

[Abstract 32]

COMBINATION THERAPY WITH RITUXIMAB AND FLUDARABINE IN WALDENSTROM'S MACROGLOBULINEMIA.

Steven P Treon¹, Andrew Branagan^{1*}, Parveen Wasi², Christos A Emmanouilides³, Stanley R Frankel⁴, Andrew Lister^{5*}, Pierre Morel⁶, Jeffrey Matous⁷, Sari Heitner Enschede⁸ and Eva Kimby⁹. ¹ Bing Program for Waldenstrom's Macroglobulinemia, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA, United States; ² Hematology Oncology, McMaster University Medical Center, Hamilton, ON, Canada; ³ Hematology Oncology, UCLA Medical Center, Los Angeles, CA, United States; ⁴ Hematology Oncology, Greenbaum Cancer Center, Baltimore, MD, United States; ⁵ Medical Oncology, St. Bartholomew's Hospital and Cancer Research, London, United Kingdom; ⁶ Clinical Hematology, Centre Hospitalier Schaffner, Lens, France; ⁷ Rocky Mountain Cancer Center, Denver, CO, United States; ⁸ Rush Presbyterian Medical Center, Chicago, IL, United States and ⁹ Hematology, Karolinska Institutet, Stockholm, Sweden.

Rituximab and Fludarabine are active in Waldenström's macroglobulinemia (WM) producing major response rates of 40-70%. Both pre-clinical and clinical studies in related low-grade B-cell malignancies suggest that additive, and even synergistic benefit with combination Fludarabine and Rituximab may result. As such, we conducted this combination study with Rituximab and Fludarabine in WM patients. WM patients who had received < 2 prior therapies, and who had not previously been treated with any nucleoside analogue or Rituximab were eligible. Intended therapy was as follows:

Weeks 1-4 Rituximab (375 mg/m²/week)
Weeks 5, 9, 13 Fludarabine daily for 5 days (25 mg/m²)
Weeks 17, 18 Rituximab (375 mg/m²/week)
Weeks 19, 23, 27 Fludarabine daily for 5 days (25 mg/m²)
Week 30, 31 Rituximab (375 mg/m²/week)

Patients were evaluated at week 12, and if they did not progress were eligible for further therapy and were evaluable for response. 43 WM patients were enrolled with a median age of 61 (range 52-75 yrs), and median prior therapies of 1 (range 0-2). 40/43 patients continued on therapy beyond week 12. Two patients (1 PR, 1 SD) died after completing protocol therapy including one elderly patient who had an influenza pneumonia and another-debilitated patient who may have had a secondary malignancy. Delays in therapy due to neutropenia were common, and 58% of patients experienced Grade III/IV neutropenia. Protocol therapy was truncated after the 4th and 5th courses of fludarabine in several patients for persistent neutropenia and/or thrombocytopenia despite delays in therapy and/or use of G-CSF support. Other complications included: Herpes zoster outbreak in 3 of the first 21 patients, before prophylactic acyclovir or equivalent was initiated; paresthesias (n=3); pneumonitis (n=2); development of bladder cancer (n=1) and a high grade lymphoma (n=1); subdural hemorrhage in a patient who had a 3-fold increase in serum viscosity following the first 4 infusions of Rituximab. On an intent to treat basis, 39/43 (90.1%) patients demonstrated a response. Response categories were as follows: CR (n=3); PR (n=32); MR (n=4). One patient remains in stable disease at 20+ months. At a median follow-up of 17 months, 36 of 39 responding patients remain in remission. Rituximab in combination with fludarabine is highly active and produces durable responses in WM.