Successful Treatment of X-Linked Lymphoproliferative Disease (XLP) with Anti-CD20 Monoclonal Antibody (Rituximab) Followed by Mismatched Unrelated Cord Blood Transplantation

TL Lee, HKW Law, GCF Chan, SY Ha, MHK Ho, KW Chan, YL Lau

Abstract
A 4-year-old boy with X-linked lymphoproliferative disease (XLP) developed life-threatening acute lymphoproliferative crisis and failed to respond to conventional treatment of dexamethasone and etoposide. With the knowledge that uncontrolled alloreactive cytotoxic T-cell responses triggered by EBV-transformed B cells is the main cause of XLP, anti-CD20 monoclonal antibody (Rituximab) which directed against B lymphocytes was used to damp down the patient's dysregulated immune response. He responded well to this novel approach and entered into complete remission with this treatment. His inherited immuno-deficient genetic defect was subsequently corrected by unrelated cord blood transplantation.

Key words
Anti-CD20 monoclonal antibody; Cord blood transplantation; Rituximab; X-linked lymphoproliferative disease

Introduction
In X-linked lymphoproliferative disease (XLP), also known as Duncan's disease, there is a failure in controlling the proliferation of cytotoxic T cells triggered by Epstein-Barr virus (EBV) infection. Patients with this disorder usually remain asymptomatic until they are infected by EBV, which usually occurs within the first five years of age. The commonest form of presentation (occurring in 75 percent of cases) is severe infectious mononucleosis, which is fatal in 80 percent of patients. The high mortality is primarily due to extensive liver necrosis caused by activated cytotoxic T cells.1

The diagnosis of XLP is mainly based on clinical criteria. It requires two or more maternally related males manifesting one or more of the following characteristic phenotypes: fulminant infectious mononucleosis (IM), malignant lymphoma or lymphoproliferative disease, and dysgammaglobulinemia.2 Most boys who survive EBV infection have global cellular immune defects, and lymphomas, aplastic anemia, or hypogammaglobulinemia will ultimately develop.

The defective gene in X-linked lymphoproliferative disease is located at Xq25 and encodes an adapter protein found in T cells and natural killer cells known as SLAM-associated adaptor protein (SAP). SAP couples with downstream signaling molecules to a cell surface protein known as signaling lymphocyte activation molecule (SLAM) found on the membrane surfaces of T and B cells. SLAM is an unusual membrane protein that serves both a growth-promoting molecule and a receptor for itself. SAP controls signaling via the SLAM family of surface receptors and plays crucial roles in T-cell and antigen presenting cell interactions during viral infections.3-5

Most conservative treatment modalities designed for the XLP including chemotherapy, antiviral agents, high-dose intravenous immunoglobulin and interferon (alpha and gamma) have been unsuccessful. Allogeneic bone marrow transplantation (BMT) is the only therapy with a proven