Essential Thrombocythaemia Guidelines

Approved by Pathway Board for Haematological Malignancies

Coordinating author: Mallika Sehkar, Royal Free London NHS Trust

Date of issue: 12.03.2015

Version number: v1.0

These guidelines should be read in conjunction with the latest National Cancer Drug Fund information, and all applicable national /international guidance.

The prescribing information in these guidelines is for health professionals only. It is not intended to replace consultation with the Haematology Consultant at the patient’s specialist centre. For information on cautions, contra-indications and side effects refer to the up-to-date prescribing information. While great care has been taken to see that the information in this section is accurate, the user is advised to check the doses and regimens carefully and if there is any uncertainty about the guidance provided, you should discuss your queries with a Haematology Consultant or Senior Pharmacist. No set of guidelines can cover all variations required for specific patient circumstances. It is the responsibility of the health care practitioners using them to adapt them for safe use within their institutions and for the individual needs of patients.
1. Investigation of patients with persistent thrombocytosis

Patients should be investigated according to the following schema:

- Persistent thrombocytosis (plts > 450 for >6 weeks); haemoglobin not elevated*

  - FBC, film, ESR, CRP, autoantibodies, iron & ferritin, JAK2 V617F, CXR

  - JAK2 negative
    - If inflammatory markers elevated or iron-deficient, investigate and treat underlying cause (or refer appropriately) then discharge
    - If inflammatory markers normal and iron replete, and thrombocytosis persists, investigate for JAK2-negative ET—do bone marrow, ultrasound abdomen, Mpl and CALR analysis (BCR-ABL if atypical features)
  
  - JAK2 positive
    - BM in keeping with ET, or positive for Mpl or CALR
    - Discharge or treat other cause

- Probable ET

*If elevated haemoglobin, investigate as for polycythaemia

Patients should fulfil the 2008 WHO criteria for the diagnosis of ET (Table 1).
2. Baseline assessment of patients with newly-diagnosed ET

- Documentation of prior thrombotic events (including TIAs, angina, amaurosis fugax), risk factors for vascular disease (diabetes, smoking, hypertension, peripheral vascular disease, hyperlipidaemia), symptoms attributable to ET (lethargy, erythromelalgia)
- Physical examination for splenomegaly & BP
- Fasting lipids & glucose
- Bone marrow if not already done (including reticulin quantification), unless very elderly or frail
- Abdominal ultrasound to measure spleen if not already done
- Red cell mass study if JAK2 V617F positive and Hct ≥ 0.48 to exclude masked PV. Available at UCL Institute for Nuclear Medicine
- *Not* for routine thrombophilia screening

All patients must be listed for multi-disciplinary team meeting consideration.

3. Risk stratification for patients with newly-diagnosed ET

**High risk:** for *thrombosis* – age >60 years OR previous thrombotic event (including angina, amaurosis fugax, TIA); for *bleeding* – platelet count ≥1500 x10^9/L.

**Intermediate risk:** patients aged 40-60 years with no high-risk features.

**Low risk:** patients aged <40 years with no high-risk features

4. Treatment of patients with newly-diagnosed ET

*Patients should be enrolled to suitable clinical studies wherever possible.*

All patients should receive aspirin 75mg daily unless they have *contra-indications* (consider clopidogrel in presence of peptic ulceration). Patients at high-risk of bleeding (previous serious haemorrhage; platelet count ≥1500 x10^9/L; and patients on anagrelide whilst platelet count is above normal range) should only receive aspirin if the benefit is felt to exceed the bleeding risk.

All patients with ET should have *co-existing cardiovascular risk factors treated aggressively* – refer to appropriate specialist if necessary.

In addition, patients in the high-risk group should receive *hydroxycarbamide (HC)*, at a starting dose of 500-1000mg daily, increased slowly to maintain platelet count <400 x10^9/L (whilst maintaining neutrophil count and haemoglobin in the normal range). Response should be classified according to the European LeukaemiaNet response criteria (Table 2).
Interferon is a reasonable alternative to HC in high-risk patients who are younger than 40 and do not wish to take HC.

HC should be avoided in women who are pregnant or lactating, and in patients planning to become pregnant or father children in the near future.

Patients in the intermediate-risk group may be considered for HC if they are symptomatic (e.g. painful splenomegaly, erythromelalgia)

Summary of treatment options:

5. Situations where alternative agents to HC may be needed
   i. *Inability to suppress platelet count to normal range without causing anaemia or neutropenia* – i.e. HC-refractory (see Table 3).
Consider relaxing platelet target to <600 x10^9/L or switching to alternative agent (see below). Combining low-dose anagrelide with HC can be effective in this setting.

ii. *Development of HC-related side-effects.*

If mild gastrointestinal symptoms or rash, consider temporarily reducing the HC dose then slowly re-increasing as necessary, with appropriate symptom-management.

For more serious effects, including ankle ulceration, actinic keratosis, squamous cell carcinoma, and nail changes, HC should be stopped and an alternative agent started.

iii. *Patient concerns re leukaemogenicity of HC*

Patients should be counselled that there is no evidence that HC is associated with an increased risk of leukaemic transformation, despite extensive experience of the drug. If patients remain reluctant to take HC, they should be offered an alternative drug.

iv. *Patients who are pregnant or lactating, or planning to become pregnant or father children in the near future*

HC should be stopped and patients offered interferon-alpha (IFNα) therapy. See section on ‘ET in pregnancy’.

6. Alternative agents to HC

A number of alternative agents are effective in ET and there is no clear ‘second-line’ drug that will suit all patients. The choice of alternative agent will depend on individual patient characteristics. The commonly-used drugs are:

**Anagrelide**

Usual starting dose 500-1000mcg daily, increased slowly to a maximum 10mg daily (max single dose = 2.5mg). Common side effects include palpitations, D&V, headaches, which usually settle after a few weeks. It can occasionally cause serious tachyarrhythmias – request ECG for all patients prior to starting anagrelide and use cautiously in patients with known cardiac disease. Whilst anagrelide is relatively platelet-specific, some patients do become anaemic.

Anagrelide is associated with a greater risk of progression to secondary myelofibrosis (MF) than is HC, so patients should be counselled appropriately and undergo bone marrow examination every 3 years (or sooner if their blood counts suddenly change). If there is evidence of MF, anagrelide should be stopped and a trial of HC (which may reverse early MF in some cases) considered.

**IFNα (non-pegylated)**

Usual starting dose 3 million IU once or twice-weekly subcutaneously, increasingly slowly to 3 million IU daily maximum. Response to the drug often takes several weeks or months and the timing of dose-adjustment should reflect this. Fatigue, myalgia, malaise and low mood are common side effects and 20-40% of patients cannot tolerate this therapy. Premedication with paracetamol may help. Avoid in patients with a history of severe psychiatric disorders unless absolutely necessary.
This is the standard therapy for ET patients needing cytoreductive treatment during lactation or pregnancy, or whilst planning to become pregnant or father children.

**IFNα (pegylated) e.g. Pegasys**

This is an alternative to non-pegylated IFNα: it benefits from once-weekly administration and a lower incidence of fatigue, myalgia etc. As with the non-pegylated form, exercise caution in patients with a history of psychiatric disorders. Usual starting dose 90mcg weekly subcutaneously. Doses can be increased slowly up to 180 mcg weekly. In some patients doses less than 90 mcg may be required. Prefilled syringes are available as 180mcg or 135mcg (which may be graduated to 45mcg, 90 mcg or 135 mcg).

**Busulfan**

Various dosing regimens exist – see BCSH guidelines. Busulfan is generally considered to be leukaemogenic (and causes pulmonary disease) so should be reserved for elderly patients – ideally those who have not received HC recently.

One dosing regimen is to give a single dose of 20-25mg busulfan and monitor blood counts carefully. If there has been no response after 4-6 weeks, a second dose can be given. If there is no response to this, the dose may be increased to a maximum of 50mg every 4-6 weeks, with regular monitoring for myelosuppression and pulmonary toxicity.

**Radioactive phosphorus (^32P)**

Rarely used, primarily because of its leukaemogenic effect, ^32P may be useful for treating selected elderly patients. As with busulfan, avoid in those who have received HC recently.

**7. ET in pregnancy**

Patients should be managed jointly by an obstetrician experienced with ‘high-risk’ antenatal patients and a haematologist. Management of pregnant women with ET should be discussed at an MDM wherever possible.

All patients should receive aspirin (unless contra-indicated) throughout pregnancy.

Low-molecular weight heparin (LMWH) should be added in at thromboprophylactic dose for six weeks post-natally, for all patients.

In addition, the following patients should receive IFNα (to achieve platelet count within the normal range) and LMWH throughout pregnancy and the puerperium:

i. Patients receiving cytoreductive therapy prior to pregnancy on the basis of being at high-risk of thrombotic or bleeding complications (see Section 3);

ii. Patients at high risk of pregnancy-related complications (see Table 4);
iii. Patients with evidence of impaired uterine arterial flow (bilateral ‘notching’ of uterine artery dopplers) at 20-24 weeks – see BCSH guideline.

Whilst IFNα does pass into breast milk, there is no evidence that this is harmful to the infant. The issue of breastfeeding whilst taking IFNα should be discussed with the mother prior to delivery, and she should be supported to make an informed decision.

8. Transformation to MF and acute leukaemia

This may be heralded by a sudden change in blood counts, development of systemic symptoms, or a general deterioration in general wellbeing. Any suspicion of transformation should prompt a bone marrow examination. Post-ET MF is diagnosed according to specific criteria (Table 5) and is managed similarly to primary MF (switching from anagrelide to HC may reverse early fibrosis in some patients). Post-ET AML is diagnosed and managed as de-novo AML, though the prognosis is generally significantly worse.

9. Patient follow-up

Patients should be regularly reviewed with FBC, LFT and renal function – the frequency of follow-up will depend on the stability of their condition. Fasting lipid and glucose screening and BP measurement should be performed annually.

10. Reactive thrombocytosis

Whilst there is no evidence to support this, some clinicians do recommend aspirin 75mg daily for patients with a reactive thrombocytosis >1000 x10⁹/L.

11. Audit

Compliance with these guidelines should be audited regularly, including effectiveness of cytoreduction where necessary and management of vascular co-morbidity. Network-wide audits should be decided and performed at least annually.

11. Multi-disciplinary team review

All new referrals should be discussed in an MPN MDT meeting and complex cases should be discussed at a network-wide MDM, including review of histology. A UCLP-wide database should be created to record all ET cases managed within the network.
Tables

Table 1 – 2008 WHO Criteria for the diagnosis of ET
(Tefferi and Vardiman 2008)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sustained platelet count ≥450x10^9/L</td>
</tr>
<tr>
<td>2</td>
<td>Bone marrow biopsy specimen showing proliferation mainly of the megakaryocytic lineage with increased numbers of enlarged, mature MKs. No significant increase or left-shift of neutrophil granulopoiesis or erythropoiesis</td>
</tr>
<tr>
<td>3</td>
<td>Not meeting WHO criteria for CML, PV, PMF, MDS or other myeloid neoplasm</td>
</tr>
<tr>
<td>4</td>
<td>Either demonstration of JAK2V617F or other clonal marker; or no evidence of reactive thrombocytosis</td>
</tr>
</tbody>
</table>

Diagnosis of ET requires fulfilment of all 4 criteria.

Table 2 – European LeukaemiaNet clinico-haematological response criteria in ET
(Barosi et al, 2009)

<table>
<thead>
<tr>
<th>Response grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>(1) Platelet count ≤ 400 × 10^9/L, AND (2) no disease-related symptoms,* AND (3) normal spleen size on imaging, AND (4) white blood cell count ≤ 10 × 10^9/L</td>
</tr>
<tr>
<td>Partial response</td>
<td>In patients who do not fulfill the criteria for complete response, platelet count ≤ 600 × 10^9/L OR decrease &gt; 50% from baseline</td>
</tr>
<tr>
<td>No response</td>
<td>Any response that does not satisfy partial response</td>
</tr>
</tbody>
</table>
Table 3 – Definition of resistance/intolerance to HC in patients with ET (Barosi et al, 2007)

Any one of:

1. Platelet count <600 x10⁹/L after 3 months of at least 2 g/day of HC (2.5 g/day in patients with a body weight>80 kg)
2. Platelet count <600 x10⁹/L and WBC less than 2500/ml at any dose of HC
3. Platelet count <600 x10⁹/L and Hb less than 10 g/dl at any dose of HC
4. Presence of leg ulcers or other unacceptable muco-cutaneous manifestations at any dose of HC
5. HC-related fever

Table 4 – Risk factors for complications in pregnancy (Harrison et al, 2010)

- Previous venous or arterial thrombosis in mother (whether pregnant or not)
- Previous haemorrhage attributed to ET (whether pregnant or not)
- Previous pregnancy complication that may have been caused by ET e.g.:
  - Unexplained recurrent first trimester loss (three unexplained first trimester losses)
  - Intrauterine growth restriction (birthweight <5th centile for gestation)
  - Intrauterine death or still birth (with no obvious other cause, evidence of placental dysfunction and growth restricted fetus)
- Severe pre-eclampsia (necessitating preterm delivery <34 weeks) or development of any such complication in the index pregnancy
- Placental abruption
- Significant ante- or postpartum haemorrhage (requiring red cell transfusion)
- Marked sustained rise in platelet count rising to above 1500 x10⁹/L
Table 5 – Diagnostic criteria for post-ET MF (Mesa et al 2007)

<table>
<thead>
<tr>
<th>Required criteria (both are required)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Documentation of a previous diagnosis of ET as defined by the WHO criteria</td>
</tr>
<tr>
<td>2 Bone marrow fibrosis grade 2–3 (on 0–3 scale) or grade 3–4 (on 0–4 scale)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Additional criteria (two are required)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Anaemia and a 20 g/l decrease from the baseline haemoglobin level</td>
</tr>
<tr>
<td>2 A leucoerythroblastic blood film</td>
</tr>
<tr>
<td>3 Increasing splenomegaly defined as either an increase in palpable splenomegaly of 5 cm; or the appearance of a newly palpable splenomegaly</td>
</tr>
<tr>
<td>4 Elevated lactate dehydrogenase level</td>
</tr>
<tr>
<td>5 Development of at least one of three constitutional symptoms:</td>
</tr>
<tr>
<td>6 10% weight loss in 6 months, night sweats, unexplained fever (&gt;37.5°C)</td>
</tr>
</tbody>
</table>

References


