Post Transplant Lymphoproliferative disorder – An update

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**Definition of PTLD**

Are lymphomas that occur after solid organ (up to 10%) or stem cell transplantation

Cause by a proliferation of lymphoid tissue

It is most common form of post transplant malignancy in children and in adults 2\(^{nd}\) most common after skin cancer

In children and adults common cause of cancer related mortality after solid organ transplantation and reported overall mortality often exceeds 50%

In Europe and US 85% are B cell lineage and most > 80% are associated with EBV infection.

Around 10-15% of PTLD are of T cell lineage around 30% which are associated with EBV
## Incidence PTLD: Adult and Paediatric

<table>
<thead>
<tr>
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<th>Adult %</th>
<th>Paediatric %</th>
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</thead>
<tbody>
<tr>
<td>Renal</td>
<td>1-2.3</td>
<td>1.2-10</td>
</tr>
<tr>
<td>Liver</td>
<td>1-2.8</td>
<td>4-15</td>
</tr>
<tr>
<td>Heart</td>
<td>1-6.3</td>
<td>6.4-19.5</td>
</tr>
<tr>
<td>Heart Lung</td>
<td>2.4-5.8</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>4.2-10</td>
<td></td>
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<tr>
<td>Small Bowel</td>
<td>20</td>
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Risk higher in Children – higher incidence of EBV
Transplanted organ or bone marrow may contain EBV
Infected cells, EBV infection very common

*Taylor et al Cr Review Oncology Haematology 2005*
## Comparison of SOT-PTLD and HSCT-PTLD

<table>
<thead>
<tr>
<th>Transplant population</th>
<th>Incidence</th>
<th>Timing of PTLD development</th>
<th>EBV demonstrated in tumour</th>
<th>PTLD origin</th>
<th>Prognosis</th>
<th>Specific risk factors</th>
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</thead>
<tbody>
<tr>
<td>SOT-PTLD</td>
<td>1–20% depending on the organ</td>
<td>Bimodal</td>
<td>Frequently EBV-positive</td>
<td>Recipient</td>
<td>Variable</td>
<td>EBV seromismatch, very young or very old recipients</td>
</tr>
<tr>
<td>HSCT-PTLD</td>
<td>&lt;2%</td>
<td>Mainly early-onset</td>
<td>Mainly EBV-positive</td>
<td>Donor</td>
<td>Variable</td>
<td>EBV seromismatch, higher grades of graft-versus-host disease, pre-transplant splenectomy</td>
</tr>
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</table>
**Classified into 4 types**

1. Early lesion – which normally regress if immune suppression reduced

2. Polymorphic PTLD (P-PTLD) lesions which contain a mixture of different types of cells

3. Monomorphic (M-PTLD) : which contains 1 type of cell and is the most common type of PTLD

   It is usually a Non Hodgkin Lymphoma- Morphologically Diffuse Large B cell lymphoma is the most common type of M-PTLD, but occasionally other types such as Burkitt lymphoma and other rarer types can occur (such as T NHL)

4. Classical Hodgkin lymphoma type – which is very rare
Histopathological markers for PTLD

**a** | CD20-positive stain in monomorphic post-transplant lymphoproliferative disease (PTLD).

**b** | Epstein–Barr virus (EBV)-encoded RNA (EBER)-positive stain in monomorphic PTLD.

**c** | Immunostaining for CD30 shows both cytoplasmic and Golgi staining characteristic of Reed–Sternberg cells in Hodgkin PTLD.

**d** | Immunostaining for CD15 shows its presence in the Reed–Sternberg cells in Hodgkin PTLD.

Clinical features

Highly variable presentation: requires high index of clinical suspicion

50% fever, 30% lymphadenopathy (solitary or multiple)

Non-specific symptoms such as tonsillitis (more in children) and weight loss / abdominal symptoms

15% emergency surgical presentation – intestinal perforation often small / large bowel

Small group fulminant presentation – disseminated disease / systemic symptoms

CNS involved into 30% of PTLD and in many of these cases the disease maybe confined to the CNS
**Diagnosis**

Histological examination of biopsy tissue

Excision is preferable to incision needle

FNA is not adequate

**Histology**

Presence of EBV by IHC and FISH

Cellular infiltrates with IHC CD Ag staining

Staging as for conventional NHL

**Imaging**

CT – C/A/P/N

PET/CT – (preferred method – excellent for extranodal disease)
Markers

IHC : Ki-67, Ig Heavy chains, CD 10, BCL 2, BCL 6, Cyclin D1, CD21, CD23, CD38, IRF4/MUM-1, PAX 5

EBV : EBV – LMP-1 or EBER ISH (if EBV LMP 1 negative, EBER ISH is recommended)

Molecular : Ig and TCR gene re arrangements

Further tests in certain circumstances

To reveal definitive histological subtype
Clinical work up

PS
LDH, U&Es, Creatinine
FBC differential
Hep B testing
C/A/P CT
Full body PET/CT

Further

Echocardiogram / MUGA
Bone marrow exam
Brain MRI with / without Contrast
EBV serology : Primary versus reactivation
EBV PCR
CMV PCR

Early lesions
Polymorphic
Monomorphic
Classical Hodgkin lymphoma
T cell PTLD
Typical case

2004

1 stone weight loss, change in BH
Central / upper abdominal pain 5/52

I/S : FK506 3mg bd

Azathioprine 150mg od
Jejunal biopsy
No evidence of Carcinoma
High power
Final diagnosis = DLBCL [EBV –ve]
Subsequent joint follow up management :: Renal and Haematology

Treatment commenced with R-CHOP

6 Further cycles well tolerated

Repeat interim CT –PET complete response

End of treatment scan CMR
Pathogenesis
Life cycle of EBV infection to PTLD development

EBV enters submucosal cells
Viral gene expression induced
B cell blasts kept in check by host CTLs
Immune suppression ↓ CTL
PTLD development

Dharnidharka, V. R. et al. (2016) Post-transplant lymphoproliferative disorders
Nat. Rev. Dis. Primers doi:10.1038/2015/
Immune response triggered by latently infected B cells with or without immunosuppression

**Normal response**

EBV Ag expression: LMP1, 2A, EBNA

Infected cell recognised by host CD4/ CD8

Apoptosis induced via FAS/FASL (Caspase 8 mediated)

**Transplant scenario**

I/S: Blunt immune response

EBV cell + IL-6 autocrine growth factor. IL-10 suppress Antiviral activity

Exhaustion via PDL-1, PD-1

c FLIP – homologue of caspase 8 – disrupts activation

Schematic diagram of EBV-mediated oncogenic signalling pathway activation in EBV-positive diffuse large B-cell lymphoma of the elderly.

Chi Young Ok et al. Blood 2013;122:328-340
Treatment
**Options**

Reduced immune suppression

Immunotherapy – Single Agent Rituximab

Chemotherapy agents

Radiotherapy

Surgery – often required for fulminant emergency presentation, excision and assessment for further adjuvant therapies above

Future: Novel agents
European PTLD trials

Dr R Trappe, Dr S Choquet

(Germany/France)
**Results**

**PTLD-1**:

70 Patients – trial examined use of single agent 4 x R followed by R-CHOP

ORR  60% after rituximab alone (20% CR)
   90% after R-CHOP
   Median PFS  4 years
   Median OS  6.6 years

Treatment related mortality 10.6%

**PTLD-2**:

Patients who received rituximab monotherapy and achieved CR – amendment made so patients received 4 further injections rituximab injections every 3 weeks and stopped (so 8 injections in total alone)

If the response was incomplete patients received 4 cycles of R-CHOP,
The results published in abstract form (ASH 2016) show similar results CR to 4R + 4- R-CHOP  but lower toxicity = termed “sequential treatment”
Trial Schema: response adapted approach

- **4R**
  - **CR**
    - Low risk
      - Further x 4R stop
  - **PR, SD, PD**
    - High Risk
      - Further 4 cycles R-CHOP21 + GCSF
Patients with a complete remission at day 50 will not receive chemotherapy and will go on with rituximab (R) single agent (8 injections in total).

Establishing the concept of “response adapted approach”
Current PTLD Management approach

**PTLD Subtype** | **First line therapy** | **Initial response** | **Second line therapy**
---|---|---|---
EARLY LESIONS | RI | Complete response | Manage IS and monitor EBV PCR

SYSTEMIC | RI | Persistent or Progressive disease | Rituximab and monitor EBV PCR

POLYMORPHIC | Ri, if possible and RT +/- Rituximab | Complete response | Monitor EBV PCR and observation or Continue RI if possible +/- Maintenance

LOCALISED | Ri, if possible and RT +/- Rituximab Surgery +/- Rituximab or Rituximab alone | Persistent or progressive disease | Chemo-immunotherapy or Clinical Trial or EBV CTL

MONOMORPHIC | Ri, if possible and or Rituximab alone | Complete response | See appropriate histology guidelines

| | Chemo-immunotherapy | Persistent or Progressive disease | RI/R/Chemo-immunotherapy Clinical Trial / EBV CTL
**Treatment Regimens**

**Sequential chemo-immunotherapy**

Rituximab 375 mg/m2 x 4 weeks

Restage with PET/CT

- If PET/CT scan negative, rituximab 375mg/m2 every 3/52 x 4 cycles
- If PET/CT scan positive, CHOP 21 every 3 weeks x 4cycles
  Prophylaxis for tumour lysis syndrome

**Concurrent immuno-therapy**

R-CHOP (rituximab , cyclophosphamide, doxorubicin, vincristine, prednisolone)

For frail patients:
R-CVP
R-CEPP
R-CEOP
PTLD in adults after SOT: What to do? a treatment algorithm

EBV-associated PTLD with EBV-reactivation and non EBV-associated PTLD

**Immunosuppression reduction (IR)**

**CD20-positive PTLD**
- Early lesion
- Polymorphic PTLD
- DLBCL-type PTLD
- Burkitt-PTLD
- pCNS PTLD

**CD20-negative PTLD**
- Plasmocytoma-like and Hodgkin-PTLD
- Plasmablastic- and T-cell PTLD

**Antiviral treatment + IR**
- Early lesion... DLBCL-type PTLD
  - no CR
  - IVIG
    - no CR
    - 4 courses rituximab
      - +/- 4 additional courses R
    - surgical resection / radiotherapy
      - 4 courses rituximab (R)
      - 4xR plus HD-MTX or 4xR plus WBRT
      - Sequential treatment (ST):
        - 4 courses rituximab (R) followed by 4 cycles of CHOP-21 + GCSF in fixed sequence
      - 4# PAD or ABVD + GCSF (if response but no CR after 4 cycles: additional cycles)

**Ann Arbor stage I**
**Ann Arbor stage II-IV**
**Ann Arbor any stage**
Serial FDG-PET/CT scans are shown from a patient presenting with a massive abdominal localization of a Burkitt non-Hodgkin post-transplant lymphoproliferative disease (PTLD) (part a)

After four weekly injections of rituximab, a complete response was obtained (part b)

The patient received 4 more rituximab injections at 21-day intervals. At the last evaluation, 5 years later, complete response was maintained (part c)
Sequential therapy

PTLD : DLBCL abdominal

Post 4 x R weekly : PR

4 Further R-CHOP : CMR

Dharnidharka, V. R. et al. (2016) Post-transplant lymphoproliferative disorders
Maximum-intensity projection $^{18}$F-FDG–PET/CT images

Baseline image showed multiple supra- and infradiaphragmatic nodal lesions and extranodal lesions in breast, intestines, and bone marrow (left);

$^{18}$F-FDG–PET/CT after 4 cycles of therapy showed a complete metabolic response in all nodal and extranodal lesions, with the exception of limited residual hypermetabolic lesions in the intestinal tract adjacent to the kidney transplant in the right iliac fossa (right).

Daan Dierickx et al. Blood 2015;126:2274-2283
Future: Use of targeted agents
“TIDAL” study

Risk-stratified sequential Treatment with Ibrutinib and Rituximab (IR) and IR-CHOP for De-novo post-transplant Lymphoproliferative disorder (PTLD) :
CI : Dr T Manne : Newcastle

Trial Design: This is a prospective, phase 2, single arm trial evaluating the addition of ibrutinib to rituximab (IR) therapy in patients diagnosed with PTLD.

Patients will receive IR combination therapy for seven weeks, after which they will receive IR (if categorised as low risk) or IR-CHOP chemotherapy (if categorised as high risk).

Objectives

Primary objective: The primary objective is to evaluate complete remission (CR) after seven weeks of therapy.

Secondary objectives: The secondary objectives are to evaluate response, event-free survival (EFS), overall survival (OS), progression-free survival (PFS), treatment-related mortality, frequency of grade III and IV leucocytopenia and grade III and IV infections and patients entering into low and high risk arms after IR therapy.
Mechanism of action of Ibrutinib – BTK inhibitor
Patient Consent

Eligibility checked (PET/CT/MUGA)

Rituximab on Day 1, 8, 15 and 22
Ibrutinib D1-49

CT Scan between 42-47

Low Risk

Four 3 weekly cycles of Rituximab on D50,71,92,113 + Ibrutinib on Days 50-133

Response assessment: PET/CT around D155 (6 post Rituximab treatment)

Patients followed up every 4/12 for 2 years
CT scan at 12 months

High Risk

Four 3 Weekly cycles of R-CHOP on D50,71,92,113
Ibrutinib on D50—133

Low Risk: Either CR or PR with initial IPI 0-1

High Risk: PR with an initial IPI 2-5 or stable or progressive disease

If at any time point clinical progressive disease is identified during initial IR therapy go to straight to high risk arm
Inclusion criteria

- Untreated CD20 positive PTLD with or without EBV association, biopsy positive upfront reduction of immune suppression with or without anti viral therapy is permissible
- PTLD with meningeal or CNS involvement can be included
- Clinically insufficient response to upfront RI
- Plts > 100 or > 50 if BM + ve, ANC > 1, independent of GCF
- CrCl ≥ 30 ml/min, AST or ALT ≤ 3 ULN, Bilirubin ≤ 1.5 ULN
- PTT / APPT ≤ 1.2 ULN
- LVEF > 50%
- ECOG ≤ 2, Age > 16
**Conclusions / Future perspectives**

Response adapted approach according to risk internationally adopted, has improved results

Integrating national registries prospectively – mandatory reporting of PTLD in all transplant trials, better capture of data

Identifying new risk factors – better assessment/ surrogates for immune suppression load and association with PTLD risk, with HLA association and Non EBV

Refining WHO 2008 classification to include impact of EBV (negative, positive, latency type, lytic activation) stromal microenvironment, molecular findings

Better preventive strategies (e.g. EBV PCR, cytokine gene polymorphisms)

Drive to create international cooperation and inclusion of patients in prospective international trials

Enhanced risk adapted strategies to pick our poor risk

Better biological understanding EBV –ve cases; why in EBV + cases primary infection carries a higher risk of PTLD versus reactivation infection
References


Thank you!