DUTCH REAL-WORLD EXPERIENCE OF IMMUNOCHEMOTHERAPY IN COLD AGGLUTININ DISEASE AND COLD AGGLUTININ SYNDROME

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Background:
Cold autoimmune hemolytic anemia (cAIHA) results from IgM autoantibodies against red blood cells with optimal reactivity at low temperatures, causing complement-mediated hemolysis and sometimes acrocyanosis. cAIHA includes cold agglutinin disease (CAD) and cold agglutinin syndrome (CAS). CAD is accompanied by a low-grade monoclonal B-cell disorder, without extramedullary involvement. If secondary to an overt malignancy, such as Waldenström macroglobulinemia (WM) or chronic lymphocytic leukemia (CLL), it is termed CAS. There is no consensus on optimal treatment. Rituximab (R) monotherapy yields short-lived responses. One prospective study demonstrated higher and more durable responses to R-bendamustine, albeit with higher toxicity. Data on other immunochemotherapy (ICT) combinations, such as R-cyclophosphamide-based combinations, are lacking. With the introduction of new therapies, such as complement- and BTK-inhibitors, expanding our knowledge of ICT regimens in CAD/CAS is important. This could help in positioning novel treatments relative to ICT.

Methods:
Clinical data were collected retrospectively for CAD/CAS patients treated with R-bendamustine or R-cyclophosphamide-based therapy after 2000. Hb response was defined as CR (to ≥12 g/dl) or PR (increase of ≥2.0 g/dl), provided transfusion independence (>3 months). AEs were graded according to CTCAE v5.0.

Results:
33 patients from 14 Dutch hospitals were included, with 39 ICT lines. Median age at diagnosis was 63 years (range 44-81) and 17 (52%) were female. All patients had a monoclonal gammopathy. Twelve patients (36%) were classified as CAS, with underlying WM (n=8) or a CLL-phenotype (n=4).
In 22 R-bendamustine treated patients, median follow-up was 26 months (range 6-94). Of 17 patients with an Hb <12g/dL at baseline, 13 (76%) reached CR and 2 (12%) PR. 2/4 patients remained transfusion dependent. Of 16 patients with acrocyanosis, 11 reported improvement with full resolution in 6. Seven patients (32%) experienced grade ≥3 AEs, including 3 (febrile) neutropenias and 2 infections.
In 17 R-cyclophosphamide treated patients, median follow-up was 23 months (range 5-128). Of 15 patients with an Hb <12g/dL at baseline, 6 (40%) reached CR and 5 (33%) PR. 3/7 patients remained transfusion dependent. Of 11 patients with acrocyanosis, 6 reported improvement with full resolution in 3. Six patients (35%) experienced grade ≥3 AEs, including 4 (febrile) neutropenias, 2 infections, and 2 cytopenias . One patient discontinued treatment due to toxicity. Suspected therapy-related MDS occurred in 1 patient.

Conclusion:

R-bendamustine and R-cyclophosphamide treatment in CAD/CAS resulted in Hb responses in 88% and 73%, respectively, and improved acrocyanosis in 69% and 55% of patients. However, 50% of transfusion dependent patients did not respond. Grade 3-4 toxicities were reported in one-third of patients. Summarizing, our data suggest that ICT is an effective fixed duration treatment for CAD/CAS, but might be less suited for transfusion-dependent patients.