Acute renal failure and disseminated intravascular coagulation following an idiosyncratic reaction to Alemtuzumab (Campath 1H) or Fludarabine

Alemtuzumab (Campath 1H) is a recombinant DNA derived humanized monoclonal antibody which targets CD52 antigens on B and T cells. It is increasingly used as a conditioning agent for bone marrow transplantation. We describe the case of a 37 year old woman who developed acute renal failure and disseminated intravascular coagulation (DIC) following one dose of Campath and Fludarabine. Campath was thought to be the most likely causal agent although Fludarabine alone or in combination with Campath cannot be excluded. Despite there being many documented side effects of Campath there are currently no reports in the literature of acute renal failure and DIC. The transplant had to be aborted and 9 months on the patient is still requiring dialysis twice a week.

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Case report

A 37 year old woman was diagnosed with chronic myeloid leukaemia (CML) in May 1999.The patient had no HLA compatible siblings and was considered unsuitable for a conventional matched unrelated donor transplant because of fatty infiltration of the liver. She was initially treated with Hydroxyurea and alpha interferon but she failed to achieve a significant cytogenetic response. In April 2001 she was commenced on imatinib mesylate, but again failed to achieve a major cytogenetic response and suffered significant hepatotoxitity. In April 2003, despite an increased dose of imatinib, haematological control was lost. A bone marrow examination continued to show morphological chronic phase CML. Cytogenetics showed Philadephia chromosome in 30/30 metaphases examined but no additional chromosomal abnormalities. A search for a matched unrelated donor commenced. A 52 year old female donor with an HLA 12/12 match was identified and the patient successfully completed a pre-transplant work up. Her glomerular filtration rate was satisfactory at 183 ml/min (132 mL/min/m^2) and no concerns arose from the remainder of her routine investigations. She had no other concomitant diseases apart from a fatty liver which led to a decision for a non-myeloablative allograft, and was not on any other medication. She was admitted on 15/10/03 and commenced her conditioning of Fludarabine 60 mg and Campath 20 mg. (Ideal surface area 1.92 metre squared). Her renal function on admission was Na+ 137 mmol/L, K+ 4.2 mmol/L, Urea 3.1 mmol/L, Creatinine 71 micromol/L. The patient tolerated the conditioning drugs satisfactorily. On the morning after admission she received a second dose of Campath 1H. There were no concerns until her daily bloods showed worsening renal function with Na+ 133 mmol/L, K+ 4.0mmol/L, Urea 9.6 mmmol/L, Creat 22Omicromol/L. She remained very well with a good urine output but repeat bloods (24 hours from first dose) showed further deterioration with a Urea 12.4mmol/L and Creat 269 micromol/L. Her clotting which had been normal on admission was also deranged with PT 20seconds (11-13), APTT 40seconds (24-39), Fibrinogen 1.8g/L (1.5-4.0), D-Dimers 310 microg/L (0-0.3) and falling platelet count consistent with disseminated intravascular coagulation (DIC). Only a few red cell fragments were evident on the blood film. The ALT was elevated at 353i.u./L (0-40). The DIC was treated with fresh frozen plasma (FFP) and platelet transfusions. A catheter was inserted and careful fluid balance monitoring began. Conditioning was aborted. That evening she became clinically unwell with a pyrexia and anuria. Renal dose Tazocin and Clarithromycin were commenced. A renal ultrasound scan was normal and she was transferred to the renal dialysis unit the following morning. The patient improved symptomatically with haemodialysis and clotting returned to normal within 48 hours with further support. She remained in the renal unit for 4 weeks and on discharge she was passing between 200 and 400 mls of urine a day. As of December 2004 she remains on haemodialysis twice a week as an outpatient. Other significant morbidity has included pulmonary emboli and difficulty with venous access for dialysis. She remains on hydroxyurea alone with no sign of acceleration of the disease.

Discussion

The authors have discussed this patient with the makers of the antibody (Schering), it's developer Dr Geoff Hales (Oxford) and transplant colleagues around the country. This adverse event was not seen in the first 5000 patients treated with Campath. There is a report with Schering of one other patient (male) with chronic myeloid leukaemia who developed DIC and acute renal failure within 12 hours of receiving 10 mg of Campath 1H as pre-conditioning for allogeneic bone marrow transplantation. He was reported as recovering after 7 days on haemofiltration. We understand that this patient had received other potentially nephrotoxic drugs and that the causality link with Campath 1H was assessed as possible. Our patient had only received one dose of Fludarabine and no other nephrotoxic drugs and causality was felt to be due to Campath although Fludarabine could not be excluded for certain. There is a paucity of literature suggesting possible mechanisms for Campath causing renal failure or DIC. Rankin et al.[1] suggested that Campath could lead to an activation of the endothelium causing disturbances in coagulation and fibrinolysis, perhaps as a direct effect or by secondary cytokine release. Wada *et al.*[2] found significantly elevated interleukin-6 and TNF levels in patients with DIC and so, however, the rarity of this reaction means that the mechanism cannot be certain at this stage. In our case the temporal link with Campath administration and the lack of concomitant medication strongly suggests that this is a rare idiosyncratic reaction to Campath therapy. As the role of Fludarabine cannot be ignored, further reporting of reactions to either drug used alone or in combination needs to occur and then be reviewed. It illustrates the necessity for close biochemical and haematological monitoring when using either agent, and has led to a change in practice on our transplant unit whereby renal function is assessed after each dose of Campath and the next dose not administered until the electrolyte results have been seen and are satisfactory. It also emphasises the importance of the yellow card reporting system to allow us to monitor and audit levels of adverse reactions to new drugs.

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