[ABSTRACT WM2.4]

OVERVIEW IN SALVAGE TREATMENT IN WALDENSTROM'S MACROGLOBULINEMIA

M.A. Gertz
Division of Hematology, Mayo Clinic, Rochester MN, USA

Waldenstrom's macroglobulinemia is characterized by the infiltration of lymphoplasmacytic cells in the bone marrow associated with an IgM monoclonal protein of any size. Only patients with symptoms manifest by anemia, thrombocytopenia, lymphadenopathy, organomegaly, hyperviscosity, neuropathy, or an IgM-associated clinical disorder should be treated. At the Second International Workshop on Waldenstrom's Macroglobulinemia, the options for first-line therapy formulated by a consensus panel included single-agent therapy with alkylating agents, nucleoside analogs, and rituximab. It was not possible at that time to recommend the use of one first-line agent over another, although it was noted that exposure to agents that would deplete stem cells should be avoided in patients who would be candidates for high-dose therapy and autologous stem cell transplantation. The option for the treatment of relapsed disease included the re-use of a front-line agent if a prior response has been obtained that was deemed durable. Alternatively, another front-line agent could be used as a single agent. Other options included combination chemotherapy, thalidomide with or without steroids, autologous transplantation, and alemtuzumab.1 A number of clinical trials exploring the use of rituximab as part of combination therapy have been performed. Rituximab as a single agent produced an objective response rate of 35%.2 A number of publications in the past 36 months have indicated the ability of rituximab in combination to produce higher response rates. Weber *et al.* reported 90 consecutive untreated patients using cladribine alone or in combination with prednisone, cyclophosphamide, and rituximab. The overall response was 94% for cladribine alone, 60% for cladribine and prednisone, 84% for cladribine and cyclophosphamide, and 94% for cladribine, cyclophosphamide, and rituximab. The only prognostic factor predicting shorter survival was hemoglobin <9 g/dL. This supports the potential role of cladribine in both untreated and treated Waldenstrom's macroglobulinemia. The use of rituximab combined with cyclophosphamide, doxorubicin, vincristine, and prednisone (RCHOP) was reported in 13 patients, ten of whom had previously been treated. Eight and six, respectively, had had prior fludarabine and rituximab. Three patients received maintenance rituximab. There were three complete responses unconfirmed, eight partial responses, and a minor response with 10 of the 11 patients who had a major response in continuous remission with a median follow-up of nine months. This is a highly active regimen for the management of refractory/relapsed Waldenstrom's macroglobulinemia, and it is currently the subject of an Eastern Cooperative Oncology Group trial.3 Other attempts to combine rituximab, a steroid, and an alkylating agent have been reported by Dimopoulos and colleagues. Patients received rituximab on day 1, cyclophosphamide orally 100 mg/m2 p.o. b.i.d. for five days, and dexamethasone 20 mg IV every 21 days for a total of six courses. Over a period of four years, 70 patients have been treated with 60 having completed the intervention. Their median age was 71 years and 70% of patients achieved a 50% reduction of serum monoclonal protein and 7% complete responses. Progressive disease was only seen in 10% of patients. The median time to response was four months, and at 24 months median, 60% of patients are progression free. There was only one treatment-related death.4 Substituting fludarabine for dexametha-sone, Vargaftig *et al.* had previously shown that fludarabine and cyclophosphamide produced a 78% response rate and subsequently added rituximab and reported on 21 patients with a median age of

65 and a median IgM level of 4090. Nineteen of the 21 had previously been treated with a median of two lines of therapy including three patients receiving autologous stem cell transplantation. Fifteen were relapsed and four were refractory. The regimen was given every four weeks and included rituximab 375 mg/m2 on day 1, fludarabine 40 mg/m2 orally days 1 through day 3, and cyclophosphamide 250 mg/m2 orally days 1 through day 3. Twenty-one patients were treated with a single cycle and 19 received two or more for a median of 4.5 cycles, maximum 6. The overall response rate was 76% with 48% partial responses, 24% minor responses, and 5% complete responses. There were five patients who had stable disease (24%), and none had progressive disease. All four patients previously treated with fludarabine responded, and two of three with previous stem cell transplant responded. Grade 3-4 neutropenia was the most common toxicity (48%). With a median follow-up of five months, 21 were alive and two had relapse. The authors concluded that rituximab and fludarabine orally and cyclophosphamide produced a response rate of 76% with acceptable toxicity.5 Tam *et al.* reported on their experience with fludarabine combination therapy used with cyclophosphamide in nine patients and with cyclophosphamide and rituximab in five patients. In the 14 patients previously treated, partial responses were obtained in 76% of patients and did not differ based on regimen. The median remission duration was 38 months. The actuarial five-year survival was 55% for previously treated patients.6 Tamburini administered the combination of fludarabine, cyclophosphamide, and rituximab to 49 patients (35 previously treated) with a 78% response rate, and only two patients had progressive disease. The median time to treatment failure was 27 months. Prognosis was influenced by age >65 and IgM <4 g/dL.7 The novel agents, thalidomide and bortezomib, both appear to have activity in the management of Waldenstrom's. Thalidomide 200 mg escalated to 400 mg each evening with rituximab weeks 2 through 5 and 13 through 16 were administered to 25 patients, five previously treated. There was one complete response, 15 partial responses, and two minor responses, for a major response rate of 70% and an overall response rate of 78%. The median duration of response is 19.6+ months.8 Dimopoulos *et al.* reported on the use of bortezomib with relapsed or refractory Waldenstrom's macroglobulinemia. Ten previously treated patients, eight of whom who had received three or more prior regimens, were treated with standard-dose bortezomib with six partial responses occurring at a median of one month. The toxicities were typical-thrombocytopenia, fever, and fatigue.9 The use of nonmyeloablative stem cell transplant for patients with refractory Waldenstrom's were reported in an effort to determine if there was a graft-versus- tumor effect. Twelve patients with refractory Waldenstrom's in the Seattle consortium were transplanted using an HLA-matched related donor in seven and an unrelated donor in five. Conditioning was low-dose total body radiation therapy with or without fludarabine. Eleven of the 12 received peripheral blood stem cells. Median time from diagnosis to allogeneic transplant was 6.6 years. Patients had received a median of 4.5 prior regimens. All patients but one achieved stable engraftment with >95% chimerism. Grades 2 through 4, acute graft-versus-host disease occurred in 58%, and extensive chronic graftversus- host disease in 58%. The treatment-related mortality was 17%. Responses were seen in 91%. Four patients achieved a complete response and only one has progressed, although one patient died of transformed large cell lymphoma. All seven sibling transplants responded. Three of the five matched unrelated donor transplants responded. The Kaplan-Meier progression-free survival at five years is estimated to be 61%. Graft-versus-tumor effects were observed in the majority of patients.10 Agents that appear promising in the management of Waldenstrom's macroglobulinemia include 131I-tositumomab which produced a response in a single

patient. This agent is limited by the extensive marrow infiltration in most patients and the potential of this agent to produce long-term myelosuppression. Imatinib has been used in the treatment of Waldenstrom's on the principle that it blocks stem cell factor signaling and induces apoptosis in Waldenstrom's mast cells thought to be important in the pathogenesis of the disease. Thirteen patients, all of whom had relapsed and refractory disease, received a median of three months of imatinib therapy. Six of 13 attained a >25% decrease in serum IgM at a median of 2.5 months. A phase I-II study of Atacicept (TACI-Ig) to neutralize APRIL and BLyS has also been reported. Four Waldenstrom's patients entered this trial, and no doselimiting toxicity was seen. Three Waldenstrom's patients had stable disease after the first cycle. One Waldenstrom's patient remains stable, and one had a minimal response. The treatment was well tolerated without dose-limiting toxicity. Perifosine is an oral Akt inhibitor which induced apoptosis in Waldenstrom's cells demonstrated by flow and did not produce cytotoxicity in healthy donor, peripheral blood mononuclear cells. Perifosine induced significant reduction in Waldenstrom's tumor growth in a mouse model suggesting it will be an active agent. There appears to be *in vitro* synergy of perifosine with rituximab and bortezomib. *Summary*. The use of combination therapy with nucleoside analogs and alkylating agents, rituximab with a nucleoside analog, and nucleoside analogs plus alkylating agents are all considered appropriate for the management of newly diagnosed and relapsed Waldenstrom's macroglobulinemia. The activity for these combinations is at least as good if not better than single-agent therapy. Alkylators plus purine nucleoside analogs, nucleoside analogs with rituximab, thalidomide and stem cell transplantation are all options to be considered in the complex management of patients with Waldenstrom's macroglobulinemia.

References

1. Treon SP, Gertz MA, Dimopoulos M, et al. Update on treatment recommendations from the Third International Workshop on Waldenstrom's macroglobulinemia. Blood 2006;107:3442-3446.
2. Gertz MA, Rue M, Blood E, Kaminer LS, Vesole DH, Greipp PR. Multicenter phase 2 trial of rituximab for Waldenstrom macroglobulinemia (WM): an Eastern Cooperative Oncology Group Study (E3A98). Leuk Lymphoma. 2004;45:2047-2055.
3. Treon SP, Hunter Z, Barnagan AR. CHOP plus rituximab therapy in Waldenstrom's macroglobulinemia. Clin Lymphoma. 2005;5:273-277.
4. Dimopoulos M, Anagnostopoulos A, Kyrtsonis MC, et al. Primary treatment of Waldenstrom's macroglobulinemia (WM) with dexamethasone, rituximab, and cyclophosphamide (Abstract 128). Blood 2006;108.
5. Vargaftig J, Pegourie-Bandelier B, Mahe B, et al. Fludarabine plus cyclophosphamide and rituximab (RFC) in Waldenstrom's macroglobulinemia (WM): Results in 21 patients (pts) (Abstract 4727). Blood 2006;108.
6. Tam CS, Wolf MM, Westerman D, Januszewicz EH, Prince HM, Seymour JF. Fludarabine combination therapy is highly effective in first-line and salvage treatment of patients with Waldenstrom's macroglobulinemia. Clin Lymphoma Myeloma 2005;6:136-139.
7. Tamburini J, Levy V, Chaleteix C, et al. Fludarabine plus cyclophosphamide in Waldenstrom's macroglobulinemia: results in 49 patients. Leukemia 2005;19:1831-1834.
8. Treon SP, Hunter Z, Patterson CJ, Branagan AR. Thalidomide in combination with rituximab is active in Waldenstrom's macroglobulinemia and may overcome poor

response determinants associated with rituximab monotherapy (Abstract 2442). Blood 2005;106.
9. Dimopoulos MA, Anagnostopoulos A, Kyrtsonis MC, Castritis E, Bitsaktsis A, Pangalis GA. Treatment of relapsed or refractory Waldenstrom's macroglobulinemia with bortezomib. Haematologica 2005;90:1655-1658.
10. Anderson LD, Sandmaier BM, Maris MB, et al. Nonmyeloablative allogeneic hematopoietic cell transplantation (HCT) for refractory Waldenstrom's macroglobulinemia (WM): Evidence for a graft-versus-WM effect (Abstract 3034). Blood 2006;108.