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Monomorphic Post-Transplant Lymphoproliferative Disorder in Pediatric Solid Organ Transplant Recipients: Treatment Approach Across Canada

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Abstract

There are no standardized pediatric treatment protocols for monomorphic post-transplant lymphoproliferative disorder (PTLD). We reviewed data from Canadian pediatric centers to determine patient characteristics, treatment approaches and outcomes. There were 55 eligible children diagnosed with monomorphic PTLD between January 2001-December 2021. Forty-nine (89%) underwent reduction of immunosuppression. The majority, 44 (80%), received rituximab, 40/44 (91%) with concurrent chemotherapy. A total of 46 (84%) children received chemotherapy: LMB-96 (48%) and low-dose cyclophosphamide with prednisone (30%) being the favored regimens. Projected 3-year event-free survival and overall survival was 62% and 77%, respectively. Approach to monomorphic PTLD treatment was relatively consistent across Canada.

Introduction

Post-transplant Lymphoproliferative Disorder (PTLD) encompasses a heterogenous group of conditions with histopathological features, characterized by the abnormal expansion of lymphoid cells, ranging from non-destructive lymphoid hyperplasia to monomorphic proliferation indistinguishable from malignant lymphoma.[1,2,3] PTLD is the most common post-transplant malignancy in children and monomorphic PTLD the largest single entity.[4-8] Up to 80% of pediatric PTLD cases have lymphoid expansion driven by Epstein Barr virus (EBV) and immunosuppressive agents, impairing T-cell surveillance, are contributory.[1,2,6-15]

Treatments employed for PTLD include reduction of immunosuppression (RIS), EBV-specific cytotoxic T-lymphocytes (EBV-CTLs), monoclonal anti-CD20 antibody rituximab, and conventional chemotherapy.[15-26] Early or polymorphic lesions are favored to respond to reduction of immunosuppression, EBV-CTLs or rituximab, conversely, monomorphic PTLD often requires a chemotherapy-based approach.[16-19,25-30] Treatment protocols for monomorphic PTLD are not standardized and little is known about how providers manage these children. This study sought to describe the characteristics associated with monomorphic PTLD, post-solid organ transplant (SOT), treatment approaches and outcomes at pediatric centers in Canada.

Method

Patients were required to fulfil the following criteria for inclusion in this retrospective study: (i) diagnosis of monomorphic PTLD, post-SOT, established by a reference pathologist in accordance with WHO Clas-

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sification of Tumours of Haematopoietic and Lymphoid Tissues, (ii) commencement of treatment between January 2001 and December 2021, (iii) age [?]19 years at time of diagnosis.

Following research ethics board approval and establishment of data sharing agreements, data abstracted included: age and gender, SOT received, immunosuppressive agents employed, subtype of monomorphic PTLD, stage at presentation (as per Murphy or Ann Arbor), EBV status, primary treatment approach, need for additional lines of treatment, and outcome data: presence or absence of allograft dysfunction, date and status at last follow-up.

Data analysis was primarily descriptive. Overall survival (OS) was defined as time from diagnosis until death from any cause. Event-free survival (EFS) was defined as time from diagnosis until relapse, progressive disease, or death from any cause. OS and EFS were determined using the Kaplan-Meier method with Cox proportional hazard modelling to compare outcomes between chemotherapy groups. P-value [?]0.05 = statistically significant. Statistical analysis was undertaken using R statistical environment (v 3.3.3).

Results

Patient Characteristics

Three of the largest Canadian pediatric centers, outside of Quebec: BC Children's Hospital, Alberta Children's Hospital and Toronto Hospital for Sick Children submitted data. There were 55 eligible children and median age at diagnosis of PTLD was 9 years (IQR 6-12 years). Patient characteristics are described in Table 1. Nine (16%) children had previously received treatment for PTLD: polymorphic n=6, non-destructive n=3. Monomorphic PTLD developed a median of 48 months (IQR 11.3-84.8) post-SOT. Forty-eight (87%) children had mature B-cell disease: 23 (42%) diffuse large B-cell lymphoma (DLBCL) and 25 (45%) Burkitt lymphoma. Majority of children, 41 (75%), presented with advanced stage III/IV disease.

Treatment Approach

Forty-nine (89%) children underwent RIS. Forty-four (80%) received rituximab: 40 (91%) with concurrent chemotherapy and 8 (18%) with surgical resection. Eleven (20%) children, 6 (55%) with non-B cell disease, did not receive rituximab: 5 received chemotherapy only, 1 received chemotherapy and radiation, 1 underwent RIS only, 2 were managed with surgical resection only, and 2 received no treatment due to instability. No patient received EBV-CTLs as treatment for first presentation of monomorphic PTLD.

Forty-six (84%) children had a chemotherapy component to their treatment plan. Twenty-two (48%) were treated according to the LMB-96 protocol and 14 (30%) received low-dose cyclophosphamide with prednisone, all low-dose cyclophosphamide with prednisone patients also received rituximab (CPR).[18,19,31] Of the 22 children receiving LMB96, 17 had Burkitt lymphoma and 5 DLBCL. Of the 14 receiving CPR, 6 had Burkitt lymphoma and 8 DLBCL. Chemotherapy received by the other 10 (22%) children included: T-cell ALL therapy n=4, cyclophosphamide/vincristine n=2, methotrexate/cytarabine n=2, cyclophosphamide/vincristine/methotrexate n=1, and Hodgkin lymphoma therapy n=1.

Fifteen children (11 with Burkitt/DLBCL and 4 with NK/T cell lymphoma) required further lines of treatment, 11 (73%) for relapse and 4 (27%) for refractory disease. Their initial treatment was not uniformly conservative: 1 received single-agent rituximab, 3 CPR, 5 LMB96 chemotherapy, and 6 received other multiagent chemotherapy.

Outcome

Median follow-up was 48 months (IQR 17-101). Three-year EFS and OS were 62% ± SE 7% (95% CI 49-77) and 77% ± SE 6% (95% CI 66-89), respectively. There was no significant difference in EFS or OS for children who received LMB-96 vs CPR as their chemotherapy regimen. Patients treated as per LMB-96 had a 3-year EFS of 69% ± SE 11% (95% CI 51-93) and those treated with CPR had a 3-year EFS of 76% ± SE 12% (95% CI 55-100), p=0.991, Figure 1. At last follow-up, 38 (69%) children were alive without evidence of PTLD, 1 (2%) was alive with PTLD. Sixteen (29%) children had died; 10 (18%) of PTLD, 4 (7%) of

allograft dysfunction, 1 (2%) of multiorgan failure and 1 (2%) of unknown cause. Of those alive, 9 (23%) had allograft dysfunction and 2 (5%) required second transplant or organ replacement therapy.

Discussion

Our primary study interest was in determining the treatment approach to monomorphic PTLD across Canadian pediatric centers. For the majority (89%) of children in our study, RIS was a component of initial management. There is widespread support for this strategy. The European Reference Network on Pediatric Transplantation surveyed 13 centers and the most common initial PTLD treatment was reduction of immunosuppression.[21] The majority of children also received rituximab with chemotherapy. LMB-96 and low-dose cyclophosphamide with prednisone were the favored chemotherapy regimens. Almost all children receiving alternate regimens had rare, non-B cell, disease. Choquet and Trappe et al demonstrated rituximab's safety and efficacy in adults with B-cell lineage PTLD and Maecker-kolhoff et al confirmed the same for children.[23,28,30] Two pediatric PTLD trials, reported by Gross et al., successfully treated children with EBV +ve PTLD, post-SOT, using low-dose cyclophosphamide and prednisone (CP), with addition of rituximab (CPR) for those with CD20 positivity. Two-year EFS rates were 67% for the CP combination and 71% for the CPR combination, however, the authors did not consistently describe histopathological subtypes treated, and included children with non-monomorphic disease, making generalizability of their findings to all children with monomorphic PTLD difficult.[18,19]

In children with B-cell monomorphic PTLD, the challenge lies in determining which patients a clinician should anticipate having a good response to low-dose cyclophosphamide with prednisone and which require more intensive chemotherapy such as LMB-96. While LMB-96 is associated with excellent survival in, otherwise, healthy children with mature B-cell lymphoma, its toxicity profile may be concerning post-SOT.[25-26,31] PTLD risk stratification, to guide allocation of therapy, is evolving. Giraldi et al. recently published a standard vs high-risk classification system, derived from age-adjusted International Prognostic Indices, with tailored treatment: RIS/rituximab vs multiagent chemotherapy.[25-26,29] We did not explore rationale used by Canadian physicians to decide treatment approach but advanced stage disease (stage III/IV), which Giraldi et al. consider 'high-risk', and the large number of Burkitt lymphoma cases, could explain prevalence of LMB-96 usage.[26] No survival benefit was observed according to chemotherapy regimen used (CPR vs LMB96), which may be explained by the small patient number in our cohort.

For monomorphic PTLD patients, with co-morbidities and risk of graft failure, chemotherapy is not always deliverable.[18-23,25-26] Prockop et al. therapeutically treated 13 SOT recipients, with EBV +ve PTLD, with EBV-CTLs; 7 (54%) were paediatric patients < 18 years of age.[24] Complete or partial remission was achieved in 7 (54%) patients.[24] An industry-sponsored EBV-CTL study is currently recruiting children with PTLD.[32] Although CTLs were not administered to patients in our cohort, it is conceivable that future management will shift to favor novel therapies, alongside aforementioned risk-stratification tools to identify children expected to derive significant benefit from polychemotherapy.[24-26,32-34]

As a retrospective study, recall bias may have impacted data collected. Further, larger Canadian pediatric centers participated but smaller centers did not, this could limit generalizability of our findings. Acknowledging limitations, our findings suggest a, relatively, consistent approach to monomorphic PTLD management. This should encourage future collaboration and development of Canada-wide treatment protocols to improve outcomes for children with this challenging disorder.

Conflict of Interest Statement

The final manuscript, submitted for publication, has been approved by all authors. No authors

disclose any competing financial interests or other conflicts of interest.

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Legends

FIGURE 1: Kaplan-Meier curves showing event-free survival (EFS) and overall survival (OS) by chemotherapy regimen received, LMB96 vs low-dose cyclophosphamide with prednisone and rituximab (CPR). Timepoint 0 is date of diagnosis. Confidence intervals (CI) are displayed as a dashed line for each respective chemotherapy regimen.

TABLE 1: Patient and disease characteristics

Patient Characteristics, n=55	
Gender, n (%)	

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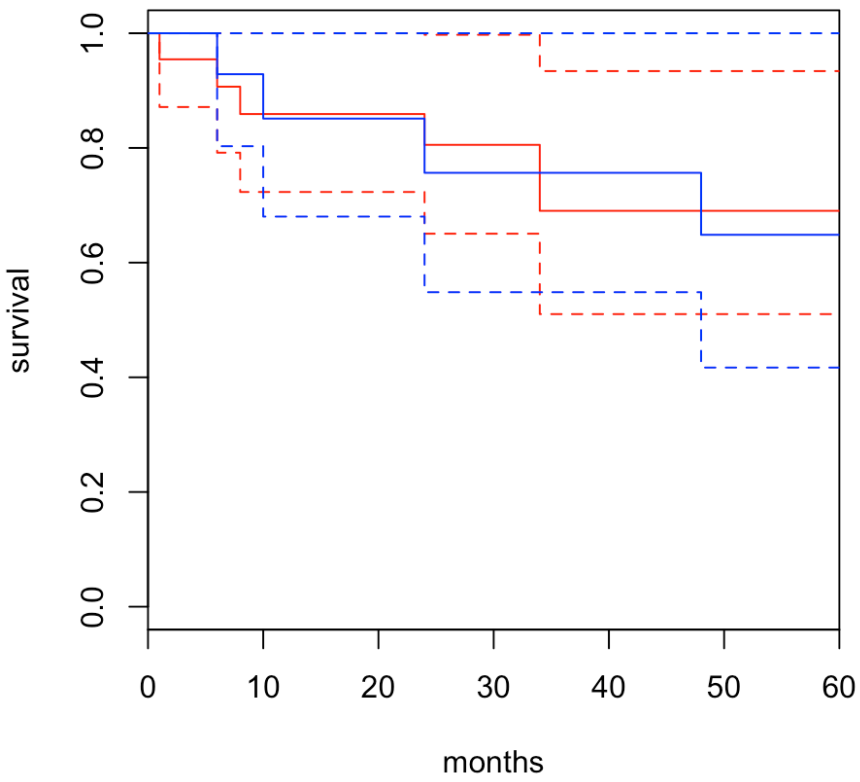
Patient Characteristics, n=55
Male
Female
Solid organ, n (%)
Heart
Kidney
Multivisceral
Liver
Lung
Immunosuppression, n (%) [?] 2 agents including tacrolimus [?] 2 agents no tacrolimus Tacrolimus only Cyclosporine only **I**
I II III IV Unknown/incomplete staging EBER positive, n (%)
Yes No
Unknown First line treatment, n (%) RIS Rituximab with chemotherapy Ritiximab without chemotherapy **Chemotherapy**

Abbreviations: PTLD- post-transplant lymphoproliferative disorder, DLBCL- diffuse large B cell lymphoma, NK- natural killer, EBER- EBV-encoded small nuclear ribonucleic acid, RIS- reduced immune suppression

FIGURE 1: Kaplan-Meier curves showing event-free survival (EFS) and overall survival (OS) by chemotherapy regimen received, LMB96 vs low-dose cyclophosphamide with prednisone and rituximab (CPR). Timepoint 0 is date of diagnosis. Confidence intervals (CI) are displayed as a dashed line for each respective chemotherapy regimen.



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