LYMPHOPROLIFERATIVE DISEASE IN CTPS1 DEFICIENCY: SINGLE CENTRE EXPERIENCE OF HAEMATOPOIETIC STEM CELL TRANSPLANTATION AND ADOPTIVE CELLULAR THERAPIES

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Introduction: CTPS1 deficiency is a rare, recently described primary immunodeficiency impairing lymphocyte proliferation and causing severe herpesvirus infections, including Epstein–Barr virus (EBV)-driven lymphoproliferative disease (LPD)[1]. Twenty cases of CTPS1 deficiency have been reported[2]. Experience with haematopoietic stem cell transplantation (HSCT) and adoptive cellular therapies, including timing, disease control and outcomes, remains limited[3].

Methods: We reviewed clinical presentations, investigations, treatments, transplant characteristics and outcomes at our tertiary paediatric centre, alongside published cases.

Patients or Material: Four locally treated patients and four published cases had CTPS1 deficiency with EBV-LPD.

Results: All patients had recurrent infections and severe EBV disease. Patient 1 developed biopsy-proven middle-ear/mastoid LPD after acute lymphoblastic leukaemia treatment. Rituximab completely controlled disease before matched unrelated donor HSCT with fludarabine, treosulfan, thiotepa and alemtuzumab; at latest follow-up he remains well and LPD-free with stable mixed lymphoid chimerism. Patient 2 required intensive care for fulminant varicella pneumonitis; subsequent pulmonary EBV-LPD caused mediastinal/hilar lymphadenopathy and bronchiectasis. Partial rituximab response allowed haploidentical αβ/CD19-depleted HSCT with the same conditioning. Post-HSCT EBV reactivation responded to rituximab; remission, full donor chimerism and immune reconstitution were achieved with chronic lung disease. Patient 3 developed disseminated EBV-driven non-Hodgkin lymphoma involving CNS, thoracic and abdominal cavities despite escalating chemotherapy and haploidentical HSCT. Post-transplant rituximab, donor-derived EBV-specific cytotoxic T lymphocytes (CTLs), systemic and intraventricular chemotherapy failed; progressive cerebral oedema and hydrocephalus caused death. Patient 4 had primary central nervous system (CNS) EBV-positive B-cell lymphoma[4] with life-threatening neurological compromise. Chemotherapy failed, but third-party CTLs induced a marked response enabling allogeneic HSCT.

Among published cases[2], one child died from aggressive CNS lymphoma before HSCT; another died after HSCT from CNS EBV reactivation, hydrocephalus and

multiorgan failure despite CTLs; an infant achieved complete CNS lymphoma control with third-party CTLs and cord blood HSCT; and one responded to rituximab alone before uncomplicated HSCT.

Conclusions: CTPS1 deficiency should be suspected in severe or atypical EBV-LPD with recurrent herpesviral or bacterial infections. High-grade, chemo-resistant, B-cell lymphoproliferative disease involving the CNS is reported. Early diagnosis, EBV-directed immunotherapy, timely HSCT referral and access to CTLs before progression or refractory disease may improve survival.

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