Post-transplant Lymphoproliferative Disease (PTLD) in Allogeneic Hematopoietic Cell Transplantation

Leslie Smith, RN, AOCNS, APRN-CNS
Objectives

1. Describe the risk factors associated with Post-transplant Lymphoproliferative Disease (PTLD).
2. Identify the clinical manifestations of PTLD.
3. Discuss strategies to prevent the development of PTLD.
4. Describe treatments for PTLD.
5. Discuss the implications for nursing practice.
Definition and Etiology

- Post transplant malignancy of B cells or T/NK cells
- One of the most common post transplant malignancies (solid organ and HCT)
- Associated most often with EBV infection (55%-65%)
- PTLD may not be associated with EBV-prognosis worse
- Caused by reactivation of EBV in B cells (lifelong dormant infection)-most common in solid organ recipients
- OR new infection (donor graft-majority of cause in HCT recipients or environmental exposure-less likely)
T-cell suppression:
- Post-transplant: Immunosuppressive pharmacologic therapy to reduce GVH: decreased T-cell immune surveillance (CD4, CD8, and NK cells important in controlling proliferation of infected B-cells)
- T-lymphocyte ablative therapy preparative regimen: allows for proliferation of infected B cells
- T-cell depleted graft (reduce risk of GVH)
Classification important for treatment and diagnosis:

- Early lesions: B-cell origin; typically EBV-positive; polyclonal
- Infectious mononucleosis-type illness; rarely transforms to malignant
- Polymorphic PTLD: EBV-positive; monoclonal:
  - Demonstrate evidence of malignant transformation but do not meet the criteria for a B or T cell lymphoma recognized in immunocompetent patients
- Monomorphic PTLD:
  - EBV positive: B-cell lymphoma (Burkitt’s, DLBCL, plasma cell myeloma, plasmacytoma-like lesion)
  - EBV-negative: T/NK cell neoplasm, PTCL not otherwise specified
- Classic HD-like PTLD: EBV positive
- Small B cell lymphomas (follicular) and MALT (mucosa associated lymphoid tissue) post transplant not considered PTLD
- Use of T-cell depleted products
- Degree of T-cell immunosuppression
- Agents that suppress T-cells associated with increased risk
  - ATG, OKT3, IL2, tacrolimus, sirolimus, calcineurin inhibitors
- EBV status of recipient
- In HCT recipients, majority is from donor
- Time post transplant: greatest risk in first year
• Age: >50 and < 10
• Ethnicity: Caucasians
• Fewer HLA match
• Second transplant
• Transplant for immunodeficiency
• Chronic GVH
• Cord blood transplants
• Haploidentical transplants
• HLA-mismatched transplants
• May be associated with HHV-8 in PEL
• Unidentified viruses
• Later onset, monomorphomic, more aggressive course

**EBV-negative disease**
• 1-2% within over 5 years in HCT

• Risk increased with one or more risk factors
• Suspected in pts. post allogenic transplant who present with adenopathy, B symptoms, unexplained hematologic or biochemical abnormalities
• Anorexia
• Fatigue
• Fevers
• Lymphadenopathy
• Multiorgan failure
• Sepsis-like syndrome
• Weight loss
• Unexplained anemia, thrombocytopenia, or leukopenia
• Elevated level of serum lactate dehydrogenase (LDH)
• Hypercalcemia
• Hyperuricemia
• Monoclonal protein in the serum or urine
• EBV load: 3225 copies/100 microml as compared to < 740 without PTLD
• PET scan positive
• Positive tissue biopsy
EBV positive B-Cells
• Degree of T-cell immunosuppression a determinant of development
• Serological testing of EBV antigens in recipient weekly
• EBV viremia arise as early as three weeks prior to disease onset
• No firm recommendations for threshold for initiation of preemptive treatment
• Primary goals of preemptive treatment: preservation of allograft and disease control
• Immunosuppression reduction considered first line treatment
• Rituximab if no decrease in EBV load
• Infusions of donor-derived EBV specific T-cells
• Manipulated DLI
• Reduction in immunosuppression as initial treatment
• Up to 40% of pts will achieve regression
• Works better for pts with polyclonal, less aggressive dz
CD 20 positive lymphoma and PTLD
Up to 69% response rate in one study (Milpied, et. al., 2000)
Relapse frequent

- Proceed to R CHOP with relapse or as up front therapy
- CHOP alone for CD20 negative dz, failure of immunotherapy reduction, clinically fulminant PTLD including CNS involvement (MTX IT)
- Antiviral therapy with ganciclovir or acyclovir or foscarnet not effective
- Interferon alpha—anecdotal reports of efficacy
  - Inhibits growth of infected B-cells
  - Suppresses helper T-cells
  - Antiviral and proinflammatory agent
• IVIG-contains EBV antibodies (EBNA)
• Adoptive immunotherapy:
  - High risk pts: EBV-specific cytotoxic T cell infusions
  - Reduction of EBV DNA in blood
  - No increased risk of GVHD
  - Higher percentage of CD4 cells did better
  - Closer HLA matching
EBV polymerase chain reaction (PCR) amplification assays:
- Monitored by whole blood EBV quantitative PCR beginning on the day of transplant and continuing for at least 3 months. At the NIH Clinical Center, the EBV PCR testing is grouped with cytomegalovirus (CMV) testing by default so essentially all patients who are monitored for CMV are monitored for EBV.

- Monitoring whole blood EBV PCR should continue after 3 months in haploidentical transplant recipients, cord blood transplant recipients, recipients with refractory GVHD, and those recipients who have on-going EBV reactivation and who remain on immunosuppression and/or have poor cellular immune reconstitution.

- Monitoring EBV PCR may be done more frequently (e.g. twice weekly) in those recipients with rising EBV viral loads.
  - It is important to note that when monitoring EBV PCR, the trajectory of a series of values (serial monitoring) is more helpful than a single result.
  - Patients with EBV viremia pre-transplant should be monitored as all other HSCT patients. No up-front intervention is usually necessary.
Consider screening HSCT recipients with imaging by CT-PET for:

- All HSCT recipients who have an increase of 5 log in EBV PCR
- High-risk HSCT recipients with an increase of 3 log in EBV PCR
- Any significant or rising EBV viremia when clinical disease consistent with PTLD (e.g. fever, lymphadenopathy) is suspected or documented on physical exam.
• Consider a reduction in immunosuppression when clinically feasible even if preemptive therapy is being considered.

• The preemptive administration of rituximab based on a rising EBV PCR may be considered in high risk HSCT recipients, particularly cord blood transplant recipients and T-cell depleted transplant recipients, especially when symptoms consistent with PTLD are present.

• In patients treated with rituximab, monitor quantitative immune globulin levels (IgG) and consider intravenous immunoglobulin (IVIG) supplementation (0.5 grams/kg/dose) to maintain an IgG level > 400 mg/dl.
Nursing Implications

- Education of patient of risk
- Education regarding serial testing
- Communication of lab results to PI/attending
- Education surrounding rationale behind treatment