Late Complications Form Changes
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Objectives

• Review how CIBMTR data are used to address long-term complications of HCT
• Review changes in CIBMTR forms that capture long-term complications of HCT
Late Effects and Quality of Life Working Committee Portfolio
Long-term survival
Second cancers
Quality of life
Late organ toxicity
Followup guidelines
Long-term Survival after HCT

- CIBMTR study of 10,632 allogeneic HCT recipients surviving ≥ 2 years in remission (median followup 9 years)

Overall survival

Non-relapse mortality

J Wingard et al, JCO 2011 ; 29: 2230
Long-term Survival after HCT

- Causes of death, ≥ 2 year survivors of allogeneic HCT
  - N = 1270 deaths
  - Chronic GVHD most common cause of death for SAA
- Main risk factors for mortality on multivariate analysis
  - Older age at HCT
  - Chronic GVHD
- Relative mortality higher than age-, gender-matched general population at 15 years followup

Causes of death (malignant diseases)

- Relapse 41%
- GVHD 12%
- Infection 11%
- Organ failure 11%
- Second cancers 7%
- Other 4%
- Unknown 14%

J Wingard et al, JCO 2011; 29: 2230
Late Complications

• Transplant survivors are at risk for late complications
  – Organ toxicity
  – Infections
  – Secondary cancers
  – Growth and development issues
  – Psychosocial, sexual, fertility and QOL issues
Risk Factors for Late Complications

Pre-HCT exposures and comorbidities

Primary therapy

Conditioning regimen

GVHD

Other exposures (infections, drugs)

Pre-HCT

HCT

Post-HCT

Genetic predisposition

Age & Gender

Lifestyle factors
Late Organ Dysfunction

- Neurologic – cognitive dysfunction, neuropathy
- Eye – sicca syndrome, cataracts
- Oral – xerostomia, caries
- Pulmonary – bronchiolitis obliterans
- Cardiovascular – coronary artery disease, metabolic syndrome, cardiomyopathy
- Liver – iron overload, hepatitis
- Kidney – HTN, chronic kidney disease
- Bone – osteoporosis, avascular necrosis
- Endocrine – hypothyroidism, growth disturbance
Late Complications in 1-year HCT Survivors with Severe Aplastic Anemia

<table>
<thead>
<tr>
<th>Late effect</th>
<th>Cumulative incidence over next 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Related donor</td>
</tr>
<tr>
<td>Stroke/seizures</td>
<td>1.8%</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.1%</td>
</tr>
<tr>
<td>Gonadal dysfunction</td>
<td>3.0%</td>
</tr>
<tr>
<td>Renal failure</td>
<td>1.4%</td>
</tr>
<tr>
<td>Avascular necrosis</td>
<td>1.8%</td>
</tr>
<tr>
<td>Cataracts</td>
<td>1.1%</td>
</tr>
<tr>
<td>Growth disturbance</td>
<td>0.5%</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>1.2%</td>
</tr>
</tbody>
</table>

D Buchbinder et al, BBMT 2012; 18: 1776
Secondary Cancers

• Cancers that occur after transplant
  – Different from the cancer for which transplant was performed
  – Cancer treatments may cause them or increase their risk

• Types of second cancers
  – Post-transplant lymphoproliferative disorders (PTLD)
  – MDS/AML
  – Solid cancers

Secondary Cancers

* Autologous recipients
** Allogeneic recipients

Risk

Day 0  1 year  10 years

Time since transplantation

MDS/AML*

PTLD**

Relapse

Second solid cancers
Secondary Solid Cancers after Allo HCT

- Study of 28,874 allogeneic HCT recipients
- Two times higher risk than general population
- Risk increased over time

Followup Guidelines

• Recommended screening and preventative practices for long-term survivors after HCT

• Co-published in:
  – Biology of Blood and Marrow Transplantation, 2012; 18: 348
  – Bone Marrow Transplantation, 2012; 47: 337
  – Hematology Oncology and Stem Cell Therapy, 2012; 5: 1
  – Revista Brasileira de Hematologia e Hemoterapia, 2012; 34: 109
Late Complications Form Changes
DISCLAIMER

• Forms revision is work in progress
• Changes have not been finalized
• CIBMTR will contact centers with updates as form changes become finalized
Forms that Capture Late Complications

• Form 2200 – 6 mos to 2 years post-HCT
• Form 2300 – yearly followup >2 years
• Form 2450 – post TED

• Iterative review process that included various stakeholders

• This presentation focuses on changes that impact late complication data (other changes also made, e.g., GVHD & DCI sections)

• Examples are shown (refer to forms for details)
Background for Changes

• Data previously collected inadequate to conduct research on some late complications
  – Need for better data to address late effects

• Balance data needed to address late complications vs. reporting burden at centers
  – Asked Late Effects Committee to identify priority areas: pulmonary & liver complications
  – Piloted questions at centers – generally positive feedback by data managers
Pulmonary Function

- IPn, ARDS, alveolar hemorrhage, bronchiolitis obliterans, COP/BOOP
- Section expanded to capture pathology report, radiology (e.g., CT scan), pulmonary function tests, bronchioalveolar lavage
298. Did the recipient develop bronchiolitis obliterans / bronchiol obliterate syndrome since the date of the last report?

☐ Yes – Go to questions 299

☐ No – Go to question 349

299. Date of diagnosis: ___ ___ ___ ___ — ___ ___ — ___ ___

         YYYY           MM       DD

300. Were any pulmonary function tests (PFTs) performed as part of the diagnostic workup?

☐ Yes – Go to question 301

☐ No – Go to question 318

301. Date of PFT: ___ ___ ___ ___ - ___ ___ - ___ ___

         YYYY           MM       DD
Specify PFT findings at diagnosis:

302. FEV₁
   - □ Known – Go to question 303
   - □ Unknown – Go to question 304

303. FEV₁: _____ . _____ liters

304. FVC:
   - □ Known – Go to question 305
   - □ Unknown – Go to question 306

305. FVC: _____ . _____ liters

306. F EV₁/FVC ratio:
   - □ Known – Go to question 307
   - □ Unknown – Go to question 308

307. F EV₁/FVC ratio: _____ . _____ liters

308. FEF 25-75:
   - □ Known – Go to question 309
   - □ Unknown – Go to question 310

309. FEF 25-75: _____ . _____ liters

310. Total lung capacity:
   - □ Known – Go to question 311
   - □ Unknown – Go to question 312

311. Total lung capacity: _____ . _____ liters

312. Residual volume:
   - □ Known – Go to question 313
   - □ Unknown – Go to question 314

313. Residual volume: _____ . _____ liters

314. Dₐ CO:
   - □ Known – Go to question 315
   - □ Unknown – Go to question 316

315. Dₐ CO: _____ . _____ □ ml CO/min/mm Hg
   - □ mmol CO/min/kPa

316. Dₐ CO adjusted for anemia:
   - □ Known – Go to question 317
   - □ Unknown – Go to question 318

317. Dₐ CO adjusted for anemia: _____ . _____ □ ml CO/min/mm Hg
   - □ mmol CO/min/kPa
### 318. Were diagnostic tests done?
- Yes – *Go to questions 319*
- No – *Go to question 325*

**Diagnosis was evaluated by:**

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>319. Bronchoalveolar lavage (BAL)</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>320. Transbronchial biopsy</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>321. Open / thorascopic (VATS) lung biopsy</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>322. Autopsy</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>323. Other diagnostic test</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

**Specify other diagnostic test: **

### 325. Is a pathology report available?
- Yes – *Go to question 326*
- No – *Go to question 337*

**Specify if any of the following changes seen on the pathology report:**

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>326. Bronchiolitis obliterans</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>327. Cryptogenic organizing pneumonia (COP / BOOP)</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>328. Diffuse alveolar damage</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>329. Diffuse alveolar hemorrhage</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>330. Granulomas</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>331. Nondiagnostic (e.g. “normal”, no pathologic alterations, no diagnostic alterations)</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>
337. Were any CT or high-resolution CT scans performed?
   □ Yes – Go to question 338
   □ No – Go to question 349

338. Date of CT scan: _______ _______ - _______ _______
       YYYY MM DD

Specify all the findings present in the chest CT radiology report:

339. Airspace consolidation / patchy or diffuse infiltrates
   □ Yes
   □ No

340. Bronchial wall thickening
   □ Yes
   □ No

341. Bronchiectasis / bronchiol dilation
   □ Yes
   □ No

342. Centrilobular opacities
   □ Yes
   □ No

343. Diffuse interstitial bilateral infiltrates
   □ Yes
   □ No
Additional Information: Pulmonary Function

• Request submission of documentation, if available:
  – Pathology report
  – Autopsy report
  – CT scan report
Liver Function

• Questions expanded to better capture liver complications
  – Cirrhosis
  – Hepatic VOD (forms 2100 & 2200)
  – Iron overload
409. Did the recipient develop non-infectious liver toxicity (excluding GVHD) since the date of last report (question 1)?
   □ Yes – Go to question 410
   □ No – Go to question 442

410. Date of diagnosis: ____________ — ______ — ______
     YYYY MM DD

Etiology:

411. Cirrhosis
   □ Yes – Go to question 412
   □ No – Go to question 420

Specify diagnosis of liver toxicity by clinical signs and symptoms / evaluation:

412. Ascites
      □ Yes
      □ No

413. Autopsy
      □ Yes
      □ No

414. Biopsy
      □ Yes – Go to question 415
      □ No – Go to question 416

415. Was the biopsy positive?
      □ Yes
      □ No

Specify labs at diagnosis of cirrhosis:

416. Serum AST (SGOT): ____________ — ______□ U/L
     □ µkat/L

417. Upper limit of normal for serum AST (SGOT): ____________ — ______□ U/L
     □ µkat/L

418. Serum ALT (SGPT): ____________ — ______□ U/L
     □ µkat/L

419. Upper limit of normal for serum ALT (SGPT): ____________ — ______□ U/L
     □ µkat/L
420. Veno-occlusive disease (VOD) / sinusoidal obstruction syndrome (SOS)

☐ Yes – Go to question 421
☐ No – Go to question 439

Specify diagnosis of liver toxicity by clinical signs and symptoms / evaluation:

421. Ascites
   ☐ Yes
   ☐ No

422. Autopsy
   ☐ Yes
   ☐ No

423. Biopsy
   ☐ Yes – Go to question 424
   ☐ No – Go to question 425

424. Was the biopsy positive?
   ☐ Yes
   ☐ No

425. Ultrasonography / doppler
   ☐ Yes - Go to question 426
   ☐ No – Go to question 427

426. Was there reversal of flow?
   ☐ Yes
   ☐ No
427. Did the recipient receive therapy for VOD (including continuation of prophylactic medications)?
   ☐ Yes – Go to question 428
   ☐ No – Go to question 434

Specify therapy:

428. Defibrotide
   ☐ Yes
   ☐ No

429. N-acetylcysteine
   ☐ Yes
   ☐ No

430. TPA
   ☐ Yes
   ☐ No

431. Ursodiol
   ☐ Yes
   ☐ No

432. Other therapy
   ☐ Yes – Go to question 433
   ☐ No – Go to question 434

433. Specify other therapy: ____________________________________________

434. Bilirubin at date of contact for this report: ________

435. Maximum known bilirubin during treatment of VOD: ________

436. Maximum known weight during treatment for VOD: ________ □ pounds
                                                      □ kilograms

437. Date maximum weight documented: ________-_______-_______
                                             YYYY      MM      DD

438. Was there concurrent multi-organ failure (e.g. renal, respiratory, neurological)?
   ☐ Yes
   ☐ No
Thrombotic Microangiopathy

• Expanded section in form 2200 (& 2100)
442. Did the recipient develop post-transplant thrombotic microangiopathy (TMA) (includes microangiopathy, thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS)), or similar syndrome?
   □ Yes – Go to question 443
   □ No – Go to question 465

443. Date of diagnosis: ___ ___ ___ ___ ___ ___ ___ ___ ___
    YYYY MM DD

444. Was TMA evaluated by biopsy?
   □ Yes – Go to question 445
   □ No – Go to question 451

Specify result(s):

445. Gastrointestinal (GI)
   □ Positive
   □ Negative
   □ Inconclusive
   □ Not done

446. Kidney
   □ Positive
   □ Negative
   □ Inconclusive
   □ Not done

447. Lung
   □ Positive
   □ Negative
   □ Inconclusive
   □ Not done

451. Was therapy given?
   □ Yes – Go to question 452
   □ No – Go to question 458

452. Defibrotide
   □ Yes
   □ No

453. Eculizumab (Soliris)
   □ Yes
   □ No

454. Rituximab (Rituxan, MabThera)
   □ Yes
   □ No

455. Plasma exchange / plasmapheresis
   □ Yes
   □ No

Specify organs involved by the TMA:

459. Renal
   □ Yes – Also complete questions ###-###
   □ No

460. Neurologic (e.g., encephalopathy, seizures, etc.)
   □ Yes – Also complete questions ###-###
   □ No
Other Organ Impairment/Disorder

• Reorganized to list questions by organ system
• Clarified terminology
  – CHF $\rightarrow$ CHF/cardiomyopathy, MI $\rightarrow$ MI/unstable angina, split seizure and stroke
• Added new relevant late complications
  – DVT/PE, osteoporosis, HTN, arrhythmia, psychological issues needing therapy (depression, anxiety, PTSD), iron overload
  – Added questions to capture solid organ transplant
Second cancers

• Split basal cell CA and squamous cell CA into separate questions
• Lymphoma/lymphoproliferative disease & Hodgkin lymphoma moved to PTLD section
• PTLD section extensively revised
Post Transplant Lymphoproliferative Disorder / EBV Reactivation

509. Did the recipient develop post-transplant lymphoproliferative disorder (PTLD) or reactivation of EBV in the blood post-transplant?

☐ Yes – Go to question 510
☐ No – Go to question 537

510. What best describes the status of the recipient:

☐ EBV reactivation only, no evidence of PTLD (elevation of blood EBV levels without any clinical and/or pathological evidence of lymphoma (e.g., bone marrow or lymph node involvement)) – Go to question 511
☐ EBV reactivation with evidence of PTLD (elevation of blood EBV levels with clinical and/or pathological evidence of lymphoma) – Go to question 511
☐ PTLD only, no reactivation of blood EBV – Go to question 518

511. Was the date of diagnosis of EBV reactivation previously reported?

☐ Yes – If recipient also had PTLD, go to question 518, otherwise go to question 530
☐ No – Go to question 512

512. Date of diagnosis: ___________ - ___________
   YYYY MM DD
513. How was EBV reactivation diagnosed?

☐ Qualitative PCR of blood – *If recipient also had PTLD, go to question 518, otherwise go to question 530*

☐ Quantitative PCR of blood – *Go to question 515*

☐ Other method – *Go to question 514*

514. Specify other method: ___________________________ - *If recipient also had PTLD, go to question 518, otherwise go to question 530*

515. Quantitative EBV viral load of blood: (at diagnosis of EBV) _____ copies/ml

516. Was a quantitative PCR of blood performed again after diagnosis?

☐ Yes – *Go to question 517*

☐ No – *If recipient also had PTLD, go to question 518, otherwise go to question 530*

517. Highest EBV viral load of blood: _____ copies/ml – *If recipient also had PTLD, go to question 518, otherwise go to question 530*

518. Was the date of diagnosis of PTLD previously reported?

☐ Yes – *Go to question 520*

☐ No – *Go to question 519*

519. Date of diagnosis: _____ _____ _____ - _____ - _____

YYYY MM DD

520. Was PTLD confirmed by biopsy?

☐ Yes

☐ No
Specify sites of PTLD involvement:

521. Bone marrow
   - Yes
   - No

522. Central nervous system (brain or cerebrospinal fluid)
   - Yes
   - No

529. Was documentation submitted to the CIBMTR? (e.g. pathology report, CT scan)
   - Yes
   - No

530. Was therapy given? (for EBV reactivation and/or PTLD)
   - Yes – Go to question 531
   - No – Go to question 537

523. Liver
   - Yes
   - No

531. Rituximab (Rituxan, MabThera)
   - Yes
   - No

524. Lung
   - Yes
   - No

532. Chemotherapy (e.g. CHOP, CVP-R)
   - Yes
   - No

525. Lymph nodes
   - Yes
   - No

533. Donor cellular infusion (DCI)
   - Yes
   - No

526. Spleen
   - Yes
   - No

534. Withdrawal of immunosuppression
   - Yes
   - No
Some Other Changes

• Capture height for pediatric patients and weight for all patients
• Capture pregnancy/fathering a child
• Capture cigarette smoking
• Removed questions on occupation and work status
Post-TED (2450) Changes

• GVHD section revised
• Reorganized 2\textsuperscript{nd} cancer section
  – Lymphoma/lymphoproliferative disease now includes Hodgkin disease, NHL, PTLD; asks about EBV positivity in tumor and blood
• Simplified questions on malignant disease evaluation
• Clarified (and more) questions to capture post-HCT therapy, disease progression and DCI
Summary

• Research on late complications is an important area of CIBMTR research
• Recognize challenges in capturing information on late complications
• Form changes reflect a balance of priority areas for future research with reporting burden at centers
Questions