Comorbidities prior to Hematopoietic Cell Transplantation
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Medical College of Wisconsin

Outline
• Clinical relevance of studying risk factors of toxicity.
• Changes in transplant-related mortality over time.
• Determinants of toxicity
  • Individual vs. collective impact on outcome.
  • Comorbidities
• Collection of Comorbidity Data

Determinants of transplant related toxicity
Transplant-related:
- Cond. intensity
- GVHD proph
- Donor type
- HLA matching
- Graft source
- Year of transplant

Disease-related:
- Prior treatment
- Disease status

Patient-related:
- Age
- Weight
- Performance score
- Comorbidities
- Genetics

Transplant activity worldwide 1980-2009

Transplant activity in the U.S. 1980-2009
Trends in transplantation by type and recipient age*
1988-2008

Allogeneic transplants in patients ≤20 years,
by donor type and graft source,
registered with CIBMTR 1991-2008

Allogeneic transplants by conditioning regimen intensity and patient age,
registered with CIBMTR 1999-2008

Number of allogeneic transplants,
by disease, registered with CIBMTR 1998-2008

Transplant Related Mortality

* Any death that occurs in the absence of disease.
* Disease relapse is a competing risk.
* Causes
  • Regimen toxicity
  • Immunesuppression
  • Graft-versus-host disease (GVHD)
Transplant Related Mortality Trends in 2 Decades: Eligibility

- Patients who
  - Had transplants performed between 1985 and 2004
  - Had AML in 1st or 2nd CR
  - Were less than 50 years
  - Received a graft from an HLA-matched sibling or an unrelated adult donor
  - Received a bone marrow or peripheral blood graft
  - Received myeloablative conditioning: TBICy (+/- other) or BU/Cy (+/- other).

Baseline Characteristics – Related Donors

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>CR1 N= 3,074</td>
<td>1124</td>
<td>1283</td>
<td>901</td>
<td>460</td>
</tr>
<tr>
<td>Median age</td>
<td>37</td>
<td>30</td>
<td>31</td>
<td>31</td>
</tr>
<tr>
<td>Unknown Cytogenetics*</td>
<td>56%</td>
<td>40%</td>
<td>25%</td>
<td>12%</td>
</tr>
<tr>
<td>Marrow graft</td>
<td>100%</td>
<td>99%</td>
<td>73%</td>
<td>43%</td>
</tr>
<tr>
<td>CR2 N= 750</td>
<td>202</td>
<td>232</td>
<td>202</td>
<td>124</td>
</tr>
<tr>
<td>Median age</td>
<td>28</td>
<td>30</td>
<td>34</td>
<td>29</td>
</tr>
<tr>
<td>Unknown Cytogenetics</td>
<td>69%</td>
<td>51%</td>
<td>22%</td>
<td>14%</td>
</tr>
<tr>
<td>Marrow graft</td>
<td>100%</td>
<td>99%</td>
<td>65%</td>
<td>29%</td>
</tr>
</tbody>
</table>

Transplant Related Mortality: Sibling Donor HCT for AML in CR1

Cumulative Incidence of TRM, %

Treatment-related Mortality: Sibling Donor HCT for AML in CR2

Adjusted Probability of Overall Survival*: Sibling HCT for AML in CR2

*Adjusted for significant changes in patient and disease characteristics.
Comparison of TRM between 2000-2004 and 1985-1989: Subgroup analysis

Determinants of Toxicity: individual vs. collective impact on outcome.

Determinants of transplant related toxicity

Obesity Trends* Among U.S. Adults
(*BMI ≥ 30, or about 30 lbs. overweight for 5’4” person)

Obesity prior to Transplant

Outcomes in Lymphoma by BMI

How does BMI influence outcomes in autologous HCT for lymphoma?

Figure 1. Cumulative incidence of transplantation-related mortality (TRM) according to body mass index.
**Outcomes in Lymphoma by BMI**

How does BMI influence outcomes in autologous HCT for lymphoma?

![Graph](image)

**Obesity in Patients with Multiple Myeloma undergoing Autologous HCT**

![Graph](image)

**Results-Multivariate Analysis**

**Related Allogeneic HCT in AML by Weight**

<table>
<thead>
<tr>
<th>BMI Group</th>
<th>Death</th>
<th>Treatment failure</th>
<th>Relapse</th>
<th>TRM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Underweight</td>
<td>1.06</td>
<td>2.08</td>
<td>2.02</td>
<td>2.22</td>
</tr>
<tr>
<td>Overweight</td>
<td>1.87</td>
<td>1.01</td>
<td>0.92</td>
<td>1.14</td>
</tr>
<tr>
<td>Obese</td>
<td>1.33</td>
<td>1.19</td>
<td>1.07</td>
<td>1.32</td>
</tr>
</tbody>
</table>

**Unrelated Allogeneic HCT in AML by Weight**

<table>
<thead>
<tr>
<th>BMI Group</th>
<th>Death</th>
<th>Treatment failure</th>
<th>Relapse</th>
<th>TRM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Underweight</td>
<td>0.86</td>
<td>0.91</td>
<td>1.04</td>
<td>0.85</td>
</tr>
<tr>
<td>Overweight</td>
<td>0.96</td>
<td>0.93</td>
<td>0.76</td>
<td>1.03</td>
</tr>
<tr>
<td>Obese</td>
<td>1.04</td>
<td>0.99</td>
<td>1.16</td>
<td>1.16</td>
</tr>
</tbody>
</table>

**Obesity and Transplant Outcomes**

- The individual impact of obesity on survival and TRM is not as distinct.
- Link of obesity with other comorbidities
- Weight is linked with disease
- Underweight and malignancies/prior treatment
- Is BMI the most appropriate measurement to define obesity?

**Better Definition of Obesity: Waist to Hip Ratio + BMI**

WHR is associated with mortality in patients with diabetes and hypertension.
Collective Impact of Different Factors

♦ Performance Score
  • Karnofsky, Lansky, Zubrod/ECOG/WHO
  • Apply to malignancies
  • Design to assess both patient and disease-specific risk factors

♦ Co-morbidities:
  • Collective impact of other diseases or condition present that may influence outcome.

Karnofsky Performance Score

<table>
<thead>
<tr>
<th>Index</th>
<th>Specific Criteria</th>
<th>General</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>Normal, no complaints, no evidence of disease.</td>
<td>Able to carry on normal activity; no special care needed.</td>
</tr>
<tr>
<td>90</td>
<td>Able to carry on normal activity, minor signs or symptoms of disease.</td>
<td>Unable to work, able to live at home and care for most personal needs, varying amount of assistance needed.</td>
</tr>
<tr>
<td>80</td>
<td>Normal activity with effort; some signs or symptoms of disease.</td>
<td>Requires considerable assistance from others and frequent medical care</td>
</tr>
<tr>
<td>70</td>
<td>Care for self, unable to carry on normal activity or to do work.</td>
<td>Requires special care and assistance.</td>
</tr>
<tr>
<td>60</td>
<td>Requires occasional assistance from others but able to care for most needs.</td>
<td>Severe disability, hospitalization indicated, but death not imminent.</td>
</tr>
<tr>
<td>50</td>
<td>Requires considerable assistance from others and frequent medical care</td>
<td>Very sick; hospitalization necessary, active supportive treatment necessary.</td>
</tr>
<tr>
<td>40</td>
<td>Disabled, requires special care and assistance.</td>
<td>Moribund</td>
</tr>
<tr>
<td>30</td>
<td>Severely disabled, hospitalization indicated, but death not imminent.</td>
<td>0 Dead</td>
</tr>
<tr>
<td>20</td>
<td>Very sick; hospitalization necessary, active supportive treatment necessary.</td>
<td>1 Moribund</td>
</tr>
<tr>
<td>10</td>
<td>Moribund</td>
<td>2 Very sick; hospitalization necessary, active supportive treatment necessary.</td>
</tr>
<tr>
<td>0</td>
<td>Dead</td>
<td></td>
</tr>
</tbody>
</table>

Charlson Comorbidity Index

<table>
<thead>
<tr>
<th>Condition</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>1</td>
</tr>
<tr>
<td>Heart disease</td>
<td>1</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>1</td>
</tr>
<tr>
<td>Cholelithiasis/cholecystitis</td>
<td>1</td>
</tr>
<tr>
<td>Malignant neoplasm</td>
<td>1</td>
</tr>
<tr>
<td>Amyotrophic lateral sclerosis</td>
<td>1</td>
</tr>
<tr>
<td>Stroke</td>
<td>2</td>
</tr>
<tr>
<td>Severe valvular heart disease</td>
<td>2</td>
</tr>
<tr>
<td>Renal failure</td>
<td>2</td>
</tr>
<tr>
<td>Solid organ transplanted</td>
<td>2</td>
</tr>
<tr>
<td>Solid tumor (�新)</td>
<td>2</td>
</tr>
<tr>
<td>Total score</td>
<td>7</td>
</tr>
</tbody>
</table>

HCT CI (n=708)

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Definition of comorbidity included in the new HCT CCI</th>
<th>HCT CI (% of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>Infection complication requiring hospitalization</td>
<td>38%</td>
</tr>
<tr>
<td>Renal failure</td>
<td>Renal failure requiring dialysis or transplantation</td>
<td>14%</td>
</tr>
<tr>
<td>Liver disease</td>
<td>Liver failure requiring transplantation</td>
<td>10%</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>Cardiac disease requiring hospitalization</td>
<td>7%</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>Pulmonary disease requiring hospitalization</td>
<td>5%</td>
</tr>
<tr>
<td>Other</td>
<td>Other comorbidities</td>
<td>4%</td>
</tr>
</tbody>
</table>

Why Collect comorbidities in the CIBMTR Forms?

♦ Important clinical question
♦ If validated may assist patient selection for transplant, or selection of transplant procedure.
♦ Use in center specific analysis to adjust on how sick patients are being transplant at a given center.
HCT-CI
Scoring comorbidities

### Cardiovascular
- **Arrhythmia (1):**
  - Atrial fibrillation (AF)
  - Atrial flutter
  - Ventricular arrhythmias (Tachycardia or fibrillation)
  - Sick sinus syndrome
- **Cardiac problems (1):**
  - Coronary artery disease
  - Myocardial infarction
  - Congestive heart failure
  - Ejection fraction (EF) ≤50%
- **Valvular disease (3):**
  - Any proven valve stenosis or malfunction with the exception of asymptomatic mitral valve prolapse
  - Prosthetic aortic or mitral valves

### Gastrointestinal
- **Inflammatory bowel disease (1):**
  - Ulcerative colitis
  - Crohn’s disease
- **Peptic ulcer (2):**
  - Previously required treatment
  - Previously bled from ulcer

### Endocrine
- **Diabetes (1):**
  - Type I
  - Type II
    - requiring treatment with oral hypoglycemic drugs or insulin

### Neurology
- **Cerebro-vascular disease (1):**
  - History of transient ischemic attacks
  - History of a cerebro-vascular accident

### Obesity (1)
- Patients with body mass index of >35 (weight in kg/ height x height in m)

### Infection (1)
- Documented or suspected and requiring treatment before, during, and after start of conditioning regimen
Psychiatric disturbances (1)
- Depression
- Anxiety
  - Previously diagnosed and receiving specific treatment
  - Diagnosed and started treatment at the time of HCT

Renal (2)
- Serum creatinine >2 mg/dl
- On dialysis
- Had prior renal transplantation

Preceding solid malignancy (3)
- Requiring treatment
- Excluding non-melanoma skin cancer

Rheumatologic (2)
- Systemic lupus erythematosis (SLE)
- Rheumatoid arthritis (RA)
- Polymyositis
- Mixed connective tissue disease
- Polymyalgia rheumatica

Hepatic
- Mild (1)
  - Chronic hepatitis
  - Bilirubin 1.5 x > upper limit of normal (ULN)
  - AST or ALT > 2.5 x ULN
- Moderate-severe (3)
  - Cirrhosis or fibrosis proved by liver biopsy
  - Bilirubin >1.5 x ULN
  - AST or ALT >2.5 x ULN

Pulmonary
- Moderate (2)
  - Diffusion capacity of CO (DLco) 80%-66%
  - FEV1 80%-66%
  - Shortness of breath on exertion
- Severe (3)
  - DLco ≤65%
  - FEV1 ≤65%
  - Shortness of breath at rest
  - Requiring supplemental oxygen

Validation of HCT-CI with CIBMTR data
- HCT CI incorporated in data collection forms in 2007
- Objectives:
  - To validate the instrument
  - Assess the impact of age
  - Reliability: who determines the score?
- To date Accrual
  - Allogeneic: RIC (n=2,604) and Myeloablative (n=6,081)
  - Autologous (n=13,424)
  - Nonmalignant diseases (n=868)
- Analysis will start this year (minimum follow up of 1 year in all patients)
Most common reported comorbidity

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>NST/RIC</th>
<th>Myeloablative</th>
<th>Autologous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other Specify</td>
<td>33%</td>
<td>25%</td>
<td>27%</td>
</tr>
<tr>
<td>Moderate Pulmonary</td>
<td>14%</td>
<td>14%</td>
<td>13%</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>13%</td>
<td>12%</td>
<td>11%</td>
</tr>
<tr>
<td>Cardiac</td>
<td>12%</td>
<td>6%</td>
<td>8%</td>
</tr>
<tr>
<td>Moderate/severe Hepatic</td>
<td>10%</td>
<td>7%</td>
<td>6%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>10%</td>
<td>7%</td>
<td>9%</td>
</tr>
<tr>
<td>Obesity</td>
<td>6%</td>
<td>6%</td>
<td>7%</td>
</tr>
</tbody>
</table>

Other Comorbidities, Examples
- Abdominal Diffuse Large B-cell lymphoma, AML, breast cancer, CLL, CML, colon cancer...
- Aortic stenosis
- Insomnia
- Heavy smoker
- Tubal ligation
- High lipids or high cholesterol
- Indigestion
- Gall bladder

Helpful hints on what to report
- Sufficient detail on the comorbidity
- Comorbidity ≠ past medical history
- Use judgement regarding relevant conditions.
- Is the comorbidity associate with the primary disease being treated?
- Is the patient receiving any medical intervention for the condition?
- If uncertain, discuss with staff.
**HCT-CI Score Assignment**
- Physician assignment along with KPS
- Post hoc assignment with chart review
- Are there any differences?
- Compare assigned scores blindly:

**Refinement of HCT-CI**
- Sorror et al:
  - Ferritin and Albumin predicted survival
- Pavlu et al (Hammersmith Hospital)
  - C-Reactive protein

![Graph](Pavlu et al Blood, 2010)

**Determinants of transplant related toxicity**

- Transplant-related:
  - Cond. intensity
  - GVHD proph
  - Donor type
  - HLA matching
  - Graft source
  - Year of transplant

- Disease-related:
  - Prior treatment
  - Disease status

- Patient-related:
  - Age
  - Weight
  - Performance score
  - Comorbidities
  - Genetics

**Conclusion**
- Presently transplants are safer than in the past.
- Better patient and donor selection, supportive care and experience of transplanters contributed to this improvement.

**Conclusion**
- Further improve will require:
  1. Refinement in patient assessments:
     - Better comorbidity assessments
     - Incorporation of laboratory markers
  2. Match best transplant approach for an individual patient according to these assessments.

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