Lung Transplantation: Where we are and Where we are going...

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Disclosure

• Vitrolife – Research support and clinical trial

• Astellas Canada – Research Grant

• CIHR/ Wyeth (Pfizer) – Chair in Transplantation Research

• Axela, Xceed Molecular – Research Grant

• Will discuss off label use of devices
OVERVIEW
Lung Transplantation

- Overview of Lung Transplantation:
  - Activity, indications outcomes

- Changing the practice of clinical lung transplantation
  - Expansion of indications
  - Bridge to transplant

- New Horizons
  - Ex vivo lung perfusion, personalized medicine for the organ, engineering “super organs”
Indications for Lung Transplantation
Adult (1983-Apr 2012)

- ILD / IPF
- BAC
- PAH
- CF
- Eisenmenger's
- COPD / Emphysema
- ReTx
- Other

N=1245 (96.3 %)
Indications for Transplantation
Pediatric (1983-Apr 2012)

N=48 (3.7%)
Total Transplants / Year
Adult vs. Pediatric
(1983-Apr 2012)-YTD

N Peds = 48
NUMBER OF LUNG TRANSPLANTS REPORTED BY YEAR AND PROCEDURE TYPE

www.ishlt.org

n = 38,119

ISHLT 2011

AVERAGE CENTER VOLUME
Lung Transplants

Average number of lung transplants per year

Number of centers

Percentage of transplants

ISHLT

ADULT LUNG TRANSPLANTS (1/1997-6/2009)
Risk Factors for 1 Year Mortality
Center Volume

Relative Risk of 1 Year Mortality

Center Volume (cases per year)

p < 0.0001

ISHLT 2011
ADULT LUNG TRANSPLANTATION

Survival comparisons by era
1988-94 vs. 1995-99: p = 0.4858
1988-94 vs. 2000-6/09: p <0.0001
1995-99 vs. 2000-6/09: p <0.0001

1988-1994: 1/2-life = 4.7 Years; Conditional 1/2-life = 7.9 Years
1995-1999: 1/2-life = 4.8 Years; Conditional 1/2-life = 7.5 Years
2000-6/2009: 1/2-life = 5.9 Years; Conditional 1/2-life = 8.0 Years

N at risk = 552
N at risk = 702
N at risk = 841

ISHLT
Survival comparisons
All p-values significant at \( p < 0.0001 \) except 18-34 vs. 35-49: \( p = 0.1708 \)

HALF-LIFE
- 18-34: 6.4 Years
- 35-49: 6.7 Years
- 50-59: 5.3 Years
- 60-65: 4.4 Years
- >65: 3.5 Years

Kaplan-Meier Survival by Age Group (Transplants: January 1990 – June 2009)

ISHLT
ADULT LUNG TRANSPLANTATION
Kaplan-Meier Survival By Diagnosis (Transplants: January 1990 – June 2009)

Survival comparisons
All comparisons with Alpha-1 and CF are statistically significant at < 0.01
COPD vs. IPF: p < 0.0001

HALF-LIFE
Alpha-1: 6.3 Years; CF: 7.4 Years; COPD: 5.3 Years;
IPF: 4.5 Years; IPAH: 4.9 Years; Sarcoidosis: 5.3 Years

ISHLT
Waiting List, Transplants and Donors (All Organs - Ontario) (Source: TGLN 1991-2011)
Death on Waiting List, Total LTx/yr & Listed/yr

2004-Jan/2012 (YTD)
Solutions to Deaths on the Wait List

• Keep the patient alive longer and in better condition ➔ Bridge to Transplant

• Increase the supply of donor organs
Selection of ECLS Support Mode / Configuration

- Hypercapnic failure
  - Hemodynamic stable
    - Support level A: Arterio-Venous (pumpless)
  - PAH (severe RV dysfunction)
    - PA-LA (pumpless)
- Hypoxic failure
  - Hemodynamic stable
    - Support level B: Veno-Venous (pump-driven)
    - Support level C: Veno-Arterial (pump-driven)
Novalung®
Novalung
Pumpless A-V Mode: Femoral Artery to Femoral Vein (extra-corporeal ventilation)
V-V ECLS

VV ECMO: Dual Cannula Circuit Model

CardioHelp Device
Novalung iLAactive
Dual Lumen Canula (Avalon®)

- One canula inserted through right internal jugular vein
- Drainage from IVC and SVC → oxygenated blood returned to right atrium
- Allows mobilisation of extubated patients

Garcia/Griffith et al J Thorac Cardiovasc Surg 2010;139:e137-9
Bridge to Lung Transplant for PAH Patients
Simple Atrial Septostomy is Unsatisfactory

RV failure $2^0$ to Pulmonary Vascular Resistance

Atrial Septostomy: $\rightarrow$ provides pressure decomposition $\rightarrow$ problem: R-L shunt, hypoxia
Novalung PA to LA
Bridge to Lung Transplant for PAH Patients
“The Oxygenating Septostomy”

1. Pumpless
2. Effectively: an oxygenating shunt → provides pressure decompression AND gas exchange

Number of days on PA-LA Novalung

Days on PA-LA Novalung

Patients

*Pediatric patients
ECLS decreases wait list mortality in iPAH patients: Toronto experience

Wait list mortality: 22% → 0%

$p=0.03$

de Perrot et al J Heart Lung Transplant 2011
ECLS Toronto Experience
2000 – 2012 (10Apr2012)
n = 100
IMPROVING SUPPLY: Focus on Organ Recovery and Repair Rather than Simply Focusing on Slowing Down Death...
NORMOTHERMIC EX VIVO LUNG PERFUSION (EVLP)

- Time to accurately assess - diagnose
- Option to treat/repair/recover
- Opportunity to reassess - confirm results of treatment
Perfusion: 40% CO
Ventilation: 7cc/kg, 7BPM, PEEP 5, FiO₂ = 21%

DEVELOPMENT OF A STABLE AND RELIABLE EX VIVO LUNG PERFUSION TECHNIQUE

HUMAN EX VIVO LUNG PERFUSION
Normothermic Ex vivo Lung Perfusion in Clinical Transplantation – HELP Trial
HELP II TRIAL
CLINICAL TRANSPLANTATION OF EX VIVO PERFUSED LUNGS
N=52 transplants to date

Toronto General Hospital OR
Bronchoscopy
LUNG X-Ray
Ex vivo treatment opportunities
Donor lung injuries

1- Pulmonary Edema
2- Brain death associated inflammation
3- Infection, Pneumonia
4- Aspiration
5- Pulmonary emboli
6- Ischemia-reperfusion injury
7- Immunologic preparation
**Survival**

**Survival Days**

0.0 0.2 0.4 0.6 0.8 1.0

0 365 730 1095 1460 1825

**Diagnose Specific Injuries:**

The expression ratio of IL-6/IL-10 in the donor lung predicts recipient outcome.

- **Low risk group**
- **Intermediate risk group**
- **High risk group**

The Wilcoxon test

P value: 0.0004

Monitoring the Response to Ex Vivo Treatment

Ziplex Inflammatory Tip Chip\textsuperscript{R} (Axela)
FUNCTIONAL REPAIR OF HUMAN DONOR LUNGS BY EX VIVO IL-10 GENE THERAPY

Delivery of IL-10 by EVLP Ad Gene Therapy to injured human donor lungs resulted in improved lung function.

Normothermic Ex Vivo Lung Perfusion in Clinical Lung Transplantation

Marcelo Cypel, M.D., Jonathan C. Yeung, M.D., Mingyao Liu, M.D., Masaki Anraku, M.D., Fengshi Chen, M.D., Ph.D., Wojtek Karolak, M.D., Masaaki Sato, M.D., Ph.D., Jane Laratta, R.N., Sassan Azad, C.R.A., Mindy Madonik, C.C.P., Chung-Wai Chow, M.D., Cecilia Chaparro, M.D., Michael Hutcheon, M.D., Lianne G. Singer, M.D., Arthur S. Slutsky, M.D., Kazuhiro Yasufuku, M.D., Ph.D., Marc de Perrot, M.D., Andrew F. Pierre, M.D., Thomas K. Waddell, M.D., Ph.D., and Shaf Keshavjee, M.D.
RESOLUTION OF PULMONARY EDEMA DURING EVLP

Donor P/F 230

Recipient P/F 420

1h EVLP

3h EVLP
Donor, EVLP and Recipient P/F (n=35)

![Graph showing P/F values over time for Donor, 1h, 2h, 3h, 4h, and ICU phases. EVLP values range from 0 to 600 mmHg.](image-url)
Overall Survival

Days after transplantation

Percent survival

Control (n=116)
EVLP (n=23)
p=0.77
median f/u 635 days
53/65 EVLP was successfully Transplanted
Operative (30 day) Mortality by year
1983-April 2012 (YTD)
THE FUTURE OF TRANSPLANTATION IS HERE…
THE “ORGAN REPAIR CENTER”
Case Report (April 2011)

• 52 y old male in US
• Viral Pneumonia
• 7 days ventilator – extubated
• Day 14 – re-intubated
• Day 22 – VV – ECMO
• Day 29 – deterioration – bleeding complications
• Day 30 urgently listed for LTx

• Day 32 – Donor is identified in another state.
• Massive pulmonary edema and P/F 230mmHg

EX VIVO LUNG PERFUSION:  
THE TORONTO EXPERIENCE

- Clinically feasible
- Increases the utilization of donor lungs (20% of our current program activity)
- Equivalent outcomes → trend to improved post transplant lung function
- Demonstrated the concept of the “organ repair center”
- New era of transplantation:
  - “Personalized medicine for the organ”:
    - More accurate assessment
    - Treatment → specific injuries
    - Lung transplantation with more predictable outcome
THE TORONTO LUNG TRANSPLANT TEAM