



Complete Summary

GUIDELINE TITLE

The management of malignant thrombocytosis in Philadelphia chromosome-negative myeloproliferative disease: guideline recommendations.

BIBLIOGRAPHIC SOURCE(S)

Matthews JH, Smith CA, Herst J, Lee D, Imrie K, Hematology Disease Site Group. The management of malignant thrombocytosis in Philadelphia chromosome-negative myeloproliferative disease: guideline recommendations. Toronto (ON): Cancer Care Ontario (CCO); 2008 Jan 15. 30 p. (Evidence-based series; no. 6-9). [50 references]

GUIDELINE STATUS

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the [Cancer Care Ontario Web site](#) for details on any new evidence that has emerged and implications to the guidelines.

COMPLETE SUMMARY CONTENT

SCOPE
METHODOLOGY - including Rating Scheme and Cost Analysis
RECOMMENDATIONS
EVIDENCE SUPPORTING THE RECOMMENDATIONS
BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS
QUALIFYING STATEMENTS
IMPLEMENTATION OF THE GUIDELINE
INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT
CATEGORIES
IDENTIFYING INFORMATION AND AVAILABILITY
DISCLAIMER

SCOPE

DISEASE/CONDITION(S)

Philadelphia chromosome-negative myeloproliferative diseases, specifically essential thrombocythemia (ET) or polycythemia vera (PV)

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Management
Treatment

CLINICAL SPECIALTY

Hematology
Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To provide information to aid clinicians in the management of patients with essential thrombocythemia (ET) and polycythemia vera (PV)
- To evaluate:
 - If there is a definable subgroup of patients who are at a high risk of either thrombosis or bleeding
 - If controlling the platelet count with cytoreductive agents improves clinical outcomes such as overall survival, major and minor thrombosis, hemorrhage, and the development of myelofibrosis
 - If cytoreductive therapy produces additional transformation to acute leukemia (AL)
 - The effect aspirin therapy has on the occurrence of thrombosis or hemorrhage

TARGET POPULATION

Patients with Philadelphia chromosome-negative myeloproliferative diseases, specifically essential thrombocythemia (ET) or polycythemia vera (PV)

INTERVENTIONS AND PRACTICES CONSIDERED

1. Low-dose aspirin
2. Cytoreductive therapy (hydroxyurea, interferon, anagrelide)

MAJOR OUTCOMES CONSIDERED

- Overall survival
- Major and minor thrombosis rate
- Hemorrhage rate
- Development of myelofibrosis
- Transformation to acute leukemia (AL)

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

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 Disease Site Group (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 randomized controlled trial (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 essential thrombocythemia (ET) or polycythemia vera (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 in the original guideline document) or reported on clinical outcomes of aspirin treatment (e.g., thrombosis/bleeding rates, mortality, or myelofibrosis) (Question 4 in the original guideline document)
2. Published research studies of any design type
3. Studies with n >20 patients

NUMBER OF SOURCE DOCUMENTS

19 retrospective, 5 prospective, 15 randomized controlled trials, and 4 clinical practice guidelines were identified

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE 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 randomized controlled trials (RCTs) reporting clinical outcome data were tabulated in tables and summarized by clinical outcome and disease type (i.e., essential thrombocythemia [ET] or polycythemia vera [PV]).

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

In its deliberations, the Hematology Disease Site Group (DSG) places particular emphasis on (a) results from published randomized controlled trials (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, the DSG 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 recommended 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. 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 essential thrombocythemia (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 acetylsalicylic acid (Aspirin) [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 polycythemia vera (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 acute leukemia (AL), strong data from randomized studies indicate that hydroxyurea is leukemogenic in patients with myeloproliferative disorders (MPD) when used after busulphan or in conjunction with 32P. There is some indication that hydroxyurea may be leukemogenic when used alone in myeloproliferative disorders (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 included in this review, are approximately equal and higher than would be anticipated in a phlebotomy-only group.

The Medical Research Council (MRC) PT1 RCT did not show any acute myeloid leukemia/myelodysplastic syndrome (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 myeloproliferative disorders is unknown. Data from the Polycythemia Vera Study Group (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 superior 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. In the absence of conclusive evidence of benefit, and with clear evidence in support of harms, the Hematology Disease Site Group 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 European Collaboration on Low-dose Aspirin in Polycythemia Vera (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 Medical Research Council 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.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Development and Internal Review

This evidence-based series was developed by the Hematology Disease Site Group (DSG) of Cancer Care Ontario's Program in Evidence-based Care (CCO's PEBC).

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.

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 of the original guideline document. On the basis of that evidence and the interpretation by members of the DSG, draft recommendations were circulated to Ontario practitioners for feedback.

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.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

All essential thrombocythemia (ET) and polycythemia vera (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" field 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" field 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.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by retrospective, prospective, randomized controlled trials, and clinical practice guidelines.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- 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 polycythemia vera (PV) treated with cytoreductive therapy. A non-randomized cohort study found a similar, though not statistically significant, effect (relative risk=0.6). Direct evidence for essential thrombocythemia (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 essential thrombocythemia 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.

POTENTIAL HARMS

Cytoreductive therapy carries with it significant leukemogenic risk

QUALIFYING STATEMENTS

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 Disease Site Group (DSG) regards this as a reasonable dosage.
- In the randomized studies, target platelet counts of both <600 and $<400 \times 10^9/L$ were shown to be safe and effective.
- Care has been taken in the preparation of the information contained in this report. Nonetheless, any person seeking to apply or consult the report is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding the report content or use or application and disclaims any responsibility for its application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Matthews JH, Smith CA, Herst J, Lee D, Imrie K, Hematology Disease Site Group. The management of malignant thrombocytosis in Philadelphia chromosome-negative myeloproliferative disease: guideline recommendations. Toronto (ON): Cancer Care Ontario (CCO); 2008 Jan 15. 30 p. (Evidence-based series; no. 6-9). [50 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2008 Jan 15

GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Provincial Hematology Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the [Cancer Care Ontario Web site](#).

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

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GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the [Cancer Care Ontario Web site](#).

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- The management of malignant thrombocytosis in Philadelphia chromosome-negative myeloproliferative disease: guideline recommendations. Summary. Toronto (ON): Cancer Care Ontario (CCO), 2008 Jan. 3 p. (Practice guideline; no. 6-9). Electronic copies: Available in Portable Document Format (PDF) from the [Cancer Care Ontario Web site](#).
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. *J Clin Oncol* 1995;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI Institute on July 16, 2008. The information was verified by the guideline developer on August 20, 2008.

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