Resident Scholarly Project
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Association between type of immunosuppression regimen and incidence of PTLD in pediatric solid organ transplant recipients.

A. STUDY PURPOSE AND RATIONALE

Background:

T cell and B cell lymphoproliferative disease (T-PTLD and B-PTLD) are rare complications of pediatric solid organ transplantation. The risk of PTLD is related to the degree of immunosuppression required to prevent allograft rejection of the transplanted organ. A majority of cases are associated with Epstein Barr virus (EBV)-driven tumor formation in B cells and are a consequence of the detrimental effect of immunosuppressive agents on the immune system's ability to control EBV. The number of available immunosuppressive agents has markedly increased in recent years. A multidrug approach involving medications with different mechanisms of action is commonly used. Among them are the calcineurin inhibitors Tacrolimus and Cyclosporine and antimetabolites such as Azathioprine and MMF. Immunosuppression protocols can be divided into induction regimens, maintenance therapy, and rejection treatment. Maintenance therapy is usually a combination of two to three immunosuppressants from separate classes such as Tacrolimus, Mycophenolate Mofetil, and a corticosteroid. Tacrolimus (FK506) has become widely popular since its introduction into clinical practice in the 1990s. However, some early studies have shown that it may increase the incidence of PTLD. In one study of pediatric liver allograft recipients, the incidence of PTLD was 18.9% in children receiving Tacrolimus compared to 2.9% in those receiving cyclosporine [1]. More recent reports of both pediatric and adult solid organ transplantation suggest that the use of Tacrolimus instead of cyclosporine is associated with a two- to five-fold increase in the risk of developing PTLD [2], [3].

Aim: The incidence of PTLD is higher in the pediatric population than in adults with 5-9% of pediatric heart transplant recipients going on to develop the disease [4]. Furthermore, it is an important contributor to mortality; lymphoma or malignancy accounting for the cause of death in 12.8% of patients surviving more than 10 years after transplant. Given these statistics it is of profound interest to be able to elucidate the effect of the immunosuppressive therapy chosen with the risk of PTLD development in the pediatric population.

B. METHODOLOGY

A retrospective review of the electronic medical record will be conducted in order to collect data on solid organ transplant recipients (heart, liver, bowel) between 2005-2017 at MS-CHONY. We will further analyze the incidence of PTLD among this cohort using WHO classification criteria based on histological biopsy findings. We will compare incidence of PTLD among two groups of solid organ transplant recipients: those who received Tacrolimus as part of their immunosuppressive regimen and those who received any other agent.

C. STATISTICAL ANALYSIS

Statistical analysis will be conducted using Microsoft Excel and R. Power analysis was conducted in anticipation of Chi-square test with N for Group 1 estimated to be 700 and Group 1 proportion of 0.09 which yielded a smallest detectable proportion for Group 2 of 0.042. We will assume a p value of <0.05 for statistical significance.

D. STUDY DRUGS: Not Applicable

E. MEDICAL DEVICES: Not Applicable

F. POTENTIAL CONFLICT OF INTEREST: No conflict of interest to declare

G. POTENTIAL RISKS: None identified.

H. POTENTIAL BENEFITS: Information collected could provide information regarding factors that can increase the risk of development of PTLD.

REFFERENCES:

[1] Cox, K. L., Lawrence-Miyasaki, L. S., Garcia-Kennedy, R., Lennette, E. T., Martinez, O. M., Krams, S. M., ... & Esquivel, C. O. (1995). An increased incidence of Epstein-Barr virus infection and lymphoproliferative disorder in young children on FK506 after liver transplantation. *Transplantation*, *59*(4), 524-529.

[2] Younes, B. S., McDiarmid, S. V., Martin, M. G., Vargas, J. H., Goss, J. A., Busuttil, R. W., & Ament, M. E. (2000). The effect of immunosuppression on posttransplant lymphoproliferative disease in pediatric liver transplant patients. *Transplantation*, *70*(1), 94-99.

[3] Cao, S., Cox, K., Berquist, W., Hayashi, M., Concepcion, W., Hammes, G., ... & Monge, H. (1999). Long-term outcomes in pediatric liver recipients: Comparison between cyclosporin A and tacrolimus. *Pediatric transplantation*, *3*(1), 22-26.

[4] Dayton, J. D., Richmond, M. E., Weintraub, R. G., Shipp, A. T., Orjuela, M., & Addonizio, L. J. (2011). Role of immunosuppression regimen in post-transplant lymphoproliferative disorder in pediatric heart transplant patients. *The Journal of Heart and Lung Transplantation*, *30*(4), 420-425.

[5] Enderby, C., & Keller, C. A. (2015). An overview of immunosuppression in solid organ transplantation. *The American journal of managed care*, *21*(1 Suppl), s12-23.

[6] Absalon, M. J., Khoury, R. A., & Phillips, C. L. (2017, August). Post-transplant lymphoproliferative disorder after solid-organ transplant in children. In *Seminars in pediatric surgery* (Vol. 26, No. 4, pp. 257-266). WB Saunders.

[7] Dharnidharka, V. R., Webster, A. C., Martinez, O. M., Preiksaitis, J. K., Leblond, V., & Choquet, S. (2016). Post-transplant lymphoproliferative disorders. *Nature reviews Disease primers*, *2*, 15088.