Anemia of Myelofibrosis: Clinical Relevance and Momelotinib

A significant proportion of patients with myelofibrosis (MF) develop anemia, with many becoming dependent on frequent red blood cell (RBC) transfusions. Anemia in MF is multi-factorial and includes disruption of the medullary erythropoietic niche due to fibrosis, anemia of inflammation, splenic sequestration, and suppression of erythropoiesis by JAK-inhibitors and other factors.

Clinical Relevance of Anemia in MF

• Anemia and transfusion dependency are among the most significant negative prognostic indicators in MF patients and, as a result, one of the most important disease consequences to address.
• Currently approved JAK inhibitor therapies are myelosuppressive and can exacerbate anemia and transfusion dependence.
• Intractable anemia depresses quality of life, portends poor outcomes, and can act to restrict access to approved JAK inhibitors in some patients.
• While progress has been made in treatment of splenomegaly and constitutional symptoms in the era of JAK inhibition, anemia remains as the major untreated negative determinant of MF-related quality of life and overall survival.

Burden of Transfusions

• 45% of MF patients are transfusion dependent within a year of diagnosis
• Transfusions are time consuming and costly
• Potential risks, acute and chronic:
  • Transfusion reactions
  • Fluid overload
  • Iron overload with subsequent end organ damage
  • Transmission of blood borne pathogens
• Benefits are transient:
  • Must be continually repeated
  • Regular blood count monitoring required

Prognostic Impact

Anemia predicts poor survival in MF.

- No anemia - N=159; median survival 7.9 years
- Mild anemia - N=384; median survival 4.9 years
- Moderate anemia - N=159; median survival 3.4 years
- Severe anemia - N=407; median survival 2.1 years

Patients with severe anemia have a significantly shortened life expectancy (ca. 2.1 years) compared with other patients.

Elevated Hepcidin predicts poor survival in MF.

- Low hepcidin
- High hepcidin

Hemoglobin <10 g/dL is an integral component of the Dynamic Prognostic Scoring System (DIPSS) for estimating prognosis in MF, with transfusion-dependency included as an additional adverse feature in the DIPSS-Plus model.
Anemia Endpoints in Momelotinib (MMB) Studies

Transfusion Dependence / Independence

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<tr>
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<th>SIMPLIFY-1</th>
<th>SIMPLIFY-2</th>
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<tbody>
<tr>
<td>Transfusion Independence, Week 24</td>
<td>66% vs. 49% (p&lt;0.001)</td>
<td>43% vs. 21% (p=0.001)</td>
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<tr>
<td>Transfusion Independence in Transfusion Dependent subset*</td>
<td>49% vs. 29% (p=0.030)</td>
<td>47% vs. 19% (p=0.005)</td>
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*Transfusion independence period of ≥ 12 weeks;
Sierra post-hoc analysis

Kaplan-Meier analysis of time to loss of TI demonstrates that the median was not reached for MMB-treated patients with > 3 years of follow up.

New analyses suggest that patients treated with ruxolitinib (RUX) have approximately twice the transfusion burden of MMB patients.

Hemoglobin, Platelet Levels

**SIMPLIFY-1 - Mean Hemoglobin and Platelets Over Time**

- MMB therapy elicited sustained increases in Hgb levels and maintained Plt counts in the randomized periods of both SIMPLIFY-1 and SIMPLIFY-2, in contrast to RUX, leading to low rates of hematological adverse events in the MMB arm and substantially higher dose intensity for MMB compared to RUX.
- Patients experienced a rapid and sustained improvement in hemoglobin and platelet levels after crossing over to extended MMB treatment, again at near full dose intensity, despite prior RUX induced myelosuppression.

**Transfusion Burden**

Kaplan-Meier Survival Function Estimates for Time to First RBC Unit

With Number of Patients at Risk and 95% Confidence Limits

- Covariate ZINB model demonstrates that a typical patient in S1 had an 82% chance of receiving no transfusions when receiving MMB vs. a 33% chance when receiving RUX.
- The odds of zero RBC units transfused were 9.3 times higher on MMB than on RUX.

**ZINB Covariate Analysis:** MMB Patients Have an Increased Odds of Zero Transfusions

References:

FOR INFORMATIONAL AND EDUCATIONAL PURPOSES ONLY; Momelotinib is an investigational agent not yet approved by the US FDA or any regulatory authority.