0.05$) or with no initial treatment (9% vs. 45%, $p<0.05$). However, no effect of hydroxyurea has been shown for stroke, myocardial infarction, or overall survival.

• Anagrelide is inferior to hydroxyurea in controlling arterial thrombosis, and its efficacy in comparison to no cytoreductive therapy has not yet been established.

Funding
The PEBC is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

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Phone: 905-527-4322 ext. 42822   Fax: 905-526-6775   E-mail: ccopgi@mcmaster.ca
The Management of Malignant Thrombocytosis in Philadelphia Chromosome-Negative Myeloproliferative Disease: Evidentiary Base

J. H. Matthews, C.A. Smith, J. Herst, D. Lee, K. Imrie, and the members of the Hematology DSG

A Quality Initiative of the Program in Evidence-based Care, Cancer Care Ontario
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QUESTIONS
This evidence summary was developed to provide information to aid clinicians in the management of patients with essential thrombocythemia (ET) and polycythemia vera (PV). The following questions were addressed:

1. Is there a definable subgroup of patients who are at a high risk of either thrombosis or bleeding?
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3. Does cytoreductive therapy produce additional transformation to acute leukemia (AL)?
4. What effect does aspirin therapy have on the occurrence of thrombosis or hemorrhage?

TARGET POPULATION
Patients with Philadelphia chromosome-negative myeloproliferative diseases, specifically ET or PV.

INTRODUCTION
Diseases: PV and ET
PV and ET are myeloproliferative disorders (MPD), a broad category of malignant bone marrow diseases that also includes chronic myeloid leukemia (1). Both diseases are characterized by an abnormal production of blood cells: PV is differentiated by a predominance of erythrocytes and ET, by thrombocytes. The major symptoms are an elevated platelet count (thrombocytosis) as well as thrombosis and bleeding. Another characteristic symptom is
erythromelalgia, a burning sensation in the hands and feet secondary to abnormal platelet aggregation in the microcirculation.

PV and ET are rare and chronic conditions with no known cure and carry a risk of thrombotic complications and transformation to myelofibrosis with myeloid metaplasia (MMM) or acute myeloid leukemia (AML). The progression of these diseases is slow, and patients often experience long asymptomatic periods punctuated by thrombotic or hemorrhagic events. The prevalence of both PV and ET has been reported as approximately 30-35 per 100,000 population, with an incidence of 1.5-2 per 100,000 (2). The risk for PV does not vary by gender but increases with age and is more common in European-born Jews. ET is twice as common in women. While the life expectancy for patients with ET does not differ from the general population, patients with PV may have a reduced survival (2).

The pathogenesis of PV and ET is particularly complex and currently not well understood. A number of different mechanisms have been implicated, including the V617F mutation in janus kinase (JAK)2, which is present in most cases of PV and found in about 50% of cases of ET. The clinical manifestation of ET varies according to whether the JAK2 mutation is present, and further complicating the issue, in a substantial number of cases, ET is not a clonal disorder (3).

Disease Management

The diagnosis of PV or ET often occurs by chance, since approximately half of patients are asymptomatic. The other half present with thrombohemorrhagic manifestations, most commonly microvascular occlusion in the central nervous system (CNS), extremities, or skin (e.g., erythromelalgia) (4). The pathogenic complexity of these diseases confounds treatment decisions and has led to varying treatment practices among clinicians. This variability was evaluated in a recent survey, conducted in 2002 among American Society of Hematology members, which found that practice patterns for PV were quite heterogeneous (5).

There is general agreement that symptomatic treatment can normalize blood and platelet counts, thereby reducing the risk of thrombotic events in patients. Phlebotomy is the standard of treatment for PV and is used to establish a safe red blood cell volume (i.e., hematocrit < 45%). Venesection is also regarded as a safe and effective therapy. However, in cases of progressive myeloproliferation, cytoreductive therapy is also used. Many clinicians feel the risk of progression to leukemia (i.e., leukemogenesis) due to cytoreductive treatment warrants caution in the application of these agents for ET or PV.

In the case of ET, current opinion is that cytoreductive agents are appropriate for patients at high risk for thrombohemorrhagic events, including those greater than 65 years of age, with a high platelet count (> 1500x10^9/L), or with symptoms of thrombosis or bleeding at diagnosis. There is less agreement over whether these profiles of ‘high risk’ are applicable to PV.

Therapy

Hydroxyurea (hydroxybarbamide) is the most commonly used cytoreductive agent in this setting and is regarded as effective and safe in reducing platelet counts. There are concerns that it is leukemogenic when used in patients with myeloproliferative disorders. Other cytoreductive options (e.g., anagrelide, interferon alpha, pipobroman, 32-phosphorus [32P]) have been used in this setting, but there is limited data available regarding their effectiveness and safety for this purpose.

Aspirin therapy is known to alleviate microvascular events such as erythromelalgia. Many clinicians prescribe low doses of aspirin to prevent thrombosis in ET and PV.

There is considerable debate over issues in the management of PV and ET and whether current practices conform to the best available evidence. In particular, there is uncertainty over which subgroups of patients with PV or ET are at an elevated risk for thrombosis or hemorrhage.
and are most likely to benefit from treatment. In addition, it is not clear what chemotherapeutic regimens are effective and safe in patients with ET or PV for improving clinical outcomes and whether there is clear evidence of benefit in terms of the occurrence of thromboses and hemorrhage, myelofibrosis, and survival. Finally, some evidence indicates that regular aspirin treatment may be beneficial for these patients. This systematic review will address these issues by reviewing the available published evidence.

**METHODS**

The evidence-based series (EBS) guidelines developed by Cancer Care Ontario's Program in Evidence-Based Care (PEBC) use the methods of the Practice Guidelines Development Cycle (6). For this project, the core methodology used to develop the evidentiary base was the systematic review. Evidence was selected and reviewed by three members of the PEBC Hematology Disease Site Group (DSG) and methodologists.

The systematic review is a convenient and up-to-date source of the best available evidence on the management of malignant thrombocytosis in Philadelphia chromosome-negative myeloproliferative disease. The body of evidence in this review is primarily comprised of mature randomized controlled trial (RCT) data; lesser quality data were also considered. That evidence forms the basis of a clinical practice guideline developed by the Hematology DSG (see Section 1). The systematic review and companion recommendations are intended to promote evidence-based practice in Ontario, Canada. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

**Literature Search Strategy**

A number of major biomedical literature databases were searched for relevant published articles. An initial search for relevant studies (e.g., systematic reviews, phase III/II randomized trials, non-random prospective and retrospective studies, conference abstracts) was conducted in July 2005. Relevant articles and abstracts were selected and reviewed by members of the Hematology DSG. The dates for the initial, and updated search where applicable, are as follows: MEDLINE (Ovid) (1966 through Jan 2007), MEDLINE In-Process & Other Non-Indexed Citations (formerly known as PREMEDLINE) (Ovid) (Jan 29, 2007), EMBASE (Ovid) (1985 through Jan 2007), and Cochrane Library (Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials (Ovid), Issue 1, 2007). Abstracts from conference proceedings were searched for reports of ongoing trials, including those of the American Society of Hematology (ASH) 1995-2006, the American Society of Clinical Oncology (ASCO) 1995-2006, and the European Hematological Society 1995-2006.

An updated search for published systematic reviews and RCT evidence was subsequently conducted in January 2007; evidence for risk factors was not included in this update search, and this data is current to July 2005.

**Study Selection Criteria**

Studies were included in this systematic review if they reported clinical outcomes of cytoreductive therapy (e.g., thrombosis or hemorrhage event rates, mortality, myelofibrosis, or rates of acute leukemia or myelodysplasia) in the treatment of patients with ET or PV and if the design of the study was an RCT. Studies were excluded if they were not published in English or did not report data primarily on patients with ET or PV. A separate search conducted for a broader range of studies than those above included the following:

1. Studies that evaluated risk factors for thrombosis/bleeding (Question 1) or reported on clinical outcomes of aspirin treatment (e.g., thrombosis/bleeding rates, mortality, or myelofibrosis) (Question 4),
2. Published research studies of any design type.
3. Studies with \( n > 20 \) patients.

Synthesizing the Evidence

Studies reporting on risk factors for malignant thrombocytosis or clinical outcomes of therapy were too heterogeneous to pool. The patients included in these studies varied widely in age, prior treatment, initial symptoms, and platelet count. Data from RCTs reporting clinical outcome data were tabulated in tables and summarized by clinical outcome and disease type (i.e., ET or PV).

RESULTS

Literature Search Results

A breakdown of the studies located through the literature searches is included in Table 1, categorized by question and study design. The review of cytoreductive therapy (Questions 2 and 3) was restricted to RCTs only. Due to the lack of RCTs investigating risk factors (Question 1) and aspirin therapy (Question 4), additional study designs such as prospective (e.g., cohort and case series) and retrospective (e.g., cohort or case audit studies) studies were located and included.

Table 1. Number of included studies by design type and question.

<table>
<thead>
<tr>
<th>Question</th>
<th>Design Type (# Abst publications)</th>
<th>Table</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Is there a definable group of patients who are at a high risk of either thrombosis or bleeding?</td>
<td>Retrospective 16(2) Prospective 4 RCT 1(1)</td>
<td>4</td>
</tr>
<tr>
<td>2. Does controlling the platelet count with cytoreductive agents improve clinical outcomes, such as overall survival, major and minor thrombosis, hemorrhage, the development of myelofibrosis?</td>
<td>NA NA 5(1)</td>
<td>5</td>
</tr>
<tr>
<td>3. Does cytoreductive therapy accelerate transformation to acute leukemia (AL)?</td>
<td>NA NA 5</td>
<td>6</td>
</tr>
<tr>
<td>4. What effect does aspirin therapy have on the occurrence of thrombosis or hemorrhage?</td>
<td>1 (1) 2</td>
<td>7</td>
</tr>
</tbody>
</table>

Notes: Values in parenthesis indicate the number of studies available in abstract form only and are in addition to the number of available full publication reports; Abst = abstract; NA = No applicable data to report; RCT = randomized controlled trial.

Systematic Reviews and Clinical Practice Guidelines

No systematic reviews were retrieved, but four clinical practice guidelines for the treatment of ET or PV were. Two were published in 2004, by the Italian Society of Hematology (SIE) and affiliates (7) and the Groupe Français de Cytogénétique Hématologique (GFCH) (8), and two in 2005, one by the Czech Hematological Society (9) and one by Campbell and Green as part of the ASH educational program (10). The GFCH guideline was not available in English, and the Czech publication was expanded in an English language publication in 2006 (11). Guideline development methods were only provided in the SIE report; a systematic review of the literature was conducted and a panel and formal consensus process used to establish recommendations. Evidence was graded and reported along several clinically relevant themes.
Data tables were not provided. The DSG addresses some of the conclusions of the SIE in the “Discussion” section (see below).

**Description and Critical Appraisal of Included RCTs**

Descriptive characteristics (e.g., patient population, treatment(s), sample size, follow-up, percentage of patients evaluable) of the RCTs included in this review are reported in Table 2.

**Table 2. Descriptive characteristics of included RCTs.**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Question(s)</th>
<th>Disease</th>
<th>Eligibility Criteria</th>
<th>Agents</th>
<th>N (% eval*)</th>
<th>FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>German ET-Study</td>
<td>1,2</td>
<td>ET</td>
<td>NR (low and high-risk ET patients were included)</td>
<td>IFN vs HU</td>
<td>55</td>
<td>6.6</td>
</tr>
<tr>
<td>2006 (12)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(abstract)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRC PT1 2005</td>
<td>2,3</td>
<td>ET</td>
<td>&gt;60 yrs, or pc &gt; 1000x10^9/L, or prior thrombosis, hemorrhage, hypertension, or diabetes</td>
<td>ASA + HU vs ASA +AA</td>
<td>407</td>
<td>408</td>
</tr>
<tr>
<td>(13,14)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECLAP 2003</td>
<td>4</td>
<td>PV</td>
<td>No clear indications or contraindications for aspirin treatment; no comorbidities</td>
<td>ASA vs @</td>
<td>518 (92)</td>
<td>~3</td>
</tr>
<tr>
<td>(15-17)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Najean 1997a (18)</td>
<td>2,3</td>
<td>PV</td>
<td>&gt;65 yrs</td>
<td>32p + HU vs 32p</td>
<td>219</td>
<td>242</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1-16;15</td>
</tr>
<tr>
<td>Najean 1997b (19)</td>
<td>2,3</td>
<td>PV</td>
<td>&lt;65 yrs and not previously treated with radiotherapy or chemotherapy</td>
<td>HU vs P</td>
<td>150</td>
<td>142</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1-17;14</td>
</tr>
<tr>
<td>Cortelazzo (20,21)</td>
<td>1995</td>
<td>ET</td>
<td>&gt;60 yrs or prior thrombosis and pc ≤ 1500x10^9/L</td>
<td>Hu vs @</td>
<td>56</td>
<td>58</td>
</tr>
<tr>
<td>(abstract)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6.1</td>
</tr>
<tr>
<td>PVSG-05 1986</td>
<td>4</td>
<td>PV</td>
<td>PSVG-01 criteria and a normal bleeding time and no history of prior bleeding disorders suggestive of either hemophilia or von Willebrand’s Disease</td>
<td>ASA vs @</td>
<td>83</td>
<td>83</td>
</tr>
<tr>
<td>(22)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.2</td>
</tr>
<tr>
<td>PVSG-01 1981</td>
<td>2,3</td>
<td>PV</td>
<td>No prior treatment (other than phlebotomy) or no prior cancer</td>
<td>Pfl vs 32p Cbl</td>
<td>153 (42)</td>
<td>162 (52)</td>
</tr>
<tr>
<td>(23,24) b</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11-18</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

*a Values in brackets are for percentages less than 100%; all other studies reported results on 100% of sample.

b Follow-up data taken for Berk et al (23) for up to 13 years.

Notes: ~ = approximately; @ = no treatment; 32p = radioactive isotope of phosphorus; AA = anagrelide; ASA = acetylsalicylic acid (aspirin); Cbl = chlorambucil; ET = essential thrombocytosis, eval = evaluable patients at time of follow-up; FU = follow-up period in median years, or a range of years where there is a hyphenation, values following semi-colon refer to time of follow-up in years; HU = hydroxyurea; IFN = interferon alpha; L = litre; N = number of patients randomized, provided by treatment arm where data was available; pc=platelet count; Pfl = phlebotomy; P = pipobroman; PV = polycythemia vera as diagnosed using the PSVG-01 diagnosis criteria; vs = versus; yrs = years.

The following paragraphs provide an assessment of the quality of the evidence forming the basis for each of the main study questions of this review, and Table 3 provides further details on the quality parameters of the included RCTs.

**Risk Factors**

Data from two RCTs, four non-randomized prospective studies, and 18 retrospective studies contributed to our evaluation of possible associations between risk factors and thrombohemorrhagic symptoms (i.e., major thrombosis or hemorrhage). In this review, major thrombosis refers to stroke, myocardial infarction, unstable angina, deep vein thrombosis, or pulmonary embolism. Most of the data are derived from studies of patients with ET (data are summarized in Table 4).
The risk factors assessed included initial symptoms (thrombosis or hemorrhage), age, platelet count during follow-up, and general vascular or genetic risk factors. Initial symptoms were assessed by comparing the occurrence of thrombohemorrhagic events at the start of therapy with events during follow-up, and advanced age, by comparing event rates in younger and older patients, with a threshold typically ranging from 60 to 65 years of age across studies. Platelet count was assessed at diagnosis, and varied somewhat across studies, but the comparison threshold was typically defined as >1000 x 10^9/L, with events compared between patients above and below this threshold. Subgroups for vascular and genetic risk factors included smokers; patients with obesity, hypercholesterolemia, or hypertension; or the presence of the Factor V Leiden and the hereditary prothrombin variants. Associations reported in studies were positive (higher values of the risk factor are associated with greater incidence of symptoms), negative (an inverse relationship, where higher values of the risk factor correlate with lower risk of symptoms), or not predictive (risk of symptoms did not vary along risk-factor strata).

In terms of the evidentiary quality of these studies, many had small sample sizes (<100 patients) and factor subgroups were sometimes unbalanced. In addition, few studies reported establishing the thresholds for comparisons between risk groups a priori (e.g., what value delineated high versus low platelet count groups).

**Outcomes of Cytoreductive Therapy to Control Platelet Count**

Data from six RCTs (13,14,18-21,23) contributed to our evaluation of outcomes of cytoreductive therapy used to control platelet counts. Two studies, one of patients with ET (20,21) and one of patients with PV (23,24), compared cytoreductive therapy against no cytoreductive therapy. The other studies compared hydroxyurea against various cytoreductive agents: interferon (IFN) (12) and anagrelide (13,14) in ‘high-risk’ patients with ET, 32P in older patients with PV (18), and pipobroman in younger patients with PV (19). The assessed outcomes included events of thrombosis or hemorrhage, the occurrence of myelofibrosis, and overall survival.

The overall quality of the RCTs was on average moderate, with three (13-17,19) of the seven trials scoring between 3 and 4 (out of a possible 5) on the modified Jadad quality scale (see Table 3). On other measures of quality that were not assessed by the scale, five trials reported intention-to-treat analyses (13-19), and four reported ethical approval (13-18). The two trials that received a Jadad score of 1 predated the other trials, having been published in the 1980s (22-24). Their lower scores may not necessarily reflect overall poorer quality but, instead, more outdated reporting practices. The Medical Research Council (MRC) PT1 RCT compared anagrelide against hydroxyurea in patients with ET who were at high risk for vascular events but was terminated early by the data-monitoring committee because of the excess numbers of deaths and vascular events in the anagrelide group. The German ET-Study was available in abstract form only, and information to perform a quality assessment was not provided (12). The authors did note that after three years of observation half of IFN patients had withdrawn from IFN therapy.

**Outcomes of Aspirin Therapy**

Three prospective studies assessed the effect of aspirin therapy on thrombosis or bleeding rates in patients with PV. Two of these studies were RCTs, while the other was a non-randomized cohort study. The ECLAP RCT (15) was stopped early because of inadequate recruitment; of the 940 patients the trial initially planned to recruit (to detect a 30% rate reduction with 95% confidence, at 80% power), only approximately 500 patients were recruited. As well, the Polycythemia Vera Study Group (PVSG)-05 RCT (22) was terminated early because the incidence of thrombosis was not reduced in the aspirin arm.
Table 3. Quality characteristics of included published RCTs.

<table>
<thead>
<tr>
<th>Study</th>
<th>Adequate Sample Size</th>
<th>Double Blinding</th>
<th>Randomization Method</th>
<th>Allocation Concealment</th>
<th>ITT Analysis</th>
<th>Losses to Follow-up</th>
<th>Withdrawal/Crossover</th>
<th>Early Termination</th>
<th>Ethical Approval</th>
<th>Jadad Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRC PT1 2005 (13,14)</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>-</td>
<td>Yes</td>
<td>0.7%</td>
<td>28%</td>
<td>Yes</td>
<td>Yes</td>
<td>3</td>
</tr>
<tr>
<td>ECLAP 2004 (15-17)</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>-</td>
<td>Yes</td>
<td>8%</td>
<td>-</td>
<td>Yes</td>
<td>Yes</td>
<td>4</td>
</tr>
<tr>
<td>Najean 1997a (&gt;65 yrs)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Yes</td>
<td>-</td>
<td>2%</td>
<td>8%</td>
<td>No</td>
<td>Yes</td>
<td>2</td>
</tr>
<tr>
<td>Najean 1997b (&lt;65 yrs)</td>
<td>-</td>
<td>Yes</td>
<td>-</td>
<td>Yes</td>
<td>-</td>
<td>0.9%</td>
<td>19%</td>
<td>No</td>
<td>Yes</td>
<td>3</td>
</tr>
<tr>
<td>Cortelazzo 1995 (20,21)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Yes</td>
<td>-</td>
<td>0%</td>
<td>25%</td>
<td>No</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>PVSG-05 1986 (22)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
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<tr>
<td>PVSG-01 1981 (23,24)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>6.4%</td>
<td>-</td>
<td>-</td>
<td>No</td>
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</tr>
</tbody>
</table>

Note: "-" indicates that the published report did not describe this characteristic of the trial; ITT = intention-to-treat; yrs = years.

Outcomes

**Question 1: Is there a definable group of patients who are at a high risk of either thrombosis or hemorrhage?**

Overall, the risk of thrombosis or hemorrhage during follow-up was low in this sample of studies. For those studies reporting the incidence of thrombotic or hemorrhagic events, the rates observed across individual studies were less than seven per 100 patient-years of evaluation with respect to thrombosis (range 0-7 per 100 patient years), and less than two per 100 patient-years of evaluation for major hemorrhage (range 0-2 per 100 patient years). Mortality or permanent impairment resulting from thrombotic or hemorrhagic events was extremely rare.

**Initial Symptoms**

One RCT (20), one prospective study (25), and seven retrospective studies (26-32) assessed the association between the frequency of initial symptoms and risk of thrombosis or hemorrhage in ET. No studies examined the associations with PV patients. Only the retrospective studies reported a positive association: six studies for initial symptoms and thrombosis (26-31) and one study for hemorrhage (26).

**Age**

One (unpublished) RCT (12), one (25) of three prospective studies, and five (27,29,31,33,34) of 10 retrospective studies reported a positive association between age and thrombosis in patients with ET. Three (33-35) of the seven retrospective studies and none of the three prospective studies (20,36,37) found a positive association between age and hemorrhage in patients with ET. This risk factor was not studied in patients with PV.

**Platelet Count**

Two (27,34) of fifteen retrospective studies (26-30,32-35,38-43) reported a relationship between platelet count and thrombosis. One study found higher initial platelet counts to be associated with a lower risk of thrombosis (27), while the other found the opposite association (34). No relationship was observed in four prospective studies (20,21,25,36). High platelet counts were associated with bleeding in one (44) of five prospective studies (20,21,25,36,37,44) and in five (33,34,39,40,42) of 13 retrospective studies. In two (39,42) of these six studies, only extremely high platelet counts (>2000 x 10^9/L) were associated with hemorrhage.
**General Vascular Risk Factors**

One RCT and one retrospective case series found smoking (20,43) to be predictive of thrombosis. One prospective study found obesity to be predictive of thrombosis (37). Hypercholesterolemia and hypertension were observed to be predictive in a retrospective chart audit study (29). The other RCT (12) reported the presence of two cardiovascular risk factors (unnamed) to be associated with higher thromboembolic risk ($p = 0.026$).

**Genetic Risk Factors**

The prothrombin variant was predictive of thrombosis in just one retrospective study (45), while Factor V Leiden was not predictive of thrombosis in either of the retrospective studies that assessed it (32, 33). These data are not reported in Table 4.
Table 4. Studies of possible risk factors for thrombosis or hemorrhage in patients with ET or PV.

<table>
<thead>
<tr>
<th>Citation</th>
<th>Population</th>
<th>Agent(s)</th>
<th>N</th>
<th>FU</th>
<th>Initial Symptoms</th>
<th>Age</th>
<th>Platelet Count</th>
<th>General Vascular</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>THR</td>
<td>HEM</td>
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<td><strong>RCTs</strong></td>
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<tr>
<td>German ET-Study 2006</td>
<td>ET</td>
<td>Hu vs. IFN</td>
<td>55</td>
<td>6.6</td>
<td>▲</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>(12)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cortelazzo 1995 (20)</td>
<td>ET</td>
<td>Hu vs. Ø</td>
<td>114</td>
<td>2.3</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td><strong>Prospective Studies</strong></td>
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<td></td>
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<td>Passamonti 2002 (25)</td>
<td>ET, high-risk</td>
<td>Pi</td>
<td>118</td>
<td>10</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
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<tr>
<td>Bazzan 1999 (36)</td>
<td>ET</td>
<td>Bu,Hu,PI,IFN</td>
<td>187</td>
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<tr>
<td>Ruggeri 1998 (37)</td>
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<td>Ø</td>
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<td>-</td>
<td>▲</td>
</tr>
<tr>
<td>Michiels 1996 (44)</td>
<td>ET,PV</td>
<td>Bu,ASA*</td>
<td>50</td>
<td>nr</td>
<td></td>
<td>▲</td>
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<td></td>
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<tr>
<td><strong>Retrospective Studies</strong></td>
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<tr>
<td>Vianelli 2005 (31)*</td>
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<td>Hu,Bu,IFN</td>
<td>205</td>
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<td>▲</td>
<td>▲</td>
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<tr>
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<td>ET</td>
<td>nr</td>
<td>306</td>
<td>8</td>
<td>▲</td>
<td>-</td>
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</tr>
<tr>
<td>Cacciola 2003 (32)</td>
<td>ET,PV</td>
<td>nr</td>
<td>42</td>
<td>1-12</td>
<td>-</td>
<td>-</td>
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</tr>
<tr>
<td>Gisslinger 2003 (45)</td>
<td>ET,PV</td>
<td>nr</td>
<td>229</td>
<td>nr</td>
<td>▲</td>
<td>-</td>
<td></td>
<td></td>
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<tr>
<td>Oltean 2003 (34)</td>
<td>ET</td>
<td>Hu,IFN</td>
<td>73</td>
<td>5</td>
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<tr>
<td>Besses 1999 (29)</td>
<td>ET</td>
<td>Hu,Bu,M,IFN</td>
<td>148</td>
<td>4.9</td>
<td>▲</td>
<td>▲</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Lengfelder 1998 (33)</td>
<td>ET</td>
<td>Bu,32P,Hu,IFN</td>
<td>143</td>
<td>6.1</td>
<td>▲</td>
<td>▲</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Watson 1992 (43)</td>
<td>ET</td>
<td>32P,HU,Mf</td>
<td>46</td>
<td>4.2</td>
<td>-</td>
<td>-</td>
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<td>-</td>
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<tr>
<td>Colombi 1991 (28)</td>
<td>ET</td>
<td>Hu,M,Bu</td>
<td>103</td>
<td>1-15</td>
<td>▲</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Chistolini 1990 (26)</td>
<td>ET</td>
<td>Hu,Bu,IFN,PI</td>
<td>100</td>
<td>3.3</td>
<td>▲</td>
<td>▲</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Cortelazzo 1990 (27)</td>
<td>ET</td>
<td>Bu</td>
<td>100</td>
<td>2.7</td>
<td>▲</td>
<td>▲</td>
<td>▼</td>
<td>-</td>
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<tr>
<td>Fenaux 1990 (42)</td>
<td>ET</td>
<td>Bu,32P,Hu</td>
<td>147</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitus 1990 (32)</td>
<td>ET, &lt;45y</td>
<td>Hu,Bu,AA,Mf</td>
<td>44</td>
<td>0.5-10</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Grossi 1988 (41)</td>
<td>MPD</td>
<td>nr</td>
<td>108</td>
<td>nr</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Bellucci 1986 (40)</td>
<td>ET</td>
<td>Hu,32P,M</td>
<td>94</td>
<td>0.19</td>
<td>-</td>
<td>-</td>
<td>▲</td>
<td></td>
</tr>
<tr>
<td>Buss 1985 (39)</td>
<td>MPD</td>
<td>Hu*</td>
<td>72</td>
<td>0-16.3</td>
<td>-</td>
<td>-</td>
<td>▲</td>
<td></td>
</tr>
<tr>
<td>Kessler 1982 (35)</td>
<td>MPD</td>
<td>Ø</td>
<td>38</td>
<td>6</td>
<td>▲</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Pearson 1978 (38)</td>
<td>PV</td>
<td>Bu</td>
<td>69</td>
<td>4.8</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Duration of follow-up given in mean number of years.

Notes: Ø = no treatment; ▲ = increased risk; ▼ = decreased risk; - = risk factor assessed, and not found to be associated with higher (or lower) rates of thrombosis (or hemorrhage); 32P = radioactive isotope of phosphorus; a = abstract; AA = anagrelide; ASA = acetylsalicylic acid (aspirin); Bu = busulfan; ET = essential thrombocythemia; FU = follow-up period in median years, or a range of years where there is a hyphenation; HEM = Hemorrhage; Hu = hydroxyurea; IFN = interferon alpha; M = melphalan; MPD = myeloproliferative disease; N = sample size; nr = not reported; Pi = pipobroman; PV = polycythemia vera, RCT = randomized controlled trial; THR = Thrombosis; vs. = versus; y = years.
Question 2: Does controlling the platelet count with cytoreductive therapy improve overall survival, major and minor thrombosis, hemorrhage, or myelofibrosis in patients with ET or PV?

**Thrombosis**

**Essential Thrombocythemia**

Three RCTs examined cytoreductive therapy in patients with ET and reported on the incidence of thrombosis (12-14,20,21).

The Cortelazzo et al RCT (20,21) compared hydroxyurea against no treatment and followed 114 patients with ET for a median duration of just over six years. The authors found that the occurrence of thrombotic complications was significantly less in the hydroxyurea group in comparison with the no cytoreductive-treatment group (9% vs. 45%, respectively; odds ratio [OR]=0.12; 95% confidence interval [CI], 0.04 to 0.35). To account for differing follow-up times between patients, the authors assessed thrombosis-free survival using the Kaplan-Meier method and by intention-to-treat and found substantially improved thrombosis-free survival in hydroxyurea-treated patients (at six years, ~88% vs. ~55%, p < .0001, respectively) Most of the excess thrombosis in the control group consisted of transient ischemic episodes and digital microvascular ischemia. There were no significant individual differences in stroke, myocardial infarction, or deep vein thrombosis, but the number of events was very small.

The MRC PT1 RCT (13,14) compared anagrelide with aspirin or acetylsalicylic acid (ASA) to hydroxyurea with ASA for a median follow-up of over three years and found arterial thrombotic events were more common in the anagrelide arm (OR=2.16; 95% CI, 1.27 to 3.69). However, there were no significant differences in stroke, unstable angina, or myocardial infarction between the treatment arms, and most of the observed difference in total arterial thrombosis was accounted for by a lower incidence of transient ischemic attacks in the hydroxyurea arm. Venous thromboembolism was less common in the anagrelide group (OR=0.27; 95% CI, 0.11 to 0.71).

The German ET-Study randomized 55 patients to either hydroxyurea or IFN and observed for a median follow-up of 6.6 years. Rates of thrombotic complications were slightly higher in the hydroxyurea arm (3.5% per 100 patient years vs. 3.2% per 100 patient years, p = 0.026). This small trial is not yet published, and a substantial number of patients (50%) withdrew from the IFN arm.

**Polycythemia Vera**

Three RCTs reported on the incidence of thrombosis in patients with PV receiving cytoreductive agents (13,14,18,19). The French Polycythemia Study Group (FPSG) reported on two separate trials in 1997, one of elderly patients (n=461) involving hydroxyurea against 32P (18) and the other of younger patients (n=292) involving pipobroman against hydroxyurea (<65 years) (19). In the former trial, at 15 years of follow-up, rates of major ‘vascular events’ did not differ significantly between hydroxyurea and 32P treated patients (47% vs. 45%, log-rank test result not reported). In the latter trial, at 14 years of follow-up, rates of major thrombosis were 26% in each treatment arm (log-rank test result not reported). The PVSG-01 trial (23,24) randomized patients (n=431) between 1969 and 1974 to no treatment (i.e., phlebotomy), 32P, or chlorambucil. At 13 years follow-up (median 5-6 years), thrombosis rates varied from 31%, to 25% and 20%, respectively (no statistical comparison reported), and were lower in the treated arms.
Hemorrhage

**Essential Thrombocythemia**

Bleeding-related outcomes were reported in three RCTs of patients with ET. In the MRC PT1 RCT (13,14), bleeding events were observed in both the anagrelide and hydroxyurea arms (5% and 2% of patients, respectively) but were significantly more common in the anagrelide arm (OR=2.61; 95% CI, 1.27 to 5.33). Hydroxyurea was not shown to be superior to no treatment in terms of bleeding; in the Cortelazzo et al RCT (20,21) comparing hydroxyurea and no treatment, the number of hemorrhagic events did not differ significantly between arms (2% vs. 7%, respectively, $\chi^2=1.8$, Fisher’s exact test, $p = 0.36$), and were generally infrequent and minor overall. The unpublished German ET-Study RCT reported no major bleed events during follow-up.

**Polycythemia Vera**

No study involving patients with PV reported data for bleeding-related outcomes.

Myelofibrosis

**Essential Thrombocythemia**

None of the studies retrieved in this review provided data regarding the incidence of myelofibrosis in untreated patients with ET. In comparison with anagrelide treatment, hydroxyurea was associated with statistically lower rates of myelofibrosis in one trial (4% vs. 1%; OR=2.92; 95% CI, 1.24 to 6.86), though for either agent overall rates of myelofibrosis were low (13,14).

**Polycythemia Vera**

Evidence pertaining to the incidence of myelofibrosis in untreated patients retrieved in this review was of limited value. Some patients enrolled in the PVSG-01 RCT (23,24) were assigned to receive phlebotomy only, and, in this group, the incidence of myelofibrosis was 10% (and not different from comparison treatment arms), but a substantial number (22%) of these phlebotomy patients later crossed over to chemotherapy arms of that trial.

Among treated patients with PV, hydroxyurea was associated with higher rates of myelofibrosis in comparison with 32P and pipobroman in two studies (18,19). In the Najeaj et al study of older patients, the incidence of myelofibrosis was 32% in patients treated with hydroxyurea and 32P versus 15% in the 32P-treated (18). In the Najeaj et al study of younger patients, rates were 17% in the hydroxyurea-treated and 2% in the pipobroman-treated (19).

Overall Survival

Five of six RCTs reported on overall survival; no significant differences between treatment arms were reported in any trial.

**Essential Thrombocythemia**

The Cortelazzo et al RCT investigating untreated patients observed 84% overall survival at a median six years follow-up in this group, which did not differ significantly from hydroxyurea-treated patients (vs. 85%, significance value not reported) (20,21). Similarly, in comparison with anagrelide-treated patients, hydroxyurea did not result in superior overall survival for patients in the MRC PT1 trial (13,14) (89% vs. 84%, OR=0.86, 95% CI 0.51 to 1.48).

**Polycythemia Vera**

The PVSG-01 RCT, reporting on survival in untreated patients, observed 66% overall survival at a median 13 years follow-up (23,24). The rates for 32P-treated and chlorambucil-treated patients were 70% and 60% (log-rank $\chi^2$, $p = 0.15$), respectively. In comparison to pipobroman (in younger patients) or 32P-treated (elderly) patients, treatment with hydroxyurea
did not result in superior overall survival for patients in the Najean et al trials (62% vs. 64%, statistical test not reported, and 22% vs. 28%, log-rank test, \( p > 0.3 \), respectively) (18,19). The trial comparing hydroxyurea versus 32P in elderly patients observed a similar median survival between the treatment arms (9.1 years vs. 11.2 years; \( p = 0.10 \), respectively).

### Table 5. RCTs reporting outcomes of cytoreductive therapy in patients with ET and PV.

<table>
<thead>
<tr>
<th>RCTs</th>
<th>Citation</th>
<th>Population</th>
<th>Agent(s)</th>
<th>N</th>
<th>FU</th>
<th>Major Thrombosis</th>
<th>Major Hemorrhage</th>
<th>MF</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>German ET-Study 2006 (12)a</td>
<td>ET, h-r</td>
<td>Hu IFN</td>
<td>27</td>
<td>28</td>
<td>6.6</td>
<td>3.5%/100 p-y</td>
<td>0%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>MRC PT1 2005 (13,14)</td>
<td>ET, h-r</td>
<td>ASA + Hu ASA + AA</td>
<td>404</td>
<td>3.3</td>
<td>8%</td>
<td>2%</td>
<td>1%</td>
<td>89</td>
<td></td>
</tr>
</tbody>
</table>
| Cortelazzo 1995 (20,21) | ET | Hu | 56 | 58 | 6.1 | 9% | 2% | NR | 85%
| Najean 1997b (18) | PV, >65y | 32P + Hu | 219 | 1-16; | 47% | NR | 32% | 22% |
| Najean 1997c (19) | PV, <65y | Hu Pi | 150 | 1-17; | 26% | NR | 17% | 62% |
| PVSG-01 1981 (23,24)c | PV | PHL | 32P+PHL | 134 | 11-18; | 31% | 10% | 66% |

- a Arterial thromboses were significantly less common in the HU group (2% vs. 3.7%); p < .05. It is not clear if the p-value is truly less than .05.
- b Arterial thromboses were significantly less common in the HU group (4.2% vs. 9.1%); p < .05.
- c In an earlier report of this trial (Berk (23)) the rates of AL differed significantly between all three groups. At the 1984 time-point measured in this study, the difference between the three treatment arms was not significant; however, the difference between the phlebotomy and the other two arms was (p < .05).

Notes: Statistics in **bold** are significant at the p < .05 level. Values in % are event rates at the end of follow-up or at the period indicated after the “;” in the FU column.

\( 32^P = \) radioactive isotope of phosphorus; AA = anagrelide; ASA = acetylsalicylic acid (Aspirin); Cbl = chlorambucil; ET = essential thrombocythemia; FU = follow-up period in median years, or a range of years for two hyphenated numbers, values following semicolon refer to year of follow-up for presented data, where applicable; h-r = high risk of thrombosis; Hu = hydroxyurea; IFN = interferon alpha; MF = myelofibrosis; N = sample size; NR = not reported; OS = overall survival, in some cases values are extracted from a figure, and therefore approximate (measurement error \(<\pm 2\%); p-y = patient-years of observation; PHL = phlebotomy; Pi = pipobroman; PV = polycythemia vera, RCT = randomized controlled trial; vs. = versus; y = years.

#### Question 3: Does cytoreductive therapy increase transformation to acute leukemia (AL) in ET or PV?

**Essential Thrombocythemia**

Two RCTs examined the effects of cytoreductive therapy on the incidence of acute AL. The Cortelazzo et al RCT (20,21) comparing hydroxyurea to no treatment found a significantly higher incidence of malignancy in the hydroxyurea arm (13% vs. 1.7%, \( p = 0.03 \)) at a median six years of follow-up (21). In total, eight patients developed malignancies: seven in the treatment group (13%) (two AML, two myelodysplastic syndrome [MDS], two lung, and one chronic lymphocytic leukemia [CLL]), and one (1.7%, breast) in the no-treatment group. The authors reported that fifteen patients in this trial had received prior busulphan and conducted an additional subanalysis on the basis of prior treatment. When patients were analyzed by prior treatment received, five of 15 (33%) patients who received both busulphan and hydroxyurea developed a malignancy, versus three of 77 (3.9%) who received hydroxyurea alone, and none of the 20 (0%) who received no prior treatment. The MRC PT1 RCT comparing hydroxyurea and anagrelide in patients receiving aspirin reported very little transformation to acute leukemia (1.2%) at 3.3 years follow-up, with no significant differences between arms (1.5% vs. 1%, \( p = 0.55 \)) (14).
**Polycythemia Vera**

Three RCTs reported on the rates of leukemogenesis with cytoreductive treatment. The Najean et al RCT that examined elderly patients by comparing hydroxyurea and 32P in combination against 32P as a single agent found a statistically significant higher incidence of leukemic transformation in the combination arm at 15 years follow-up (31% vs. 23%, respectively, \( p < 0.05 \)) (18). The PVSG-01 RCT (23,24) found a significantly higher rate of leukemogenesis in treated patients (10%-13.5%, vs. 2%, respectively, \( p < 0.05 \)) over a follow-up ranging from 11 to 18 years (23). The Najean et al RCT comparing hydroxyurea against pipobroman in younger patients reported similar rates of leukemogenesis in both arms (10%, log-rank test, \( p > 0.30 \)) at 14 years follow-up (19).

### Table 6. Acute leukemia in RCTs of chemotherapeutic agents in patients with ET and PV.

<table>
<thead>
<tr>
<th>Citation</th>
<th>Population</th>
<th>Agent(s)</th>
<th>N</th>
<th>FU</th>
<th>AL%</th>
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<tr>
<td>MRC PT1 2005 (13,14)</td>
<td>ET, h-r</td>
<td>ASA + Hu vs ASA +AA</td>
<td>404</td>
<td>3.3</td>
<td>1.5</td>
</tr>
<tr>
<td>Cortelazzo 1995 (20,21)</td>
<td>ET</td>
<td>Hu vs</td>
<td>56</td>
<td>6.1</td>
<td>13</td>
</tr>
<tr>
<td>Najean 1997b (18)</td>
<td>PV, &gt;65y</td>
<td>32P + Hu vs 32P</td>
<td>219</td>
<td>1-16;15</td>
<td>31</td>
</tr>
<tr>
<td>Najean 1997c (19)</td>
<td>PV, &lt;65y</td>
<td>HU vs Pi</td>
<td>150</td>
<td>1-17;14</td>
<td>10</td>
</tr>
<tr>
<td>PVSG-01 1986 (23,24)</td>
<td>PV</td>
<td>Phl vs 32P + Phl</td>
<td>134</td>
<td>11-18</td>
<td>1.5a</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cbl + Phl</td>
<td>141</td>
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<td>13.5</td>
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</table>

*In an earlier report of this trial (Berk (23)) the rates of AL differed significantly between all three groups. At the 1984 time-point measured in this study, the difference between the three treatment arms was not significant; however, the difference between the phlebotomy and other 2 arms was \( p < .05 \).*

Notes: Statistics in **bold** are significant at the \( p < 0.05 \) level; \( 32P \) = radioactive isotope of phosphorus; AA = anagrelide; ASA = acetylsalicylic acid (Aspirin); ET = essential thrombocythemia; FU = follow-up period in median years, where there are values following “;” the result refer to follow-up at that number of years; h-r = high risk of thrombosis; Hu = hydroxyurea; N = sample size; Phl = phlebotomy; Pi = pipobroman; PV = polycythemia vera; y = year.

**Question 4: What effect does aspirin therapy have on the risk of major thrombosis or hemorrhage? (Table 7)**

**Essential Thrombocythemia**

No RCTs reported on the effects of aspirin in patients with ET. A single retrospective chart audit study \( n=68 \) found that patients treated with aspirin (either alone or in combination with cytoreductive therapy, \( n=57 \)) had a lower incidence of thrombosis in comparison to those who did not receive aspirin \( n=11 \) \( 2.8 \) vs. \( 20.7 \) events/100 patient years, respectively) (47).

**Polycythemia Vera**

Three studies, two RCTs and one prospective trial, investigated the use of aspirin therapy in PV. In the ECLAP RCT (15) comparing low-dose aspirin \( 100 \) mg/day) against no aspirin in patients receiving cytoreductive therapy, the risk of the primary combined end point of nonfatal myocardial infarction, nonfatal stroke, pulmonary embolism, major venous thrombosis, or death from cardiovascular causes was significantly reduced in the aspirin arm \( RR=0.40; 95\% CI, 0.18 \) to 0.91; \( p = 0.03 \)). The PVSG-05 RCT compared high-dose aspirin \( 900 \) mg/day) against cytoreductive therapy directly and found that aspirin was not superior to cytoreductive therapy in reducing the risk of thrombosis (in fact, the risk was slightly, though not significantly, elevated in the aspirin group, with 7/83 vs. 2/83 patients affected, respectively, \( p > 0.05 \)) (22).

One additional small non-randomized prospective study of aspirin in PV patients \( n=159 \) was retrieved in abstract form and supported the findings of the ECLAP study. In this study, patients received phlebotomy or cytoreductive therapy and either aspirin or no aspirin.
Thrombosis was less common in the patients who received aspirin (OR = 0.6, significance level not reported), and hemorrhagic events were more common (25 events for ASA vs. five events for no ASA, risk value not reported) (48).

Table 7. Thrombohemorrhagic outcomes of aspirin therapy in patients with ET or PV.

<table>
<thead>
<tr>
<th>Citation</th>
<th>Design</th>
<th>Treatment(s)</th>
<th>N</th>
<th>FU</th>
<th># Events</th>
<th>RR</th>
<th># Events</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>van Genderen 1997</td>
<td>R</td>
<td>ASA+/−cr</td>
<td>68</td>
<td>3.1</td>
<td>5</td>
<td>NA</td>
<td>14</td>
<td>NA</td>
</tr>
<tr>
<td>Randi 2001</td>
<td>P</td>
<td>ASA +Phl+cr</td>
<td>159</td>
<td>7.5</td>
<td>15</td>
<td>0.6</td>
<td>25</td>
<td>1.08</td>
</tr>
<tr>
<td>PVSG-05 1986</td>
<td>RCT</td>
<td>ASA +di+Phl</td>
<td>83</td>
<td>1.2</td>
<td>7</td>
<td>3.5</td>
<td>6</td>
<td>13.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>32P +Phl</td>
<td>83</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Duration of follow-up given in mean number of years.
b The rate of thrombosis was 2.8 events per 100 patient-years of follow-up.
c The rate of hemorrhage was 7.8 events per 100 patient-years of follow-up.
d Patients in both arms of this trial received other recommended treatments, including phlebotomy and cytoreductive drugs.
e This value is an odds ratio and was reported in the abstract; insufficient data was provided to allow for the calculation of the relative risk.

Notes: Values in **bold** are significant at the 95% confidence level, i.e., $p < .05$. $\approx$ approximately; $\varnothing$ = no treatment; $^{32}P$ = radioactive isotope of phosphorus; a=abstract; ASA = acetylsalicylic acid (Aspirin); cr = cytoreductive therapy; di = dipyridamole; FU = follow-up period in median years; N = sample size; NA = not applicable; P = prospective; Phl = phlebotomy; R = retrospective; RCT = randomized controlled trial; RR = relative risk.

DISCUSSION

In its deliberations, the Hematology DSG places particular emphasis on (a) results from published RCTs (where available) and (b) the recognition of a hierarchy of outcomes that should influence treatment decisions, with priority being given to therapies found to improve clinically important outcomes.

Because there was not much strong evidence to inform the question of possible risk factors for thrombosis or hemorrhage, we sought consistency across study findings, regardless of design type, as an indicator of a predictive relationship. While, among prospective trials, the presence of initial thrombotic symptoms was not predictive of subsequent events, most retrospective studies found initial symptoms to be predictive. The magnitude of the platelet count at diagnosis, or during treatment, did not predict for thrombosis. Patients with a very high platelet count may be at a higher risk of bleeding overall, but the incidence of major bleeds reported in this series is low, and there is very little evidence of mortality or permanent morbidity. Age and other vascular risk factors were inconsistently predictive. Other groups, notably the Italian Society of Hematology, have recommend platelet-lowering treatment for patients over 60 years of age, for those with platelet counts over $1500 \times 10^9/L$, or for patients aged 40-60 with counts over $1000 \times 10^9/L$ and with cardiovascular risk factors (7). However, in light of the available evidence, the DSG feels a definite group at high risk of bleeding or thrombosis cannot be identified with strong certainty, though the evidence seems to suggest initial symptoms are a predictor of subsequent thrombosis.

Several quality RCTs addressed the possible benefit of cytoreductive therapy for controlling thrombocytosis with respect to outcomes such as major thrombosis and hemorrhage, myelofibrosis, or survival. There is good evidence to show that hydroxyurea results in a reduction in the incidence of total arterial thrombosis in ET when compared with anagrelide or with no treatment. However, no effect of hydroxyurea has been shown for stroke, myocardial
infarction, or overall survival. In one of the RCTs of patients with ET, the biggest reduction was in the incidence of transient ischemic attacks, and, in the other, both transient ischemic attacks and digital microvascular ischemia. Anagrelide is inferior to hydroxyurea in controlling arterial thrombosis, and its efficacy in comparison to no cytoreductive therapy has not been established. It does not prolong overall survival in ET. Although venous thrombosis was reduced in the anagrelide arm of the study comparing anagrelide with ASA to hydroxyurea with ASA, it is unclear whether the rate was increased by hydroxyurea or decreased by anagrelide.

There was no published evidence to show that controlling thrombocytosis with any of the agents reviewed reduces the incidence of major or minor bleeding. Serious bleeding was increased with anagrelide in the study comparing anagrelide with ASA to hydroxyurea with ASA. This is likely to have been caused by the functional inhibition of platelets by anagrelide. Similarly, there is very little evidence available on the use of agents in non-elderly patients. Two studies observed thrombosis rates greater than 20% in treated patients with long-term follow-up, showing elevated risk in this population as well.

Unlike ET, there is no randomized placebo-controlled trial of hydroxyurea in PV. The two RCTs by the French PV study group evaluated hydroxyurea in comparison to 32P and pipobroman, and observed no differences between agents in terms of thrombohemorrhagic outcomes. The DSG regards hydroxyurea as an efficacious agent in the PV population because of the biologic similarity between it and ET and because of the benefit established for hydroxyurea in the latter population.

The incidence of myelofibrosis in PV patients treated with phlebotomy alone is no different than for those who are treated with cytoreductive therapy. In addition, in randomized studies of patients with PV, hydroxyurea is not different from 32P and inferior to pipobroman, with respect to the subsequent rate of myelofibrosis. The natural history of myelofibrosis in ET is unknown. In the RCT that compared anagrelide and hydroxyurea, there was less myelofibrosis in the hydroxyurea arm. Whether hydroxyurea or anagrelide is responsible for this is not known.

With regard to the potential for cytoreductive therapies to induce transformation to AL, strong data from randomized studies indicate that hydroxyurea is leukemogenic in patients with MPD when used after busulphan or in conjunction with 32P. There is some indication that hydroxyurea may be leukemogenic when used alone in MPD; the Cortelazzo et al RCT found an elevated risk in the treatment group (in comparison to no-treatment controls). The leukemogenic potential of hydroxyurea and pipobroman in previously untreated younger patients with polycythemia vera, as reported in the RCT from Najean et al (19) included in this review, are approximately equal and higher than would be anticipated in a phlebotomy-only group.

The MRC PT1 RCT did not show any AML/MDS in patients treated with either agent alone. However, the median follow-up in this study was only just over three years, which is probably too short to exclude a leukemogenic effect. Whether or not hydroxyurea is leukemogenic in individuals without MPD is unknown. Data from the PVSG-01 RCT showed that both chlorambucil and 32P are leukemogenic, and anagrelide and interferon are believed to be non-leukemogenic from their mechanism of action.

The evidence shows that cytoreductive therapy carries with it significant leukemogenic risk and should not, therefore, be used unnecessarily. There are no studies confirming benefit in terms of superiority rates of major thrombohemorrhagic events, myelofibrosis, or overall survival for asymptomatic patients, although there is an observed benefit of hydroxyurea in terms of the reduction of arterial thrombosis. The Italian Society of Hematology recommended hydroxyurea as first-line therapy in all patients over 60 years of age, and in patients aged 40-60 without childbearing potential and with a previous thrombotic event (7). In the absence of conclusive evidence of benefit, and with clear evidence in support of harms, the Hematology DSG adopts a somewhat more conservative stance and recommends that treatment without cytoreductive therapy in the asymptomatic population is reasonable.
In patients with PV, high-dose aspirin (900 mg/day) was not found to be beneficial, and data suggested the possibility for harm. Short-term follow-up data from the ECLAP RCT showed a benefit for low-dose aspirin (100 mg/day) in reducing thrombotic events. There is little evidence to inform this issue for patients with ET (the one retrospective study reported a low event rate of 2.4 events/100 patient years in aspirin-treated patients; this rate is comparable to rates observed in studies of cytoreductive therapy-treated patients, notably the randomized MRC PT1 trial whose patients received aspirin therapy with cytoreductive therapy). Because PV and ET are similar diseases, clinical observations showing that ASA relieves the symptoms of microvascular occlusion and that low-dose aspirin therapy has a low risk of harm make it reasonable to anticipate that they would also be effective in this population.

RECOMMENDATIONS

- All ET and PV patients with thrombocytosis should be managed with low-dose aspirin. Special precautions should be taken in the case of patients with greater bleeding risk, or allergies (see “Qualifying Statements” for additional information).
- Management without cytoreductive therapy is a reasonable option for asymptomatic patients.
- Cytoreductive therapy should be considered as an option for patients with thrombocytosis who have thrombosis. Hydroxyurea is the preferred agent and should be administered to maintain a platelet count of less than 600 x 10^9/L (see “Qualifying Statements” for additional information).
- If treatment with hydroxyurea is not appropriate, then either interferon or anagrelide are options. Physicians who choose anagrelide to reduce the risk of arterial thrombosis should be aware that there are data to suggest that it is inferior to hydroxyurea, and its efficacy in comparison to no cytoreductive therapy has not been established. Other than reducing the platelet count, interferon is of unknown efficacy.

QUALIFYING STATEMENTS

- Hydroxyurea should be regarded as a possible leukemogen in patients with myeloproliferative disease.
- The ECLAP 2003 study used a 100 mg dose of aspirin. However, only an 81 mg pill is available in Canada for use in adults, and the Hematology DSG regards this as a reasonable dosage.
- In the randomized studies, target platelet counts of both <600 and <400 x 10^9/L were shown to be safe and effective.

ACKNOWLEDGEMENTS

The Hematology DSG would like to thank Drs. John Matthews, Jordan Herst, David Lee, and Kevin Imrie and Mr. Christopher Smith for taking the lead in drafting this systematic review.

For a complete list of the Hematology DSG members please visit the CCO Web site at http://www.cancercare.on.ca/
Funding
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Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca
REFERENCES


Evidence-based Series #6-9: Section 3

The Management of Malignant Thrombocytosis in Philadelphia Chromosome-Negative Myeloproliferative Disease: EBS Development Methods and External Review Process

J. H. Matthews, C.A. Smith, J. Herst, D. Lee, K. Imrie, and the Hematology Disease Site Group

A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)
Developed by the Hematology Disease Site Group (DSG)

Report Date: January 15, 2008

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, called Disease Site Groups (DSGs) and Guideline Development Groups (GDGs), as well as other groups or panels called together for a specific topic, all mandated to develop the PEBC products. These panels are comprised of clinicians, other health care providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based guidelines, known as Evidence-based Series (EBS) reports, using the methods of the Practice Guidelines Development Cycle (1,2). The EBS report consists of an evidentiary base (typically a systematic review), in the province for whom the topic is relevant. an interpretation of and consensus agreement on that evidence by our Groups or Panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original clinical practice guideline information.
The Evidence-based Series: A New Look to the PEBC Practice Guidelines
Each Evidence-based Series is comprised of three sections.

- **Section 1: Guideline Recommendations.** Contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the Group or Panel involved and a formalized external review in Ontario by review participants.
- **Section 2: Evidentiary Base.** Presents the comprehensive evidentiary/systematic review of the clinical and scientific research on the topic and the conclusions reached by the Group or Panel.
- **Section 3: EBS Development Methods and External Review Process.** Summarizes the guideline development process and the results of the formal external review of the draft version of Section 1: Recommendations and Section 2: Evidentiary Base.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES
Development and Internal Review
This evidence-based series was developed by the Hematology DSG of CCO's PEBC. The series is a convenient and up-to-date source of the best available evidence on the management of malignant thrombocytosis in Philadelphia chromosome-negative myeloproliferative disease, developed through systematic review, evidence synthesis, and input from practitioners in Ontario.

The findings of the systematic review were discussed at the DSG meeting of October 2005. The DSG agreed to the recommendations presented in Sections 1 and 2 of this series and subsequently approved through email thereafter. A minority later expressed concern with the recommendation that asymptomatic patients with thrombocytosis be managed without the use of cytoreductive therapy, regardless of their age, platelet count, and the presence of other thrombotic risk factors. This minority noted that the recommendation challenged the recommendations of other guidelines and standard practice in many centres.

Report Approval Panel (RAP)
Prior to the submission of this evidence-based series report for external review, the report was reviewed and approved by the PEBC Report Approval Panel, which consists of two members, including an oncologist, with expertise in clinical and methodology issues. One member of the panel was involved in preliminary discussions related to the report and did not participate in this review. The principal concerns of the RAP had to do with the types of evidence included in the report, and the rationale behind certain recommendations, and the extent to which they were directly supported by available evidence. Initially, the report included evidence from phase III RCTs, other prospective studies, and data from retrospective chart audits. There was concern that the latter two types of evidence did not help inform clinical recommendations, particularly since higher quality evidence was available as well. In response, the DSG revised the report to include only phase III RCTs for questions dealing with clinical outcomes (for questions related to risk factors, and the role of aspirin, a broader scope of evidence was included). On the issue of evidence and recommendation rationale concordance, the DSG supplemented the “Discussion” section to better articulate how the available evidence did in fact directly inform the practice recommendations made. In one case, the concern on the part of RAP that there was a lack of concordance between disease-specific evidence (i.e., ET and PV) and multi-disease recommendations was resolved by explaining that, from the perspective of clinicians, the diseases were regarded and treated similarly.
External Review by Ontario Clinicians

The systematic review on the management of malignant thrombocytosis in Philadelphia chromosome-negative myeloproliferative disease is reported in Section 2. On the basis of that evidence and the interpretation by members of the DSG, draft recommendations were circulated to Ontario practitioners for feedback. This section comprises the results from Practitioner Feedback, any changes made to the draft document, and final recommendations that were submitted to the PEBC Report Approval Panel for review and final approval.

<table>
<thead>
<tr>
<th>BOX 1: DRAFT RECOMMENDATIONS (approved for external review on May 13, 2007)</th>
</tr>
</thead>
</table>
| **Target Population**  
Patients with Philadelphia chromosome-negative myeloproliferative diseases, specifically essential thrombocythemia (ET) or polycythemia vera (PV). |
| **Recommendations** |
| • All ET and PV patients with thrombocytosis should be managed with low-dose aspirin. Special precautions should be taken in the case of patients with greater bleeding risk or allergies (see “Qualifying Statements” for additional information). |
| • Management without cytoreductive therapy is a reasonable option for asymptomatic patients. |
| • Cytoreductive therapy should be considered as an option for patients with thrombocytosis who have thrombosis. Hydroxyurea is the preferred agent and should be administered to maintain a platelet count of less than 600 x 10^9/L (see “Qualifying Statements” for additional information). |
| • If treatment with hydroxyurea is not appropriate, then either interferon or anagrelide are options. Physicians who choose anagrelide to reduce the risk of arterial thrombosis should be aware that there are data suggesting that it is inferior to hydroxyurea, and its efficacy in comparison to no cytoreductive therapy has not been established. Other than reducing the platelet count, interferon is of unknown efficacy. |
| **Qualifying Statements** |
| • Hydroxyurea should be regarded as a possible leukemogen in patients with myeloproliferative disease. |
| • The European Collaboration on Low-dose Aspirin in Polycythemia Vera (ECLAP) 2003 study used a 100 mg dose of aspirin. However, only an 81 mg pill is available in Canada for use in adults, and the Hematology DSG regards this as a reasonable dosage. |
| • In the randomized studies, target platelet counts of both <600 and <400 x 10^9/L were shown to be safe and effective. |

**Methods**

Feedback was obtained through a mailed survey of 102 practitioners in Ontario who treat hematological malignancies (hematologists and medical oncologists). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. The survey was mailed out on June 14, 2007. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Hematology DSG reviewed the results of the survey.
**Results**

Forty-three responses were received out of the 102 surveys sent (42% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the practitioners who responded, 65% indicated that the report was relevant to their clinical practice, and they completed the survey. Key results of the practitioner feedback survey are summarized in Table 1.

**Table 1. Responses to eight items on the practitioner feedback survey.**

<table>
<thead>
<tr>
<th>Item</th>
<th>Number (%)*</th>
<th>Strongly agree or agree</th>
<th>Neither agree nor disagree</th>
<th>Strongly disagree or disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>The rationale for developing a guideline, as stated in the &quot;Introduction&quot; section of the report, is clear.</td>
<td>27 (96)</td>
<td>1 (4)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>There is a need for a guideline on this topic.</td>
<td>26 (93)</td>
<td>2 (7)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>The literature search is relevant and complete.</td>
<td>26 (93)</td>
<td>0</td>
<td>2 (7)</td>
<td></td>
</tr>
<tr>
<td>The results of the trials described in the report are interpreted according to my understanding of the data.</td>
<td>24 (86)</td>
<td>3 (11)</td>
<td>1 (4)</td>
<td></td>
</tr>
<tr>
<td>The draft recommendations in the report are clear.</td>
<td>25 (89)</td>
<td>3 (11)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>I agree with the draft recommendations as stated.</td>
<td>21 (75)</td>
<td>4 (14)</td>
<td>3 (11)</td>
<td></td>
</tr>
<tr>
<td>This report should be approved as a practice guideline.</td>
<td>22 (79)</td>
<td>2 (7)</td>
<td>4 (14)</td>
<td></td>
</tr>
</tbody>
</table>

*Percentages may not add to 100% due to rounding.

**Summary of Written Comments**

Fourteen respondents (50%) provided written comments. The main points contained in the written comments were:

1. The recommendations differ from those of other important guidelines: in particular, they do not recommend cytoreductive therapy for patients deemed at high risk of thrombosis by reason of age, other thrombophilic disorders, and platelet count.
2. JAK-2 testing has become important, and should have been discussed.
3. The target platelet count of less than 600 x 10^9/L cannot be justified.
4. The management of thrombocytosis in pregnancy was not discussed.
5. Extremes of thrombocytosis may cause acquired Von Willebrand disease (VWD) and bleeding, so management with cytoreductive therapy should have been addressed for this group.
6. Phlebotomies should have been recommended for patients with PV.
7. The evidence favouring a leukemogenic effect of hydroxyurea is not strong, and no increase in leukemia has been seen in the ECLAP cohort of patients.
8. The conclusions about anagrelide cause some discomfort.
9. Interferon may prevent myelofibrosis.

**Modifications/Actions**

1. The Hematology DSG acknowledges that our recommendations differ from those of other guideline development groups. After a careful review of the literature, we found the evidence that a group of asymptomatic patients can be identified at high risk of thrombosis is weak and inconsistent. Similarly, the DSG took into account that
cytoreductive therapy has not been shown to prolong overall survival or reduce the incidence of major thrombosis. We have revised the discussion to better explain the difference in recommendations with other guidelines.

2. The group concurs that JAK-2 testing is important, but feels that there is insufficient evidence to use the results to guide therapy. Further study of the predictive value of JAK-2 mutational status on thrombosis risk and response to treatment are needed.

3. Target platelet counts of both 600 and 400 $\times 10^9$/L have been used in clinical trials. Both appear satisfactory, and the group simply chose the more conservative.

4. The group acknowledges that the management of pregnant patients with thrombocytosis is challenging but indentified insufficient evidence to make evidence-based recommendations.

5. The DSG recognises that acquired VWD is reported to occur in some patients with extreme thrombocytosis. Given the rarity with which bleeding is observed we did not feel that a recommendation for cytoreduction to reduce bleeding risk was warranted.

6. As the guideline focuses on the management of thrombocytosis, we did not address phlebotomy, which the DSG concurs is standard management for hematocrit control in PVera.

7. We agree that the evidence indicating a leukemogenic effect of hydroxyurea in patients with myeloproliferative disease is inconclusive, and we have been careful to word the recommendations appropriately. Approximately half of the ECLAP cohort of patients received hydroxyurea, and no increased incidence of AML/MDS was found. However, allocation to hydroxyurea therapy was not randomized, and so firm conclusions cannot be drawn.

8. The evidence that anagrelide is inferior to hydroxyurea in preventing arterial thrombosis is robust. Significantly fewer venous thromboses occurred in the anagrelide arm of the MRC PT1 study, but arterial thrombosis is the main clinical concern.

9. The DSG acknowledges that myelofibrosis can occur in patients with malignant thrombocytosis and that there have been suggestions that interferon use may be associated with lower incidence of this complication. However, the systematic review identified insufficient evidence to allow for a recommendation to use interferon for this reason.

Policy Review

It is estimated that between 3,800 and 4,400 people in Ontario have ET or PV, with the majority being over 60 years of age. The progression of these diseases is slow, and patients often experience long asymptomatic periods punctuated by thrombotic or hemorrhagic events. In fact, over half of patients are asymptomatic and diagnosed by chance. Two conventional beliefs have guided practice for a number of years: (i) older patients and those with higher platelet counts are thought to be a greater risk for adverse thrombohemorrhagic outcomes and (ii) cytoreductive therapy used to lower platelet count is effective in reducing these adverse events. Therefore, the majority of these supposed higher risk patients currently receive cytoreductive therapy. However, the pathologic complexity of these diseases, and uncertainty around the merits of cytoreductive agents, contributes to much practice heterogeneity in this area. The recommendations of the DSG on this topic, specifically that asymptomatic patients not be treated with cytoreductive therapy and that all patients be managed with aspirin amount to an important change in practice. If followed, this guideline could have an impact on drug usage by reducing the number of hydroxyurea treatments provided to patients as well as the therapy provided for cases of related leukemogenic transformation.
Funding
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