

Rituximab, Fludarabine and Alkylating Agents In Peripheral Neuropathies Related To IgM Monoclonal Gammopathy with Autoantibody Activity Against Myelin-Associated-Glycoprotein: A Retrospective Study of 15 Patients.

Karlin L, Arnulf B, Galicier L, Asli B, Malphettes M, Fieschi C, Cereja S, Oksenhendler E, Fermand JP and Brouet JC.

Immuno-hematology Department, Saint-Louis Hospital, Paris, France.

Treatment of peripheral neuropathies (PN) related to IgM monoclonal (MIgM) gammopathy with anti-MAG antibodies remains unsatisfactory. Reducing the serum level of MIgM is a reasonable goal because of its auto-antibody activity against antigens expressed on peripheral nerve.

Rituximab (R) in combination with Fludarabine (F) and Alkylating agents is a highly effective regimen in Waldenström's Macroglobulinemia but has been poorly evaluated in MIgM anti-MAG antibody-related PN. We retrospectively studied a cohort of 15 patients (pts) treated with such association or with R alone.

Median age was 64 years, 13/15 pts had MIgM with kappa-light-chain. All had sensory symptoms, 3 had motor involvement. Median Overall Neuropathy Limitations Scale (ONLS) score was 4 (2-12). Median MIgM level was 5.9 g/L (1.8-28). No pt had evidence for an overt lymphoid proliferation. Electrophysiologic evaluation showed a demyelinating, axonal or mixed neuropathy in 8, 2 and 5 pts, respectively. Nine pts had been previously treated (7 with alkylating agents alone, 2 with intravenous immunoglobulins) but none had improvement. Median interval time between PN diagnosis and treatment with R +/- chemotherapy was 25.6 months (range, 1-159).

Twelve pts received a combination of R + chemotherapy (7 R + F + Cyclophosphamide (C), 4 R + C or chlorambucil, 1 R + F), 3 received R alone. Significant and durable improvement occurred in 7 pts, all treated with R + chemotherapy. Among those, 5 had major reduction (>90%) of the serum MIgM level. On the opposite, no response was observed with R alone. Seven pts experienced drug-induced cytopenias (4 grade III-IV neutropenia, 1 grade III thrombopenia). Treatment-related infections occurred in 3 pts (2 herpes zoster, 1 cytomegalovirus retinitis). Two pts (treated with F containing regimen) developed secondarily malignancy, 1 died from cardiac arrest during a surgical procedure for lithiasic cholecystitis.

In conclusion, combination of R, F and Alkylating agents in MIgM anti-MAG antibodies-related PN provides high rates of durable clinical improvement, even in first-line refractory pts. Toxicity is acceptable but adding F implies immunosuppressive consequences that should be carefully evaluated. Although this remains to be formally demonstrated, R + chemotherapy seems to be more effective than R alone.