# Rituximab and fludarabine combination therapy results in high response rates and durable responses in chronic cold agglutinin disease (CAD)

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Probably <5% of patients with Waldenstrom's macroglobulinemia (WM) have cold agglutinin disease (CAD), while a high proportion of patients traditionally diagnosed with 'primary' CAD can also be classified as having WM. Although not all CAD patients require pharmacologic treatment, counseling and avoidance of cold is insufficient as sole therapeutic measure in a majority. The only well-documented drug therapy is infusions of rituximab, leading to partial response (PR) in 45-60% of the patients. Complete responses (CR) are rare, and the median response duration is only 11 months. We wanted to improve on these results by studying the potential of fludarabine and rituximab combination therapy. In a prospective, uncontrolled multi-center trial, eligible patients received rituximab infusions, 375 mg/m$^2$ day 1, 29, 57 and 85; and fludarabine orally, 40 mg/m$^2$ day 1-5, 29-34, 57-51 and 85-89. Twenty-nine patients were treated, 12 men and 17 women, aged median 73 years (range, 39-87). Median hemoglobin level was 8.7 g/dL. Twenty-two patients (76%) responded to therapy, including 6 (21%) CR and 16 (55%) PR. Seven patients (24%) were non-responders. Among 10 patients who had previously received rituximab monotherapy without response, 1 achieved CR and 6 PR following the combination therapy. Median time to response was 4 months. Median increase in hemoglobin level was 3.1 g/dL among the responders and 4.0 g/dL in those who achieved CR. At a follow-up of median 33 months after achieving remission, the median or even the lower quartile of response duration has not yet been reached. Grade 3 or 4 hematologic toxicity occurred in 12 patients (41%), including grade 4 toxicity in 4 (14%). Seventeen patients (59%) experienced infection which was successfully treated. In conclusion, fludarabine and rituximab combination therapy is very efficient in patients with CAD. Toxicity is more prevalent as compared with rituximab monotherapy, and potential benefits should be carefully weighed against risks in the youngest as well as the old and frail patients.