Autoimmune haemolytic anaemia emerging during Campath treatment in a patient with CD5 negative chronic lymphocytic leukaemia

Paul R. J. Ames · Darren Aw · Mervin G. Rainey

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Abstract Campath is being employed for the treatment of autoimmune haemolytic anemia (AIHA) whether or not associated to B cell chronic lymphoid leukaemia (CLL). CD5 negative CLL is relatively uncommon and runs an indolent course. We report a CD5 negative CLL patient who developed AIHA associated with cytomegalovirus infection reactivation whilst on treatment with Campath for progressive disease.

Keywords Campath · CMV · Haemolytic anemia · Lymphoid leukaemia

Introduction

Campath is a humanized monoclonal antibody against CD52 expressed on the surface of normal and malignant B and T cells [1] used in pre-treated as well as un-treated B cell chronic lymphocytic leukaemia (CLL) [reviewed in 2]. Its usefulness extends to autoimmune cytopenias [3], at times developing in the course of CLL [4, 5]. The CD5 negative variant of B CLL ranges in frequency between 7 % and 20 % according to series [6, 7], is associated with Binet stage A and splenomegaly at diagnosis [8] and runs an aggressive clinical course [9]. Herein we describe a case of progressive CD5 negative B CLL complicated by

autoimmune haemolytic anaemia (AIHA) at the 8th week of Campath treatment.

Case Report

A 70-year-old man was diagnosed with Binet stage A CLL in May 2005 (lymphocytes $66 \times 10^9/L$) that progressed to stage C within a year. In March 2006 a marrow biopsy revealed nodular and diffuse infiltration and B cell phenotype on marrow blood revealed CD19 96 %, CD23 66 %, CD5 negative, CD5/19 negative, CD38/19 negative, lambda 81 %, kappa negative. Despite four courses of chlorambucil (10 mg/day for 10 days for the first two monthly courses extended to 14 days for the last two monthly courses) and two courses of fludarabine (60 mg/day for 5 days) his lymphocyte count had increased to $160 \times 10^9/L$ with persisting nodular and diffuse marrow infiltration. He then received dexamethasone (40 mg/day for 4 days) until October 2006 with no durable effect (lymphocytes $201 \times 10^9/L$). In March 2007 he developed splenomegaly, confirmed by CT scan that also showed retroperitoneal and celiac axis adenopathy, while a repeat marrow still showed diffuse and nodular infiltration. Intravenous (IV) Campath was started escalating from 3 to 10 mg and finally 30 mg during the 1st week and then 30 mg three times a week. After 4 weeks lymphocytes were not detectable in peripheral blood and the diffuse part of the infiltration in the marrow had cleared leaving the residual nodular component. Repeat B cell markers on marrow blood revealed CD19 14 %, CD5 6 %, CD5/19 negative but CD38/19 was positive at 25 %. In early June 2007, at the 8th week of Campath treatment haemolytic anaemia developed in synchrony with CMV reactivation and Campath was stopped. The patient was admitted to

P. R. J. Ames · D. Aw · M. G. Rainey
Department of Haematology, Inverclyde Royal Hospital,
Larkfield Road, Greenock PA16 0XN, Scotland, UK

P. R. J. Ames (✉)
Centre for Sports and Exercise Medicine, William Harvey
Research Institute, Queen Mary University of London,
327 Mile End Rd, London E1 4NS, UK
e-mail: paxmes@aol.com

Fig. 1 Evolution and treatment of autoimmune haemolytic anaemia after Campath cessation

hospital (Fig. 1). A direct anti-human globulin test was positive for IgG and C₃, and a free warm auto-anti-C and -e were detected by enzyme treated erythrocytes a week later. Haptoglobin was not measurable, LDH was raised at 2,200 IU/L as well as reticulocytes and bilirubin (90 % unconjugated). The patient received an IV pulse of 500 mg methylprednisolone on the 5th of June 60 mg prednisolone orally from the 6th to the 20th of June tapering down 5 mg every 3 days. He received an IV pulse of cyclophosphamide (1 g) on the 15th of June followed by IV immunoglobulins (20 g total) on the 21st June. G-CSF (300 µg/SC × 5 doses) was administered for post-cyclophosphamide neutropenia and Ganciclovir for the eradication of CMV. The haemolysis eventually settled and the patient was event free until November 2007 when he presented with right axillar adenopathy. In March 2008 lymphocyte counts had increased to $200 \times 10^9/L$ and further adenopathy was noted in the neck. A CT scan showed extensive mediastinal, pre-tracheal, para-aortic and subcarinal adenopathy with marked splenomegaly and abdominal adenopathy. He was commenced on pulsed methylprednisolone (1 g IV fortnightly) for six courses decreased to 0.5 g IV at the same time interval that kept the lymphocyte count within $160\text{--}180 \times 10^9/L$ until December 2008 when the lymphocyte count decreased gradually to $20 \times 10^9/L$ on the same regimen until March 2009. The Hb level also improved to a maximum of 11.5 g/dL having been persistently around 9–10 g/dL in the previous months in the absence of haemolysis. These changes prompted further investigations: cell markers on peripheral blood revealed CD20 98 %, CD23 89 %, FMC 12 %, CD5/19 negative, CD38/19 34 % alongside high expression of ZAP70 (by immunofluorescence), FISH was negative for cytogenetic abnormalities and the CT findings were similar to those of

March 2008. Over the ensuing 6 months though, his Hb and platelet progressively decreased for marrow infiltration and the patient passed away for multi organ failure secondary to sepsis.

Discussion

Campath has proven efficacy for the management of AIHA: of three patients with AIHA from a British series of autoimmune cytopenias without CLL two responded (though one relapsed mildly) and one died [3] and in a further patient coincidental AIHA and CLL were suppressed for 10 months when the patient succumbed to a widespread infection [4]. Our patient developed AIHA at the 8th week of Campath treatment. Auto-antibodies may appear after Campath treatment: anti-cardiolipin antibodies (in one case associated with thrombosis) and anti-erythrocyte antibodies (without haemolysis) emerged in patients with autoimmune cytopenia treated with Campath [3], and anti-thyroid antibodies developed in multiple sclerosis patients treated with the same agent [10]. It is possible that Campath destroys lymphocytes subsets capable of limiting autoimmunity allowing the emergence of auto-reactive clones. Moreover, CD38 expression had increased on out patient's lymphoid cells after Campath treatment. One study noted that CD38 expression increased after treatment on residual cells in few patients variably treated with chlorambucil, epirubicin and fludarabine [11]. This leads to the possibility of autoimmune clones emerging within the CD38 positive population. Alternatively, CMV reactivation might have induced the same mechanism and contribute directly to haemolysis. Indeed CMV is known to be associated with autoimmune disorders including AIHA in

immune compromised [12] and less commonly in immune competent individuals [13]. CD5 negative CLL generally follows an aggressive course with a median survival similar to those of CD5 positive patients [8]. Having progressed from Binet stage A to C in almost a year our patient did not achieve marrow clearance with conventional therapy and achieved only a partial response to Campath treatment. This was not too surprising as clearance of marrow involvement occurs in less than 50 % of CLL patients [14] and the previous lack of response to fludarabine was a poor prognostic indicator in itself. In CD5 positive CLL the simultaneous expression of CD38 and ZAP70 correlates with stage, diffuse marrow infiltration and raised lymphocyte counts [15–17] and thus predicts a poorer prognosis that may well apply to CD5 negative cases. Despite the lack of CD5 expression, CD5 negative B CLL co-expressing unfavourable prognostic markers may behave as aggressively as conventional CD5 positive B CLL.

The emergence of AIHA associated with CMV reactivation during treatment of CLL with Campath has not been described before: we are aware of a CMV re-activation instance followed by AIHA in a patient with systemic lupus erythematosus [18] and as such this case adds to the wide spectrum of autoimmune conditions directly or indirectly linked to CMV in immune compromised and immune competent subjects.

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