CLINICAL VIGNETTE

Refractory Cold Agglutinin Disease Responsive to Sutimlimab

Maxwell J. Kroloff, MD and Steven C. Tsai, MD

Introduction

Cold agglutinin disease (CAD) is an acquired form of autoimmune hemolytic anemia (AIHA) in which IgM autoantibodies target the red blood cell antigens at cold temperatures. The IgM-antigen complex further activates the classical complement pathway resulting in predominantly extravascular hemolysis.[1] In comparison to warm-AIHA, CAD is rarer, accounting for roughly 15% of AIHA's.[2] The distinction is typically made via a positive Coombs test for anti-C3 antibodies and negative anti-IgG, though the anti-IgG antibody detection is more variable. Following the Coombs test, a cold agglutinin titer is performed to confirm the diagnosis of cold agglutinin disease as opposed to paroxysmal cold hemoglobinuria, which represents an alternative form of cold-AIHA primarily seen in children following a viral illness.

In most patients, the cold agglutinin is produced by a clonal B-cell lymphoproliferative disorder.[3] Occasionally, patients may not need treatment and are monitored. Treatment becomes necessary for symptomatic anemia or cold-induced circulatory symptoms in 70-80% of patients.[4] Because of the rarity of CAD, large randomized, controlled trials do not exist. Treatment aims to target the pathogenic B-cell clone in the bone marrow responsible for production of the cold agglutinin. In contrast to warm-AIHA, steroids have shown limited efficacy.[5] Thus, the cornerstone of therapy has remained rituximab, either as monotherapy or in combination with chemotherapy (typically bendamustine or fludarabine).

If patients fail to respond to combination B-cell therapy, there are few evidence-based therapies. Given that CAD is dependent on complement-mediated hemolysis, complement inhibition represents a novel treatment approach. Sutimlimab is a monoclonal antibody designed to target C1s, which is responsible for activation of the classic complement pathway.[6] We present a patient with concurrent chronic lymphocytic leukemia (CLL) and a clonally unrelated diffuse large b-cell lymphoma (DBLCL) with refractory CAD despite rituximab monotherapy, plasmapheresis, combined rituximab/cytotoxic therapy, and acalabrutinib. He eventually achieved rapid response to sutimlimab, allowing successful completion of his definitive DLBCL-directed therapy.

Case Presentation

A 79-year-old male with no significant past medical history initially presented with progressive anemia. Evaluation revealed hemolysis with a positive Coombs test (IgG-antibody negative, C3-antibody positive). Subsequent cold agglutinin titer was 20,480. A bone marrow biopsy four months after presentation demonstrated CLL involving 40-50% of marrow cellularity with a negative FISH. IgHV was mutated. At that time, he deferred treatment despite active hemolysis, given the asymptomatic nature of his cold agglutinin disease.

About one year later, the patient presented to the emergency department on with right upper quadrant pain. CT of the abdomen/pelvis demonstrated a 9 x 5 cm, solid right liver mass. Additional outpatient evaluation was scheduled and he presented to hematology five weeks after ED visit. He was found to have a hemoglobin of 6.8 g/dL with evidence of ongoing hemolysis. Lactate dehydrogenase (LD) was 942 U/L and haptoglobin was undetectable. Coombs test confirmed an anti-C3 antibody positive (3+) and anti-IgG antibody negative process with a cold agglutinin titer of 1:1024, consistent with active cold agglutinin disease.

The patient was admitted to the hospital for emergent management of his cold agglutinin disease and expedited evaluation of his liver lesion. He underwent daily plasmapheresis for 5 days and started weekly rituximab. The biopsy of his liver mass demonstrated DLBCL, which was felt to be clonally unrelated given CD10+ disease on immunohistochemistry. Repeat bone marrow biopsy confirmed chronic lymphocytic leukemia without evidence of large cell transformation. Flow cytometry demonstrated CD5+, CD19+, CD23+, CD10- disease.

The patient received his third weekly infusion of rituximab followed by cycle 1, day 1 of R-pola-CHP (rituximab, polatuzumab, cyclophosphamide, doxorubicin and prednisone) for intermediate-high risk DLBCL based on an international prognostic index of 3. He had evidence of ongoing hemolysis including a hemoglobin 10 g/dL, LD 512 U/L, undetectable haptoglobin and total bilirubin of 2.2 mg/dL. Unfortunately, he required admission with acute on chronic hemolytic anemia with a hemoglobin of 4.6 g/dL. He received emergent plasmapheresis for 5 days, which was continued twice weekly on an outpatient basis with anticipation that the cytotoxic chemotherapy would ultimately lead to resolution of his refractory cold agglutinin disease. He had favorable response noted on PET/CT with significant decrease in size of the segment 5/6 hepatic mass with Lugano 3 classification consistent with a complete metabolic response. However, cycles 2, 3, and 4 were

all complicated by severe, refractory anemia approximately 7-10 days following chemotherapy administration, requiring admission. This temporally correlated with his bone marrow suppression, with inability to compensate to ongoing hemolysis, despite prolonged treatment with rituximab followed by 4 cycles of cytotoxic chemotherapy. During this period, a Bruton's Tyrosine Kinase inhibitor, acalabrutinib was also added with hopes of suppressing the CLL clone and resultant cold agglutinin titer. However, this also failed to achieve any response in terms of his cold agglutinin disease with a persistent titer of 1:1024 and ongoing undetectable haptoglobin.

Two months later, sutimlimab was administered at a dose of 6500mg. With the first dose, there was a decrease in active hemolysis, reflected by haptoglobin 26 mg/dL, LD 331 U/L and total bilirubin of 0.7 mg/dL within 3 days. Following 2 doses, his hemoglobin had increased from 8.6 g/dL to 11.7g/dL within two weeks. Cycle 5 of R-pola-CHP was resumed without complications and no recurrent hemolytic anemia requiring transfusion of warmed red blood cells.

The patient successfully completed his 6th and final cycle, with his final sutimlimab held 2 weeks later. His end of treatment PET scan confirmed a further decrease in the size of his liver mass measuring 29 x 12mm with mild FDG uptake (Lugano 2), which was consistent with a complete metabolic response.

Discussion

Given the relative rarity of CAD and heterogeneous disease course, there are few randomized controlled trials and no standardized, evidence-based treatment approach. In contrast to a warm-AIHA, response rates to high dose corticosteroids are no higher than 10-15%, necessitating need for alternative therapies.[7] Treatment has primarily focused on targeting the B-cell clone responsible for production of the IgM antibodies and resultant CAD.

Rituximab monotherapy was the first effective therapy demonstrated via prospective study.[8] In a cohort of 27 patients, rituximab monotherapy administered at a dose of 375 mg/m2 weekly for 4 weeks demonstrated an overall response rate of 54% with a median increase in hemoglobin levels of 4.0 g/dL. There was only 1 complete response and median time to response was 1.5 months. Unfortunately, the durability of response was limited to a median of 11 months.

In order to improve the response rate and durability, subsequent studies investigated the combination of rituximab with chemotherapy, including bendamustine or fludarabine. The prospective Nordic study evaluated the combination of rituximab plus bendamustine for 4 cycles in 45 patients.[9] The combination therapy increased overall and complete response rates to 71% and 40% respectively. Similarly, the median observed response duration was 32 months. Compared with rituximab plus fludarabine, the side effect profile was also more favorable with rates of grade 3-4 neutropenia in 33%. Interestingly, the data are even more impressive in a retrospective review of 232 patients.[3] Patients that responded to rituximab plus bendamustine, had not reached the median response duration after 88 months with an estimated 5-year sustained remission rate of 77%. Patients receiving rituximab plus fludarabine appeared to have similar outcomes in terms of response and durability, but had a higher risk of long-term adverse effects including developing secondary malignancies in of 31% compared to 9% with rituximab plus bendamustine.

The evidence in more novel therapies is even more limited. A small, prospective study examined bortezomib monotherapy administered as a single cycle in 21 individuals with CAD refractory to at least 1 prior line of therapy.[10] Only 32% of patients demonstrated a response, which was defined as transfusion independence or a 2g/dL increase in hemoglobin level. Finally, use of ibrutinib, a Bruton's Tyrosine Kinase (BTK) – inhibitor, has also been investigated in a small retrospective study of 10 participants, though all 10 appeared to demonstrate a response.[11]

Our patient was particularly challenging because of ongoing hemolysis despite multiple lines of therapy including plasmapheresis, rituximab monotherapy, rituximab in combination with cytotoxic therapy and cytotoxic therapy combined with a BTK inhibitor. In addition, he had concurrent DLBCL requiring definitive therapy. DLBCL would ultimately be fatal without completion of treatment. The initial treatment of combined rituximab and cytotoxic therapy would simultaneously treat the DLBCL and underlying B-cell clone responsible for his CAD. However, treatment resulted in myelosuppression and prevented adequate compensatory reticulocytosis in the setting of his complement-mediated hemolysis.

He required a more effective method to reduce hemolysis as repeated plasmapheresis had failed to accomplish. Sutimlimab represents a first-in-class monoclonal antibody, which targets C1s and is responsible for activating the classic complement pathway. The CADENZA study enrolled 42 patients with CAD to receive sutimlimab or placebo with an overall response rate of 73% in the treatment arm.[12] Remarkably, the effect of sutimlimab was near immediate in responders with normalization of bilirubin within 1 week. Fortunately, our patient had a near immediate response, with >3 g/dL increase in his hemoglobin within 2 weeks, which allowed completion of his definitive cytotoxic therapy. Interestingly, vaso-occlusive extremity symptoms persisted while on the sutimlimab, since this phenomenon is not complement-mediated.

Conclusion

It is critical to consider sutimlimab as a treatment option in patients with refractory CAD, as well as those requiring urgent correction of their complement-mediated hemolysis. It is important to note that upon cessation of the medication, hemolysis will resume once the classic complement pathway is no longer inhibited. Thus, additional novel therapies are required to more definitively eradicate the B-cell clone responsible for the CAD.

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