Reporting Data- FAQs & Answers
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Wed. Feb. 21, 2018
Topics

1. Autologous Boosts/Rescues
2. Minimal Residual Disease (MRD)
3. Molecular Marker Reporting
4. FLT3 Mutations
5. MDS/MPN Reporting
6. Related Donor Reporting
7. VOD/SOS
Reporting Autologous Boosts/Rescues
Autologous “Boosts/Rescues”

• Performed for engraftment reasons following a HCT
  ➢ No hematopoietic recovery
  ➢ Partial hematopoietic recovery
  ➢ Graft failure

• Autologous boosts/rescues are HCTs
  ➢ Purpose is to restore hematopoiesis

• Purely to reduce the reporting burden on centers, forms will not start over.
Autologous “Boosts/Rescues”

- Performed for any other reason would be reported as a subsequent HCT & forms would start over
- Indications include-
  - Persistent primary disease
  - Recurrent primary disease
  - Planned second HCT, per protocol
  - New malignancy
  - Stable, mixed chimerism
  - Declining chimerism
Minimal Residual Disease
Minimal Residual Disease (MRD)

- MRD is detected by molecular (e.g., PCR) and multi-parameter flow cytometric (MFC) techniques.
  - MFC uses 6-10 colors
- MRD in acute lymphoblastic leukemia (ALL) is defined by the presence of 0.01% or more ALL cells.
MRD Reporting for AML

- F2402 r3 AML Q87

Status at transplantation:

85. What was the disease status (based on hematological test results)?
- Primary induction failure - Go to question 89
- 1st complete remission (no previous bone marrow or extramedullary relapse) (include CRI) - Go to question 86
- 2nd complete remission - Go to question 86
- ≥ 3rd complete remission - Go to question 86
- 1st relapse - Go to question 88
- 2nd relapse - Go to question 88
- ≥ 3rd relapse - Go to question 88
- No treatment - Go to question 89

86. How many cycles of induction therapy were required to achieve 1st complete remission? (includes CRI)
- 1
- 2
- ≥ 3

87. Was the recipient in remission by flow cytometry?
- Yes
- No
- Unknown
- Not applicable

88. Date of most recent relapse: YYYY / MM / DD

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TRAINING & DEVELOPMENT | 8
MRD Reporting for ALL

- F2402 r3 ALL Q149

Status at transplantation:

147. What was the disease status (based on hematological test results)?
- Primary induction failure - Go to question 151
- 1st complete remission (no previous marrow or extramedullary relapse) (include CR1) - Go to question 148
- 2nd complete remission - Go to question 148
- ≥ 3rd complete remission - Go to question 148
- 1st relapse - Go to question 150
- 2nd relapse - Go to question 150
- ≥ 3rd relapse - Go to question 150
- No treatment - Go to question 151

148. How many cycles of induction therapy were required to achieve 1st complete remission (includes CR1)?
- □ 1
- □ 2
- □ ≥ 3

149. Was the recipient in remission by flow cytometry?
- □ Yes
- □ No
- □ Unknown
- □ Not applicable

150. Date of most recent relapse: ____/____/____ YYY/MM/DD
MRD Reporting on CRFs

- AML F2010 r4 Q58
  
  58. Was the recipient MRD negative following this line of therapy?  
      □ Yes  □ No

- ALL F2011 r5 Q52
  
  52. Was the recipient MRD negative following this line of therapy?  
      □ Yes  □ No
Molecular Marker Reporting
Molecular Markers

• What are they & why do we care?
  ➢ NCI definition- A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease.
  ➢ The presence of a molecular marker may be associated with favorable or unfavorable survival.
  ➢ Can be used to monitor minimal residual disease (MRD) in post-HCT patients.
Molecular Markers

- **AML**: CEBPA, FLT3, IDH1-2, KIT, NPM1
- **APML**: PML-RARA, t(15;17)
- **ALL**: BCR-ABL, t(9;22); TEL-AML1
- **CML**: BCR-ABL, t(9;22)
- **NHL**: BCL-1, t(11,14); BCL-2, t(14;18); BCL-6; Immunoglobulin heavy (IgH) chain rearrangement; TCR gene rearrangement
Molecular Marker Reporting on F2402 at Diagnosis

• Can be determined using a FISH or PCR/NGS method

• Molecular markers (e.g., BCR-ABL) for ALL assessed by **FISH** should be reported in Q99 on F2402 r3

• Molecular markers (e.g., BCR-ABL) for ALL assessed by a **molecular method** (e.g., PCR) should be reported in Q108 on F2402r3
Molecular Marker Reporting

- F2402 ALL Disease Classification - FISH

95. Were cytogenetics tested (karyotyping or FISH)? (at diagnosis)
   - Yes
   - No
   - Unknown

96. Were cytogenetics tested via FISH? (at diagnosis)
   - Yes
   - No

97. Results of tests: (at diagnosis)
   - Abnormalities identified
   - No abnormalities

99. Specify abnormalities: (check all that apply)
   - -7
   - +4
   - +8
   - +17
   - +21
   - t(1;19)
   - t(2;8)
   - t(4;11)
   - t(5;14)
   - t(8;14)
   - t(8;22)
   - t(9;22)
   - t(10;14)
Molecular Marker Reporting

- F2402 ALL Disease Classification - PCR
Molecular Marker Reporting

• Patient Scenario

A patient with Ph+ ALL in CR1 (molecular & cytogenetic CR) at time of HCT, is undergoing their 6 month evaluation post-HCT.

A BM aspirate & biopsy are obtained during the 6 month evaluation with the following results-

- BM- remains in morphologic CR
- Karyotyping- negative for t(9;22)
- BCR-ABL by FISH- 100 of 500 cells are positive for BCR-ABL; BCR-ABL by PCR not done
Reporting Molecular Markers

Where to report the BCR-ABL findings on the ALL Post-Infusion F2111 r4…….

<table>
<thead>
<tr>
<th>Disease Detection Since the Date of Last Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indicate if disease was detected since the date of last report – including relapsed disease, persistent disease, and minimal residual disease.</td>
</tr>
</tbody>
</table>

62. Were cytogenetic abnormalities identified via FISH?
- [ ] Yes
- [X] No

63. Date sample collected: YYY/MM/DD

64. Specify abnormality (check all that apply)
- [ ] -7
- [ ] +4
- [ ] +8
- [ ] +17
- [ ] +21
- [ ] t(1;19)
- [ ] t(2;8)
- [ ] t(4;11)
- [ ] t(5;14)
- [ ] t(8;14)
- [ ] t(8;22)
- [X] t(9;22)
- [ ] t(10;14)
- [ ] t(11;14)
Molecular Marker Reporting

- Karyotype

Diagram:

66. Were cytogenetic abnormalities identified via karyotyping?
   - Yes
   - No

67. Date sample collected: YYYY-MM-DD

68. Specify abnormalities (check all that apply)
   - 7
Reporting Disease Status

• What is the current disease status for this recipient at 6 months post-HCT?

129. What is the current disease status?

Complete remission (CR) – All of the following response criteria without progression for at least four weeks: < 5% blasts in the bone marrow, no blasts with Auer rods, no extramedullary disease (e.g., central nervous system or soft tissue involvement)

Not in complete remission
FLT3 Mutations
FLT3 Mutations

- There are two FLT3 mutations
  - FLT3 ITD & FLT3 TKD
- FLT3 mutations occur in ~30% of AML cases
- FLT3+ AML patients have a worse outcome and response to chemotherapy
- The FLT3 ITD mutation is the most prevalent & clinically significant of the two
  - Increased incidence of relapse & decreased overall survival
FLT3 Allelic Ratio

- FLT3 allelic ratio (or signal ratio) compares the # of ITD-mutated alleles to the # of wild-type alleles (normal alleles)

- Examples-
  1. FLT3 ITD mutant allele frequency = 70% by NGS
     FLT3 wild-type alleles (normal) = 30%
     Ratio = 2.3 (70:30)
  2. FLT3 ITD mutation detection by PCR
     Positive with a signal ratio of 0.352
FLT3 Allelic Ratio Reporting

- Reporting FLT3-ITD allelic ratio of F2402 r3
  - Example 1
  - Example 2
MDS/MPN Questions
Myeloproliferative Disorders

• Essential Thrombocytosis (ET)
  ➢ A myeloproliferative neoplasm (MPN)
  ➢ Characterized by sustained thrombocytosis ($\geq 450 \times 10^9/L$), increased # of large mature megakaryocytes in the marrow and episodes of thrombosis and/or hemorrhage.
  ➢ After many years, some ET patients may develop BM fibrosis associated with myeloid metaplasia
Myeloproliferative Disorders

• Polycythemia Vera (PV)
  ➢ A myeloproliferative neoplasm (MPN)
  ➢ Characterized by increased production of RBCs independent of mechanisms that normally regulate erythropoiesis
  ➢ Virtually all have the JAK2 mutation
Myeloproliferative Disorders

• Polycythemia vera (PV) continued
• Three phases of PV
  ➢ Pre-polycythemic phase
    Characterized by borderline to mild erythrocytosis
  ➢ Polycythemic phase
    Significantly increased red cell mass
  ➢ Post-polycythemic myelofibrosis phase (post-PV MF)
    Cytopenias (including anemia) are associated with ineffective hematopoiesis, BM fibrosis, extramedullary hematopoiesis & hypersplenism
Myeloproliferative Disorders

• The development of fibrosis/myelofibrosis in ET & PV patients would be considered **secondary** myelofibrosis

• For reporting purposes, when ET & PV patients develop marrow fibrosis, indicate “Primary Myelofibrosis” as the primary disease for HCT.
Reporting ET or PV on F2402 r3

• Disease Classification

➢ Q167 What was the MDS/MPN subtype at diagnosis? Report “ET” or “PV”

➢ Q212 Did the recipient progress or transform to a different MDS/MPN subtype between diagnosis and the start of the prep regimen? Report “Yes”

➢ Q213 Specify the MDS/MPN subtype after transformation: Report “Primary Myelofibrosis”
Related Donor Reporting
Reporting Related Donor Information

• Related Donors
  • Specify related donor type
    • Syngeneic (monozygotic twin)
    • HLA-identical sibling (includes fraternal twin)
    • HLA-matched other relative
    • HLA-mismatched relative
Related Donor Definitions

• **Syngeneic**-
  - Monozygotic (identical) twins only

• **HLA-identical sibling**-
  - Non-monozygotic (fraternal) twins
  - Siblings who aren’t twins, but have HLA identical types.
  - Does **not** include “half-siblings” who are HLA-identical. Report as “HLA-matched other relative”
Related Donor Definitions

• **HLA-matched other relative**-
  - All HLA-matched blood-related relatives, other than siblings
  - Includes parents, aunts, uncles, children, cousins, half-siblings

• **HLA-mismatched relative**-
  - Non HLA-identical siblings & other blood-related relatives with at least one HLA mismatch
  - Includes haploidentical donors
  - Includes parents, aunts, uncles, children, cousins, half-siblings
Case Study #1

Jane D is scheduled for an allogeneic HCT from her sibling. Based on the following HLA typing, what related donor type would be reported on F2400 r5 Q40?

<table>
<thead>
<tr>
<th>HLA locus</th>
<th>A_1</th>
<th>A_2</th>
<th>B_1</th>
<th>B_2</th>
<th>C_1</th>
<th>C_2</th>
<th>DRB1_1</th>
<th>DRB1_2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipient</td>
<td>0201</td>
<td>3402</td>
<td>1516</td>
<td>3501</td>
<td>0401</td>
<td>0601</td>
<td>1102</td>
<td>1503</td>
</tr>
<tr>
<td>Donor</td>
<td>0201</td>
<td>3402</td>
<td>1516</td>
<td>3501</td>
<td>0401</td>
<td>1601</td>
<td>1102</td>
<td>1503</td>
</tr>
</tbody>
</table>
Case Study #1

A) HLA-identical sibling
B) HLA-matched other relative
C) HLA-mismatched relative
Case Study #1

- F2400 r5 Q31

31. Specify donor:
   - Autologous - Go to question 46
   - Autologous cord blood unit - Go to question 35
   - NMDP unrelated cord blood unit - Go to question 32
   - NMDP unrelated donor - Go to question 33
   - Related donor - Go to question 40
   - Related cord blood unit - Go to question 35
   - Non-NMDP unrelated donor - Go to question 34
   - Non-NMDP unrelated cord blood unit - Go to question 35

   - Related donor

- F2400 r5 Q40

40. Specify the related donor type:
   - Syngeneic (monozygotic twin)
   - HLA-identical sibling (may include non-monozygotic twin)
   - HLA-matched other relative
   - HLA-mismatched relative

   - HLA-mismatched relative
Case Study #2

John D is scheduled for an allogeneic HCT from his half-sibling. Based on the following HLA typing, what related donor type would be reported on F2400 r5 Q40?

<table>
<thead>
<tr>
<th>HLA locus</th>
<th>A_1</th>
<th>A_2</th>
<th>B_1</th>
<th>B_2</th>
<th>C_1</th>
<th>C_2</th>
<th>DRB1_1</th>
<th>DRB1_2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipient</td>
<td>0201</td>
<td>0602</td>
<td>3501</td>
<td>5101</td>
<td>1602</td>
<td>1604</td>
<td>0101</td>
<td>1601</td>
</tr>
<tr>
<td>Donor</td>
<td>0201</td>
<td>0602</td>
<td>3501</td>
<td>5101</td>
<td>1602</td>
<td>1604</td>
<td>0101</td>
<td>1601</td>
</tr>
</tbody>
</table>
Case Study #2

A) HLA-identical sibling
B) HLA-matched other relative
C) HLA-mismatched relative
Case Study #2

- F2400 r5 Q31

31. Specify donor:
   - Autologous - Go to question 46
   - Autologous cord blood unit - Go to question 35
   - NMDP unrelated cord blood unit - Go to question 32
   - NMDP unrelated donor - Go to question 33
   - Related donor - Go to question 40
   - Related cord blood unit - Go to question 35
   - Non-NMDP unrelated donor - Go to question 34
   - Non-NMDP unrelated cord blood unit - Go to question 35

- F2400 r5 Q40

40. Specify the related donor type:
   - Syngeneic (monozygotic twin)
   - HLA-identical sibling (may include non-monozygotic twin)
   - HLA-matched other relative
   - HLA-mismatched relative
VOD/SOS
Hepatic Sinusoidal Obstruction Syndrome

Also known as veno-occlusive disease (VOD)

• Triad:
  – Hepatomegaly with RUQ pain
  – Third spacing fluid retention (e.g., ascites)
  – Jaundice (total bili >2 with cholestatic picture)

• Ancillary features
  – Weight gain (≥5%)
  – Increased platelet transfusion requirements
  – Coagulopathy
SOS- Pathophysiology

- Damage to endothelial lining of hepatic sinusoids
- Intrahepatic thrombosis & hemostasis
- Centrilobular hemorrhagic necrosis
  - This finding distinguishes it from alcoholic cirrhosis which involves the portal triad
- Portal vein obstruction
- Liver failure with coagulopathy
- Hepatorenal syndrome
SOS- Risk Factors

- Risk Factors
  - Pre-existing liver conditions: Hepatitis (Hepatitis B, drug induced), Cirrhosis
  - Prior therapy: second HCT
  - Conditioning regimen: Ablative regimens (high doses of RT, use of busulfan), sirolimus in patients undergoing ablative HCTs
SOS- Treatment

• Prevention:
  – Low-dose heparin
  – Ursodiol (ursodeoxycholic acid)
  – Defibrotide

• Treatment
  – Defibrotide
Incidence

- The overall incidence of VOD/SOS is ~14% based on an analysis of 135 studies published between 1979 & October 2007

- Reference-
SOS- Diagnosis

• Diagnosis
  – Clinical suspicion
  – Ultrasound: ascites, abnormal portal vein waveform, reversal of flow in portal vein
  – Liver biopsy
Clinical Criteria for Diagnosis of VOD

• Seattle Criteria (1984)
  Presence before Day 30 post-HCT of 2 or more of the following-
  ➢ Bilirubin $\geq 2$ mg/dL ($\sim 34$ μmol/L)
  ➢ Hepatomegaly, RUQ pain
  ➢ Ascites with or without unexplained weight gain $> 2\%$ over baseline

• Modified Seattle Criteria (1993)
  Presentation of the clinical features of VOD before Day 20 (instead of Day 30) post-HCT
Clinical Criteria for Diagnosis of VOD

• Baltimore Criteria (1987)
  Bilirubin $\geq$ 2 mg/dL before Day 21 post-HCT and at least 2 of the following-
  ➢ Hepatomegaly (usually painful)
  ➢ Ascites
  ➢ Weight gain $>5\%$ over baseline
VOD/SOS Severity Classification

• Mild-
  ➢ No adverse effects of liver disease
  ➢ No medications required for diuresis or hepatic pain
  ➢ Have completely reversible signs, symptoms & lab abnormalities
VOD/SOS Severity Classification

• Moderate-
  - Experience adverse effects from liver disease
  - Require sodium restriction & diuretics to minimize signs of fluid excess (e.g., edema)
  - Require medication to manage the pain from hepatomegaly
  - Eventually demonstrate complete resolution of all signs of liver damage (i.e., return to baseline weight, decrease in liver size & decrease in total bili to <2.0 mg/dL)
VOD/SOS Severity Classification

• Severe-
  - Experience adverse effects from liver disease
  - Signs, symptoms & lab values do not resolve before Day +100 or death occurs

• Mortality rate from severe VOS/SOS 84.3%
  - Majority of patients had multi-organ failure
VOD/SOS Severity Classification

• Multi-organ Failure (MOF)
  ➢ Oxygen requirement
    ▪ O2 saturation ≤ 90% on RA and/or ventilator dependence; and/or
  ➢ Renal dysfunction
    ▪ Defined as doubling of baseline creatinine and/or dialysis dependent; and/or
  ➢ Encephalopathy in addition to liver failure
Complete Resolution Criteria

• Resolution of VOD/SOS is defined as:
  - **Bilirubin** < 2.0 mg/dL (34 µmol/L)
  - **Serum creatinine** < 1.5 times the upper limit of normal OR less than the upper limit of normal based on patient’s age.
  - Increase of greater than 80% in **creatinine clearance/GFR** compared to values at time of diagnosis and not currently on dialysis.
  - Greater than 90% **oxygen saturation** on room air AND no supplemental oxygen or ventilator requirements.
Form 2553 VOD/SOS Insert

- Triggered from 2450/2100 diagnosis question.

F2450r4:

F2100r4:
Form 2553 VOD/SOS Insert

- Inserts may be assigned at 100 Days.
  - A Six Month insert will also be completed if VOD/SOS persists at Day 100
- Reporting Sections
  - Tests/Labs at diagnosis of VOD/SOS
  - Therapy
  - Maximum severity
  - Most recent labs and status of VOD/SOS
  - Late sequelae
  - Hospital stay
Questions