13. Post-transplant Lymphoproliferative Disorder

Allen UD, Preiksaitis JK. Epstein-Barr virus and posttransplant lymphoproliferative disorder in solid organ transplantation. Am J Transplant. 2013;13 Suppl 4:107-20. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/23465004

- AST Infectious Diseases Community of Practice summary of recommendations and supporting data that guide the prevention, diagnosis and treatment of PTLD in the solid organ transplant recipient. Relevant aspects of non-PTLD EBV syndromes are also addressed.

Blaes AH, Peterson BA, Bartlett N, Dunn DL, Morrison VA. Rituximab therapy is effective for posttransplant lymphoproliferative disorders after solid organ transplantation: results of a phase II trial. Cancer. 2005;104(8):1661-7. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/16149091

- Retrospective review of 11 transplant recipients (4 kidney, 1 heart, 1 kidney-pancreas, 4 single-lung, and 1 bilateral lung) at two U.S. centers diagnosed with PTLD treated with rituximab. Immunosuppressive therapy was reduced in dose or discontinued in all patients at the discretion of the managing physician. Three patients received a course of acyclovir.
- The overall response rate was 64% (6 complete remission, 1 partial remission, 2 progressive disease, and 2 deaths) and 55% complete remission rate.

Choquet S, Leblond V, Herbrecht R, et al. Efficacy and safety of rituximab in B-cell post-transplantation lymphoproliferative disorders: results of a prospective multicenter phase 2 study. Blood. 2006 Apr 15;107(8):3053-7. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/16254143

- Phase 2 study conducted at 15 French and 4 Belgian centers between May 2000 and December 2001. Forty-six patients with untreated B-PTLD that were not responding to tapering of immunosuppression were included and 43 patients (18 kidney, 11 heart, 7 liver, 4 lung, and 3 heart-lung) were analyzed.
- Treatment consisted of 4 weekly injections of rituximab at 375 mg/m^2. Immunosuppressive drugs were stopped if possible, or dosage reduced by at least 50% and/or the number of drugs reduced to no more than two. At day 80, 37 (86%) patients were alive and the response rate was 44.2%, including 12 complete response. The overall survival rate at 1 year was 67%.

Dharnidharka, Vikas R. Comprehensive review of post–organ transplant hematologic cancers. Am J Transplant. 2018;18(3):537-549. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/29178667

- Comprehensive review of hematologic cancers, including PTLD, following solid organ transplant.

DeStefano CB, Desai SH, Shenoy AG, et al. Management of post-transplant lymphoproliferative disorders. Br J Haematol. 2018;182(3):330-343. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/29741774

- Comprehensive review of PTLD following solid organ transplant and hematopoietic stem cell transplant with a focus on management. Provides overview of ongoing clinical trials of novel agents.

Dierickx D, Habermann TM. Post-Transplant Lymphoproliferative Disorders in Adults. N Engl J Med. 2018;378(6):549-562. Retrieved from: http://www.nejm.org/doi/full/10.1056/NEJMra1702693

- A comprehensive review of PTLD in adult transplant recipients, including solid organ transplant and bone marrow transplant.

Ghobrial IM, Habermann TM, Macon WR, et al. Differences between early and late posttransplant lymphoproliferative disorders in solid organ transplant patients: are they two different diseases? Transplantation. 2005;79(2):244-7. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/?term=15665775

- Retrospective review of SOT patients diagnosed with PTLD at a single U.S. center between December 1970 and May 2003. Early PTLD was defined as PTLD that occurs within 1 year post-transplant. The authors concluded that patients with early PTLD were likely to be EBV+, CD20+, and more commonly involved the grafted organ.

Jain AB, Marcos A, Pokharna R, et al. Rituximab (chimeric anti-CD20 antibody) for posttransplant lymphoproliferative disorder after solid organ transplantation in adults: long-term experience from a single center. Transplant. 2005;80(12):1692-8. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/16378063

- A report of a single U.S. center's utilization for rituximab in PTLD as salvage therapy on long-term outcomes. The authors found poor response rates and survival rates compared to other studies. The patients in the analysis had a high tumor burden and did not receive surgical interventions prior to rituximab.

Johnson SR, Cherikh WS, Kauffman HM, et al. Retransplantation after post-transplant lymphoproliferative disorders: an OPTN/UNOS database analysis. Am J Transplant. 2006;6(11):2743-9. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/17049062

- The Organ Procurement and Transplant Network/United Network for Organ Sharing database was reviewed for individuals who developed PTLD and underwent retransplant from 1987 through 2004.

Oertel SH, Verschuuren E, Reinke P, et al. Effect of anti-CD 20 antibody rituximab in patients with post-transplant lymphoproliferative disorder (PTLD). Am J Transplant. 2005;5(12):2901-6. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/16303003

- A multi-center, prospective study investigated the use if rituximab in 17 patients with PTLD (5 heart, 4 kidney, 4 lung, and 4 liver) between 1999 and 2002. Patients were treated with four weekly doses of 375 mg/m^2 of rituximab. Immunosuppressive therapy was reduced in all patients prior to their entry into the study protocol. Complete remission was achieved in 9 patients (52.9%) with a mean duration of 17.8 months; interestingly, these 9 PTLD cases were EBV-associated. The mean overall survival period was 37.0 months with 11 patients still living at the time of publication.

Martínez-Calle, N, Alfonso A, Rifón J, et al. First-line use of rituximab correlates with increased overall survival in late post-transplant lymphoproliferative disorders: retrospective, single-centre study. Eur J Haematol. 2017;98(1):38-43. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/27232286

- A retrospective study evaluating the impact of rituximab on PTLD response and survival in a single center cohort. PTLD cases between 1984 and 2009, including heart, kidney, liver, and lung transplant recipients were included (n=24). Chemotherapy regimen was up to physician's choice along with reduction in immune suppression. Nearly 50% of patients were switched to sirolimus for immunosuppression after PTLD diagnosis but the authors did not find this change to impact response to treatment or survival within the study time period. The median time to diagnosis in this series was beyond 5 years after transplantation.

- Overall response rate (ORR) was 62% (66% rituximab vs. 50% non-rituximab; p = 0.5). R-CHOP-like regimens were used most frequently (72% of patients treated with rituximab). Median overall survival was 64 months (CI 95% 31-96). OS was significantly increased in patients treated with rituximab (p = 0.01; CI 95% rituximab 58-79 months; non-rituximab 1-30 months).

Reshef R, Vardhanabhuti S, Luskin MR, et al. Reduction of immunosuppression as initial therapy for posttransplantation lymphoproliferative disorder(★). Am J Transplant. 2011;11(2):336-47. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/21219573

- Retrospective review of solid organ recipients diagnosed with PTLD between August 1988 and June 2008 at a single U.S. center. Of 162 adult patients diagnosed, 148 were evaluated. Patients were treated with either reduced immunosuppression (RI) alone (n=67), surgical excision followed by RI (n=30), or other first line therapies with or without RI (n=51).
- The study demonstrated a 45% response rate from RI alone, with the majority being complete response. There was a 32% acute rejection rate with RI-containing regimens with some requiring a second transplant. Of note, monomorphic PTLD was diagnosed in 63% patients treated with RI alone vs. 39% patients treated with other first-line therapies, implying a selection of patients with monomorphic PTLD for treatment with RI alone (p=0.011). The study also identified the following risk factors for poor response: bulky disease, advanced stage, and older age.

Parker A, Bowles K, Bradley JA, et al. Management of post-transplant lymphoproliferative disorder in adult solid organ transplant recipients–BCSH and BTS Guidelines. Br J Haematol. 2010;149(5):693-705. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/20408848

- PTLD guidelines from a joint working group established by the Haemato-oncology subgroup of the British Committee for Standards in Haematology (BCSH) and the British Transplantation Society (BTS). This review details the therapeutic options recommended including reduction in immunosuppression, transplant organ resection, radiotherapy and chemotherapy.

Rouphael B, Lankireddy S, Lazaryan A, et al. Outcomes of kidney retransplantation in recipients with prior post-transplant lymphoproliferative disorder. Clin Transplant. 2016;30(1):60-5. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/?term=26497471

- A retrospective review of 8 kidney transplant recipients who developed PTLD and subsequently underwent retransplantation from 1963 to December 2012 at a single U.S. center. After a median follow-up of 62.5 months (range 2-125 months) allograft survival was 87.5% (7 functioning grafts, 1 failed graft from chronic rejection), with no recurrence of PTLD. Three patients died from causes other than PTLD.

Stanley K, Friehling E, Ranganathan S et al. Post-transplant lymphoproliferative disorder in pediatric intestinal transplant recipients: a literature review. Pediatr Transplant. 2018; 22(5):e13211. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/29745058

- A comprehensive review of PTLD in pediatric intestinal transplant recipients in regard to pathology, presentation, and management. Also provides a summary of cases reviewed from the literature.

Swinnen, Lode J., et al. Prospective study of sequential reduction in immunosuppression, interferon alpha-2B, and chemotherapy for posttransplantation lymphoproliferative disorder. Transplantation. 2008 Jul 27;86(2):215-22. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/18645482

- A multi-center, prospective, phase II study of 16 patients with biopsy-proven PTLD after any organ allograft (excluding lung) transplantation. A sequential approach was used in this study, starting with reduction in immunosuppression, escalating to interferon alpha2b, and finally to chemotherapy. The response rate to reduced immunosuppression was 0/16 complete remission and 1/16 (6%) partial remission. Six of the 16 patients (38%) had documented rejection during the period of reduced immunosuppression. 13 patients underwent treatment with IFN alpha with 2/13 (15%) complete remission and 2/13 (15%) partial remission. Lastly, 7 patients proceeded to ProMACE-CytaBOM chemotherapy with 67% complete remission.

Trappe RU, Dierickx D, Zimmermann H, et al. Response to Rituximab Induction Is a Predictive Marker in B-Cell Post-Transplant Lymphoproliferative Disorder and Allows Successful Stratification Into Rituximab or R-CHOP Consolidation in an International, Prospective, Multicenter Phase II Trial.(★) J Clin Oncol. 2017;35(5):536-543. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/?term=27992268

- Prospective, multicenter, open-label, phase II trial evaluating 152 CD20+ PTLD patients who failed reduced immunosuppression. All patients received rituximab whereby on day 50, if patients were complete responders would continue rituximab monotherapy. All others would receive R-CHOP. The study concluded that treatment stratification into rituximab or R-CHOP consolidation on the basis of response to rituximab induction is safe and effective.

Trappe R, Oertel S, Leblond V, et al. Sequential treatment with rituximab followed by CHOP chemotherapy in adult B-cell post-transplant lymphoproliferative disorder (PTLD): the prospective international multicenter phase 2 PTLD-1 trial. Lancet Oncol. 2012;13(2):196-206. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/?term=22173060

- International multicenter open-label phase 2 trial, treatment-naive adult solid-organ transplant recipients diagnosed with CD20-positive PTLD who had failed to respond to upfront immunosuppression reduction received four courses of rituximab (375 mg/m^2 IV) once a week followed by 4 weeks without treatment and four cycles of CHOP every 3 weeks. In case of disease progression during rituximab monotherapy, CHOP was started immediately.
- The primary endpoint was treatment efficacy measured as response rates in all patients who completed treatment with rituximab and CHOP, per protocol, and response duration, in all patients who completed all planned therapy and responded. Secondary endpoints were frequency of infections, treatment-related mortality, and overall survival.

Tsai DE, Hardy CL, Tomaszewski JE, et al. Reduction in immunosuppression as initial therapy for posttransplant lymphoproliferative disorder: analysis of prognostic variables and long-term follow-up of 42 adult patients. Transplantation. 2001;71(8):1076-88. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/11374406

- Retrospective review of 42 adult patients treated with either reduced immunosuppression (RI) with or without surgical resection of all known disease. 63% (19/30) responded to RI alone with multivariate analysis indicating elevated LDH, organ dysfunction, and multi-organ involvement as risk factors for poor responders of RI. At the median follow-up of 147 weeks, 55% of patients were alive with 50% in complete remission.