How to improve long term outcome after liver transplantation?

François Durand  
Hepatology & Liver Intensive Care  
University Paris Diderot  
INSERM U1149  
Hôpital Beaujon, Clichy

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Long term outcome after liver transplantation in France 1994-2014

10% decrease in early mortality

Data from Agence de la Biomédecine (www.agence-biomedecine.fr)
Decreased mortality: reasons for improvements

• Better selection of candidates
• Better preparation for transplantation
• Improvements in surgical techniques
• Improvement in procurement and preservation solutions
• Improvements in immunosuppression
• Better post-operative care
  - Earlier management of infection
  - Management of acute kidney injury...
Long term outcome after liver transplantation in France 1994-2014

Data from Agence de la Biomédecine (www.agence-biomedecine.fr)
Causes of late mortality: mainly unrelated to the liver

United States
- Hepatic: 28%
- De novo malignancy: 22%
- Infections: 9%
- Cardiovascular: 11%
- Renal failure: 6%
- Miscellaneous: 24%

Europe
- Hepatic: 22%
- De novo malignancy: 18%
- Cardiovascular: 14%
- Infections: 20%
- Miscellaneous: 26%

Late mortality in liver transplantation: multifactorial
Expected trends in liver transplantation

- More patients with NASH
  - More comorbidities
  - Cardiovascular risk
- Less patients with HCV cirrhosis
- Older age at transplantation
- More patients with impaired renal function
  - Impact of the MELD score

Post-transplant survival according to pre-transplant creatinine clearance

Improve the results of LT: target #1

Prevent/treat disease recurrence

Prevention/eradication of HCV ≈ 100%

- Recurrence of HCC
  - 10-15%
- Primary sclerosing cholangitis
  - 10-30%
  - no treatment
- Primary biliary cholangitis
  - 10%
- Auto-immune hepatitis
  - Not uncommon

Improve the results of LT: target # 2

Management of dysmetabolic syndrome

Post-transplant

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>33%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>60%</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>50%</td>
</tr>
<tr>
<td>Obesity</td>
<td>30%</td>
</tr>
</tbody>
</table>

NASH: second leading cause of cirrhosis in candidates for LT

Improve the results of LT: target # 3

Prevent/cure de novo malignancy


**Standardized incidence ratio**
- Skin cancer: 30
- Lymphoma: 20

**Malignancy by underlying liver disease**
Prevent/cure de novo malignancy

Modifiable risk factors

Risk of lung, head and neck, esophageal, kidney and urinary tract cancer according to smoking status

## De novo malignancy: mTOR inhibitors

### Controlled trials in kidney transplantation

<table>
<thead>
<tr>
<th>Authors</th>
<th>Campistol JM</th>
<th>Alberu J</th>
<th>p value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immunosuppression</strong></td>
<td>SRL + CsA + St</td>
<td>SRL + St</td>
<td>CNI</td>
<td>SRL</td>
</tr>
<tr>
<td>Patients</td>
<td>215</td>
<td>215</td>
<td>275</td>
<td>555</td>
</tr>
<tr>
<td>Follow up</td>
<td>5y</td>
<td>5y</td>
<td>2y</td>
<td>2y</td>
</tr>
<tr>
<td>Skin cancer</td>
<td>7.4%</td>
<td>3.7%</td>
<td>4.3%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Non skin cancer</td>
<td><strong>9.6%</strong></td>
<td>4%</td>
<td>2.1%</td>
<td>1%</td>
</tr>
</tbody>
</table>

## Limitations of mTOR inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Tacrolimus ± MMF 1 month</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TAC standard</td>
<td>EVR + TAC reduced</td>
</tr>
<tr>
<td>Patients</td>
<td>243</td>
<td>245</td>
</tr>
<tr>
<td>Acute rejection</td>
<td>7%</td>
<td>3%</td>
</tr>
<tr>
<td>Composite acute rejection,</td>
<td>9.7%</td>
<td>6.7%</td>
</tr>
<tr>
<td>graft loss, death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GFR 1 year (mL/min/1.732)</td>
<td>70</td>
<td>81</td>
</tr>
<tr>
<td>Wound healing problems</td>
<td>14%</td>
<td>18%</td>
</tr>
</tbody>
</table>

* Enrollment prematurely discontinued: too high rate of rejection

Target # 4: protect the kidney

- Treat pre-transplant episodes of AKI
  - Pre-transplant AKI impacts on post transplant outcome
- Delayed introduction of CNIs in patients with post-operative AKI
  - Basiliximab + steroids + MMF without CNIs during the first 7-14 days
- CNIs minimization
  - Low target trough levels
  - Adjunction of MMF
- Control of hypertension
- Control of diabetes
- Nephroprotective approaches
# Target # 5: Humoral rejection and DSA

## 1270 patients

*Multivariate analysis on the risk of death*

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td>Preformed DSA</td>
<td>1.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AA recipient</td>
<td>1.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HCV</td>
<td>1.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Donor age &gt; 50</td>
<td>1.4</td>
<td>0.006</td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preformed iGg3 DSA</td>
<td>2.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AA recipient</td>
<td>1.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HCV</td>
<td>1.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Donor age &gt; 50</td>
<td>1.4</td>
<td>0.01</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>No DSA</th>
<th>Preformed iGg3 DSA</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver-related death</td>
<td>6%</td>
<td>12%</td>
<td>0.004</td>
</tr>
</tbody>
</table>


**Which therapy?**
Take home messages

- Significant improvements in early mortality have been achieved
- Improvements in late mortality still need to be achieved
- HCV cure will improve long term outcomes
- NASH as a growing indication will negatively impact on long term outcomes
- Late deaths are mainly unrelated to the liver
  - Comorbidities need a multidisciplinary approach
- The role of humoral rejection needs to be better understood
- The pool of donors is limited
  - Think about transplant benefit in the selection of candidates