# HSCT provides effective treatment for lymphoproliferative disorders in children with primary immunodeficiency

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**Summary**

In a national cohort, we demonstrate the safety and efficacy of tailored chemo-immunotherapy followed by RIC HSCT for PID-associated lymphoproliferative disorders in children.

**Key words:** primary immunodeficiencies, lymphoproliferative disorders, lymphoma, allogeneic stem cell transplantation.

*To the editor*,

Patients affected by primary immunodeficiencies (PID) have a well-recognized risk of malignancy. In children, approximately half are of lymphoid origin, representing a 8-10 fold increased risk.[1] Within this patient group, lymphoproliferative disorders (LPD) present specific diagnostic/management challenges, including increased sensitivity to chemotherapy and pre-existing comorbidities making supportive care more challenging and HSCT more complex.[2] Consequently, overall survival (OS) is 40-50%, substantially lower than for children without PID. Allogeneic haematopoietic stem cell transplantation (HSCT) is a curative treatment option for PIDs, with survival approaching 80-90%.[3] Whilst data on the role of HSCT in PID patients presenting with LPD are scarce, existing reports are not encouraging, with mortality rates nearing 70%.[4,5] Across the UK's two accredited centres for paediatric immunological HSCT we have adopted a strategy of LPD cytoreduction, followed by reduced-intensity conditioning (RIC) HSCT to re-establish immunocompetence. Here we analyse the presentation, management and outcomes of children affected by PID and LPD.

We studied 36 patients <18 years old, with PID and histologically proven LPD, who were referred for HSCT between 2000 and 2016. Patients had a broad spectrum of PID diagnoses (Table E1)[6]. Median age at LPD diagnosis was 5.5 years (range 0.2–17.2). The majority (30/36, 83%) of patients had advanced (stage III/IV) disease at diagnosis, 4/36 (11%) patients had central nervous system involvement (Table E2). Thirty-eight histological diagnoses were made across the 36 patients, including both polymorphic and monomorphic lesions, with two patients experiencing two separate LPD diagnoses pre-HSCT[7]. All but two were destructive polymorphic or frankly lymphomatous lesions (Figure 1A and Table 1). The lesional lymphoid cells were EBV-positive in 22/34 (65%) patients tested. The majority of patients presented comorbidities at LPD onset, with chronic lung disease (33%), neurological impairment (14%) or chronic enteropathy (11%) being most common (Table E2 and Table E3).

LPDs were predominantly treated with reduced-dose chemo-immunotherapy, modified according to underlying PID, type of LPD, disease stage and patient co-morbidities. Treatments were mostly based on the UK post-transplant lymphoproliferative disorder recommendations of rituximab (+/- corticosteroids) escalating to COP or UKCCSG protocol 901/GRAB, or classic Hodgkin lymphoma regimens (ChLVPP or OEPA/COPDAC) (Table E3). Response to these therapies was varied, with 16/36 (44%) of the patients requiring

multiple lines of treatment and 13/34 (38%) evaluable patients having non-responsive/progressive disease as their best response (Table 1 and Table E2). Five patients had one or more LPD relapses prior to HSCT. Three patients received EBV specific cytotoxic T lymphocytes and five received radiotherapy as part of their LPD therapy pre-HSCT. Employing the approach of lower intensity chemo-immunotherapy, only five patients experienced notable toxicity during initial LPD treatment (Table E3), facilitating rapid transition to HSCT.

Amongst 36 referred patients, 6 did not proceed to HSCT. Four of these six had progressive LPD, amongst whom three had additional complications and were judged unfit for transplant (Table 1). One patient died of pneumonia and sepsis prior to HSCT. One patient was not transplanted having achieved a complete remission (CR), due to clinician decision, and remained in CR when censured at three months follow-up.

HSCT was performed in 30 patients at a median of 180 days from LPD diagnosis and a median age of 7.6 years (range 0.6–17.7). In 93% of cases RIC conditioning was used. Transplant details, including conditioning, chimerism and toxicity are given in Table 1 and Table E5. Transplant-related mortality was observed in 4/30 (13%) patients, due to infection, cerebral infarct and/or pulmonary veno-occlusive disease. At the time of HSCT, 43% of the patients were in CR, 23% in partial remission (PR) and 30% had either no response (NR) or progressive disease (PD) (Table 1).

With a median follow up of 3.6 years (range 0.1–18.1) from LPD diagnosis, 3-year overall survival (OS) across the entire cohort was 74% (95% CI, 55%–85%). The survival of patients who did not receive HSCT was poor and significantly worse than that of those who received HSCT (3-year OS 0% v 86%, $p<0.001$, Figure 1B). Neither sex, age, genetic definition of PID, having aggressive B-NHL, LPD stage at diagnosis, EBER positivity, pre-HSCT comorbidity nor HSCT characteristics influenced OS. LPD treatment response pre HSCT approached a significant association with 3-year OS (93%, 73% and 54% respectively for patients in CR, PR and NR/PD, $p=0.06$, Figure 1C), however, in a Cox multivariate regression analysis, only failure to proceed to HSCT remained associated with an inferior OS (HR 2.8, 95% CI 2.0-53.5, $p=0.005$) (Table E4).

Within the transplanted group, median follow up was 3.8 years post HSCT (0.02–14.8). 3-year relapse free survival (RFS) was 79% (95% CI, 58%–90%). No patient, LPD or

transplant related (donor match, GVHD prophylaxis, stem cell source) variables were associated with 3-year RFS. Notably, LPD treatment response was not significantly associated, with 3-year RFS of 92%, 83% and 56% respectively for patients in CR, PR and NR/PD, p=0.11 (Figure 1D). This finding is in keeping with the ability of HSCT to salvage chemotherapy resistant LPD, as evidenced by 7/9 patients transplanted with unresponsive LPD being alive in remission at last follow-up.

Only two patients relapsed post-transplant (Table 1). PT9 was transplanted with non-responsive LPD, remitted post-transplant but relapsed at day +146 in the setting of secondary graft failure. He was successfully re-induced and received a second, successful HSCT. PT29 was transplanted with non-responsive disease and developed a progressive intracranial mass at day +85, despite full donor chimerism. This was successfully excised. Both patients were alive and disease-free at last follow-up.

Our study shows that RIC-HSCT is a well-tolerated and effective therapy for PID associated LPD. Importantly, the value of RIC-HSCT was not affected by the absence of a genetically defined PID diagnosis. It is noteworthy that our cohort included only one patient with a defined DNA repair disorder and one with increased chromosomal breakage but no defined underlying PID. DNA repair disorders are reported to carry a poorer outcome[8] and therefore require separate consideration in a dedicated study. Because of both the ability of HSCT to salvage chemo-immunotherapy non-responsive cases, and the occurrence of LPD relapse following graft failure in one case, we postulate that the primary therapeutic role of HSCT in this setting is to restore immune competence. This may have multiple effects, including control of oncogenic viruses, normalization of aberrant microenvironmental inflammation and effective immune surveillance[9]. However, we cannot exclude that classical allo-HSCT mechanisms such as cytotoxic conditioning or graft versus lymphoma effect may contribute. We believe that HSCT should be considered in all cases of PID associated LPD, irrespective of disease response, but contingent on individualized assessment of patient status and co-morbidities. Despite the lack of association between LPD response and RFS, this finding may relate to the relatively small cohort size and larger international studies are required to address this question. Only with those data might we be able to define the optimal pre-HSCT cytoreductive therapy, providing a balance between depth of response and risk of additional toxicity.

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**Figure 1. Histopathological classification and Kaplan-Meier estimates of survival**. **A,** Diagnostic histopathology. **B,** estimate of 3-year overall survival. **C**, estimate of 3-year overall survival according to LPD disease response. **D**, estimate of 3-year relapse free survival according to LPD disease response. NHL – non-Hodgkin lymphoma; LPD, lymphoproliferative disease; PTCL – peripheral T cell lymphoma; ENMZL – extranodal marginal zone lymphoma; IM – infectious mononucleosis; EBV – Epstein Barr virus; HSCT, hematopoietic stem cell transplantation; CR, complete remission; PR, partial remission, NR/PD - no-response/progressive disease.

**Table 1. Clinical summary of LPD, treatment response and HSCT outcome.** PT – patient, DLBCL – diffuse large B cell lymphoma, poly B-LPD – polymorphic B cell lymphoproliferative disorder, HGBL NOS – high grade B cell lymphoma not otherwise specified, B-NHL – B cell non-Hodgkin lymphoma, cHL – classic Hodgkin lymphoma, IM – infectious mononucleosis, EBV – Epstein Barr virus, PTCL – peripheral T cell lymphoma, ENMZL – extra nodal marginal zone lymphoma, CR – complete remission, PR – partial remission, NR/PD – no response/progressive disease, HHV6 – human herpes virus 6, VOD – veno-occlusive disease, CMV – cytomegalovirus, AIT – autoimmune thrombocytopenia, N – no, Y – yes, A – alive, D – dead, RSV – respiratory syncytial virus

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## Online Repository methods

### Case reviews

Children (<18 years) who had been referred to either Great Ormond Street Hospital or The Great North Children's Hospital for HSCT in the setting of PID were reviewed. Additional cases who were not transplanted were identified by collaborating centres. Histopathology specimens and reports were assessed by an expert haematopathologist (CMB) and LPDs were classified, according to the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues (Revised 4th Edition). Epstein Barr virus (EBV) was detected in tissue by *in situ* hybridisation for EBV-encoded early RNAs (EBER) or in one single case by immunohistochemistry for LMP1. Radiographic imaging was blindly reviewed by two expert paediatric radiologists to establish LPD disease stage at presentation and pre-HSCT (KMcH and CG). The Lugano classification was used for staging of classic Hodgkin lymphoma and the International Paediatric Non-Hodgkin Lymphoma Staging System was used for other LPDs.

Relevant post-transplant events including acute and chronic graft versus host disease (GVHD), LPD recurrence, graft failure and treatment related toxicity as per Common Terminology Criteria for Adverse Events (CTCAE) Version 4 were identified for each patient. Treatment outcomes were assessed as overall survival (OS), defined as the time from diagnosis of LPD to death from any cause and relapse-free survival (RFS), defined as the time from transplant to relapse or death from any cause. Transplant related mortality (TRM) was defined as death from infection or other transplant-associated toxicity, excluding LPD, following allogeneic HSCT.

### Statistical analysis

All study variables were treated as categorical. The population, LPD and HSCT characteristics have been reported as median and ranges or as frequency and percentages. The Kaplan-Meier method was used to estimate 3-year OS and RFS rates. Differences in survival were assessed by the log-rank test. All surviving patients were censored at the date of last follow up. Associations between study variables were investigated using Fisher's exact test.

Univariate Cox proportional hazards regression was used to determine the prognostic significance of study covariates, and multivariate modelling was used to adjust for potential confounding and effect modification from study variables found to be significant on univariate analysis. Interactions were tested for within the Cox regression framework by including the product of dichotomised HSCT status (i.e. HSCT "Yes" and "No") with LPD treatment response in the models and using the likelihood ratio test for the nested models with and without the interaction term. The validity of the Cox regression models was investigated using Schoenfeld residuals and the global score test of proportional hazards. STATA version 14.0 was used for all statistical analysis.

## Ethical Considerations

The study has been conducted in full conformance with principles of the “Declaration of Helsinki”, Good Clinical Practice (GCP) and within the laws and regulations of the United Kingdom. All patients/families had given written informed consent for data collection and use for research. Ethical approval for the study was obtained from the National Health Service Health Research Authority (reference 17/WA/0064) and the Great Ormond Street Hospital Clinical Research Adoptions Committee (reference 17WA09).