Managing Myelofibrosis in 2019

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Evolution of Myelofibrosis

Symptoms/Splenomegaly

Early MF  Overt MF/secondary MF  Terminal stage

Years after diagnosis

Thrombocytopenia/Anemia
Leukoerythroblastosis
Peripheral blasts

Marrow fibrosis grade

MF0  MF1 RETICULUM OSTEOSCLEROSIS  MF2  MF3 COLLAGEN FIBROSION

EARLY DEATH

18% BM insufficiency
31% Acute Leukemia
13% Thrombosis
11% Infections
17% Second neoplasia
5% Bleedings

### Primary MF Diagnosis

#### Requirement for diagnosis
- All 3 major criteria AND ≥ 1 minor criteria

#### Major criteria
1. Megakaryocytic proliferation and atypia, **without reticulin fibrosis > grade 1 (prefibrotic PMF)** or **with reticulin and/or collagen fibrosis grade 2/3 (overt fibrotic PMF)**
2. **JAK2, CALR, or MPL** mutation, presence of other clonal markers* OR absence of reactive MF
3. Not meeting WHO criteria for other myeloid malignancies

#### Minor criteria
1. Anemia not attributed to a comorbid condition
2. Leukocytosis ≥ 11 × 10⁹/L
3. Palpable splenomegaly
4. LDH increased above ULN
5. **Leukoerythroblastosis (overt fibrotic PMF)**

* eg, ASXL1, EZH2, TET2, IDH1/IDH2, SRSF2, SF3B1.

Disease Progression - ET vs. prePMF

International Study on 1,104 Patients

Transformation to overt MF

Risk of leukemic transformation

The heterogeneous clinical spectrum of prefibrotic myelofibrosis
Treatment algorithm in prefibrotic myelofibrosis for the thrombotic and bleeding risk

No previous thrombosis or bleeding

Observation only, or Low-dose ASA in selected patients*

Previous thrombosis

Low-dose ASA (if arterial) or Oral anticoagulation (if venous) and Cytoreduction** (if thrombocytosis or leukocytosis)

Previous bleeding

Avoid ASA and use Cytoreduction** (if thrombocytosis or leukocytosis)

* Age > 60 yrs., or CV risk factors, or JAK2V617F mutation, or leukocytosis or microvascular symptoms and low bleeding risk

** Hydroxyurea as first choice, rIFNα in HU resistant or intolerant patients
Diagnosing PPV- or PET-MF

<table>
<thead>
<tr>
<th>PV</th>
<th>ET</th>
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<tr>
<td>10% transformation rate per 10 years(^2)</td>
<td>&lt;4% transformation rate per 10 years(^2)</td>
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Post-PV or Post-ET Myelofibrosis\(^1\)

**IWG Diagnostic Criteria for Post-PV Myelofibrosis**

**REQUIRED CRITERIA**

- Documentation of previous diagnosis of PV or ET as defined by WHO criteria
- Grade 2 or 3 bone marrow fibrosis (0-3 scale) or grade 3 or 4 bone marrow fibrosis (0-4 scale)

**Additional Criteria (2 Required)**

- Anemia or sustained loss of need for either phlebotomy or cytoreductive therapy
- Leukoerythroblastosis
- ≥5 cm increase in palpable splenomegaly or new splenomegaly
- Development of ≥1 of 3 constitutional symptoms\(^3\)

**Additional Criteria (2 Required)**

- Anemia and a decrease of ≥2 mg/mL from baseline hemoglobin level
- Leukoerythroblastosis
- ≥5 cm increase in palpable splenomegaly or new splenomegaly
- Increased serum LDH level
- Development of ≥1 of 3 constitutional symptoms\(^3\)

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ET = essential thrombocythemia; IWG = International Working Group; LDH = lactate dehydrogenase; PET-MF = post-essential thrombocythemia myelofibrosis; PPV-MF = post-polycythemia vera myelofibrosis; PV = polycythemia vera; WHO = World Health Organization.

NCCN Guideline for Treatment of MF: Based on Risk and Symptoms/Signs

- **Low Risk**: Observation or ruxolitinib (if symptomatic) or clinical trial
- **Intermediate-1**: Observation or ruxolitinib (if symptomatic) or clinical trial or allogeneic HSCT (selected pts)
- **Intermediate-2**
  - Transplant candidate ➔ Allogeneic HSCT or
  - Transplant ineligible/symptomatic ➔ ruxolitinib or clinical trial
- **High Risk**
  - Transplant ineligible/anemia ➔ anemia rx or clinical trial

Low risk = 0 on IPSS, DIPSS-Plus, or DIPSS
INT-1 risk = IPSS = 1, DIPSS-Plus = 1, DIPSS = 1 or 2
INT-2 risk = IPSS = 2, DIPSS-Plus = 2 or 3, DIPSS = 3 or 4
High risk = IPSS = 3, DIPSS-Plus = 4 to 6, DIPSS = 5 or 6

IFN for First-Line MF Treatment: Consideration in Early Hyperproliferative Stage

Impact of Use

| Early | • Blood count control  
|       | • Address splenomegaly, when modest  
|       | • Reduction in thrombosis risk |
| Late  | • Anticlonal activity  
|       | • Potential for regression of histologic changes and delayed transformation? |

• Consider IFN use in selected pts
  – With preserved performance status and limited comorbidities
  – Who are earlier in disease course
  – When splenomegaly modest
  – Without additional non-JAK2 mutations (?)

• Limitations:
  – Potential for short-term negative impact on QoL
  – Tolerable in the long term?

Aproach to the Treatment of Anemia in MF

EPO (erythropoietin) level

- ADEQUATE ≥ 500 mIU/mL
  - Danazol, Thalidomide, Lenalidomide

- INADEQUATE < 500 mIU/mL
  - ESA x 3 mos
  - No response
  - Response

NCCN guidelines, 2017
MF: What does ruxolitinib do?

It is good for spleen and symptoms.
Early-Stage MF May Have a Significant Clinical Burden

- DIPSS low-risk MF patients are moderately to highly symptomatic in 44% of the cases
- The reduction of quality of life and social/working activity is similar in low and high risk categories
## Ruxolitinib in IPSS-1 Patients

### Higher response rate and lower toxicities

Intermediate-1 risk patients may possibly achieve higher response rates and experience lower toxicities than patients with higher-risk disease.

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<tbody>
<tr>
<td>COMFORT-I (n = 155)</td>
<td>41.9%</td>
<td>45%</td>
<td>13%</td>
<td>≈ 50%</td>
<td>21%</td>
</tr>
<tr>
<td>COMFORT-II (n = 146)</td>
<td>32%</td>
<td>42%</td>
<td>8%</td>
<td>≈ 50%</td>
<td>38%</td>
</tr>
<tr>
<td>JUMP INTM-1 (n = 163)</td>
<td>56.9%</td>
<td>24.5%</td>
<td>11%</td>
<td>40%</td>
<td>19.6%</td>
</tr>
<tr>
<td>ROBUST trial (n = 14)</td>
<td>50%</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Italian study (n = 70)</td>
<td>54.7%</td>
<td>21.7%</td>
<td>2.9%</td>
<td>17.1%</td>
<td>17.1%</td>
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Overall survival of patients by degree of spleen length reduction on ruxolitinib

Ruxolitinib Efficacy by Titrated Dose

- Avoid starting with low dose!
- Start dosing per guidelines and modify based on platelets if needed
- Doses less than 10mg BID are not effective long term

COMFORT-1 study; Verstovsek S et al. OncoTargets and Therapy 2014;7:13-21
Summary on Ruxolitinib in MF

- Indicated for splenomegaly or MF-related symptoms (regardless of a risk of dying)
- Early stage MF patients may achieve better therapeutic results with respect to IPSS intermediate-2/high-risk patients
- Also, toxicity (myelosuppression) could be lower due to better global health status and better bone marrow reserve (better CBC)

- Anemia is NOT contraindication; starting dose based on platelet number
- Avoid ‘prophylactic underdosing’ - maintain maximum tolerated dose to achieve larger reductions in splenomegaly early during treatment
- Development of anemia DOES NOT affect benefits of JAK2 inhibitor
  - Manage anemia as alternative to early dose reductions
- Avoid abrupt interruption of ruxolitinib in patients responding well
- Monitor for skin cancer
- Be aware of rare possibility of opportunistic infections
Outcome of patients with MF after ruxolitinib

In chronic phase patients, survival probability may be improved by the use of medical therapies that are still in the experimental phase.

Overall survival according to the type of medical treatment after ruxolitinib discontinuation (N=171)
NCCN Guideline for Treatment of MF-AP or MF-BP/AML

**Workup**
- BM aspirate and biopsy with trichrome and reticulin stain
- BM cytogenetics (karyotype ± FISH)
- Flow cytometry
- Molecular testing

**MF-AP**
- Peripheral blood or BM blasts 10-19%

**MF-BP/AML**
- Peripheral blood or BM blasts ≥20%

**Transplant candidate**: *
- Induce remission with hypomethylating agent (HMA) or intensive induction chemotherapy

**Not a transplant candidate**: *
- Clinical trial OR
- HMA or low-intensity induction chemotherapy

*Consider ruxolitinib to control splenomegaly and systemic symptoms*

HMA: azacitidine and decitabine

MF-AP: myelofibrosis in accelerated phase; MF-BP/AML – myelofibrosis in blast phase or transformation to AML
THANK YOU

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