Neoplasie Mieloproliferative Croniche
Report dei gruppi di lavoro

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9° EDITION
Highlights from EHA
Firenze 16-17 Settembre 2016
Domande del gruppo di lavoro

☐ La classificazione WHO 2016
☐ Inserire le nuove conoscenze nella terapia
  - ET
  - PV
  - MF
Dynamics of the disease process in PV

Evolution → Manifestation → Transformation

**masked PV**
- positive WHO 2008 criteria (hb > 18.5 / 16.5 g/dL)
- ~10%-15% mimicking "ET"

**JAK2 +/-**
- EECs + EPO ↓

**definite increase in red cell mass**

Fibrosis

10 - 15 yrs.

(t)

Splenomegaly

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

Pre-polycythemic stage

Polycythemic stage

Terminal stage

Imaging results:
Dopo la classificazione WHO 2008 le nuove scoperte genetiche e i risultati di studi epidemiologici hanno consentito di descrivere una nuova epidemiologia delle MPN.

- earlier diagnosis,
- different clinical and hematologic features at presentation
- different rates of thrombo-hemorrhagic event, progression to myelofibrosis or transformation to blast phase.

Consequently, the relevant clinical outcomes registered in contemporary cohorts of patients with MPN enrolled in several observational studies, were not concordant with the findings obtained before the 2008 WHO.
Underdiagnosis of PV
RCM demonstrated PV (RCM > 25% of predicted value) in patients with hemoglobin or hematocrit below WHO 2008 requirement

- Johansson et al 2005
  Hemoglobin: male 65% ; female 37%

- Cassinat et al 2008
  Hemoglobin or hematocrit: 46%

- Alvarez-Larrán et al 2012
  Hemoglobin: male 42%; female 52%

- Silver et al 2013
  Hemoglobin or hematocrit 29%

Silver et al 2013 Blood 122 (11):1881-1886
Bone marrow morphology was consistent with WHO-PV but hemoglobin or hematocrit were below WHO 2008 criteria in 397 JAK2 mutated patients classified as PV.

(centrally re-reviewed by JT completely blinded to outcome data)

- **257 (65%)** met the full WHO-2008 criteria.
- **140 (35%)** were classified and treated as PV, although they did not meet the hemoglobin level threshold that is required for the diagnosis of WHO-defined PV.

These patients were operationally defined as «**masked PV**».

* International study including patients from Italy, Austria and Mayo Clinic

Barbui T et al, Leukemia 2013
Hematocrit is a better indicator of raised RCM than Hemoglobin

A1: High haematocrit (>0.52 in men; >0.48 in women) OR raised red cell mass (>25% above predicted) and Presence of JAK2 mutation

Barbui et al, Leukemia 2014
The best cut-off of Hb and HCT in males and females for the discrimination between PV and ET JAK2 positive patients

Females
Hb ≥ 16.0 g/dL
HCT ≥ 48%

Males
Hb ≥ 16.5 g/dL
HCT ≥ 49%

Barbui T et al, AJH 2013
Thrombosis-free in masked and overt PV patients by WHO and BCSH classification

All patients were treated as overt PV

Barbui T et al, AJH 2013
Therapeutic relevance of recognizing mPV

An excess of thrombosis in 62 patients with mPV and age < 40 years was associated to less intensive therapy.

Lussana et al, BJH 2014
Major criteria:
1. Hb > 16.5 g/dL in men, Hb > 16.0 g/dL in women OR, Hct > 49% in men, Hct > 48% in women OR, Increased red cell mass
2. Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic and megakaryocytic proliferation with pleomorphic megakaryocytes (differences in size)
3. Presence of JAK2 mutation

Minor criterion:
Subnormal serum EPO level

Diagnosis of PV requires meeting either all three major criteria, or the first two major criteria and the minor criterion
UPDATE - WHO criteria for PV

- In cases with sustained absolute erythrocytosis (Hb levels >18.5 g/dL, Hct >55.5 % in men or >16.5 g/dL, 49.5% in women, bone marrow biopsy may not be necessary for diagnosis if major criterion 3 and the minor criterion are present.

- However, only by performing a bone marrow biopsy an initial myelofibrosis (up to 20%) may be detected that indicates a more rapid progression to overt myelofibrosis (post-PV MF). (Barbui T et al. Blood 2012;119:2239-2241)
**Initial bone marrow reticulin fibrosis in PV exerts an impact on clinical outcome** (Barbui et al. Blood, 2012, 119)

### Progression to overt MF in PV

<table>
<thead>
<tr>
<th>Grade at diagnosis</th>
<th>Incidence per 100 pts./yrs.</th>
<th>IRR</th>
<th>cumulative incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>MF-0</td>
<td>0.8</td>
<td>2.7</td>
<td>1.3</td>
</tr>
<tr>
<td>≥ MF-1</td>
<td>2.2</td>
<td></td>
<td>7.8</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th></th>
<th>10 yrs.</th>
<th>15 yrs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>MF-0</td>
<td>6.9</td>
<td>15.4</td>
</tr>
<tr>
<td>≥ MF-1</td>
<td>22.0</td>
<td>20.1</td>
</tr>
</tbody>
</table>

**Thrombosis-free survival**

**Myelofibrosis-free survival**

- **BM fibrosis**
- **No BM fibrosis**
ESMO Practical Guidelines for MPN
Domande del gruppo di lavoro

- La classificazione WHO 2016
- **Inserire le nuove conoscenze nella terapia**
  - ET
  - PV
  - MF
La terapia della ET nel 2016

Valuta il rischio cardiovascolare

Basso Rischio
- Observation only
- LD-Asa (case-by-case)

Alto Rischio
- **First line cytoreduction**
  - HU
  - IFN-α
- Asa or anticoagulants (if prior venous event)
- **Second line** (IFN-α, HU, anagrelide or busulphan)
- Consider clinical trials for resistant/refractory to conventional agents

Vannucchi A et al, Linee guida ESMO 2015
Influence JAK2 mutation status on the rate of vascular events in a cohort of 1019 conventionally defined low and high risk patients with ET

Conventionally defined low risk patients' subgroups according to the presence or absence of cardiovascular risk factors and JAK2 mutation

Barbui T et al, BCJ 2015
La terapia della PV nel 2016

Valuta il rischio cardiovascolare

Basso Rischio
- Phlebotomy
- LD-Asa (all)

Alto Rischio
- Phlebotomy
- LD-Asa
- **First line cytoreduction**
  - HU
  - IFN-α
- Anticoagulants (if prior venous event)
- **Second line** (IFN-α, HU or busulphan)
- Consider *Jak*-inhibitors (for resistant/refractory to conventional agents)

Vannucchi A et al, Linee guida ESMO 2015
Rates of incident thrombosis in conventionally defined low and high risk PV by calendar period of diagnosis (N= 1,545)

<table>
<thead>
<tr>
<th></th>
<th>LOW RISK N=</th>
<th>HIGH RISK N=</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dx before 2005</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IR per 100</td>
<td>IR: 2.03 % pts/yr; 95% CI: 1.58-2.61</td>
<td>IR: 4.01 % pts/yr; 95% CI: 3.28-4.90</td>
</tr>
<tr>
<td>person/hrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dx after 2005</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IR per 100</td>
<td>IR: 2.24 % pts/yr; 95% CI: 1.33-3.78</td>
<td>IR: 2.93 % pts/yr; 95% CI: 1.89-4.54</td>
</tr>
<tr>
<td>person/hrs</td>
<td></td>
<td></td>
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</table>

Barbui T et al, AJH 2015, Feb 14, Epub, ahead of print
Overall survival in PV with criteria of resistance/intolerance

1A: resistance / intolerance to HU (dotted line) or not (solid line) p=0.8.
1B: development of **cytopenia** (dotted line) or not (solid line) p=0.026.

Development of cytopenia was defined as an absolute neutrophil count < 1 x109/L or Hb level < 100 g/L or platelet count < 100 x 109/L at the lowest dose of HU required to achieve a complete or a partial response.

Alvarez-Larràn A, Brit J Haematol 2016, 172, 786-703
Primary Response: Hct Control at Week 28

Significantly more patients randomized to ruxolitinib achieved Hct control without phlebotomy (primary endpoint) compared with those randomized to BAT.

\[ P < .0001 \]
\[ OR, 7.28 \]
\[ (95\% CI, 3.43-15.45) \]
RESPONSE Study

Improvement in symptoms (week 32)

Percentage of Patients with a ≥ 50% Improvement in MPN-SAF Symptom Score at Week 32

**MPN-SAFTotal Symptom Score**

<table>
<thead>
<tr>
<th></th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruxolitinib</td>
<td>49/74</td>
</tr>
<tr>
<td>BAT</td>
<td>5/81</td>
</tr>
</tbody>
</table>

**Cytokine Symptom Cluster**

- Tiredness
- Itching
- Muscle ache
- Night sweats
- Sweating while awake

<table>
<thead>
<tr>
<th></th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruxolitinib</td>
<td>64/74</td>
</tr>
<tr>
<td>BAT</td>
<td>11/80</td>
</tr>
</tbody>
</table>

**Hyperviscosity Symptom Cluster**

- Headache
- Dizziness
- Skin redness
- Vision problems
- Ringing in ears
- Concentration problems
- Numbness/tingling in hands/feet

<table>
<thead>
<tr>
<th></th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruxolitinib</td>
<td>37/71</td>
</tr>
<tr>
<td>BAT</td>
<td>13/80</td>
</tr>
</tbody>
</table>

**Splenomegaly Symptom Cluster**

- Fullness/early satiety
- Abdominal discomfort

<table>
<thead>
<tr>
<th></th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruxolitinib</td>
<td>62/63</td>
</tr>
<tr>
<td>BAT</td>
<td>17/71</td>
</tr>
</tbody>
</table>

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In patients with scores at both baseline and week 32

MPN-SAF, Myeloproliferative Neoplasm Symptom Assessment Form

Preliminary evidence shows that ruxolitinib may reduce the rate of thromboembolic events.

RESPONSE study

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Ruxolitinib (n = 110)</th>
<th>BAT (n = 111&lt;sup&gt;a&lt;/sup&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure, Patient-Years</td>
<td>227.7</td>
<td>73.6</td>
</tr>
<tr>
<td>Number of Patients (Rate per 100 Patient-Years of Exposure)</td>
<td>All Grades</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>All thromboembolic events</td>
<td>4 (1.8)</td>
<td>2 (0.9)</td>
</tr>
</tbody>
</table>

Preliminary evidence of the lower rate of thromboembolic events observed in the ruxolitinib arm vs the BAT arm. Consistent with the observed effects of ruxolitinib on hematocrit, WBC counts, and C-reactive protein levels, which are all associated with thromboembolic risk.

Kiladjian et al, EHA 20th Congress, Vienna 2015, abstract 5447
The impact of ruxolitinib on thrombosis in patients with polycythemia vera and myelofibrosis: a meta-analysis.

Method
Comfort-1 and 2, Response 1 were identified. In Comfort-1 and 2 trials rates of thrombosis were provided by Incyte. Primary outcomes: thrombosis (arterial, venous as defined by investigators.

Conclusion JAK1/JAK2 inhibition may reduce the risk of thrombosis in MPN. This finding warrants prospective trials

_Samuelson BT _al _Blood Coagul Fibrinolysis_. 2014 Nov 13. [Epub ahead of print]
Calcola IPSS score

- Basso rischio o Int-1
  - Symptomatic
    - NO: Observation
    - YES: Conventional treatment, Ruxolitinib (se sintomi)

- Int-2 e Alto rischio
  - AlloSCT eligible?
    - NO: Ruxolitinib, Drugs for anaemia, Clinical trial
    - YES: Allo SCT
      - Conventional
      - Reduced intensity

Vannucchi A et al, Linee guida ESMO 2015
A cutoff criteria of the worst single symptom being >5/10 may differentiate between which patients will most benefit from symptom-based treatment.

We propose that JAK2 inhibitor treatment be strongly considered in any JAK2-inhibitor naïve MF patient with an individual symptom score >5.
Which patients with myelofibrosis should receive ruxolitinib therapy?

ELN-SIE evidence-based recommendations

Marchetti Monia¹, Barosi Giovanni², Cervantes Francisco³, Birgegård Gunnar⁴, Griesshammer Martin⁵, Harrison Claire⁶, Hehlmann Rüdiger⁷, Kiladjian Jean-Jacques⁸, Kröger Nicolaus⁹, McMullin Mary Frances¹⁰, Passamonti Francesco¹¹, Vannucchi Alessandro¹², Barbui Tiziano¹³.

Leukemia, accepted 2016

Ruxolitinib was strongly recommended

- for improving symptomatic or severe (>15 cm below the costal margin) splenomegaly in patients with an IPSS/DIPSS risk INT2 or high
- for improving systemic symptoms in patients with a MPN10 score higher than 44, refractory severe itching, unintended weight loss not attributable to other causes or unexplained fever.
- because of weak evidence, the panel does not recommend ruxolitinib therapy for improving survival.
- the recommendations given above do not necessarily apply to patients who are candidates for allogeneic stem cell transplant.