Managing ET in 2019
Tiziano Barbui  MD
(tbarbui@asst-pg23.it)

Hematology and Foundation for Clinical Research,
Hospital Papa Giovanni XXIII
Bergamo, Italy
Managing ET in 2019

Establish diagnosis

Risk Stratification

Personalize therapy

Disease progression

Future research
UPDATE - Essential thrombocythemia (ET)

Major criteria:
1. Platelet count equal to or greater than 450 x 10^9/μL
2. Bone marrow biopsy showing proliferation mainly of the megakaryocyte lineage with increased numbers of enlarged, mature megakaryocytes with hyperlobulated nuclei.
   No significant increase or left-shift of neutrophil granulopoiesis or erythropoiesis and very rarely minor increase in reticulin fibers.
3. Not meeting WHO criteria for BCR-ABL1+ CML, PV, PMF, myelodysplastic syndromes, or other myeloid neoplasms
4. Presence of JAK2, CALR or MPL mutation

Minor criteria:
Presence of a clonal marker or absence of evidence for reactive thrombocytosis

Diagnosis of ET requires meeting all four major criteria or the first three major criteria and one of the minor criteria
Recognizing ET from Early-Phase PV in JAK2 mutated patients

**PV: WHO 2008 diagnostic criteria**

Dynamics of the disease process in PV

- **Evolution** → **Manifestation** → **Transformation**
  - **masked PV**
    - positive WHO 2008 criteria (hb > 18.5 / 16.5 g/dL)
    - JAK2 +/- JAK2 +++
    - EECs + EPO ↓↓
  - **definite increase in red cell mass**
  - Fibrosis
  - 10 - 15 yrs.
  - Splenomegaly

- **Transformation**
  - Post-polycythemic myeloid metaplasia (post-PV MF)
  - ~ 20%
  - Post-PV MF with blastic transformation
  - ~ 10%

- **Pre-polycytemic stage**
- **Polycytemic stage**
- **Terminal stage**
Recognizing ET from Prefibrotic-PMF

**Clinical implications:**
- Clinical presentation is different (anemia, leukytosis, LDH, splenomegaly)
- Thrombosis is similar to ET
- Time to disease progression is shorter in pre-PMF
- Prefibrotic-PMF is associated with an almost double rate of hemorrhage compared to ET
- Careful with aspirin

Survival estimates for patients with essential thrombocythemia and early/prefibrotic primary myelofibrosis

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**ET**

- ET and prefibrotic-PMF are distinct entities in the 2016 WHO classification.

**pre-PMF**

Managing ET in 2019

- Establish diagnosis
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- Disease progression
- Future research
The ET disease burden

**Symptoms**

- **Cytokine**: fatigue, pruritus, constitutional symptoms, bone pain
- **Vascular**: headache, dizziness, numbness, decreased concentration, low mood, sexuality problems
- **Disease evolution**: splenomegaly, constitutional symptoms

ELN recommendations for Risk stratification in ET/PV

The conventional prognostic systems in ET/PV are based upon age and previous history of thrombosis that separate patients into low- (age <60 years and no history of thrombosis) or high-risk (age ≥ 60 years or prior thrombosis) categories.
Jak2 mutation status is an independent factor for total thrombosis in ET (n= 891)*

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 60</td>
<td>1.50</td>
<td>(1.00-2.25)</td>
</tr>
<tr>
<td>CV risk factors</td>
<td>1.56</td>
<td>(1.03-2.36)</td>
</tr>
<tr>
<td>Previous thrombosis</td>
<td>1.93</td>
<td>(1.27-2.91)</td>
</tr>
<tr>
<td>JAK2 V617F</td>
<td>2.04</td>
<td>(1.19-3.48)</td>
</tr>
</tbody>
</table>

* Multivariate model adjusted for: sex, Hb, WBC and plt counts, HU and aspirin

*Leukocytosis associated with arterial and not venous thrombosis

CALR Mutated patients have lower rate of thrombosis in Essential thrombocythemia

Thrombosis Free-Survival

Hazard Ratio: Wild type patients were taken as a reference population

<table>
<thead>
<tr>
<th>Mutated</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>JAK2</td>
<td>1.78</td>
<td>1.06-3.18</td>
</tr>
<tr>
<td>MPL</td>
<td>1.65</td>
<td>1.70-3.92</td>
</tr>
<tr>
<td>CALR</td>
<td>0.74</td>
<td>0.33-1.00</td>
</tr>
</tbody>
</table>

P = 0.008

Time (months)

Thrombosis–free survival in patients with ET who were triple-negative or harbored JAK2 or CALR mutations (n=290)

Gangat et al, European J Hematology, 2014
IPSET-Thrombosis Model

• Model in WHO-defined ET
  • **Factors**: age > 60 years (1 point), thrombosis history (2 points), cardiovascular risk factors (1 point), and JAK2 V617F (2 points).
  • **Model**: LR if < 2 points; IR if 2 points; HR if > 2 points
  • **Risk of thrombosis**: 1.03% p/y (LR), 2.35% p/y (IR) 3.56% p/y (HR)
  • This model better predicts thrombosis than conventional one and is not affected by CALR-mutation (Finazzi et al, Blood 2015)
Validation of IPSET-thrombosis model in 585 patients with ET (Mayo Clinic)
Revised IPSET-Thrombosis. Influence of risk factors on the rate of vascular events in a cohort of 1019 conventionally defined low and high risk patients with ET

Validation of the revised International Prognostic Score of Thrombosis for Essential Thrombocythemia (IPSET-thrombosis) in 585 Mayo Clinic patients

P < 0.0001

Am J Hematol 2016
ELN and NCCN recommendations for Risk stratification in ET

In ET, the IPSET system that includes age, previous thrombosis, cardiovascular risk factors, and JAK2V617F mutation, is the recommended prognostic system and it should be scored in all patients at diagnosis.

Barbui T et al, JCO 2011; Leukemia 2018 Mesa et al, National Comprehensive Cancer Network® (NCCN®)
Managing ET in 2019

- Establish diagnosis
- Risk Stratification
- Personalize therapy
  - Disease progression
  - Future research
Managing ET in 2019

- Establish diagnosis
- Risk Stratify
- Personalize therapy
  - Treat disease progression
  - Future research

- Future research
Low dose aspirin by risk of thrombosis in patients with ET

**Very low thrombotic risk: No aspirin**
- No history of thrombosis
- Age <60 years
- JAK2V617F-unmutated
- No cardiovascular risk factors (CVR)

**Low thrombotic risk: Yes aspirin**
- No history of thrombosis
- Age <60 years
- JAK2V617F-mutated and/or CVR present

**High thrombotic risk: Aspirin twice?**
- History of thrombosis and/or Age ≥ 60 years
- JAK2V617F-mutated and/or CVR present
“Personalized” Aspirin Treatment: 0, 1, 2 daily?

- In **CALR-mutated patients**, antiplatelet therapy did not affect the risk of thrombosis but was associated with a higher incidence of bleeding (12.9 vs. 1.8 x1000 pt-yrs, p=0.03).
- In **JAK2V617F-mutated patients**, low-dose aspirin was associated with a reduced incidence of thrombosis with no effect on the risk of bleeding.
- In **pre-PMF** aspirin is associated with increase risk

A randomized trial (ARES) is ongoing.

Cytoreductive therapy for LOW-RISK with levels of platelets up to $1500 \times 10^9/l$?

No treatment for low-risk thrombocythaemia: results from a prospective study (Ruggeri M….Barbui T. BJH 1998)

We conclude that the thrombotic risk in young ET patients, with no thrombotic history and a platelet count $<1500 \times 10^9/l$, is not increased compared to the normal population and that a conservative therapeutic approach should therefore be considered in these patients.

Comments by UK Investigators (Letter, BJH 1998)
This clearly has relevance to the study design of the current Medical Research Council Primary Thrombocythaemia (MRC PT1) study (TC Pearson et al, 1998)
Hydroxycarbamide Plus Aspirin Versus Aspirin Alone in Patients With Essential Thrombocythemia Age 40 to 59 Years Without High-Risk Features

CONCLUSION

In patients with ET age 40 to 59 years and lacking high-risk factors for thrombosis or extreme thrombocytosis, preemptive addition of hydroxycarbamide to aspirin did not reduce vascular events, myelofibrotic transformation, or leukemic transformation.

Patients age 40 to 59 years without other clinical indications for treatment (such as previous thrombosis or hemorrhage) who have a platelet count, $1,500 \times 10^9 \text{L}$ should not receive cytoreductive therapy.
Randomized Clinical Trials in ET

Phase III studies in high-risk ET
(Age and/or prior events)

1995 (PVSG)
Cortelazzo et al.
HU vs.
no myelosuppressive therapy

HU better than no myelosuppressive therapy

target < 600x10^9/L

Thrombosis incidence
3.6% vs. 24%
(at 27 months)

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2005 (PVSG)
Harrison et al.
PT-1
HU+ASA vs. AG+ASA

HU+ASA superior to AG+ASA*

target < 400x10^9/L

Incidence of thrombosis
4% vs. 8%
(at 2 years)
Randomized Clinical Trials in ET

Phase III studies in high-risk ET
(Age and/or prior events)

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target < 400x10^9/L

2013 (WHO 2008) Gisslinger et al.
ANAHYDRET
HU vs. AG

AG not inferior to HU
target ≤ 450x10^9/L

Thrombosis incidence
3.6% vs. 24%
(at 27 months)

Incidence of thrombosis
4% vs. 8%
(at 2 years)

Thrombosis rate
3.3% vs. 3.4%
(at 2 years)

The Panel agreed on recommending hydroxyurea and INFα as first-line therapy agents.

However, even though the majority of the experts indicated anagrelide as an appropriate choice for first-line therapy in ET, the panel did not reach a consensus on recommending the agent in this setting, arguing that the evidence of non-inferiority with hydroxyurea was of insufficient quality, and the risk-benefit ratio unfavourable.
HU resistant and intolerant patients

Non hematologic toxicities
- Leg ulcers or
- other unacceptable HU-related non-hematological toxicities, gastrointestinal symptoms, pneumonitis or fever at any dose of hydroxycarbamide

Hematologic toxicities
- Neutrophil count <1,000/mL
- platelet count <100,000/mL
- Hb <10 g/dL
Treatment options for hydroxyurea intolerant or refractory patients

- Pegylated interferon-α (IFN-α)
- Anagrelide
- Busulfan
- Ruxolitinib
Ruxolitinib for essential thrombocythemia refractory or intolerant of hydroxyurea

**Phase II study** (Vertovsek et al Blood 2014)
Hydroxyurea resistant ET patients can achieve clinically meaningful and durable reductions in platelet and WBC counts and **improvements in ET-related symptoms** with ruxolitinib treatment.

**RCT Ruxo vs BAT** (Harrison et al Blood 2017)
Ruxolitinib **significantly improved some disease-related symptoms**, but rates of thrombosis, hemorrhage, or transformation were not different.

**Editorial** (Finazzi, Blood 2017)
At variance to patients with PV, ruxolitinib does not represent the first choice for most ET patients resistant or intolerant to HC, with the possible exception of those **severely symptomatic, particularly for pruritus.**
Addressing Symptoms

- Assessment of symptoms (in provider’s office) at baseline and during FU is recommended in all patients.
- MPN-SAF or MPN-SAF TSS is assessed by the patients themselves.
- Changes in symptom status can be a sign of disease progression.
- Symptom response to treatment can justify continued use of drugs.

NCCN Guidelines v2.2018

Managing ET in 2019

- Establish diagnosis
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- Personalize therapy

Disease progression
Future research
Diagnosis and Cumulative Incidence of Myelofibrosis in “true ET” vs prefibrotic MF

REQUIRED CRITERIA
1. Prior WHO Diagnosis of PV or ET
2. Bone marrow fibrosis 2-3/ 3 scale (3-4 on 4 scale)

ADDITIONAL CRITERIA (2 Required)
1. Anemia, decreased cytoreduction
2. Leukoerythroblastic peripheral blood picture
3. Increasing splenomegaly
   - Increase >5cm (palpable)
   - New palpable splenomegaly
4. Development of constitutional symptoms
   - >10% weight loss
   - Night Sweats
   - Unexplained Fever >37.5°C

Barbui et al, JCO 2011
The Leukemia controversy in MPNs: Is AML a natural progression of myeloproliferative disorders, a secondary sequela of therapy or a combination of both?

- Leukemic transformation may occur in untreated ET and PV patients (25%)
- HU alone does not seem to increase the natural risk of AML/MDS
- A significant association with AML/MDS is observed when HU is used in patients previously or sequentially treated with alkylating agents

Cumulative Incidence of Leukemia and role of cytoreductive drugs in “True ET vs pre-PMF”

Barbui et al, JCO 2011
Cumulative Incidence of Death and risk factors in “True ET and Pre-PMF”

<table>
<thead>
<tr>
<th>Parameters at diagnosis</th>
<th>HR (95%CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BM histology (PMF vs ET)</td>
<td>1.60 (1.05-2.44)</td>
<td>0.03</td>
</tr>
<tr>
<td>Age &gt; 60 years</td>
<td>6.70 (4.34-10.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male Gender</td>
<td>1.30 (0.91-1.86)</td>
<td>0.15</td>
</tr>
<tr>
<td>WBC &gt; 11 x10^9/L</td>
<td>2.01 (1.39-2.90)</td>
<td>&lt;0.0002</td>
</tr>
<tr>
<td>HB &lt; 12 g/dL</td>
<td>2.95 (1.73-5.04)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PLT &gt; 1000 x10^9/L</td>
<td>1.30 (0.90-1.90)</td>
<td>0.16</td>
</tr>
<tr>
<td>JAK2^{V617F}</td>
<td>1.48 (0.80-2.76)</td>
<td>0.21</td>
</tr>
<tr>
<td>Reticulin fibrosis grade 1</td>
<td>1.06 (0.57-1.98)</td>
<td>0.85</td>
</tr>
<tr>
<td>Previous thrombosis</td>
<td>2.81 (1.95-4.06)</td>
<td>&lt;0.0001</td>
</tr>
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Barbui et al, JCO 2011
Managing ET in 2019

- Establish diagnosis
  - Risk Stratification
    - Personalize therapy
      - Disease progression
      - Future research
Annual rate of first incident vascular event (per 100 persons per year) in general population* and in MPN

General population without risk factors* 0.5%

General population with multiple CV risk factors** 0.9%

ET (n=1,019)§ ...... 1.1-2.4 %
PV (n=1,545) §§ ...... 2.0-3.1 %
PMF (n=707) §§§ ...... 2.2 %

Arterial thrombosis (60-70%) (cerebral, acute myocardial infarction and peripheral arterial occlusion); Deep venous thrombosis and pulmonary embolism; Splanchnic and cerebral vein thrombosis

§§§ Barbui et al, Blood 2010;115:778-782
Summary (1)

- ET diagnosis should be differentiated from early PV and pre-PMF
- Standard risk classification is IPSET thrombosis
- Patients at low-risk with thrombocytosis up to $1.5 \times 10^9$ should not be treated with cytoreductive drugs
- Low-dose aspirin is not for every patient
Summary (2)

- Hydroxyurea is the standard cytoreductive therapy in high risk patients
- IFN in younger patients should be preferred
- Angrelide is recommended for patients refractory or intolerant to HU.
- Ruxolitinib does not seem to reduce the vascular events. It could benefit patients with severe symptoms.
- Investments from the companies in developing clinical trials with new molecules and hard endpoints.