The ABCs of PTLD: A Review of Post Transplant Lymphoproliferative Disorder

Melissa Laub, PharmD
PGY1 Pharmacy Resident
Mayo Clinic Hospital – Rochester, MN
Pharmacy Grand Rounds
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Objectives

1. Explain the risk factors and pathologic classification of PTLD.
2. Review treatment options for PTLD based on disease category.
3. Describe considerations for prevention of PTLD in patients at risk for developing the disease.
Background

- Hyper-proliferation of B-cells
- Occurs in immunosuppressed patients
- Spectrum of clinical presentations
  - Most commonly associated with EBV but EBV-negative disease can also occur
  - Ranging from benign processes to fatal malignancies
  - Donor and recipient derived
  - B-Cell and T-cell derived
  - Early and late onset
5 Year Cumulative Incidence

- **Intestinal or multi-organ**: 11-33%
- **Lung**: 2-9%
- **Heart**: 2-6%
- **Renal**: 1-3%
- **HCT and Liver**: 1-2%

HCT: Hematopoietic stem cell transplant

Curtis RE. Blood. 1999 Oct 1;94(7):2208-16.
Epstein-Barr Virus

- Immunocompetent patients
  - Primary infection
    - Often asymptomatic
    - Infectious mononucleosis is most common manifestation
  - Transitions to latent infection
    - > 90% adults seropositive
- HCT and organ transplant patients
  - Primary infection or reactivation can lead to PTLD
Pathophysiology

EBV

Epithelium

T-Cells

Latent infection

Lysogenetic

Reactivation

Lytic

PTLD

B-Cell

Risk Factors

PTLD

- EBV serostatus
- Net level of immunosuppression
- Time from transplant
- CMV Infection
- Donor marrow T-Cell depletion (HCT)
- Graft versus host disease (HCT)

EBV: Epstein Barr virus
CMV: Cytomegalovirus
HCT: Hematopoietic stem cell transplant
Epstein-Barr Virus and PTLD Risk

<table>
<thead>
<tr>
<th>EBV Serostatus</th>
<th>Immunity?</th>
<th>PTLD Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>No</td>
<td>High</td>
</tr>
<tr>
<td>or</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>Yes</td>
<td>Intermediate</td>
</tr>
<tr>
<td>+</td>
<td>No</td>
<td>Low</td>
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<tr>
<td>or</td>
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Epstein-Barr Virus and PTLD Risk

- EBV-seronegative recipients are 5-12 times more likely to develop PTLD compared to EBV-seropositive recipients
- Pediatrics at higher risk for primary EBV infection
- EBV-negative disease more likely to occur in older patients

Net Level of Immunosuppression

- Given around time of transplant
- Varying degrees of intensity based on risk factors
- Intensification of maintenance
  - Long-term immunosuppression
  - Combination of 2-3 medication classes
  - More aggressive upfront and tapered over time

GVHD: Graft versus host disease
Induction Immunosuppression

- PTLD risk theoretically increases with greater T-cell depletion
- T-Cell depleting agents:
  - Anti-thymocyote globulin
    - Thymoglobulin (rATG, Rabbit)
    - ATGAM (Equine)
  - Alemtuzumab
- Non T-Cell depleting agents:
  - Basiliximab
  - Daclizumab
  - Eculizumab

Induction Immunosuppression

<table>
<thead>
<tr>
<th>Design</th>
<th>Retrospective review</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>59,560 kidney transplant patients in OPTN/UNOS database, 2000-2004</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Rate of PTLD within 730 days of transplant</td>
</tr>
</tbody>
</table>

- **Incidence of PTLD**
  - No induction
  - Thymoglobulin: P <0.01
  - Alemtuzumab
  - Basiliximab
  - Daclizumab

**Comments**
- Doses of induction agents not reported
- Alemtuzumab
  - Lower risk may be associated with B-cell depleting effects
  - Only used in 3% of subjects
- Maintenance regimen varied among groups

OPTN: Organ Procurement and Transplantation Network
UNOS: United Network for Organ Sharing
Maintenance Immunosuppression

- Difficult to assess contribution of single agents
- Depletion of B-cells in addition to T-cells may decrease risk of PTLD

<table>
<thead>
<tr>
<th>Class or Agent</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimetabolites</td>
<td>• Azathioprine risk &gt; mycophenolate mofetil</td>
</tr>
<tr>
<td>Calcineurin inhibitors</td>
<td>• Tacrolimus risk &gt; cyclosporine</td>
</tr>
<tr>
<td>mTOR inhibitors</td>
<td>• Conflicting data</td>
</tr>
<tr>
<td></td>
<td>• Mouse studies show inhibition of proliferation</td>
</tr>
<tr>
<td></td>
<td>• Early clinical studies show increased PTLD risk</td>
</tr>
<tr>
<td></td>
<td>• Long term data to be determined</td>
</tr>
<tr>
<td>Belatacept</td>
<td>• Clinical trials showed PTLD rate of 0-4%</td>
</tr>
<tr>
<td></td>
<td>• Black box warning for PTLD risk</td>
</tr>
<tr>
<td></td>
<td>• Only used in EBV seropositive patients</td>
</tr>
</tbody>
</table>
Time from Transplant

- >80% of cases
- EBV-positive disease most common

- EBV-negative disease
- Multifactorial
- Poorer prognosis

Limitations of Risk Studies

- PTLD incidence is low
- Databases have limited information
  - Doses
  - Induction vs. rejection treatment
- Inadequate duration of follow up
- Era effect
- Varying combinations of immunosuppressants
- Confounding patient factors

Summary: Risk Factors

• Recipient EBV-negative serostatus is major risk factor

• Overall level of immunosuppression is more important than specific agents
  • Anti-thymocyte globulin may infer higher risk

• Most cases occur within first year but later disease is also possible
Which of the following EBV serostatus types represents the highest risk for developing PTLD in solid organ or bone marrow transplant? (D=Donor, R=Recipient)

A. D+/R+
B. D+/R-
C. D-/R+
D. D-/R-
Clinical Presentation

- Non-specific
- "B Symptoms"
  - Fever
  - Weight loss
  - Fatigue
  - Night sweats
- Lymphadenopathy

- Organ graft dysfunction
- Extranodal involvement
  - GI tract
  - Skin
  - Bone marrow
  - CNS
Clinical Presentation

Images retrieved from: http://www.cancertherapyadvisor.com
Diagnosis: WHO Classification

- Early lesions (mononucleosis-like PTLD)
- Polymorphic PTLD
- Monomorphic PTLD
- Classical Hodgkin lymphoma-like PTLD

Treatment Algorithm: 2010 Guidelines

Clinical and laboratory assessment, WHO classification, stage, EBV status, MDT discussion

1. RIS if possible
   - Multifocal
   - Low clinical risk disease persisting post RIS
   - High & intermediate clinical risk disease persisting post RIS

2. Rituximab
   - Persistent/progressive disease
   - Complete remission
   - Relapse
   - Continue reduced IS & monitor

3. Rituximab + chemotherapy
   - Persistent/progressive disease
   - Complete remission
   - Continue reduced IS & monitor
   - Relapse
   - Chemotherapy
   - Palliation

CNS
- Radiotherapy/chemotherapy
- Localized
- Relapse
- Local excision/radiotherapy
Reduction in Immunosuppression

• Mainstay of therapy in SOT
  • Approximately 50% response rate and recurrence is high
  • Risk factors for non-response:
    • Age > 50 years old
    • Multi-organ involvement
    • B symptoms
    • Late-onset PTLD

• Usually ineffective alone in HCT

Reduction in Immunosuppression

- Renal and liver: more aggressive reduction
- Heart and lung: less aggressive reduction

PTLD Progression

Risk of Rejection
Reduction in Immunosuppression

• Limited disease:
  • 25% reduction in immunosuppression goal ranges

• Extensive disease not critically ill:
  • Decrease calcineurin inhibitor goal range by 50%
  • Discontinue azathioprine/mycophenolate
  • Continue prednisone 7.5–10 mg/day

• Extensive disease and critically ill
  • Stop all agents except prednisone 7.5–10 mg/day

Rituximab

- Monoclonal antibody against CD20
  - CD20 is expressed on B lymphocytes
  - Can be used in CD20+ PTLD
- Induction of partial remission in 45-65% of PTLD patients
- Recurrence is high
- Median overall survival ranges from 1.2-3.5 years
- Side effects
  - Infusion reactions
  - Opportunistic infections
  - Hepatitis B reactivation

Rituximab

• Risk factors for non-response to rituximab monotherapy
  • Age >60 years
  • ECOG performance status 2-4
  • Raised LDH

<table>
<thead>
<tr>
<th>Number of risk factors</th>
<th>1 year</th>
<th>2 year</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>100%</td>
<td>88%</td>
</tr>
<tr>
<td>2</td>
<td>79%</td>
<td>50%</td>
</tr>
<tr>
<td>3</td>
<td>36%</td>
<td>0%</td>
</tr>
</tbody>
</table>
Chemotherapy

- Most common:
  - Cyclophosphamide + doxorubicin + vincristine + prednisone (CHOP)

- Guidelines recommend with rituximab:
  - No response or progression on rituximab monotherapy
  - Initial severe disease
  - Many risk factors for poor prognosis

- Recommended alone:
  - CD20-negative disease

Chemotherapy

- Effective for inducing complete remission
- Toxicities are significant
  - Neutropenia
  - Infection
  - Cardiotoxicity
- Retrospective review of PTLD patients receiving chemotherapy +/- rituximab:
  - Overall survival = 3.5 years
  - 57% achieved complete remission
  - 52% hospitalized for toxicity
  - 26% died from treatment-related causes

Elstrom RL. Am J Transplant. 2006 Mar;6(3):569-76.
### Sequential Rituximab + CHOP

<table>
<thead>
<tr>
<th><strong>Background</strong></th>
<th>Attempt to maintain remission longer with fewer side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td>Prospective, open label (n=74)</td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td>Treatment naïve CD20+ PTLD after SOT</td>
</tr>
<tr>
<td></td>
<td>Failure to respond to RIS</td>
</tr>
<tr>
<td></td>
<td>Measurable disease &gt;2 cm</td>
</tr>
<tr>
<td></td>
<td>ECOG performance status ≤ 2</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>Rituximab 375 mg/m² once weekly x 4 weeks</td>
</tr>
<tr>
<td></td>
<td>CHOP (1 month after rituximab) x 4 cycles</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td><strong>Primary:</strong></td>
</tr>
<tr>
<td></td>
<td>• Response rates (partial or complete remission)</td>
</tr>
<tr>
<td></td>
<td>• Duration of response</td>
</tr>
<tr>
<td></td>
<td><strong>Secondary:</strong></td>
</tr>
<tr>
<td></td>
<td>• Infections</td>
</tr>
<tr>
<td></td>
<td>• Treatment-related mortality</td>
</tr>
<tr>
<td></td>
<td>• Overall survival</td>
</tr>
</tbody>
</table>

SOT: Solid organ transplant  
RIS: Reduction of immunosuppression  
ECOG: Eastern Cooperative Oncology Group  
CHOP: Cyclophosphamide, doxorubicin, vincristine, prednisolone

Sequential Rituximab + CHOP

• **Efficacy:**
  - 63% achieved complete or partial remission after rituximab and 93% after sequential treatment
  - Median overall survival: 6.6 years
  - Median time to progression: 6.4 years

• **Safety:**
  - 11% treatment related death due to CHOP
  - Treatment related death higher in rituximab non-responders than rituximab responders

Future Directions in Treatment
Brentuximab

- Monoclonal antibody targeting CD30
- CD30 expressed by B-cells in 70-80% of PTLD cases
- Ongoing phase I/II studies in combination with rituximab showed 71% complete remission rate
- Exact role in therapy unclear
- Promising option for:
  - Patients with poor performance status who cannot tolerate chemotherapy

Gandhi M. Blood 2014;124(21).
Immunotherapy

- Infusion of cytotoxic T-Cells
  - SOT: Autologous
  - HCT: Allogeneic
    - Risk of graft versus host disease
- Complex process, reserved for patients who fail initial approaches


SOT: Solid organ transplant
HCT: Hematopoietic stem cell transplant
Summary: Treatment

• Guidelines:
  • Reduction in immunosuppression is standard
  • Rituximab followed by chemotherapy for non-response or progression
    • Rituximab well tolerated but short time to progression
    • Chemotherapy effective but toxic

• More recent data:
  • First line sequential therapy may be more effective
  • Newer modalities may decrease toxicities
Patient Case

• 45 year old female s/p kidney transplant 8 months ago (EBV D+/R-)

• EBV serum PCR is positive

• Symptoms of fatigue, night sweats, lymphadenopathy but overall stable

• Diagnosed with early lesions of PTLD on pathology report, no extra nodal involvement

• Immunosuppression regimen:
  • Tacrolimus 3 mg BID, goal trough 7-10 ng/mL (Most recent level = 8 ng/mL)
  • Prednisone 5mg daily
  • Mycophenolate mofetil 1,000mg BID
What is your first step in management of this patient’s PTLD?

A. Initiate rituximab
B. Decrease tacrolimus by 50%
C. Discontinue prednisone
D. Switch tacrolimus to belatacept
E. B & C
### Antiviral Prophylaxis

**Background**
- No consensus on antiviral prophylaxis
- Certain antivirals may have *in-vitro* effects against EBV

**Design**
- Systematic review and meta-analysis

**Studies Included**
- Evaluating universal or preemptive antiviral prophylaxis in SOT patients with any of the following:
  - Acyclovir
  - Valacyclovir
  - Famciclovir
  - Ganciclovir
  - Valganciclovir
  - Foscarnet

Antiviral Prophylaxis

Conclusion: Antiviral prophylaxis does not affect the incidence of PTLD

Mayo Three-Site Protocol for EBV D+/R-

- Minimize immunosuppression from day 1
- Universal antiviral prophylaxis not recommended
- Quantitative EBV serum PCR:
  - Once monthly for 1 year
  - Every 3 months for second year
- For patients with EBV PCR positivity:
  - Consult with Infectious Disease Service
  - Reduce immunosuppression
  - Consider valganciclovir 900 mg PO BID
  - Evaluate for PTLD, as clinically indicated
  - Hematology consultation, if PTLD suspected
All EBV D+/R- patients should receive which of the following antiviral prophylaxis therapies to prevent PTLD?

A. Valganciclovir 900mg BID
B. Acyclovir 400mg BID
C. Valacyclovir 1,000mg daily
D. None of the above
Retransplant

- Retransplant should be considered if PTLD caused graft failure
- Review of retransplants due to PTLD in OPTN/UNOS database

<table>
<thead>
<tr>
<th>Time from PTLD to retransplant</th>
<th>Percent of population (n=69)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 year</td>
<td>33%</td>
</tr>
<tr>
<td>1-3 years</td>
<td>22%</td>
</tr>
<tr>
<td>3-5 years</td>
<td>22%</td>
</tr>
<tr>
<td>5-10 years</td>
<td>22%</td>
</tr>
<tr>
<td>&gt;10 years</td>
<td>1%</td>
</tr>
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- At least 1 year from PTLD control may be appropriate

Summary

• PTLD is a heterogeneous disease state
• Major risk factors are EBV D+/R- serostatus and higher intensity immunosuppression
• Cornerstones of treatment:
  • Reduction in immunosuppression
  • Rituximab +/- CHOP
• Antiviral prophylaxis generally not recommended
• Retransplant can be considered in graft loss
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