Acute and Chronic Rejection

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The R-------- Word

- Know the difference between acute and chronic rejection
- Understand how each is diagnosed
- Understand treatment options
Columbia-Presbyterian Medical Center Kaplan-Meier - Patient Survival Estimates Lung Transplantation – 7/01/1997 to 6/30/2001 (n = 92)

Pre-Program Restructure

<table>
<thead>
<tr>
<th>Interval</th>
<th>% Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Month</td>
<td>85%</td>
</tr>
<tr>
<td>6 Month</td>
<td>67%</td>
</tr>
<tr>
<td>1 Year</td>
<td>61%</td>
</tr>
<tr>
<td>UNOS 1Year</td>
<td>79 %</td>
</tr>
<tr>
<td>3 Year</td>
<td>42%</td>
</tr>
<tr>
<td>UNOS 3 Year</td>
<td>62%</td>
</tr>
</tbody>
</table>

Columbia-Presbyterian Medical Center Kaplan-Meier - Patient Survival Estimates Lung Transplantation – 7/01/2001 to 12/08/2005 (n = 136)

Post Program Restructure

<table>
<thead>
<tr>
<th>Interval</th>
<th>% Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Month</td>
<td>98%</td>
</tr>
<tr>
<td>6 Month</td>
<td>94%</td>
</tr>
<tr>
<td>1 Year</td>
<td>93%</td>
</tr>
<tr>
<td>UNOS 1Year</td>
<td>79 %</td>
</tr>
<tr>
<td>3 Year</td>
<td>78%</td>
</tr>
<tr>
<td>UNOS 3 Year</td>
<td>62%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CAUSE OF DEATH</th>
<th>0-30 Days (N = 1146)</th>
<th>31 Days - 1 Year (N = 1,717)</th>
<th>&gt;1 Year - 3 Years (N = 1,428)</th>
<th>&gt;3 Years - 5 Years (N = 800)</th>
<th>&gt;5 Years (N = 829)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRONCHIOLITIS</td>
<td>5 (0.4%)</td>
<td>82 (4.8%)</td>
<td>378 (26.5%)</td>
<td>231 (28.9%)</td>
<td>225 (27.1%)</td>
</tr>
<tr>
<td>ACUTE REJECTION</td>
<td>63 (5.5%)</td>
<td>35 (2.0%)</td>
<td>25 (1.8%)</td>
<td>4 (0.5%)</td>
<td>5 (0.6%)</td>
</tr>
<tr>
<td>LYMPHOMA</td>
<td>1 (0.1%)</td>
<td>47 (2.7%)</td>
<td>32 (2.2%)</td>
<td>11 (1.4%)</td>
<td>27 (3.3%)</td>
</tr>
<tr>
<td>MALIGNANCY, OTHER</td>
<td>1 (0.1%)</td>
<td>44 (2.6%)</td>
<td>78 (5.5%)</td>
<td>60 (7.5%)</td>
<td>70 (8.4%)</td>
</tr>
<tr>
<td>CMV</td>
<td>0</td>
<td>65 (3.8%)</td>
<td>20 (1.4%)</td>
<td>4 (0.5%)</td>
<td>3 (0.4%)</td>
</tr>
<tr>
<td>INFECTION, NON-CMV</td>
<td>245 (21.4%)</td>
<td>639 (37.2%)</td>
<td>352 (24.6%)</td>
<td>162 (20.3%)</td>
<td>150 (18.1%)</td>
</tr>
<tr>
<td>GRAFT FAILURE</td>
<td>331 (28.9%)</td>
<td>307 (17.9%)</td>
<td>244 (17.1%)</td>
<td>137 (17.1%)</td>
<td>127 (15.3%)</td>
</tr>
<tr>
<td>CARDIOVASCULAR</td>
<td>121 (10.6%)</td>
<td>72 (4.2%)</td>
<td>50 (3.5%)</td>
<td>36 (4.5%)</td>
<td>46 (5.5%)</td>
</tr>
<tr>
<td>TECHNICAL</td>
<td>96 (8.4%)</td>
<td>44 (2.6%)</td>
<td>11 (0.8%)</td>
<td>2 (0.3%)</td>
<td>3 (0.4%)</td>
</tr>
<tr>
<td>OTHER</td>
<td>283 (24.7%)</td>
<td>382 (22.2%)</td>
<td>238 (16.7%)</td>
<td>153 (19.1%)</td>
<td>173 (20.9%)</td>
</tr>
</tbody>
</table>
PERCENTAGE OF ADULT LUNG TRANSPLANT RECIPIENTS TREATED FOR REJECTION IN 1ST YEAR
Stratified by Type of Induction (Transplants: January 1, 2000 - June 30, 2003)
NUMBER OF REJECTION EPISODES FOR ADULT LUNG TRANSPLANT RECIPIENTS TREATED FOR REJECTION IN 1ST YEAR

Stratified by Type of Induction (Transplants: January 1, 2000 - June 30, 2003)

Average number of rejection episodes

- Overall
- 18-34
- 35-49
- 50-64
- 65+

IL2R-antagonist
Acute Lung Rejection

A0  No infiltrates
A1  Rare perivascular infiltrates
A2  Perivascular infiltrates notable at low magnification
A3  Infiltrates extend into septae
A4  Diffuse infiltrates and alveolar damage

- With/Without Grade B
Minimal Acute Cellular Rejection

A
B
C
D

AJT 2005, 5; 2022-2030
Clinical Features

- Asymptomatic
  - Surveillance transbronchial biopsy

- Nonspecific
  - Fever
  - Malaise
  - Dyspnea
  - Cough
  - Sputum
Clinical Findings

- Chest radiograph
  - Clear
  - Focal infiltrate
  - Diffuse hazy opacities

- Spirometry
  - Normal
  - Decline from post-operative baseline
Differential Diagnosis

- Acute Rejection
- Infection
  - Bacterial
  - Viral
    - CMV
  - Fungal
- Graft dysfunction
  - Vascular
Diagnosis

- Fiberoptic bronchoscopy
  - Bronchoalveolar lavage
  - Transbronchial biopsy
    - 10-12 specimens
    - At least 5 pieces, >100 alveoli, bronchioles

- Concomitant diagnoses
  - Concurrent infection
    - CF
    - CMV
Treatment

- Oral corticosteroids
  - Boost with taper
- Intravenous methylprednisolone
  - 10-15 mg/kg/day (500-1000 mg/day)
- Augmentation of immunosuppression
  - Change calcineurin inhibitor
  - Add mycophenolate
- Lympholytic therapy
**LARGO**

- Lung Allograft Gene Expression Observational Study
- 14 centers U.S., Canada, Europe
- Enrolled > 600 patients

**CARGO**

- AlloMap™
  - NPV 98-99%
## POST-LUNG TRANSPLANT MORBIDITY FOR ADULTS

Cumulative Prevalence in Survivors within 1 and 5 Years Post-Transplant (Follow-ups: April 1994 - June 2004)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Within 1 Year</th>
<th>Total number with known response</th>
<th>Within 5 Years</th>
<th>Total number with known response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>51.1% (N = 6,994)</td>
<td>85.9% (N = 1,490)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal Dysfunction</td>
<td>25.7% (N = 7,008)</td>
<td>39.4% (N = 1,596)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal Creatinine &lt; 2.5 mg/dl</td>
<td>16.2%</td>
<td>22.7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine &gt; 2.5 mg/dl</td>
<td>7.6%</td>
<td>12.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic Dialysis</td>
<td>1.9%</td>
<td>3.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal Transplant</td>
<td>0.0%</td>
<td>0.7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>17.7% (N = 7,362)</td>
<td>46.8% (N = 1,645)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>21.5% (N = 6,995)</td>
<td>30.9% (N = 1,467)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchiolitis Obliterans</td>
<td>8.8% (N = 6,407)</td>
<td>33.0% (N = 1,178)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Obliterative Bronchiolitis

- Narrowing of the small airways
- Little inflammatory infiltrate
- Irreversible
- Progressive airflow obstruction
Diagnosis of OB

- Diagnosis of EXCLUSION
  - Exclude infections
  - Exclude airway abnormalities
  - Exclude acute rejection

- Reduction in PFTs from the BEST post-transplant baseline
PFTs post-transplant

- What should your lung function be?
  - Age
  - Gender
  - Height
  - Donor?

- When are the PFTs “the BEST”.
BOS – Bronchiolitis Obliterans Syndrome

- Once all other diagnoses are excluded
- Many names:
  - BOS, Chronic rejection, Graft failure
- Clinical Diagnosis
  - Transbronchial biopsy cannot detect the changes
- Treatment
Treatment Options

- Augment immunosuppressive medications
- Anti-inflammatory medication
  - Advair
  - Lipitor
  - Azithromycin
- Anti-lymphocyte therapy
  - Photopheresis
- Re-transplant
Thank You