Remission of cold hemagglutinin disease induced by rituximab therapy

Cold hemagglutinin disease is a chronic hemolytic anemia that is refractory to the usual treatments for hemolytic anemia mediated by a warm-reactive antibody; it may be associated with a low-grade lymphoma. Two previous case reports point to a possible role for this agent in the treatment of cold hemagglutinin disease.[1,2] Rituximab is an anti-CD20 monoclonal antibody of proven efficacy in the treatment of low-grade B-cell lymphomas.[3] We report a remission of cold hemagglutinin disease in response to single-agent therapy with rituximab.

In 1987, a 39-year-old man presented with idiopathic acquired cold hemagglutinin disease. Physical examination revealed pallor and jaundice. There was no lymphadenopathy or organomegaly. He had a hemoglobin concentration of 67 g/L, a hematocrit of 20.1% and a reticulocyte count of 9.7%. His white blood cell count was 5.1×10^9/L with 62% neutrophils, 35% lymphocytes, 2% monocytes and 1% eosinophils. Hemagglutination was noted and improved with prewarming. The direct antiglobulin test was positive to complement 4+. The titre of cold agglutinins was persistently greater than 1:2048 and the thermal amplitude was reactive in saline and albumin to 37°C. The bilirubin concentration was 86 μmol/L (normally 0–17 μmol/L) and the lactate dehydrogenase concentration was 306 U/L (normally 90–180 U/L). The bone marrow biopsy specimen was hypercellular with no abnormal infiltrates. The chest x-ray film and the CT scan of the abdomen appeared normal.

The patient was given folic acid and a regimen to minimize cold exposure. He failed to respond to chlorambucil and showed minimal responsiveness to prednisone on occasions when hemolysis was severe. His condition was managed in a symptomatic fashion until 1996, when he failed a trial of cyclosporin A. He was reassessed in 1998 and was noted to have an enlarged spleen. Bone marrow aspiration showed a dry tap, and the bone marrow biopsy demonstrated replacement with a small-cleaved follicular centre cell lymphoma. At the time of his reassessment the patient was taking 50 mg of prednisone daily, and his hemoglobin level had improved transiently. A course of oral chlorambucil therapy (4 mg/d) resulted in a drop in his hemoglobin concentration to 51 g/L and was discontinued.

Rituximab therapy (375 mg/m^2 weekly for 4 weeks) was begun on Dec. 15, 1999. The dose of prednisone was reduced from 50 mg/d to 30 mg/d alternating with 15 mg/d on alternate days over 4 weeks. Prednisone was withdrawn completely over 4 months. At the time this treatment was initiated, the patient's hemoglobin level was 82 g/L; it increased to 125 g/L by the 18th day after treatment began. One year later his hemoglobin concentration was 93 g/L; the patient was off all treatment and exhibited no symptoms.

This successful induction of remission suggests that rituximab may be an effective treatment for chronic and refractory cold hemagglutinin disease occurring in association with follicular centre cell lymphoma. The use of this agent to treat idiopathic acquired cold hemagglutinin disease requires evaluation.

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Escherichia coli infections and hemolytic-uremic syndrome

Each outbreak of verotoxigenic *Escherichia coli* infection renews interest in interventions to prevent the complication of hemolytic-uremic syndrome. Donald Farquhar reviewed in *CMAJ*[1] a paper by Wong and colleagues that raises important concerns about risk factors for the progression to hemolytic-uremic syndrome.[2] Although the authors' concerns about antibiotic use in this context may be valid, it is critical that their conclusions not dissuade investigators from performing prospective, controlled antibiotic studies.

Wong and colleagues concluded that the association between antibiotic use and progression to hemolytic-uremic syndrome was strong, but the 95% confidence interval of the adjusted relative risk is extremely wide for antibiotic use within the first 3 days after onset of illness (1.4–737).[2] If the next 1 or 2 patients with hemolytic-uremic syndrome had not received an antibiotic, the significance level might not have been maintained in the multivariate analysis. Both youth and the use of antimotility agents did not prove to be risk factors, contrary to previous findings.[3–5] In addition, the authors did not find an association between antibiotic use and progression to hemolytic-uremic syndrome in a previous study with much larger numbers of patients.[5] These discordances could be a function of inadequate patient numbers in the latest study.[2]

Perhaps more importantly, I am concerned that the approach taken to categorize antibiotic use may not have