POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDER

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Discussant: Bob Richard
Case: GM

69M followed in oncology clinic at PSVA

- Initially presented to medical attention in 2005 for HA/AMS
  - IgM m-spike 4g/dL; BMBx with 10% lymphoplasmacytoid cells
  - Dx: Waldenstrom’s; tx: DRC x4 → VGPR, resolution of sx
- 11/2009: OLT for ESLD; EBV seropos host/donor; tacrolimus/pred/MMF IST
- 4/2012: presented with weight loss, fatigue, LAD, increasing m-spike

Excisional LN biopsy:

- Flow cytometry c/w with initial LPL
- Morphology LPL population as well as ‘epitheliod granulomas with central necrosis’
  - AFB and GMS negative
  - Multifocal EBER staining, polymorphic infiltrate (*serum EBV PCR neg)
- Diagnosis: recurrent WM and new concurrent polymorphic PTLD
- Tx: taper of tacrolimus, rituxan x4 weekly followed by q3mo x6

Repeat CT with resolution of diffuse LAD, m-spike ‘too small to quant’
Case: GM

- Followed in clinic with serial SPEP, EBV and clinical monitoring
  - 10/2015: new abdominal pain; CT with diffuse small volume abdominal LAD
  - SPEP with markedly increased m-spike (1.4), IgM 3600. sEBV: negative
  - IR unable to biopsy

- What next?...
PTLD: Overview

- History, epidemiology, risk factors
- Pathogenesis: PTLD as a prototype for EBV-associated oncogenesis
- Monitoring and prevention strategies
- Treatment: PTLD as a model for EBV-directed therapies
- Special scenarios
- Case discussion
- Cute picture of my kid
PTLD: origins

- Malignant lymphomas in transplantation patients (Penn, et al. Transplant Proc. 1969)
- Pseudolymphoma in renal allograft recipients (Geis, et al Arch Surg. 1978)
  - “Cyclosporin lymphomas”
- Reversibility of lymphomas and lymphoproliferative lesions developing under cyclosporin-steroid therapy (Starzl, et al. Lancet 1984)
  - “Post-transplant lymphoproliferative disorder”
PTLD: defined

• WHO 2008:
  • 1) Early-type PTLD (10%)
    • Non-destructive lymphoplasmacytic proliferation
  • 2) Polymorphic PTLD (5-10%)
    • Destructive lymphoplasmacytic proliferation
    • Monoclonal or polyclonal
      • Typically comprised of small population of B-cell blasts in background of lymphocytes, histiocytes and plasma cells
    • Does not meet definition of monomorphic PTLD
  • 3) Monomorphic PTLD (70-80%)
    • Destructive, monoclonal lymphoid proliferation
    • Fulfills definition of WHO B or T cell lymphoma
      • Most common: DLBCL
  • 4) Post-transplant classical Hodgkin lymphoma (<5%)
PTLD: defined

- A heterogenous group of lymphoid and plasmacytic proliferations of variable malignant potential arising in immunocompromised post-solid organ or allogeneic transplant patients
PTLD: epidemiology and risk factors

• Incidence is widely variable; dependent on transplant type...

<table>
<thead>
<tr>
<th>SOT</th>
<th>HSCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney: 1-1.5%</td>
<td>MRD: 1%</td>
</tr>
<tr>
<td>Pancreas: 2%</td>
<td>MMRD: 3%</td>
</tr>
<tr>
<td>Lung: 2-3%</td>
<td>MURD: 4%</td>
</tr>
<tr>
<td>Liver: 5%</td>
<td>MMURD: 11%</td>
</tr>
<tr>
<td>Heart/lung, multivisceral: up to 33%</td>
<td>Haplo: up to 20%</td>
</tr>
</tbody>
</table>

• ...and modified by several risk factors:
  • Transplanted lymphoid mass (SOT)
  • Allograft T-cell depletion (HSCT)
  • T-cell directed host immunosuppression (OKT-3, ATG, CNIs)
  • Intensity and duration of IST (GVHD)
  • EBV- recipient with EBV+ donor (peds)
PTLD: epidemiology and risk factors

- Highest incidence in first year post-transplant
  - Likely directed related to degree of IST immediately post-transplant
  - 60-80% post HSCT LPD, 50-60% post SOT LPD
- Strong association with EBV
  - 90-100% in early lesions, 50-80% for more advanced lesions
  - More common in early vs late PTLD (>2yrs post-transplant)
- Incidence is increasing
  - Likely in context of more robust transplant programs

- In SOT: PTLD is typically of recipient origin
- In HSCT: PTLD of donor origin
PTLD: clinical features

- Majority of patients present with advanced disease (~70%)
- Extranodal involvement is common
  - ~80% of patients have EN involvement
  - GI tract most common (30-40%)
  - CNS involvement (20-25%)
  - Allograft involvement in SOT
- Presenting symptoms
  - Non-specific systemic sxs: fatigue, malaise, weight loss
    - Acute mononucleosis-like syndrome
  - Graft dysfunction
  - LAD
PTLD pathogenesis: a brief foray into EBV virology

• EBV: a wolf in sheep’s clothing?
  • gamma herpesvirus (HHV-4)
  • 172 Kbp genome; 100 genes
  • >90% seropositivity in adults worldwide
    • Subclinical infection vs infectious mononucleosis (later age of exposure)
    • Salivary transmission (“kissing disease”)
  • Host cells: predominately B cells; also T cells, NP epithelial cells
  • Robust immune response to initial infection (‘lytic program’)
    • Mononuclear cells of mononucleosis (‘atypical lymphocytes’) are the cytotoxic
      T-cells responding to the highly antigenic lytic phase of the virus
  • Lifelong persistence (memory B-cells) via activation of ‘latency program’
PTLD pathogenesis: a brief foray into EBV virology

- EBV: a day in the life
PTLD pathogenesis: a brief foray into EBV virology

• EBV: getting with the program
  • Lytic program: robust viral replication; unsustainable (host cell destruction)
  • Latency programs:
    • Drive ligand-independent B cell activation/maturation
    • Establish life-long persistence in memory B cells (immune evasion)
    • Create viral reservoir capable of reactivation/transmission
PTLD pathogenesis: a brief foray into EBV virology

• EBV: getting with the program
  • Latency programs:
    • 10 genes, differentially expressed
    • pattern of expression establishes type/function of latency:

### Table 1. Five Transcription Programs Used by EBV to Establish and Maintain Infection.

<table>
<thead>
<tr>
<th>Type of Infected B Cell*</th>
<th>Program</th>
<th>Genes Expressed</th>
<th>Function of the Program</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naive cell</td>
<td>Growth (Latency III)</td>
<td>EBNA-1 through EBNA-6, LMP-1, LMP-2A, and LMP-2B</td>
<td>Activates B cell</td>
</tr>
<tr>
<td>Germinal-center cell</td>
<td>Default (Latency II)</td>
<td>EBNA-1, LMP-1, and LMP-2A</td>
<td>Differentiates activated B cell into memory cell</td>
</tr>
<tr>
<td>Peripheral-blood memory cell</td>
<td>Latency (Latency 0)</td>
<td>None</td>
<td>Allows lifetime persistence</td>
</tr>
<tr>
<td>Dividing peripheral-blood memory cell</td>
<td>EBNA-1 only (Latency I)</td>
<td>EBNA-1</td>
<td>Allows viral DNA in latency-program cell to divide</td>
</tr>
<tr>
<td>Plasma cell</td>
<td>Lytic</td>
<td>All lytic genes</td>
<td>Replicates virus in plasma cell</td>
</tr>
</tbody>
</table>
PTLD pathogenesis: a brief foray into EBV virology

- **EBV latency: meet the players**
  - EBNA1: maintains viral DNA replication (*not expressed on MHC I*)
  - EBNA2: master regulator of viral gene expression (eg, LMP1 & LMP2)
  - LMP1: upregulates Bcl-2, A20, cFLIP (anti-apoptosis) and activates NF-kB, MAPK, PI3K/Akt pathways (pro-proliferation).
  - LMP2: antigen independent BCR signaling modulation
  - EBER1/2: non-polyadenylated RNAs, induce secretion of IL-10 (suppression of cytotoxic T-cells). Abundant in latently infected cells (IHC staining).
PTLD pathogenesis: a brief foray into EBV virology

- EBV: a transformative experience
  - First human virus implicated in oncogenesis
  - Immortalization of B cell lines *in vitro* after EBV infection
  - LMP1 identified as oncogene in nude mouse model
PTLD pathogenesis: a brief foray into EBV virology

• EBV: a transformative experience
  • Associated with myriad human malignancies
    • B cell: Burkitt lymphoma, Hodgkin lymphoma, DLBCL, primary effusion lymphoma, primary CNS lymphoma, PTLD
    • T/NK cell: extranodal NK/T lymphoma, aggressive NK leukemia, AITL
    • Carcinoma: nasopharyngeal carcinoma, gastric adenocarcinoma
  • Immunocompetent and immunodeficient hosts
    • Disease-specific latency programs; role of driver vs cofactor

<table>
<thead>
<tr>
<th>Latency type</th>
<th>EBER</th>
<th>EBNA-1</th>
<th>EBNA-2</th>
<th>EBNA-3</th>
<th>LMP1</th>
<th>LMP2</th>
<th>BARTs</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Burkitt lymphoma</td>
</tr>
<tr>
<td>II</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td>+</td>
<td>HL, T-cell lymphoma, PEL</td>
</tr>
<tr>
<td>III</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>LPD, AIDS, infectious mononucleosis</td>
</tr>
<tr>
<td>IV</td>
<td>+</td>
<td>±</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Healthy carrier, ?, not known</td>
</tr>
</tbody>
</table>

EBNA, EBV nuclear antigen; LMP, latent membrane protein; EBER, EBV-encoded RNA; BARTs, Bam HI rightward transcripts; HL, Hodgkin lymphoma; PEL, primary effusion lymphoma; LPD, lymphoproliferative disease; AIDS, acquired immunodeficiency syndrome with LPD; ?, not known.
PTLD as a prototype for EBV lymphomagenesis

- 60-80% EBV positive (~100% in early lesions)
- Type III latency program (full expression of transforming proteins)
- GCB origin (typically L1/2 in healthy carriers)

- Immune suppression (esp cytotoxic CD8 T-cells) → unchecked L3 gene expression → pro-growth/anti-death program → lymphoid hyperplasia (early-lesions) → further expansion/ somatic hypermutation in GC → additional transforming events → oligoclonal expansion (polymorphic PTLD) → monoclonal malignancy (monomorphic PTLD)

- Underscores potential utility of monitoring/ pre-emptive tx
- Provides insight for pathogenesis-driven treatment options
EBV monitoring and early intervention

- No prospectively established monitoring programs
  - Omar, er al (Transpl Infect Dis, 2009)
  - Risk adapted quant EBV monitoring in post-HSCT patients:

<table>
<thead>
<tr>
<th></th>
<th>Study group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High risk</td>
<td>Standard risk</td>
</tr>
<tr>
<td>Totals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCR samples per patient</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>No. (% of EBV-positive patients)</td>
<td>21/53 (39.6%)</td>
<td>19/78 (24.3%)</td>
</tr>
<tr>
<td>EBV loads (minimum–maximum, median)</td>
<td>(50–1.4 × 10^6)</td>
<td>(50–2.3 × 10^6)</td>
</tr>
<tr>
<td>Patients who received rituximab</td>
<td>9/53 (17%)</td>
<td>3/78 (3.8%)</td>
</tr>
<tr>
<td>Total rituximab doses (doses/patient)</td>
<td>29 (1–6 doses)</td>
<td>6 (1–4 doses)</td>
</tr>
<tr>
<td>Patients treated with CTL</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Patients who developed PTLD</td>
<td>3/53 (5.6%)</td>
<td>1/78 (1.3%)</td>
</tr>
<tr>
<td>Patients who died of PTLD</td>
<td>1/53 (1.9%)</td>
<td>1/78 (1.3%)</td>
</tr>
</tbody>
</table>

PCR, polymerase chain reaction; EBV, Epstein–Barr virus; CTL, cytotoxic T lymphocytes; PTLD, post-transplant lymphoproliferative disease.
EBV monitoring and early intervention

• Wide variation in practice
  • Gil, et al (Contemp Oncol, 2012)

### Table 1. Indication for monitoring of EBV-DNA according to type of transplant

<table>
<thead>
<tr>
<th>Type of transplant</th>
<th>Number of centers (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>all alloSCT</td>
<td>32/64 (50.0%)</td>
</tr>
<tr>
<td>MUD-SCT</td>
<td>49/64 (76.5%)</td>
</tr>
<tr>
<td>T-depletion in vitro</td>
<td>40/64 (62.5%)</td>
</tr>
<tr>
<td>T-depletion in vivo</td>
<td>53/64 (82.8%)</td>
</tr>
<tr>
<td>family mismatched SCT</td>
<td>46/64 (71.9%)</td>
</tr>
<tr>
<td>cord blood SCT</td>
<td>48/64 (75.0%)</td>
</tr>
<tr>
<td>other (SAA, EBV mismatch, autoimmune disease)</td>
<td>3 (SAA, EBV mismatch, autoimmune disease)</td>
</tr>
</tbody>
</table>

*alloSCT* – allogeneic stem cell transplantation; *MUD* – matched unrelated donor; *SAA* – severe aplastic anemia; *EBV* – Epstein-Barr virus

### Table 2. Threshold value of EBV-DNA copies as an indicator for preemptive treatment with rituximab

<table>
<thead>
<tr>
<th>Number of EBV-DNA copies/ml</th>
<th>Number of centers</th>
</tr>
</thead>
<tbody>
<tr>
<td>$1 \times 10^3$</td>
<td>19 (31.7%)</td>
</tr>
<tr>
<td>$5 \times 10^3$</td>
<td>1 (1.7%)</td>
</tr>
<tr>
<td>$1 \times 10^4$</td>
<td>20 (33.3%)</td>
</tr>
<tr>
<td>$4-5 \times 10^4$</td>
<td>6 (10%)</td>
</tr>
<tr>
<td>$1 \times 10^5$</td>
<td>9 (15%)</td>
</tr>
<tr>
<td>other (risk factors, increasing value)</td>
<td>5 (8.3%)</td>
</tr>
</tbody>
</table>

*EBV-DNA* – Epstein-Barr virus deoxyribonucleic acid
EBV monitoring and early intervention

• No standard intervention:
  • San Juan, et al (Clinical Microbiology and Infectious Diseases, 2015):
    • Survey of 69 transplant centers across 15 European countries
      • 85% of centers performed routine monitoring
      • 75% routine pre-emptive intervention based on EBV DNAemia:
        • RI: 51%
        • Switch CNI to mTOR: 31%
        • Rituxan: 14.5%
      • 10% pursued additional diagnostics (PET, biopsy)
EBV monitoring and early intervention

• Conclusions:
  • No prospective evidence to guide monitoring/pre-emptive therapy
  • Tends to be an institutionally idiosyncratic algorithm
PTLD: pathogenesis-driven treatment approach

• Basic principles:
  • Eradicate the premalignant lesion/malignant clone
  • Preserve graft function
  • Minimize toxicity

• Essential strategies:
  • Reduction of immunosuppression
  • Rituxan +/- chemotherapy
  • EBV as a therapeutic target

• Future approaches:
  • Pathway targeted therapies
PTLD: pathogenesis-driven treatment approach

- Reduction of immunosuppression
  - Core tenet of PTLD therapy
  - Most effective in early lesions
  - Maximal reduction will vary with transplant type/timing
  - Balanced with risk of graft rejection/GVHD
PTLD: pathogenesis-driven treatment approach

- Reduction of immunosuppression
  - Reshef, et al. (Am J Transplant, 2011)
    - 67 SOT PTLD patients (1988-2008), managed with RI alone
      - 37% polymorphic, 63% monomorphic
      - 70% EBV+
    - ORR 45% (CR 37%, PR 8%)
    - Acute rejection rate: 32%
    - mOS: 44mo
PTLD: pathogenesis-driven treatment approach

- Eradication of the malignant clone: role of rituxan
    - First prospective treatment trial in PTLD
    - 43 patients with SD/PD despite RI treated with rituxan monotherapy (375mg/m2 weekly x4weeks)
    - 10% polymorphic PTLD, 65% monomorphic

- ORR: 44% (27% CR); 1 year OS: 67%, mOS: 15mo
  - Only factor predictive of response: LDH wnl
PTLD: pathogenesis-driven treatment approach

• Eradication of the malignant clone: role of (more) rituxan
  • Gonzalez-Barca, et al. (Haematologica, 2007)
    • Multi-center, prospective phase II trial
    • 38 patients: all prior RI; 18% P-PTLD, 82% M-PTLD (90%DLBCL); 70% EBV+
    • Adaptive trial design with initial +/- additional rituxan course

```
<table>
<thead>
<tr>
<th>Registered n=41</th>
</tr>
</thead>
<tbody>
<tr>
<td>Included 1st rituximab course n=38</td>
</tr>
<tr>
<td>Failure N=8</td>
</tr>
<tr>
<td>PR N=17</td>
</tr>
<tr>
<td>CR N=13</td>
</tr>
<tr>
<td>Progression N=5</td>
</tr>
<tr>
<td>Included for 2nd rituximab course N=12</td>
</tr>
<tr>
<td>PR N=2</td>
</tr>
<tr>
<td>CR N=10</td>
</tr>
<tr>
<td>R-chemotherapy n=3</td>
</tr>
<tr>
<td>R-chemotherapy n=3</td>
</tr>
<tr>
<td>R-chemotherapy n=2</td>
</tr>
</tbody>
</table>

34% CR
83% CR
60.5% CR ITT |
```
PTLD: pathogenesis-driven treatment approach

- **Eradication of the malignant clone: chemoimmunotherapy**
  - 74 SOT PTLD pts with SD/PD after RI
    - P-PTLD: 4%, M-PTLD: 96% (81% DLBCL); EBV+ 44%
  - Rituxan weekly x4, followed by CHOP-21 x4
    - Sequential therapy to reduce R-CHOP TRM in PTLD (up to 31% in retrospective reports)
  - ORR: 90% (CR in 68%), TRM 11%, mOS 79mo
  - No diff in OS for EBV+ vs EBV- (although improved PFS for EBV+)
  - Favorable outcomes when compared to prior rituxan-only patients who relapsed and then went on to receive combination R-chemo
    - Upfront sequential rituxan→CHOP is superior to R then R-CHOP at relapse
PTLD: pathogenesis-driven treatment approach

PTLD: pathogenesis-driven treatment approach

- Eradication of the malignant clone: chemoimmunotherapy
  - Trappe, et al (JCO 2012, abstract 8030)
    - 2007 trial amendment: Risk-Stratified Sequential Treatment (RSST)
      - N=91 pts, 87% M-PTLD, 45% EBV+
      - All pts received rituxan 375mg/m2 weekly x4
        - If CR (low risk; 27%) → rituxan ‘consolidation’ 375mg/m2 q3weeks x4
        - If no CR (high risk; 73%) → RCHOP-21 x 4
    - ORR 93% (CR 78%)
    - No difference in relapse for low risk pts tx’d with R consolidation (13%) vs CHOP
    - For high risk patients, RCHOP outperformed CHOP (65% CR vs 27%CR)
    - 3yr OS for RSST vs ST with trend toward improvement (70% vs 61%), non-sig p
PTLD: pathogenesis-driven treatment approach

- Eradication of the malignant clone: chemoimmunotherapy
  - NCT02042391 (PI: Trappe)
    - Risk stratify based on response to rituxan as well as IPI
      - Low risk: CR with R or PR with R and IPI 0-2 → rituxan consolidation
      - High risk: SD/PD with R or PR with R and IPI>2 → RCHOP x4
  - Enrolling 90pts, open 12/2014
PTLD: pathogenesis-driven treatment approach

- Initial treatment summary:
PTLD: pathogenesis-driven treatment approach

- EBV as a therapeutic target: adoptive immunotherapy
  - 5 pts post TCD alloBMT with development of EBV+ M-PTLD (DLBCL)
  - Treated with unseparated DLI

### Table 1. Characteristics of the Patients and Outcome of Treatment.

<table>
<thead>
<tr>
<th>No</th>
<th>Sex/ Age (Yr)</th>
<th>Diagnosis</th>
<th>Type of Graft</th>
<th>Conditioning Regimen</th>
<th>EBV VCA IgG Titer</th>
<th>Onset of EBV-Associated LPHD</th>
<th>Donor Leukocyte Infusion</th>
<th>Patient</th>
<th>Donor</th>
<th>Day of Treatment</th>
<th>Dose</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F/20</td>
<td>ALL</td>
<td>HLA-matched, unrelated donor</td>
<td>30 mg/kg/day on days -5, -4</td>
<td>1:1280</td>
<td>1:80</td>
<td>90</td>
<td>0.55 x 10^6</td>
<td>Clinical and pathological response; 2nd biopsy on day 139 showed no evidence of disease; alive and well with limited chronic GVHD on day 300</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>M/29</td>
<td>CML</td>
<td>HLA-matched, related donor</td>
<td>30 mg/kg/day on days -5, -4</td>
<td>1:80</td>
<td>1:60</td>
<td>74</td>
<td>1.0 x 10^6</td>
<td>Died of respiratory failure on day 94; autopsy showed no evidence of lymphoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>F/52</td>
<td>ANLL</td>
<td>HLA-matched, related donor</td>
<td>15 mg/kg every other day on days 5, 7, 9, 11, 13</td>
<td>1:80</td>
<td>1:60</td>
<td>107</td>
<td>1.0 x 10^6</td>
<td>Died of respiratory failure on day 130; autopsy showed no evidence of lymphoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>M/43</td>
<td>CML</td>
<td>HLA-matched, related donor</td>
<td>30 mg/kg/day on days -5, -4</td>
<td>1:10</td>
<td>1:20</td>
<td>113</td>
<td>0.8 x 10^6</td>
<td>Complete response; a 2nd biopsy on day 142 showed no evidence of disease; chronic GVHD of oral mucosa; alive 18 mo post-transplantation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>F/33</td>
<td>ANLL</td>
<td>HLA-matched, related donor</td>
<td>None</td>
<td>1:320</td>
<td>1:80</td>
<td>127</td>
<td>1.0 x 10^6</td>
<td>Complete response; chronic GVHD, alive post-transplantation</td>
<td></td>
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</tbody>
</table>
PTLD: pathogenesis-driven treatment approach

• EBV as a therapeutic target: adoptive immunotherapy
    • 10pts s/p TCD alloBMT; EBV seropositive
      • 3 with EBV viral reactivation, 1 with M-PTLD
    • All pts received **EBV-specific donor lymphocytes**
    • None of 7 EBV VL negative patients experienced EBV reactivation, PTLD or GVHD at 11mo f/u from infusion
  • Of the 3 EBV VL+ patients:
PTLD: pathogenesis-driven treatment approach

• EBV as a therapeutic target: adoptive immunotherapy
  • Haque, et al (Blood 2007)
    • First prospective trial evaluating safety/efficacy of allogeneic CTLs in PTLD
    • 33 patients (31 SOT, 2 HSCT)
      • All with EBV+ PTLD, refractory to initial therapy
    • Weekly infusion of $2 \times 10^6$ EBV-specific CTLs/kg x 4 weeks
  • ORR 64% at 5 weeks, 52% at 6 months
    • 12 pt in CR at 5 weeks, 14 pts in CR at 6 mo
    • 13/14 CR patients remained disease free at 1-7.5 years follow up
  • No difference in response by type of PTLD (E-PTLD, P-PTLD, M-PTLD)
    • Improved response with increased CD4+ cells/kg and tighter HLA matching
PTLD: pathogenesis-driven treatment approach

• EBV as a therapeutic target: adoptive immunotherapy
  • Haque, et al (Blood 2007)
PTLD: pathogenesis-driven treatment approach

• EBV as a therapeutic target: CTL adoptive immunotherapy
  • Potential promise in EBV+ PTLD
    • Possible role as pre-emptive strategy
  • Limited by institutional availability and cost
  • Additional trials ongoing
PTLD: pathogenesis-driven treatment approach

- Vaccine therapy (pre-emptive and therapeutic)
- Lytic inducers coupled with antiherpesvirus agents
  - Drive memory B-cell out of latent phase, then eliminate virus with ACV/GCV
- Targeted approaches:
PTLD: a word on EBV negative disease

• Incidence is on the rise:
PTLD: a word on EBV negative disease

- Similar response to therapy as EBV+ disease:

<table>
<thead>
<tr>
<th>Table 2: Best response to initial therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response</td>
</tr>
<tr>
<td>All patients</td>
</tr>
<tr>
<td>Complete response, n (%)</td>
</tr>
<tr>
<td>Partial response, n (%)</td>
</tr>
<tr>
<td>Stable disease, n (%)</td>
</tr>
<tr>
<td>Progressive disease, n (%)</td>
</tr>
<tr>
<td>Unknown, n</td>
</tr>
<tr>
<td>RI only</td>
</tr>
<tr>
<td>Complete response, n (%)</td>
</tr>
<tr>
<td>Partial response, n (%)</td>
</tr>
<tr>
<td>Stable disease, n (%)</td>
</tr>
<tr>
<td>Progressive disease, n (%)</td>
</tr>
<tr>
<td>Unknown, n</td>
</tr>
<tr>
<td>Rituximab with or without RI</td>
</tr>
<tr>
<td>Complete response, n (%)</td>
</tr>
<tr>
<td>Partial response, n (%)</td>
</tr>
<tr>
<td>Stable disease, n (%)</td>
</tr>
<tr>
<td>Progressive disease, n (%)</td>
</tr>
<tr>
<td>Unknown, n</td>
</tr>
<tr>
<td>Chemo ± RI ± Rituximab</td>
</tr>
<tr>
<td>Complete response, n (%)</td>
</tr>
<tr>
<td>Partial response, n (%)</td>
</tr>
<tr>
<td>Stable disease, n (%)</td>
</tr>
<tr>
<td>Progressive disease, n (%)</td>
</tr>
<tr>
<td>Unknown, n</td>
</tr>
</tbody>
</table>

EBV, Epstein–Barr virus; PTLD, posttransplantation lymphoproliferative disorder; RI, reduction of immunosuppression.
PTLD: a word on EBV negative disease

- Similar survival outcomes as EBV+ disease:

![Graph showing comparison between EBV positive and EBV negative survival outcomes](image-url)
Back to the case...

• GM

  • Assessment:
    • Relapsed WM (SPEP, IgM, PB flow)
    • ?relapsed PTLD (LAD in similar pattern as prior)
      • Unable to biopsy
      • Role of PET unclear given known concurrent WM
      • On minimal tacro dose
    • Needs semi-urgent treatment for WM
    • Prior good response to rituxan monotherapy

• Plan
  • Treat relapsed WM +/- component of PTLD with chemoimmunotherapy
PTLD: Take home points

• Heterogenous group of disorders ranging from benign hyperplasia to aggressive lymphoma
• Prototype for EBV-driven oncogenesis and model disease for EBV-directed therapies
• RI is mainstay of therapy, R +/- combination chemotherapy for high risk disease
• EBV directed therapies present future promise for refractory EBV+ dz
• More research into pathogenesis of EBV negative disease is needed
References


Thank you

• Questions?
PTLD pathogenesis: a brief foray into EBV virology