[ABSTRACT WM2.1]

INDICATIONS FOR TREATMENT AND THE ROLE OF ALKYLATING AGENTS IN WALDENSTROM'S MACROGLOBULINEMIA (WM)

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The presence of constitutional symptoms such as weakness, fatigue, fever, night sweats, or weight loss are indications for beginning therapy for WM. The presence of progressive symptomatic lymphadenopathy, hepatomegaly, and/or splenomegaly is also indication for treatment. The occurrence of anemia (hemoglobin < 10 g/dL) or thrombocytopenia (platelets < 100·109 due to marrow infiltration) are also indications for therapy. Development of the hyperviscosity syndrome, sensorimotor peripheral neuropathy, autoimmune hemolytic anemia, the presence of amyloidosis or symptomatic cryoglobulinemia also require the institution of therapy. Initiation of therapy should not be based on the IgM level *per se* since this may not correlate with the clinical manifestations of WM (Kyle, *et al.*, 2003). Treatment for systemic complications of WM is evolving as newer chemotherapeutic agents are utilized. Therapeutic options include rituximab, fludarabine, cladribine (2-chlorodeoxyadenosine), 2-CdA and alkylating agents as well as autologous stem cell transplantation (Dimopoulos, *et al.*, 2005, Gertz 2005, Dimopoulos, *et al.*, 2005). This discussion will be limited to the use of alkylating agents. Chlorambucil continuously has been a standard therapy for WM for more than four decades. It is usually given in an initial oral dosage of 6-8 mg/day. The dose is then reduced usually to 2-4 mg/day depending upon the leukocyte and platelet counts and patient response. Chlorambucil with or without prednisone may be given in an intermittent schedule, at a dosage of 0.3 mg/kg/day for 7 days every 4-6 weeks. Therapy should be continued until the patient reaches a plateau state defined as the resolution of constitutional symptoms and serum IgM protein reaching a stable state. Facon *et al.* described 167 patients with WM oral chlorambucil over a 19-year period. The median survival was 60 months. Age, gender, and hemoglobin value had no impact on the outcome. In addition, the presence of organomegaly and the percentage of marrow lymphoid cells did not predict a shorter survival (Facon, *et al.*, 1993). There has been one prospective randomized study comparing continuous oral with intermittent administration of chlorambucil. Forty-six patients with WM requiring therapy because of anemia or other laboratory abnormalities, hepatosplenomegaly, lymphadenopathy, or constitutional symptoms were randomized to chlorambucil 0.1 mg/kg/day orally (continuous) or chlorambucil 0.3 mg/kg orally for 7 days repeated every 6 weeks (intermittent). The two patient groups were not different according to age, symptom of fatigue, weight loss, bleeding or purpura, hepatosplenomegaly or lymphadenopathy, performance score, hemoglobin, leukocyte or platelet values, serum creatinine, calcium, serum albumin, serum viscosity, bone marrow plasma cells, size, light chain type of serum monoclonal protein, the amount and type of urine monoclonal light chain. Twenty-two percent had either monoclonal gammopathy of undetermined significance (MGUS) or smoldering macroglobulinemia before protocol entry. Of the 46 patients, 39 (85%) had an M-spike ≥ 3 g/dL at study entry. Of the 7 patients with an M-spike < 3 g/dL, 4 had anemia, 3 had a malignant proliferative process with hemoglobin of 11.7 g/dL and an Mspike of 2.8 g/dL (1 patient), systemic amyloidosis (1), and a massive pleural effusion from plasmacytoid lymphocytes involving the pleura (1). Forty-one of the 46 patients (89%) had a hemoglobin value of ≤ 12 g/dL; 57% had a hemoglobin level of ≤ 10 g/dL. The median

age was 63 years and 70% were males. Fatigue was present initially in 52% and weight loss was noted in 22%. Bleeding was present in 17%. The liver was palpable in 24%, and the spleen was palpable in 20%, while lymphadenopathy was noted in 15% at study entry. The median hemoglobin value was 9.9 g/dL (range 5.4-15.4 g/dL). Platelets were less than 100·109/L in 9%, while the serum albumin was < 3 g/dL in 20%. Viscosity was more than 1.9 cp in 8 of the 31 patients in whom viscosity was measured (median 3.5 cp); 39% had a serum viscosity > 4 cp. Size of the monoclonal protein ranged from 1.7-9.2 g/dL (median 4.2 g/dL). IgA and IgG immunoglobulins were reduced in 94% of patients. Seventy-eight percent had IgM kappa. Monoclonal light chains were found in the urine in 72%, but only 14% had an M-protein value of more than 1 g/24h. Criteria for response included > 50% reduction in the serum monoclonal protein, an increase in the hemoglobin level of ≥ 2 g/dL without transfusion, ≥ 50% decrease of urine monoclonal protein, reduction in the size of the liver or spleen of ≥ 2 cm, or a reduction of ≥ 2 cm in the size of the lymph nodes(Kyle, *et al.*, 2000). Of the 24 patients receiving continuous chlorambucil, 75% had a reduction in serum monoclonal protein of ≥ 50% unrelated to plasmapheresis. Ten other patients had an objective response of the monoclonal protein but had progression of their macroglobulinemia and were considered nonresponders. The median duration from randomization to the time of objective response was 18 months, with a median duration of response of 26 months. Hemoglobin increased by more than 2.0 g/dL without transfusion in 53%. The duration of the hemoglobin response was 17 months. Nineteen of the 24 patients (79%) had objective improvement measured by either a reduction of the serum monoclonal protein or an increase in hemoglobin. Of these 19 patients, only 3 had a reduction of serum monoclonal protein and no improvement in the hemoglobin value. The urine monoclonal protein decreased by ≥ 50% in 5 of the 7 patients with a measurable monoclonal protein. In addition to the seven patients, two others had a reduction in the serum monoclonal protein, but their disease progressed. Of the 22 patients receiving intermittent chlorambucil, 64% had a serum monoclonal protein decrease of ≥ 50% unrelated to plasmapheresis. Median duration from randomization to response was 21 months, while the median duration of response was 46 months. Fifty-nine percent (13 of 22 patients) had an increase in hemoglobin of ≥ 2 g/dL without benefit of transfusion. Median duration from randomization to an increase in the hemoglobin level of ≥ 2 g/dL was 7 months. Median duration of the hemoglobin response was 5 months. Fifteen (68%) had an objective reduction of the monoclonal protein or an increase in the hemoglobin value. Five of seven patients with an initial value of >50 mg/24h. had a reduction in urine monoclonal protein of ≥ 50%. With either continuous or intermittent chlorambucil, the liver decreased by ≥ 2 cm in 6 of 11(55%), while the spleen decreased by ≥ 2 cm in 6 of 9 patients (67%). Lymphadenopathy decreased in 71% of 7 patients. Two patients with pleural effusion requiring repeated thoracenteses had resolution with chlorambucil. The median survival was 5.4 years with no survival difference between continuous and intermittent chlorambucil. Eighty-nine percent have died from *macroglobulinemia* (13 patients), infection,5 cardiac (4), myelodysplasia/leukemia,3 gastrointestinal bleeding ,3 cerebrovascular accident,2 injury from a fall,2 other malignancy,2 and miscellaneous causes.7 In summary, 79% had an objective response to continuous chlorambucil, and 68% had an objective response to intermittent chlorambucil. The addition of corticosteroids does not seem to increase response rate or survival although they may be useful in patients who have autoimmune hemolytic anemia. Optimal duration of chlorambucil administration has not been defined. In some studies, treatment is continued

until a maximum reduction of monoclonal protein is reached (plateau state), and then patients are followed without treatment until there is evidence of disease progression. In other studies, chlorambucil has been administered for 1 to 2 years and then discontinued. There is no evidence that maintenance therapy prolongs survival. Prolonged treatment with alkylating agents increases the possibility of myelodysplasia or acute leukemia(Dimopoulos, *et al.*, 2005). Combinations of alkylating agents may also be of benefit, such as the M2 protocol (BCNU, cyclophosphamide, vincristine, melphalan, and prednisone) at 4- to 5-week intervals. Twenty-seven of 33 patients (82%) showed response (Case, *et al.*, 1991). In another report, 72 patients were treated with melphalan (6 mg/m2), cyclophosphamide (125 mg/m2), and prednisone (40 mg/m2) daily on days 1 through 7 every 4 to 6 weeks for a maximum of 12 courses. Patients with responsive or stable disease were then given chlorambucil (3 mg/m2) orally each day and prednisone (6 mg/m2) daily until progression. Fifty-five of 71 (77%) of evaluable patients obtained a response. No grade III or IV toxicities were seen. The major side effects consisted of transient nausea, vomiting, and mild neutropenia(Annibali, *et al.*, 2005). An interesting prospective study is comparing oral chlorambucil 8 mg/m2 for 10 days every 28 days for a maximum of 12 cycles with oral fludarabine at a dosage of 40 mg/m2 or IV fludarabine 25 mg/m2. The results of this study are eagerly awaited (Johnson, *et al.*, 2005).

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