Rituximab in the Treatment of Pemphigus: Outcome in 38 Patients Treated in Texas

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Pemphigus: Background

- Current treatment unsatisfactory
- Oral corticosteroids often fail to produce long term remission
- Oral corticosteroids have many adverse effects
- Rituximab successful for refractory pemphigus in several small reports
- Long term data on rituximab is lacking
Background

- Indications for rituximab therapy from previous studies
  - Patients who have failed treatment with high-dose prednisone (1-1.5 mg/kg/d) for > 3 weeks with or without adjuvant therapies (mycophenolate mofetil, azathioprine)
  - Severe contraindications to corticosteroid or immunosuppressive therapy

Leshem YA, Hodak E, David M, Anhalt GJ, Mimouni D. JAAD 2013; 68:404-411
Background

• Dosing of rituximab for autoimmune blistering disorders:
  – Initial cycle:
    • Rheumatoid Arthritis dosing: **Two 1000mg IV given 2 weeks apart**
    • Chronic Lymphocytic Leukemia Dosage: **4 weekly doses of 375 mg/m² IV**
  – Subsequent cycles given if disease activity persists or if unable to discontinue systemic therapy
    • **500 mg IV every 6 months**
Definitions/Outcome Measures

– **Complete Remission (CR)**: Absence of new or established lesions while off all therapy for > 2 months

– **CR on minimal therapy**: Absence of lesions on prednisone < 10mg/d and/or minimal adjuvant therapy (half the standard dose) for at least 2 months

Definitions/Outcome Measures

- **Partial Remission (PR):** Clear of lesions off all therapy except for transient new lesions that resolve within 1 week
- **PR on minimal therapy:** Clear except for transient new lesions that resolve within 1 week and on prednisone < 10mg/d and/or minimal adjuvant therapy (half the standard dose) for at least 2 months
- **Relapse/Flare:** Appearance of >3 lesions/month after patient achieves disease control that do not heal spontaneously within 1 week

Study Design

• Aim
  – To determine the efficacy of Rituximab for the treatment of pemphigus vulgaris and foliaceus

• Methods
  – Retrospective chart review of patients with PV or PF who have received rituximab at UT Southwestern and have had at least 9 months follow-up
  – 45 Patients screened
    • 38 patients qualified
    • 7 disqualified because of lack of sufficient follow-up
Results- Demographics

- Mean age at infusion: 50 years (range 19 - 77 years)
- 20 Females, 18 Males
- 30 PV, 8 PF
- Median duration of disease before first rituximab infusion
  - 33 months (range 2-187 months)
- Median follow-up time after 1st Infusion
  - 22 months
Results: Cycle 1

• 23 received RA dosing, 15 received CLL dosing
• **26/38 (68%) patients achieved remission**
  - CR in 16 (42%) patients (13 off all therapy, 3 on minimal therapy)
  - PR in 10 (26%) patients (4 off all therapy, 6 on minimal therapy)
  - Time to remission: **3 months** (1 - 7.5 months)
• No response in 12 patients (continued disease or unable to reduce all systemic therapies)
• 28/38 (73%) on adjuvant therapy at time of infusion
• **Mean prednisone dose**
  - 34 mg (4-100mg) at time of infusion → 5 mg at 3-6 months follow-up (75% decrease)
Results: Cycle 2

- n=29, 25 analyzed (4 lost to follow-up)
- **18/25 (72%) patients achieved remission**
  - CR in 10 (40%) patients (8 off all therapy, 2 on minimal therapy)
  - PR in 8 (32%) patients (4 off all therapy, 4 on minimal therapy)
  - Time to remission: 3 months (1-5)
- No response in 7 patients
- Mean prednisone dose at time of infusion
  - 12 mg (0-60mg)
- 16/25 (64%) on adjuvant therapy at time of infusion
Results: Cycle 3

• **8/10 (80%)** patients achieved remission
  – CR in 2 (20%) patients (1 off therapy, 1 minimal therapy)
  – PR in 6 (60%) patients (4 off therapy, 2 minimal therapy)
  – Time to remission mean: 3 months (2-4 range)

• No response in 2 patients

• Mean prednisone dose at time of infusion
  – 5 mg (0-25)

• **5/10 (50%)** on adjuvant therapy at time of infusion
Results: Cycle 4

• 6/6 (100%) patients in remission
  – CR in 2 patients (1 off therapy, 1 on minimal therapy)
  – PR in 4 patients (2 off therapy, 2 on minimal therapy)
• 3/6 (50%) on adjuvant therapy at time infusion
• Mean daily dose of prednisone at time of infusion
  – 0 mg
Relapse Rates

- After cycle 1: 17/26 (65%), mean 11 months
- Cycle 2: 3/18 (18%), mean 12 months
- Cycle 3: 2/8 (20%), mean 12 months
- Cycle 4: 0/5
## Patients Receiving additional cycles

<table>
<thead>
<tr>
<th>Reason for additional dose</th>
<th>Cycle</th>
<th>Remission</th>
<th>Remission type</th>
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</thead>
<tbody>
<tr>
<td>No remission in previous cycle</td>
<td>Second (N = 11)</td>
<td>6/11 (54%)</td>
<td>CR= 4 PR= 2</td>
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<tr>
<td></td>
<td>Third (N = 5)</td>
<td>4/5 (80%)</td>
<td>CR=1 PR=4</td>
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<tr>
<td></td>
<td>Fourth (N = 2)</td>
<td>2 (100%)</td>
<td>PR=1 CR=1</td>
</tr>
<tr>
<td>Relapse after previous cycle</td>
<td>Second (N = 12)</td>
<td>10/12 (83%)</td>
<td>CR=5 PR=5</td>
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<tr>
<td></td>
<td>Third (N = 3)</td>
<td>2/3 (67%)</td>
<td>CR=1 PR=1</td>
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<tr>
<td></td>
<td>Fourth (N = 2)</td>
<td>2/2 (100%)</td>
<td>CR=1 PR=1</td>
</tr>
</tbody>
</table>
Remission Rates Overall

Remission Rates (per protocol, n=33)

- CR OFF: 48%
- CR ON: 6%
- PR OFF: 15%
- PR ON: 21%
- None: 9%

Legend:
- No Response
- CR on therapy
- CR off therapy
- PR on therapy
- PR off therapy
Remission Rates

Cycle 1
- Remission: 6
- No response: 13

Cycle 2
- Remission: 4
- No response: 8

Cycle 3
- Remission: 2
- No response: 1

Cycle 4
- Remission: 2
- No response: 1
Mean oral Prednisone Dose

Prednisone (mg), P <0.05

Cycle 1
Cycle 2
Cycle 3
Cycle 4

Prednisone (mg)

- Cycle 1: 34 mg
- Cycle 2: 12 mg
- Cycle 3: 5 mg
- Cycle 4: 0 mg
Summary

- 38 patients treated, 5 lost to follow up
- **Overall remission rate: 90% (30/33)**
- 3 patients with pemphigus foliaceus never achieved remission
  - All 3 patients had substantial improvement of lesions
- **Rituximab side effects**
  - 2 patients developed Herpes Zoster
  - 6 others with fatigue, myalgias, arthralgias, nausea that resolved shortly after infusion
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