BMT for MPNs

MPN Advocacy and Education
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Overview

- What is BMT?
- When is transplant recommended in MPNs?
  - Disease factors
  - Patient factors
  - Transplant factors
- Post-transplant complications
- Future directions
What is BMT?

- BMT =
  - Blood and marrow transplant
  - Bone marrow transplant
  - Stem cell transplant
  - Peripheral blood stem cell transplant
  - Hematopoietic stem cell transplant
  - Hematopoietic cell transplant (HCT)
What is BMT?

• Autologous transplant
  – High dose chemotherapy followed by autologous (self) stem cell support
  – Used to treat lymphoma, multiple myeloma

• Allogeneic transplant
  – Chemotherapy preparative regimen with adoptive immunotherapy
  – Acute and chronic leukemia, bone marrow failure syndromes, myelofibrosis
What is BMT?

• **Autologous transplant**
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• **Allogeneic transplant**
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What is BMT?

• Allogeneic transplant:
  – Deliver chemotherapy to kill abnormal cells
  – Provide a source (donor) of hematopoietic (blood) cells to replace bone marrow
  – Provide an immune effect to mediate a graft (donor) versus “tumor” activity
Allogeneic HCT
(Cells from a donor)

- **Transplant types**
  - **Graft source**
    - Peripheral blood stem cells
    - Umbilical cord blood
    - Bone marrow
  - **Donor source**
    - Related donor
    - Unrelated donor
    - HLA matched sibling
    - Haplo-identical
    - HLA matched unrelated
  - **Conditioning**
    - Myeloablative
    - Reduced intensity or non-myeloablative
    - Umbilical cord blood
What is BMT?

Donor search

Patient selection

Patient work up

Collect stem cells

Conditioning regimen

Infuse stem cells

Replace recipient bone marrow with donor cells
• Primary or secondary (from polycythemia vera or essential thrombocytosis)
• Characterized by low blood counts (cytopenias), abnormal production of blood cells outside of the bone marrow (extramedullary hematopoiesis), bone marrow fibrosis/scarring, and constitutional symptoms (fevers, sweats, itching, large spleen/liver, bone aches, etc.) due to high levels of inflammatory proteins (cytokines)
• Heterogenous: indolent to rapidly progressive
Myelofibrosis- treatment overview

• Initial treatment goal primarily to relieve symptoms and reduce risk of complications (e.g. ruxolitinib/Jakafi, JAK inhibitors, hypomethylating agents)

• Allogeneic transplantation is the only potentially curative treatment
  – Potentially high risk of complications

• Risk adapted
  – Patient, disease, and transplant factors
Myelofibrosis (MF)- Transplant

• In early era of transplant for MF, relatively small number of patients were reported—establishing feasibility and curative potential

• Splenomegaly and marrow fibrosis resolved slowly in the majority after successful engraftment; however toxicity from transplant was high
Myelofibrosis (MF) - Transplant

A

Number of transplants

250

200

150

100

50

0


Ruxolitinib EMA approval
Ruxolitinib FDA approval
When is BMT recommended for MF?

- Challenges regarding optimal timing of HCT
- Heterogenous disease:
  - Many have prolonged life expectancy and enjoy reasonable quality of life; while others may develop cytopenias (low blood counts), symptomatic splenomegaly, and troublesome symptoms; or transform to AML.
When is BMT recommended for MF?

- **Disease factors**
  - Prognostic scoring systems (IPSS, DIPSS, DIPSS-plus, MIPSS)
    - blood counts (low platelets, anemia), blasts, splenomegaly, symptoms; cytogenetics
    - Other complications- portal hypertension
    - “accelerated phase”

- **Patient factors**
  - Age
  - presence of other medical issues (“co-morbidities”)
  - general well-being/functional status (“performance status”)

- **Transplant factors**
  - Donor source/availability
  - Preparative regimens
When is BMT recommended for MF?

Risk of toxicity

Disease risk
Transplant for MF - Disease factors

• Risk stratification strategies: with goal of maximizing benefit-risk ratio.
  – **IPSS** (age>65, hgb<10, WBC>25x10⁹/L, peripheral blood blasts >1%, constitutional symptoms (at diagnosis)
  – **DIPSS** (time dependent)- development of anemia, higher risk
  – **DIPSS-plus**- incorporation of cytogenetics, transfusion dependence
  – **MIPSS**- incorporation of mutation data
  – **MIPSS-plus**- incorporation of cytogenetics and mutation data
## Transplant for MF- Disease factors: DIPSS

<table>
<thead>
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<th>Prognostic variable</th>
<th>0 points</th>
<th>1 point</th>
<th>2 points</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>≤ 65</td>
<td>&gt; 65</td>
<td>--</td>
</tr>
<tr>
<td>White blood cell count (x10^9/L)</td>
<td>≤ 25</td>
<td>&gt; 25</td>
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</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>≥ 10</td>
<td>--</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>Peripheral blood blasts (%)</td>
<td>&lt; 1</td>
<td>≥ 1</td>
<td>--</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td>No</td>
<td>Yes</td>
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<table>
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<tr>
<th>DIPSS score</th>
<th>DIPSS risk category</th>
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<tr>
<td>0</td>
<td>Low</td>
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<tr>
<td>1-2</td>
<td>Intermediate-1</td>
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<td>3-4</td>
<td>Intermediate-2</td>
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<tr>
<td>5-6</td>
<td>High</td>
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- No benefit from transplant
- Benefit from transplant
Transplant for MF- Disease factors

- Further improvement in models
  - Cytogenetics
  - Mutations
    - \textit{JAK2, CALR, MPL (driver mutations)}
    - \textit{ASXL1, SRSF2, EZH2, IDH1/2}
### Transplant for MF - Disease Factors: MIPSS

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<td>--</td>
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<tr>
<td>Peripheral blood blasts (%)</td>
<td>&lt; 2</td>
<td>≥ 2</td>
<td>--</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
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<td>Yes</td>
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</tr>
<tr>
<td>Bone marrow fibrosis</td>
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<td>≥ 2</td>
<td>--</td>
</tr>
<tr>
<td>CALR type 1 driver mutation</td>
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<td>No</td>
<td></td>
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<tr>
<td>White blood cell count (x10^9/L)</td>
<td>≤ 25</td>
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<tr>
<td>Platelets (x10^9/L)</td>
<td>≥ 100</td>
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<td>&lt;100</td>
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<tr>
<td>High risk molecular mutations</td>
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- MIPSS70-Plus: incorporating cytogenetics
- GIPSS: primarily based on genetic markers
- MTSS: transplant outcomes
Transplant for MF - Patient Factors

- Patient age
  - Median age for patients with MF >65
  - No significant difference in outcomes for patients 60-65 and 66-78 (bias of “fit” older patients)
  - Biologic age >> chronologic age, should not be denied solely based on age

- Patient fitness/“performance status”
  - May be related to disease (JAK inhibitor therapy)

- Patient co-morbidities (other medical problems)
  - HCT-co-morbidity index (lung, heart, liver, function) assesses risk
Transplant for MF- Transplant Factors

• Donor selection
  – Related
  – Unrelated donors

• Preparative chemotherapy regimens
  – Myeloablative
  – Reduced intensity

• Stem cell grafts
  – Bone marrow
  – Peripheral blood stem cells
Donor selection

- Matched sibling donors >> matched unrelated donors
- Not a lot of data for haplo-identical donors (increasingly used successfully) and cord blood donors (not generally recommended)
- Mismatched donors poorer outcomes
- No head-to-head comparative data
Myelofibrosis (MF)- Transplant

• Advances in supportive care, conditioning regimens, GVHD prophylaxis, and high resolution typing to identify and select unrelated donors have improved the safety and outcomes of HCT

• Application of reduced-intensity conditioning/chemotherapy (RIC) expands the scope of HCT to older patients and those with co-morbidities
Transplant for MF

C

% of transplants


URD  URD  URD  URD  URD

Median age

≤ 40 years  41-60 years  > 60 years

C
Transplant for MF- Stem cell graft
Transplant for MF - type of chemotherapy

- No optimal conditioning regimen for transplant in MF patients
Transplant for MF- Optimal timing

• Optimal timing is yet to be determined
• Discussion regarding early versus delayed HCT, individualized decisions in those responding well to JAK inhibitors
JAK inhibitors prior to transplant

- May improve pre-HCT performance status by controlling MF-related symptom burden
- Response to ruxolitinib prior to transplant (better performance status) → more favorable outcome of HCT?
- Decreased spleen size can help with faster hematologic recovery
- Association with decreased graft-versus-host disease?
- Ruxolitinib should be continued until close to time of conditioning regimen initiation, tapering is generally recommended, as stopping may cause rapid return of MF-related symptoms
- Drug interactions
- Infection risk?
Transplant for MF- splenectomy?

- Controversial
- Spleen size can be a risk factor for poorer transplant outcomes
- Complications of splenectomy include bleeding, infection and clotting
- Generally not recommended, but potentially considered in select cases.
Transplant for MF- Post transplant challenges

- **Graft failure**
  - May depend on donor source (higher with unrelated donors)
  - Risk factors not clear

- **Liver toxicity**
  - Related to enlarged liver and higher pressures prior to transplant?

- **Graft-versus-Host Disease**
  - Common complication post transplant
  - Unclear if patients with MF have higher rates of GVHD (inflammatory cytokines)

- **Disease**
  - Monitoring of “minimal residual disease” of mutations (JAK2)
Transplant for MF

• Decision can be complex and requires individualized decision making
• Patient, disease, transplant factors should be considered, as well as timing
• Due to chronic nature of MF, consideration of transplant can be revisited throughout disease course
Transplant for MF - Future

• Role of novel JAK inhibitors prior to and post-transplant
• Optimizing chemotherapy preparative regimens
• Alternative donor sources (haplo-identical transplants)
• Comparison with non-transplant therapies
Thank you and Questions?