

LETTER TO THE EDITOR

Prolonged remission in a case of Richter's transformation of B-cell chronic lymphocytic leukaemia following adoptive immunotherapy

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The clinical course of B-cell chronic lymphocytic leukaemia (B-CLL) is highly variable. However, a number of clinical and biological parameters have been identified that predict prognosis.¹ The outlook for patients with high-grade (Richter's) transformation is particularly poor, with a median survival of 5–8 months.² We report a case of poor risk B-CLL and Richter's transformation in which prolonged complete remission was entirely attributable to adoptive immunotherapy. A 53-year-old man presented with advanced B-CLL. Treatment with chlorambucil, fludarabine and CHOP chemotherapy gave partial responses of less than 6 months. Investigations before salvage therapy revealed unmutated immunoglobulin variable (IgVh) genes, CD38 expression in 70% of leukaemic cells and a 17p deletion in 80% of metaphases. Alemtuzumab, the humanised monoclonal antibody against CD52, at a dose of 30 mg 3 × weekly for 3 months resulted in a good partial response. A reduced intensity allogeneic haematopoietic stem cell transplant (allo-HSCT) was then performed using the BCNU, etoposide, cytarabine and melphalan (BEAM) alemtuzumab conditioning regimen (see Figure 1). Haematopoietic reconstitution was prompt, but 25 days following the transplant he developed an acute abdomen. Computed tomography (CT) scan assessment showed extensive intra-abdominal and retroperitoneal lymphadenopathy, in addition to inflammatory changes localised to the gall bladder and cystic duct. Laparotomy revealed cholecystitis and cystic duct obstruction owing to lymphadenopathy. Histology of the lymph nodes showed Richter's transformation with the appearances of a diffuse large B-cell non-Hodgkins lymphoma. *In situ* hybridisation for Epstein–Barr virus RNA was negative. Subsequently, the patient developed a progressive leucocytosis, and immunophenotyping of the peripheral blood cells showed a CLL phenotype of the lymphocytes with expression of CD38. He proceeded to therapy with rituximab (anti-CD20 monoclonal antibody 375 mg/m² weekly × 4), which resulted in only transient stabilisation of the lymphocyte count. At 100 days post transplant, incremental dose donor lymphocyte infusions (DLI) and further rituximab 375 mg/m² were commenced (see Figure 1). On completion of therapy, bone marrow (BM) evaluation showed continuing infiltration with CLL, and, although there was some resolution of the volume of disease, persistent axillary, abdominal and inguinal lymphadenopathy was evident on CT. Following DLI, acute grade 3 gastrointestinal and skin graft-versus-host disease

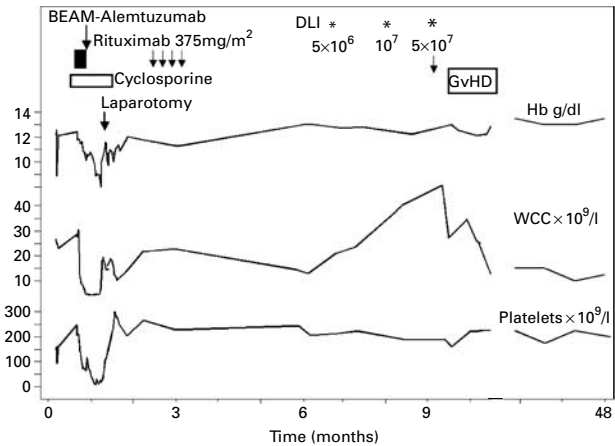


Figure 1 A reduced intensity allo-HSCT was performed using the BEAM-alemtuzumab conditioning regimen (carmustine 300 mg/m² day -6; cytarabine 400 mg/m² day -5 to -2; etoposide 200 mg/m² day -5 to -2; melphalan 140 mg/m² day -1; alemtuzumab 20 mg day -5 to -1). Peripheral blood stem cells from a male matched sibling donor (3.5×10^6 CD34 cells/kg) were reinfused on day 0. Richter's transformation was documented histologically 28 days post transplant and treated by cessation of cyclosporine, administration of rituximab 375 mg/m² × 4 and DLI in doses from 10^6 – 5×10^7 CD3 cells/kg. A single dose of rituximab 375 mg/m² was given with the final dose of DLI.

(GvHD) developed, necessitating therapy with cyclosporine, intravenous methylprednisolone (2 mg/kg) and parenteral nutrition. The onset of GvHD coincided with complete resolution of the lymphadenopathy and normalisation of the peripheral blood counts. The BM aspirate and trephine biopsy showed no evidence of CLL and minimal residual disease (MRD) was undetectable using a sensitive four-colour flow cytometric assay.³ The patient remains well and in complete clinical, haematological, radiological and MRD remission more than 4 years post transplant.

There is increasing evidence of a potent graft-versus-leukaemia effect in B-CLL. In a recent study of nine patients with poor prognosis B-CLL and unmutated IgVh genes, seven were still free of MRD at 2 years, although disease progression was observed in a case with 17p deletion.⁴ Response of Richter's transformation to allo-HSCT has been reported previously.⁵ However, it is difficult to distinguish the contribution of conditioning therapy and the allogeneic effect in this study. In the present case, disease progression in the early post transplant period unequivocally demonstrated that the prolonged remission was induced by adoptive immunotherapy. There are theoretical grounds to suggest that Rituximab therapy may have been synergistic with the DLI in initial remission induction. However, the peripheral lymphocytosis remained until the onset of GVHD, and fell consistently before the

introduction of steroid therapy. In summary, effective remission was achieved in this patient at the onset of GVHD induction, despite progressive disease early post transplant.

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