Introduction

Chronic myeloproliferative neoplasms (MPNs) represent a group of heterogeneous blood stem cell disorders characterized by clonal proliferation of any number of myeloid lineages

- Chronic myeloid leukemia (CML), characterized by the presence of the Philadelphia chromosome (Ph)

- Ph negative (Ph-) MPNs,
  - polycythemia rubra vera (PV) → R/ phlebotomy, hydroxyurea
  - essential thrombocytosis (ET) → R/ hydroxyurea
  - myelofibrosis (MF) → R/ JAK2 inhibitors, allogeneic stem cell transplantation (alloSCT)
    - primary myelofibrosis (PMF)
    - secondary myelofibrosis (SMF)

- Chronic myelomonocytic leukemia (CMML) → mixed myeloproliferative/myelodysplastic neoplasm
Hematopoiesis
Allogeneic stem cell transplantation (alloSCT)

• Remains the only currently available curative option for Ph- MPNs

• Who and when to transplant?

• Specific difficulties
  o Portal hypertension
  o massive splenomegaly
  o extensive bone marrow fibrosis
Scoring systems for PMF

DIPSS = Age + WBC + Hb + Blasts + Constitutional symptoms

<table>
<thead>
<tr>
<th>DIPSS point count</th>
<th>DIPSS risk category</th>
<th>DIPSS-Plus points</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Low risk</td>
<td>0</td>
</tr>
<tr>
<td>1 to 2</td>
<td>Intermediate-1 risk</td>
<td>1</td>
</tr>
<tr>
<td>3 to 4</td>
<td>Intermediate-2 risk</td>
<td>2</td>
</tr>
<tr>
<td>5 to 6</td>
<td>High risk</td>
<td>3</td>
</tr>
</tbody>
</table>

DIPSS-Plus = Plt + anemia + Karyotype + adjusted DIPSS

<table>
<thead>
<tr>
<th>DIPSS-Plus score</th>
<th>DIPSS-Plus risk group</th>
<th>Median survival (all patients)*</th>
<th>Median survival (patients &lt;60 years)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Low risk</td>
<td>15.4 years</td>
<td>20 years</td>
</tr>
<tr>
<td>1</td>
<td>Intermediate-1 risk</td>
<td>6.5 years</td>
<td>14.3 years</td>
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<tr>
<td>2 to 3</td>
<td>Intermediate-2 risk</td>
<td>2.9 years</td>
<td>5.3 years</td>
</tr>
<tr>
<td>4 to 6</td>
<td>High risk</td>
<td>1.3 years</td>
<td>1.7 years</td>
</tr>
</tbody>
</table>

Other prognostic factors:
(JAK2, CALR, MPL) negative
ASXL1, SRSF2, EZH2 mutations

- There is a general consensus that all patients with intermediate-2 or high risk PMF by DIPSS or DIPSS-plus who are young (< 70 yrs) and fit should be referred for HSCT
Allogeneic stem cell transplantation

1/ Hematopoietic stem cells
- Donor cells
- Thymic maturation
- Peripheral expansion
- Immune reconstitution of T cells
- New pool of naive T lymphocytes
  - Slow reconstitution
  - Complete repertory
  - Response to infections
  - Self tolerance
- Memory and effector T lymphocytes
  - Immediately available to fight microbes
  - Incomplete repertory
  - React with minor histocompatibility antigens → GVHD
  - React with Tumor associated antigens (TAA) → GVL

2/ Mature T lymphocytes
- T lymphocyte precursors
- Microbes
- Minor histocompatibility antigens
- Tumor associated antigens
JAK2 inhibitors

Are helpful for symptoms splenomegaly and constitutional symptoms
Show a survival benefit over best available therapy

→ if a DIPSS high risk patient responds well to a JAK inhibitor, should he/she still undergo HSCT?

= JAK2 inhibitors may be best used as a “bridge” to get a patient with MF to HSCT
  o Reduction of spleen size (as an alternative to splenectomy or splenic irradiation)
  o Improvement of patient’s performance status
  o Reduction of hepatic extramedullary hematopoiesis, portal hypertension, ascites, and the patient’s overall risk for hepatorenal complications after HSCT

How to manage JAK2 inhibitors during conditionning?
  o taper prior to conditioning ?
  o early after HSCT ?
Conditioning intensity

• Younger, fit patients should be considered for myeloablative conditioning (MAC) alloSCT to optimize relapse and graft failure rates

• Targeted Bu/Cy regimens may be superior to TBI based MAC regimens

• If using RIC, more intense regimens such as Flu/Mel may provide an advantage over lower intensity Bu/Flu RIC or NMA regimens

• Debulking before conditioning
Donor lymphocyte infusions

1/ Hematopoietic stem cells

Donor cells

T lymphocyte precursors

Immune reconstitution of T cells

New pool of naive T lymphocytes
- Slow reconstitution
+ complete repertory
+ response to infections
+ self tolerance

Memory and effector T lymphocytes
+ immediately available to fight microbes
- incomplete repertory
- react <> minor histocompatibility antigens → GVHD
+ react <> Tumor associated antigens (TAA) → GVL

2/ Mature T lymphocytes

<> microbes
<> minor histocompatibility antigens
<> Tumor associated antigens
Thank you for your attention