

International Phase III study of chlorambucil versus fludarabine as initial therapy for Waldenstrom macroglobulinemia and related disorders: results in 414 patients.

Owen RG¹, Johnson SA², Lejeune J³, Tournilhac O⁴, Morel P⁵, Ewings M², Chevret S³ and Leblond V⁶.

1. HMDS Laboratory, St James's Institute of Oncology, Leeds, UK. 2. Department of Haematology, Taunton and Somerset NHS Foundation Trust, Taunton, UK. 3. Department of Biostatistics, Saint Louis Hospital, Paris, France. 4. Department of Haematology, Hotel Dieu Hospital, Clermont Ferrand, France. 5. Department of Haematology, Schaffner Hospital, Lens, France. 6. Department of Haematology, Pitié -Salpêtrière Hospital, Paris, France.

Waldenstrom macroglobulinemia (WM) and related-disorders (splenic marginal zone lymphoma: MZL, and non-immunoglobulin M lymphoplasmacytic lymphoma: LPL) are rare diseases with very few randomized trials having been reported. Most commonly patients with WM are initially treated with an alkylating agent, such as chlorambucil with response rates of 50-60% or with a nucleoside analogue such as fludarabine or cladribine, with higher reported response rates of 70-90%. A number of small phase II studies have reported the efficacy of combination chemotherapy with monoclonal antibodies but a clear demonstration of a survival advantage over single agent therapy remains lacking. The WM1 study was a prospective international randomized open-label study that included patients with symptomatic and previously untreated WM, MZL and LPL. At registration, patients were stratified as having WM, MZL or LPL, and were randomized in the two arms. The aim of the study was to compare the efficacy of oral chlorambucil at a dose of 8 mg/m² (6 mg/m² for those >75 years of age) for 10 days every 28 days to a maximum of 12 cycles with oral fludarabine at a dose of 40 mg/m² orally (30 mg/m² orally for those >75 years of age) for 5 days every 28 days to a maximum of 6 cycles. Primary endpoints were response to therapy and duration of response; secondary endpoints were improvement in hematologic parameters, toxicity of therapy, quality of life, and overall survival. 416 patients were enrolled into the study in 8 years (07/01 to 12/09) and 414 received at least one course of chemotherapy. There were 337 WM, 34 MZL and 43 LPL, 277 males and 137 females with a median age of 68 years (40-89). 207 patients were randomized to receive fludarabine (169 WM, 17 MZL and 21 LPL) and 207 chlorambucil (168 WM, 17 MZL and 22 LPL). At inclusion, the median values for haemoglobin (g/dl), platelets (10⁹/l), albumin (g/l) and beta 2 microglobulin (mg/l) were 10, 218, 37 and 3.49 respectively. Analysis of the results are ongoing and will be presented at the meeting.