Setting the stage for Transplant in MPN

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What will be covered

What is a bone marrow transplant?
When to start thinking about bone marrow transplant
Timing of transplant
Understanding disease risk
Bone marrow transplantation

- Involves high dose/intermediate dose chemotherapy followed by hematopoietic stem cell infusion.
  - Chemotherapy helps reduce disease + suppress immune system
  - New blood system works better
  - New stem cells fight off underlying disease ‘graft versus myelofibrosis’

- Autologous: uses patients own stem cells, allows use of high dose chemotherapy
- Allogeneic: uses donor stem cells, either related or unrelated
Alternative names

- Alternative names:
  - Peripheral blood stem cell transplant
  - Hematopoietic stem cell transplant
  - Bone marrow transplant

- Bone marrow vs peripheral blood
  - Refers to how the hematopoietic stem cells are collected:
    - Bone marrow: through bone marrow harvest, a procedure performed in the OR
    - Peripheral blood collection: collected after giving neupogen via leukopheresis
How does transplant work

The Allogeneic Transplant Process

1. **Collection**
   - Stem cells are collected from the patient's bone marrow or blood.

2. **Processing**
   - Bone marrow or peripheral blood is taken to the processing laboratory where the stem cells are concentrated and prepared for the freezing process.

3. **Cryopreservation**
   - Bone marrow or blood is preserved by freezing (cryopreservation) to keep stem cells alive until they are infused into the patient's bloodstream.

4. **Chemotherapy**
   - High dose chemotherapy and/or radiation therapy is given to the patient.

5. **Infusion**
   - Thawed stem cells are infused into the patient.

Conditioning

Important facts of transplant

• Live near the transplant center for 3-4 months

• 1 month in the hospital (or daily appointments at the hospital), very frequent appointments for another (at least) 2 months

• Significant financial implications:
  • Time off work for you and your caregiver
  • Expensive medications

• Risk of being really sick or even dying
WHY WOULD I WANT TO DO THIS TO MYSELF?

SHOULD I PURSUE A CLINICAL TRIAL INSTEAD?
What are common concerns about transplant?

- Survey done on patients with MPN
- Less than half the patients were referred for transplant
- Of those who saw a transplant specialist, less than half planned on proceeding with transplant due to the following concerns
  - Quality of life
  - Financial implications
  - Caregiver
  - Graft versus host disease
- WHY??
  - Further studies ongoing to understand the thought process around transplant
Other considerations

• Physicians are human and have biases as well
  • Transplant physicians
  • Hematologists

• Blogs
  • Everyone experiences transplant differently
  • People like to share their experiences
Clinical trials and medical treatment

- There are good clinical trials and treatments in MF
  - No curative options yet
- This is a very individualized decision
When do I see a transplant specialist?

- Important to see a transplant specialist early in the disease course— even if you aren’t sure whether you will proceed with transplant or not
  - Understand and plan for the different resources needed for transplant
    - Caregiver
    - Financial
    - Lodging
  - Understand the process of transplant
- Have time to **process** all the information related to transplant
Who should I see?

• Helpful to see a transplant specialist who has knowledge regarding transplants for MF

  • The timing of transplant is a **SHARED** decision making process

  • There is no one answer that is correct for anyone

• Even if you don’t get a transplant at the center, good to have the discussion/opinion
What to expect during a bone marrow transplant consultation

• Bring a family member/friend

• Be prepared to be scared

• If you can, record the consultation

• If you have any doubts get a second opinion
So, when should I get a transplant?

• Generally transplant is reserved for higher risk patients

• It is important to KNOW YOUR RISK

• Can be dependent on life events
HOW DO WE DEFINE RISK?
Dynamic International Prognostic Scoring System

DIPSS scores/risk:

• 0 pts: low risk
• 1-2 pts: Intermediate – 1
• 3-4 pts: Intermediate – 2
• 5-6 pts: High risk

<table>
<thead>
<tr>
<th>DIPSS</th>
<th>DIPSS plus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia (hgb &lt;10) (2 pts)</td>
<td>DIPSS score</td>
</tr>
<tr>
<td>WBC &gt;25</td>
<td>Platelets &lt;100</td>
</tr>
<tr>
<td>Blasts &gt;1%</td>
<td>Transfusion dependant</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td>poor risk cytogenetics: complex karyotype or any sole or two abnormalities including +8, -7/7q-, -5/5q-, inv(3), i(17q), 12p-, 11q23 rearrangement</td>
</tr>
<tr>
<td>Age &gt;60</td>
<td></td>
</tr>
</tbody>
</table>

DIPSS plus scores/risk:

• 0 pts: low risk
• 1 pt: intermediate-1
• 2-3 pts: intermediate-2
• 4-6 pts: high risk
Clarification of risks

• Anemia–low red blood cell count. Hemoglobin (hgb) is consistently less than 10
• Thrombocytopenia- low platelet (plt) count, less than 100.
• Leukocytosis – high white blood cell count (WBC), consistently greater than 25
• Blasts – immature white blood cells
  • Note this does not mean you have leukemia unless blast % greater than 20%
• Abnormal karyotype
• Constitutional symptoms- fatigue, weight loss, decreased appetite, night sweats
Stem cell transplant spectrum timing tool

- This tool uses DIPSS score to give a sense of when a transplant should be considered

- Even in the case of low risk disease- good to start the conversation

- http://www.mpntransplant.com/
When to **think about a transplant**

- **DIPSS low risk or Int-1 risk**
- **DIPSS Int-2 risk**
- **DIPSS High risk, advanced disease with organ dysfunction**

**Diagnosis of disease**
When to do transplant

Too early! DIPSS low risk or Int-1 risk

Just right

DIPSS Int-2 risk

Too late! DIPSS High risk, advanced disease with organ dysfunction

Diagnosis of disease
Other factors that contribute to risk

- Driver mutation
- Cytogenetics
- Molecular mutations
Driver mutation

• Mutations that CAUSE the disease
  • JAK-2
  • MPL
  • CAL-R type 1 and 2
• CAL-R type 1 is GOOD
• No mutations is unfavorable
Cytogenetics

- Cytogenetics (abnormal chromosomes found in your bone marrow)
  - complex karyotype (3 or more abnormalities) or sole or 2 abnormalities that include +8, −7/7q−, i(17q), inv(3), −5/5q−, 12p−, or 11q23 rearrangement

*These are not inherited... they are changes that occur only in disease cells*
Molecular mutations
“next generation sequencing”

Prognostically important genes, other than JAK2/CALR/MPL, in essential thrombocythemia (ET), polycythemia vera (PV) and primary myelofibrosis (PMF)

- SRSF2
- ASXL1
- IDH2
- EZH2
- TP53
- U2AF1

PV
ET
PMF
CBL
SF3B1
SH2B3
When to do transplant

Too early!
DIPSS low risk or int-1 risk

Just right

High risk chromosomes /mutations

Absence of high risk chromosomes /mutations

Too late!
High risk, advanced disease with organ dysfunction
Other considerations

• Symptom burden

• Ruxolitinib (Jakafi©) and other JAK-inhibitors

• Transfusion dependence

• What gives you points??
Example #1

- 64 year old gentleman with primary myelofibrosis

- CAL-R type 1 positive

- On 1/5/22 WBC 23K, 2% blasts, hgb 9.7, platelets 115
  - (DIPSS: 3 points- Intermediate -2)
- On 2/5/22 WBC 26K, 0 blasts, hgb 10.2, platelets 150
  - (DIPSS: 1 points- Intermediate -1)

- Would this change if JAK2 positive?
- ASXL1 positive?
Example #2

- Patient is 58 year old female with post-essential thrombocytethemia myelofibrosis
- MPL positive
- Hgb 7, requires transfusion every month, WBC 6.7, Blasts 0
  - DIPSS: Intermediate 1
  - DIPSS plus: Intermediate 2
Example #3

• 65 year old woman with primary myelofibrosis

• JAK2 positive

• Hgb 9.5, WBC 7.2, blasts 0, platelets 165
  • DIPSS: 3 points- Intermediate-2
Other questions to consider

- I feel SO good on Jakafi-- should I proceed with transplant??

- These newer agents in clinical trial may reduce my mutation burden and fibrosis- will these cure the disease?

- Should I do a clinical trial first, then transplant?
Summary

• Bone marrow transplant is a curative option for myelofibrosis

• When the best time to undergo transplant is still under investigation

• Know your risk! The risk of disease as characterized by cytogenetics, molecular mutations etc