Lupus and Your Kidneys

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Kidney Inflammation and Abnormal Function as a Result of Lupus (Lupus Nephritis)

- Types of lupus nephritis
- Current treatment options
  - Latest clinical study results
  - Newer therapies
- Predicting treatment response
Major Types of Lupus Nephritis

- Lupus nephritis is grouped into 6 major types or classes (Class I-VI)
  - Class I and II: Mesangial
  - Class III: Focal
  - Class IV: Diffuse
  - Class V: Membranous
  - Class VI: Advanced sclerotic

- The higher the Class number, the more advanced the disease

- Injuries to the kidney (lesions) are also labeled as “active” or “chronic”
  - Active lesions can be treated, chronic lesions cannot

- Advanced kidney disease is also known as end-stage renal disease
How does my doctor determine if I have lupus nephritis and what type of lupus nephritis I have?
Tests to Determine Class of Lupus Nephritis

- Blood tests provide clues
  - Elevation in serum creatinine or BUN levels
  - Greater the amount of anti-dsDNA
  - Lower the amount of complement
  - More protein appears in urine

These changes alert the physician to be more aggressive with diagnosis and treatment

- Tissue sample (kidney biopsy)
  - amount of inflammation
    (potentially reversible, treatable)
  - amount of scarring
    (irreversible)
Lack of correlation of Anti-DNA Antibody Levels and Severity of Lupus Nephritis

Treatment for Lupus Nephritis
Treatment - Lupus Nephritis Options

- Steroids
  - Methylprednisolone (IV) or prednisone (oral)
  - May be given at intervals (pulsed)
  - Dose typically reduced over time
- Cytoxan (cyclophosphamide)
  - Intravenous (IV) or oral
- Imuran (azathioprine)
- CellCept (mycophenolate mofetil MMF)
- Other immunosuppressive medication
- Clinical Trials
Prevention of Advanced Renal Disease
Combination Therapy is Superior

Long-term Follow-up

- **Likely that therapy would succeed**
- **Likely that therapy would fail**

Months From Study Entry

- Combination therapy
- Cytoxan alone
- Solumedrol alone

Combination therapy still more effective after 10 years

Long-term Follow-up of Protocol Completers in WHO Class IV LN

*14 of 24 patients received CY after study completion

Standard Treatment 2001/2002

- Pulse of IV Cytoxan with a pulse of Solumedrol every month for 6 months then again every every third month thereafter

![Diagram showing time in months from 0 to 14 with pulses indicated at months 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14]
Long-term Cytoxan Therapy Improves Remission Rates

In one study, the longer patients were on Cytoxan the more likely they were to go into remission.

Starting Cytoxan Early Reduces Relapse Rates

<table>
<thead>
<tr>
<th>Event</th>
<th>Cytoxan (n = 21)</th>
<th>Combination Therapy (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/n</td>
<td>n/n</td>
</tr>
<tr>
<td>High blood pressure</td>
<td>10/20</td>
<td>10/20</td>
</tr>
<tr>
<td>Heart disease limiting blood flow to heart</td>
<td>1/19</td>
<td>4/19</td>
</tr>
<tr>
<td>Elevated fat in blood (hyperlipidemia)</td>
<td>7/20</td>
<td>8/19</td>
</tr>
<tr>
<td>Heart disease affecting flaps that regulate blood flow through the heart</td>
<td>9/19</td>
<td>7/21</td>
</tr>
<tr>
<td>Tissue death resulting from lack of blood supply</td>
<td>6/21</td>
<td>6/20</td>
</tr>
<tr>
<td>Bone fragility (osteoporosis)</td>
<td>4/18</td>
<td>3/19</td>
</tr>
<tr>
<td>Premature menopause</td>
<td>9/16</td>
<td>10/18</td>
</tr>
<tr>
<td>Major infections</td>
<td>7/21</td>
<td>9/20</td>
</tr>
<tr>
<td>Herpes zoster infection</td>
<td>6/21</td>
<td>5/20</td>
</tr>
</tbody>
</table>

What are the factors that determine who will respond well to drug therapy for lupus nephritis?
“Predicting” Results

- Some groups of patients respond better to therapy than others

- Risk factors for progression to renal disease and renal failure
  - Higher initial blood values of creatinine
  - Mild anemia
  - African-American
  - Severe “activity” and “chronicity” (kidney biopsy)

“Predicting” Results (Cont’d)

- Tissue extractions (biopsies) are important predictors of outcome

- Follow up biopsy in individuals that do not respond is important for future treatment

If the biopsy after 6 months of treatment still shows that the disease is progressing, you may be placed on a different therapy

Kidney function was less likely to be maintained in African-American patients.

What about alternative approaches to induction?

Do we always need to treat with Cytoxan?
CellCept vs Oral Cytoxan Plus Imuran (Cont’d)

Both treatments were effective, but fewer infections with CellCept

Relapse-free Survival After Achieving Remission in Patients with DPLN

Induction and Maintenance Therapy for Lupus Nephritis?
Probability of Freedom From Death or Chronic Renal Failure

- CellCept
- Imuran
- IV Cytoxan

Similar Benefit Over Cytoxan

Months:
- 0
- 12
- 24
- 36
- 48
- 60
- 72

Y-axis:
- 0
- 0.25
- 0.50
- 0.75
- 1.00

Renal failure:
- less likely
- more likely

## Side Effects of Therapy

<table>
<thead>
<tr>
<th></th>
<th>Hospital Days Per Patient Year</th>
<th>Loss of Menstruation (%)</th>
<th>Infection (%)</th>
<th>Major (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV Cytoxan</td>
<td>13</td>
<td>32</td>
<td>68</td>
<td>12</td>
</tr>
<tr>
<td>Imuran</td>
<td>1*</td>
<td>7.5*</td>
<td>28*</td>
<td>3</td>
</tr>
<tr>
<td>CellCept</td>
<td>1*</td>
<td>6.1*</td>
<td>21*</td>
<td>3</td>
</tr>
</tbody>
</table>

Oral CellCept vs IV Cytoxan

- Patients randomly assigned to groups
- Multiple centers involved
- Mostly female African-American patients with Class III or IV lupus nephritis

- Treatment groups
  - Oral CellCept
  - IV Cytoxan

- Measured remissions and partial remissions

CellCept vs Cytoxan Remission Rates

More complete remissions with CellCept

Percent (%) Responding

- Complete Remission: 16/71 (CellCept), 4/69 (IV Cytoxan)
- Partial Remission: 21/71 (CellCept), 17/69 (IV Cytoxan)
- Complete + Partial Remission: 37/71 (CellCept), 21/69 (IV Cytoxan)

P = NS

Similar results when African-American patients analyzed separately

ALMS Trial - Primary Endpoint: Responders at Month 6

Response judged by blinded Clinical Endpoint Committee:

Decrease in proteinuria to <3g if baseline nephrotic (≥3g/d), or by ≥50% in patients with subnephrotic (<3g/d) proteinuria

and

Stabilization of serum creatinine level (24-week level ± 25% of baseline), or improvement

MMF was not superior to IVC (p = 0.575)
Novel Approaches - Lupus Nephritis

- Directed antibody therapy
  - Anti-CD20
  - Anti-BLyS
  - Anti-CD40
  - Anti-C5
  - Anti-IL10
  - Anti-IFN-γ

Biomarkers
Take Home Messages

- Early diagnosis and therapy are important
- Combination therapy with steroids and immunosuppressive agents (e.g. cytoxan, MMF, immuran) improves results (e.g. better survival and fewer side effects)
- Outlook for African-Americans is better than ever
- New treatments are being developed and tested, and many look promising