3. Streszczenie w języku angielskim

Introduction

Post-transplantation lymphoproliferative disease (PTLD) affects solid organ and hematopoietic cell transplant recipients. PTLD is most frequent in multiorgan and intestinal transplant recipients, through lung, pancreas, liver, and heart transplant recipients and the lowest in kidney transplant recipients. It is widely accepted, that the intensity and duration of immunosuppressive treatment otherwise known as the cumulative dose of immunosuppression as well as EBV infection are the most important risk factors. Despite novel treatment modalities, the disease still possesses high mortality rates, owing to non-specific symptoms, difficult diagnostics and rapid progression in immunosuppressed patients.

Through the scope of its overall frequency in the general population, we can recognize PTLD as a rare disease. Currently we do not possess satisfactory epidemiological data, as the low frequency of the disease combined with the high number of transplantation centers worldwide make it difficult to assemble large cohorts suitable for analysis. Thus each research project focusing on PTLD is so valuable.

Methodology

Solid organ transplant recipients (SOTRs), both paediatric and adult, with histologically confirmed PTLD were included in this retrospective observational research. Hematopoietic cell transplant recipients as well as patients with lesions not meeting the diagnosis criteria of PTLD were excluded from this study.

All patient data were anonymized, including the data received from other participating transplantation centers. The required approvals of the Bioethics Committee of the Medical University of Warsaw were collected (No. AKBE/90/2022 and No. KB/75/2023).

The project was divided into two stages. The first stage was conducted on kidney (KTRs) and liver transplant recipients (LTRs) who were under observation at the Department of Immunology, Transplantation and Internal Medicine MUW in a time period between 2002 and 2017. The results were published (publication No. 2, page 50).

In order to verify the results of the first stage of the project and to possibly discover new insights, the second stage of the project was conducted. Five additional Polish transplantation centers were invited to participate in this stage:

a) Department of Nephrology, Transplantation, and Internal Medicine, Medical University of Gdańsk (prof. dr hab. n. med. Alicja Dębska-Ślizień, dr hab. n. med Sławomir Lizakowski)
b) Department of Nephrology and Transplantation Medicine, Wroclaw Medical University (prof. dr hab. n. med. Dorota Kamińska, dr n. med. Paweł Poznański)
c) Department of Nephrology, Medical University of Lublin (prof. dr hab. n. med Wojciech Załuska, dr n. med. Izabela Zakrocka)
d) Department of Hepatology, Transplantation and Internal Medicine, Medical University of Warsaw (prof. dr hab. n. med. Joanna Raszeja-Wyszomirska)
e) Silesian Center for Heart Diseases (dr hab. n. med. Marek Ochman, dr hab. n. med. Anita Stanjek-Cichoracka)

Kidney, liver and lung transplant recipients with histologically verified PTLD diagnosed between 2000 and 2023 were included in this stage. The significance of organ-specific risk and prognostic factors was analyzed using univariate (dr Magdalena Zielenkiewicz) and multivariate analysis (dr Wojciech Lesiński) (publication No. 3).

The monograph chapter included in this dissertation describes the clinical landscape of hematological disorders in solid organ transplant recipients, with a particular focus on PTLD. The review paper included in this dissertation aimed at researching novel diagnostic and treatment modalities in neoplasms, and particularly PTLD. Thus, the viability of 3D bioprinting in tumor microenvironment research (including PTLD) was assessed.

During this project we established a multicentre database, which as of September 2024 (the month paper No. 3 was submitted for review) contained the data of 103 patients with confirmed PTLD out of a total of 13 263 kidney, liver or lung transplant recipients from six participating transplantation centres. The database is continuously updated in terms of the number of patients (currently 128) and data.

Results

1. The dynamics of PTLD development differ between kidney, liver and lung transplant recipients. LngTRs were earliest to develop PTLD (median of 5 months post-LngTx), KTRs developed PTLD latest (median of 117 months post-KTx, $p < 0.001$)

2. Age at transplantation was the most important risk factor for KTRs (HR = 1.04, 95% CI 1.01 – 1.07, p = 0.003). Additionally, age at transplantation was also determined to be a negative prognostic factor (HR = 1.03, 95% CI 1.00 – 1.07, p = 0.045). In paper No. 2 male sex (p = 0.029), use of tacrolimus (TAC, p = 0.002) and age > 45 years at KTx (p = *0.004)* were found to be significant risk factors among KTRs
3. Among LTRs patients receiving TAC were later to develop PTLD (HR = 0.21, 95% CI 0.05 - 0.95, p = 0.042) and patient survival was inferior in patients diagnosed with plasmacytic hyperplasia PTLD (HR = 10.2, 95% CI 2.2 – 47.48, p = 0.003).
4. Anti-thymocyte globulin (administered either as induction or as acute rejection treatment, $p < 0.001$ and p = 0.004, respectively) was found to negatively impact SOTR survival. Focal disease (Lugano I, p = 0.005) and surgical treatment (p = 0.014) were found to be positive prognostic factors.
5. 3D bioprinting seems to be a technology that allows for research on tumor microenvironment, evaluation of novel treatment modalities, with potential applications in PTLD.

Conclusions

The dynamics and risk factors of PTLD development differ in relation to solid organ transplant type. Based on our research, the LngTRs are at the highest risk of PTLD development, LTRs at intermediate risk and KTRs at lowest risk. Among KTRs patients who are of older age at transplantation, males, and those treated with TAC are at the highest risk. Among LTRs the highest risk concerns patients treated with cyclosporin. Focal disease (Lugano I) and surgical treatment were found to be positive prognostic factors in SOTR, whereas ATG use had a negative impact on patient survival. Future research of the epidemiology of PTLD should include organ specific analyses. The multicenter database of Polish patients with PTLD created for the purpose of this project is a starting point for future research. 3D bioprinting is a technology that seems to allow for future research of PTLD and novel methods of its treatment.