Current and Future Myelofibrosis Treatments

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Disease Course and Complications in Patients with Myelofibrosis

Abbreviations: EMH, extramedullary hematopoiesis; ET, essential thrombocythemia; PMF, primary myelofibrosis; PS, performance status; PV, polycythemia vera; QOL, quality of life.

Current MF Treatment is Based on Risk and MF-related Symptoms/Signs

- **Low Risk**: Minimally symptomatic → Observation or Interferon. Many symptoms → JAK2 inhibitor.
- **Intermediate-1**: JAK2 inhibitor or anemia treatment or allogeneic HSCT.
- **Intermediate-2**: Allogeneic HSCT or JAK2 inhibitor or anemia treatment.
- **High Risk**: Allogeneic HSCT or JAK2 inhibitor or anemia treatment.

HSCT, hematopoietic stem cell transplantation.

# Main Clinical Problems in Myelofibrosis

<table>
<thead>
<tr>
<th>Clinical need</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia (Hb &lt;10 g/dL)</td>
<td>36%</td>
</tr>
<tr>
<td>Leukocytosis (&gt;25x10⁹/L)</td>
<td>10%</td>
</tr>
<tr>
<td>Thrombocytopenia (&lt;100x10⁹/L)</td>
<td>16%</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>83%</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>65%</td>
</tr>
<tr>
<td>Extramedullary hematopoiesis</td>
<td>1-3%</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>7.2%</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td>27%</td>
</tr>
<tr>
<td>Leukemia transformation</td>
<td>13%</td>
</tr>
</tbody>
</table>

Patients are treated for specific problems, not based on prognosis

Medicines for Anemia
- Prednisone
- Androgens (danazol)
- EPO
- Thalidomide or Lenalidomide +/- prednisone

Medicines for Spleen
- Ruxolitinib
- Hydroxyurea
- Busulfan
- Cladribine
- Splenectomy
- Splenic Radiation

Medicines for Symptoms
- Ruxolitinib
- Prednisone
Initial Approach to the Treatment of Anemia of Myelofibrosis

EPO levels

ADEQUATE

Danazol
others

INADEQUATE

EPO preparation

x 3 months

No response

Response

Phase II Study of Sotatercept (ACE-011) in Myeloproliferative Neoplasm-Associated Myelofibrosis and Anemia

ASH Abstract 478

Sotatercept in MF

- Efficacy: ~40% response rate using 0.75 mg/kg dose Q3W

73-year-old female, PMF, MF-3, *MPL* W515L+, del7q, del13q, transfusion-dependent DIPSS int-2, previous therapies pomalidomide and momelotinib (4 years)

Splenectomy in Myelofibrosis

ASSOCIATED RISKS
- up to 40% morbidity
- up to 10% mortality
- Liver enlargement and failure
- Higher acute transformation rate?
- Average survival post splenectomy: 18 months

MAIN INDICATIONS
- Symptomatic splenomegaly unresponsive to treatment
- Severe refractory anemia and thrombocytopenia
- Unresponsive constitutional symptoms
- Uncontrollable hemolysis
- Portal hypertension

CONTRAINDICATION
- Thrombocytosis
Splenic Irradiation in Myelofibrosis

INDICATIONS
- Symptomatic splenomegaly in poor candidates to surgery
- Severe pain from splenic infarction

RESULTS
- Dose: variable, median 2.8 Gy, fractioned
- Effect duration: median 6 mos.

CONTRAINDICATION
As preparation for splenectomy

ASSOCIATED RISK
Long-lasting cytopenias (43%)
• Not selective for mutated JAK2V617F enzyme (ATP binding inhibitors)
• Inhibit JAK-STAT pathway
• Lowering of platelets and red blood cells is expected side effect due to inhibition of wild type (normal) JAK2
• Elimination of the disease very unlikely
Patient with Myelofibrosis
MF Patient after 2 Months of Therapy
## British Guidelines for myelofibrosis & use of JAK inhibitors

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Spleen</th>
<th>Haematological toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear</td>
<td>Clear</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Suboptimal</td>
<td>Yes</td>
</tr>
<tr>
<td>Suboptimal</td>
<td>Clear</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Suboptimal</td>
<td>No</td>
</tr>
<tr>
<td>Minimal</td>
<td>Equivocal</td>
<td>Yes</td>
</tr>
<tr>
<td>None</td>
<td>None</td>
<td>Yes</td>
</tr>
</tbody>
</table>

British guidelines for Myelofibrosis & use of JAK Inhibitors

- Target spleen and symptom reduction will be **individual** for each patient

- Starting dose selected based on platelet number; anemia is NOT contraindication for use of JAK2 inhibitors

- Dose should be modified to the **maximum** tolerated where response is not adequate, and treatment should be continued for 6 months

- Decision to stop ruxolitinib will depend upon a **combination** of different factors, including benefit and presence or absence of toxicity

- Avoid abrupt interruption of ruxolitinib in patients responding well to therapy

- Development of anemia **DOES NOT** affect benefits of JAK2 inhibitor
Overall survival of patients by degree of spleen length reduction on ruxolitinib

Hazard ratio = 0.22*
95% CI: 0.10–0.51
p-value = 0.0001

- <25% Reduction (n=23)
- ≥25% but <50% Reduction (n=13)
- ≥50% Reduction (n=61)

Present time

Almost 9 years
The risk of death was reduced by 30% among patients randomized to ruxolitinib compared with control patients (median overall survival (OS): ruxolitinib, 5.3 years; control, 3.8 years; HR (ruxolitinib vs control), 0.70; 95% CI, 0.54-0.91; P = .0065)

Results: OS Among Ruxolitinib-Treated Patients, Stratified by IPSS Risk Status

Among patients randomized to ruxolitinib, intermediate-2 (int-2) patients had longer median OS than those with high-risk disease (median OS: int-2, not reached, estimated, 8.5 years; high-risk, 4.2 years; HR (high risk vs int-2), 2.86; 95% CI, 1.95-4.20; P<.0001)


IPSS, International Prognostic Scoring System
ReTHINK: prevention study in early MF

Objectives & Study design

**Primary Objective**: Progression-free survival

**Secondary Objectives**: Time to progression in spleen/symptoms, Safety, Overall Survival,

**Screening**
- IPSS Low-risk MF Patients
- Spleen ≤ 5 cm below LCM
- HMR+ (ASXL1, EZH2, SRSF2 or IDHI1/2)
- N = 320

**Treatment Phase**
- Ruxolitinib 10 mg bid
- Placebo
- 1:1
- PFS1*
- Ruxolitinib 15/20 mg bid
- Ruxolitinib 15/20 mg bid
- Survival Follow up
<table>
<thead>
<tr>
<th>Clinical need</th>
<th>Drugs / Intervention</th>
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<tr>
<td>Anemia</td>
<td>Prednisone, Danazol, erythropoietin, Thalidomide, Lenalidomide</td>
</tr>
<tr>
<td>Symptomatic splenomegaly</td>
<td>Ruxolitinib, Hydroxyurea, Cladribine, IMIDs, Splenectomy</td>
</tr>
<tr>
<td>Extramedulary hematopoiesis</td>
<td>Radiation therapy</td>
</tr>
<tr>
<td>Hyperproliferative (early) disease</td>
<td>Interferon</td>
</tr>
<tr>
<td>Risk of thrombosis</td>
<td>Low-dose ASA</td>
</tr>
<tr>
<td>Constitutional symptoms/ QoL</td>
<td>Ruxolitinib, Prednisone</td>
</tr>
<tr>
<td>Accelerated/blastic Phase</td>
<td>Hypomethylating agents</td>
</tr>
<tr>
<td>Improved survival</td>
<td>Allo SCT, Ruxolitinib</td>
</tr>
</tbody>
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JAK Inhibitors and Status of Development:
Myelofibrosis as lead indication

- Ruxolitinib (FDA Approved)
- Pacritinib (SB1518)
- Momelotinib (CYT387)
- NS-018
- INCB039110 (JAK1)
- LY2784544
- BMS-911543
- Fedratinib (SAR302503)
- CEP 701
- XL019
- AZD1280

- No Longer in Development For MPNs
Key eligibility criteria

- Primary/secondary MF
- Platelets ≤100,000/µL,
- Prior JAK2 inhibitors allowed

1:1:1 Randomization (N = 311)

- PAC 400 mg daily
- PAC 200 mg 2x/day
- BAT (including RUX)

Co-primary endpoints (week 24)
- % of patients achieving ≥35% SVR
- and
- % of patients achieving ≥50% reduction in TSS*

- Crossover from BAT (best available therapy) allowed after progression (anytime) or at week 24

- **Study objectives:**
  - ** Primary: Efficacy of pooled PAC arms vs. BAT

Key Efficacy Results From PERSIST-2

**Phase 3**

- PERSIST-2 trial met one of its two primary endpoints
  - Patients treated with pacritinib demonstrated a statistically significant response rate in spleen volume reduction in patients with myelofibrosis treated with pacritinib compared with BAT, including ruxolitinib
  - The primary endpoint of ≥ 50 percent reduction in total symptom score was not met

- HOWEVER: PAC 2x/day appeared more effective than PAC daily versus BAT for BOTH spleen and symptom control
- Plan for more studies to define proper dose and schedule of PAC
Phase 3 SIMPLIFY Studies of Momelotinib for Myelofibrosis

JAK inhibitor naïve
- Randomized, Double Blind

Previous JAK inhibitor exposure
- Randomized, Open Label
- Allows continuation/restart of ruxolitinib on BAT arm

**N = 420**
1:1 randomization

Momelotinib + placebo

Ruxolitinib + placebo

**N = 150**
2:1 randomization

Momelotinib

Best Available Therapy

Day 1
Week 24
Year 5
Phase 3 SIMPLIFY Studies (Momelotinib): Top-line Results, November 2016

• SIMPLIFY-1: Momelotinib vs ruxolitinib
  – Met primary endpoint of splenic response BEING SIMILAR between two treatments
  – Did not meet secondary endpoint: was LESS effective for symptom control
  – Improvement in anemia-related endpoints with momelotinib

• SIMPLIFY-2: Momelotinib vs BAT
  – Did not meet primary endpoint: was NOT better for spleen than BAT

Gilead, Nov 2016 press release
Thank You

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