



Clinicopathologic spectrum of Waldenstrom's Macroglobulinemia: a single center experience

Raihan Said*, Sarah S**, Usman Shaikh*,
Salman N Adil*

*Section of Hematology

Department of Pathology and Microbiology

Aga Khan University

** Dow Medical College DUHS

Introduction

Waldenstrom's Macroglobulinemia (WM) is a B cell neoplasm characterized by infiltration of the bone marrow by a lymphoplasmacytic infiltrate and an IgM monoclonal gammopathy

It is a rare disorder with incidence of approximately 3 per million per year in western countries

Epidemiological data for Pakistan is not available as only occasional case reports of this disease are published in this part of the world

Diagnostic criteria

The lymphoma classification of World health organization (WHO) defines WM as a subset of lymphoplasmacytic lymphoma (LPL) with bone marrow involvement and IgM monoclonal gammopathy of any concentration

IgM monoclonal gammopathy of any concentration, bone marrow infiltration by small lymphocytes, plasmacytoid cells and plasma cells in a diffuse, interstitial or nodular pattern, and a surface Ig(+), CD19(+), CD20(+), CD5(-), CD10(-), CD23(-) immunophenotype proposed by Owen et al in 2003

Clinical presentation

- **asymptomatic**
- **symptomatic**
 - **weight loss**
 - **fatigue**
 - **lymphadenopathy**
 - **hepatosplenomegaly**
 - **sensorimotor peripheral neuropathy**
 - **hyperviscosity syndrome**
 - **generalised neurologic dysfunction (coma)**
 - **bleeding diathesis (impaired platelet function)**
 - **hypervolemia (progressing to congestive heart failure)**
 - **retinal changes (haemorrhages)**

WM

- **Laboratory findings**
 - anaemia, thrombocytopenia
 - hyperproteinemia
 - prolongation of APTT, PT
- **Diagnosis**
 - monoclonal IgM
 - lymphoplasmatic cells in bone marrow and peripheral blood
- **Treatment**
 - chemotherapy (chlorambucil, CHOP)
 - plasmapheresis

WORKUP

- H&P
- CBC, differential, platelets
- BUN/creatinine, electrolytes
- Quantitative immunoglobulins
- SPEP/immunofixation
- Liver function tests
- Serum viscosity^a
- Unilateral bone marrow aspirate + biopsy
- Chest x-ray
- Chest/abdominal/pelvic CT
- Hepatitis serology
- Cryocrit^b

Generally useful tests:

- Cold agglutinins

Indications for treatment:

- Symptomatic hyperviscosity
- Anemia, pancytopenia
- Bulky adenopathy
- Symptomatic organomegaly
- Symptomatic cryoglobulinemia or neuropathy

PRIMARY TREATMENT

Plasmapheresis for symptomatic hyperviscosity and

- Alkylating agents or
- Nucleoside analogs^c
 - 2-CdA
 - Fludarabine
- or
- Clinical trials
- or
- Rituximab^{d,e}
- or
- Thalidomide
- or
- Bortezomib^f

[See Surveillance and Follow-up \(WALD-2\)](#)

Proposed Criteria for the Diagnosis of WM

- IgM monoclonal gammopathy of any concentration
- Bone marrow infiltration by small lymphocytes, plasmacytoid cells, and plasma cells
- Diffuse, interstitial, or nodular pattern of bone marrow infiltration
- Surface Ig+, CD5-, CD10-, CD19+, CD20+, CD23- immunophenotype

Reprinted from Seminars in Oncology, Volume 30(2), Owen, RG, Developing Diagnostic Criteria in Waldenström's Macroglobulinemia, 196-200, Copyright (2003), with permission from Elsevier.

^aMost patients with serum viscosity of less than 4 cP will not have symptoms of hyperviscosity.

^bIf cryocrit positive, then initial and follow-up sample should be measured under warm conditions.

^cAvoid nucleoside analogs if a stem cell transplant is considered.

^dPreliminary data indicate significant response with minimal toxicity. Long-term results are unknown.

^eFor patients with M-protein > 5 g/dL, use of rituximab alone is discouraged, reports of transient increase in M-protein have been noted with use of rituximab alone.

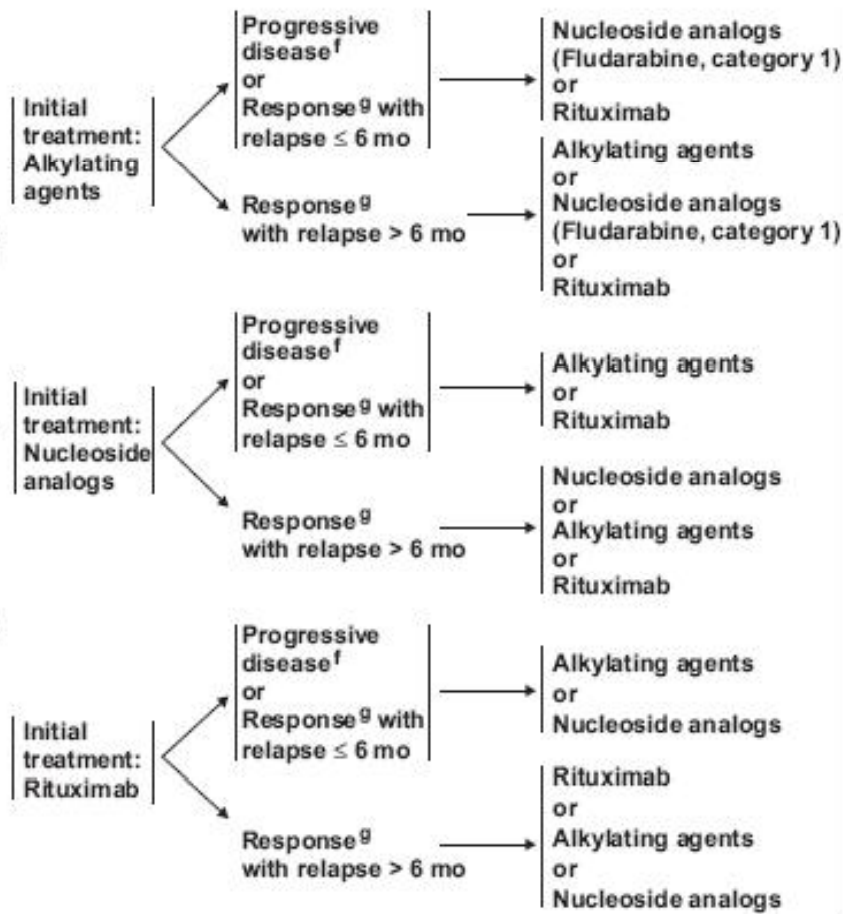
^fConsider herpes zoster prophylaxis for patients treated with bortezomib.

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

SURVEILLANCE

- Every 2 cycles:
 - CBC
 - SPEP
 - Quantitative immunoglobulins
- Every 3-6 mo:
 - CT scan (if abnormal at presentation)
- If symptomatic then serum viscosity generally useful



FOLLOW-UP

^fDisease progression: Defined by a sustained $\geq 25\%$ rise in M protein in serum or urine, adenopathy or organomegaly.
^gDisease partial response: Defined by at least 50% reduction in all measureable disease confirmed by a second measurement at ≥ 4 weeks later.

Note: All recommendations are category 2A unless otherwise indicated.
 Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Study Rationale

No study from Pakistan has been published and there are just few published case reports of this disease

We did a retrospective analysis of this disease at our center for the last 15 years with analysis of clinicopathologic spectrum, treatment given and outcomes in this cohort of patients.



Patients and Methods



Patients and Methods

The demographic and relevant data was retrieved using an in-house questionnaire maintaining full confidentiality for the patients

The data included clinicopathologic features, laboratory parameters, treatment protocols and outcomes.

Patients and Methods

Overall Survival (OS) was considered from the time of diagnosis to death.

To assess the patient's response to treatment, the criteria developed by "The International working group on WM Patients" were followed

The response to therapy was evaluated at 6 and 12 months

Patients and Methods

Complete response (CR) was defined as disappearance of monoclonal protein by immunofixation, resolution of any organomegaly or lymphadenopathy and resolution of any signs or symptoms attributable to WM.

Partial response (PR) was defined as 50 percent or more reduction in serum monoclonal IgM concentration, 50 percent or more decrease in marrow lymphocytosis, at least 50 percent decrease in lymphadenopathy or organomegaly, if present and no new symptoms or signs of the disease.

Patient was considered to have a Minor response (MR) when there was less than 50%, but at least 25% reduction in serum monoclonal IgM concentration.



Patients and methods

- Finally, Progressive disease (PD) was defined as 2 measurements showing an at least 25 percent increase in serum monoclonal IgM, increase in size/ number or lymph nodes or organomegaly, development of cytopenias and an increase in symptoms attributable to WM.
- Stable disease (SD) was considered when the patient did not fulfill criteria for MR or progressive disease.

Results

- Total Patients= 18
- clinicopathologic features are summarized in table I
- Neurological symptoms were seen in almost 95 %
- while B symptoms were present in almost 80 % of patients.
- More than two third of patients were anemic at the time of presentation
- More than 90% showed bone marrow infiltration with lymphoplasmacytoid cells

Total number of patients

18

Age (years)

Median

65

Range

38-86

Male/female (n)

12/6

Percentage of light chain

Kappa (%)

55

Lambda (%)

12

B symptoms (%)	78
Hepatomegaly (%)	27.8
Lymphadenopathy (%)	6
Palpable Splenomegaly	27.8
Neurological symptoms (%)	95
Anemia (<10 g/dl) (%)	77
Lymphocytosis (%)	55
Thrombocytopenia (<150 x10 ⁶ /dl) (%)	22.2
Serum Ig M level (g/dl)	
Median	32.4
Range	4.7-129.9



Treatment and outcomes

- Anemia, B symptoms, splenomegaly and neurological symptoms were the primary reasons in the majority of patients to initiate treatment.
- Chlorambucil was the primary treatment in more than half the patients
- CVP (cyclophosphamide, vincristine and prednisolone) was given in five, Fludarabine in one and R-CHOP (Rituximab, Cyclophosphamide, Vincristine, Doxorubicin and prednisolone) in one patient respectively.



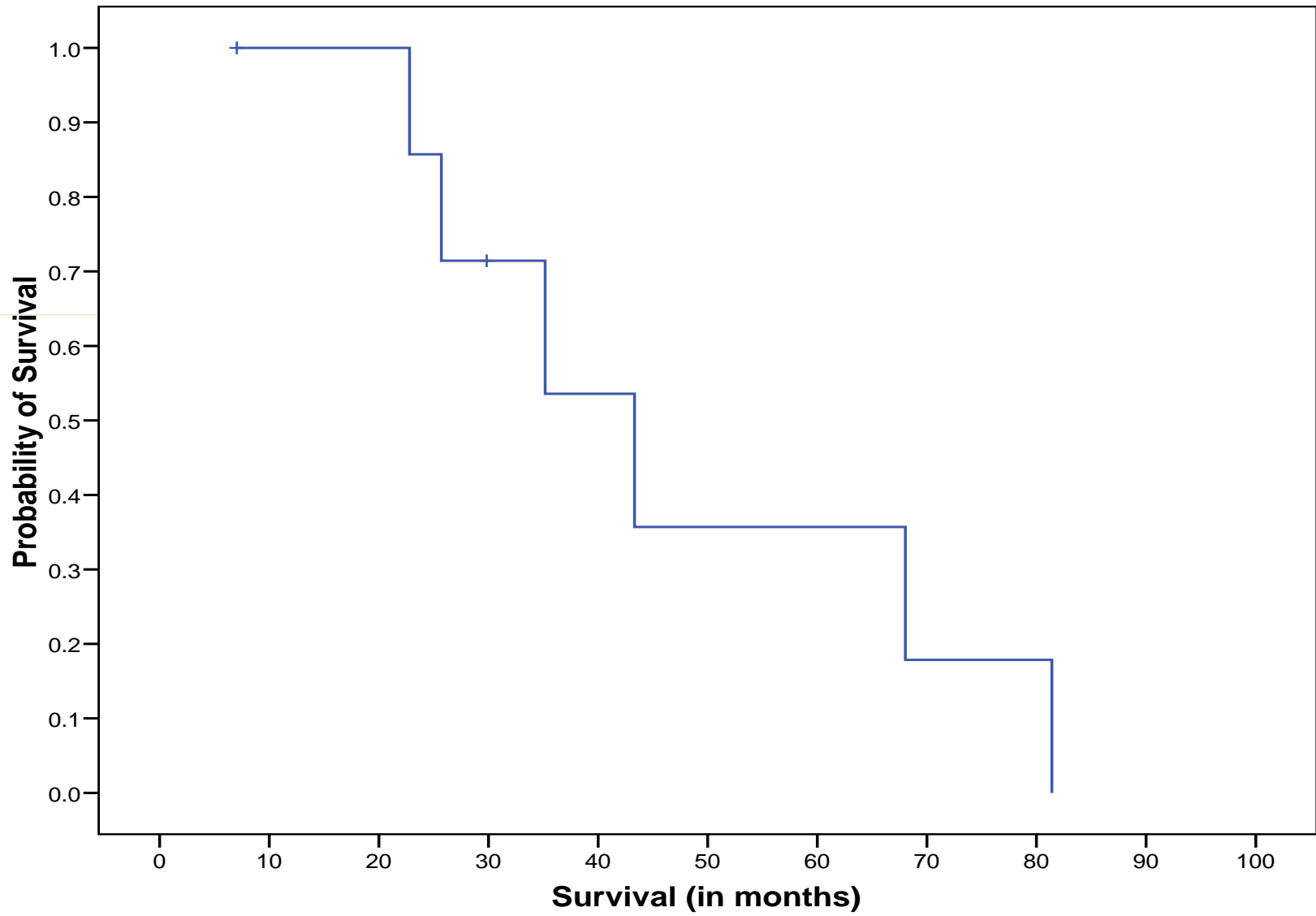
Treatment and outcomes

- Complete response was seen in only one patient
- Two patients had minor responses
- One had progressive disease despite treatment
- Two showed stable disease
- There was no difference in response rates among various regimens.



Outcomes

- The median overall survival in all patients was 29 months (range 22-81 months).
- Plasmapheresis was done in 10 patients with a median of 4 sessions per patient.
- Only one patient was alive in remission, whereas one patient had relapsed disease, eight patients had died and eight patients were lost to follow up at the time of data analysis
- Sepsis was the most common cause of death in four patients followed by cardiopulmonary arrest in two, pneumonia in one and mucormycosis in one patient respectively





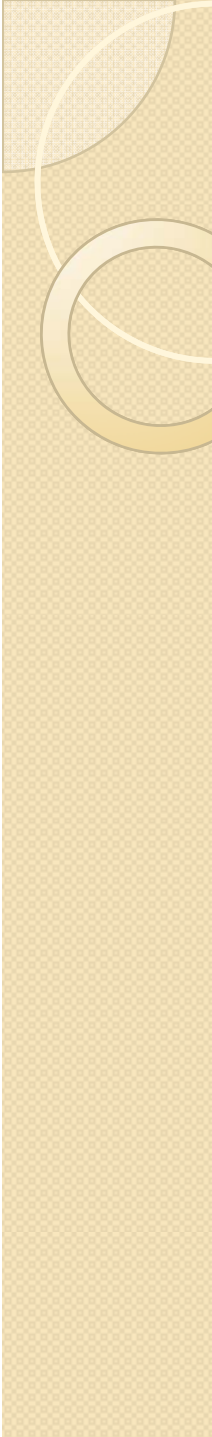
Discussion

- 18 patients over 15 year period indicated that WM is a rare disorder
- Median age of the patients was 65 years with M:F 2:1 which is similar in other studies



Discussion

- First line Chlorambucil and CVP were found to be well tolerated and led to symptom control.
- The median survival of patients with WMM ranges between 5 and 10 years in different studies ^{15,20}. As observed in this study, the median survival was much lower, being 29 months (2.4 years) only, with a range of 22-81 months.
- The most common cause of death was Sepsis. No significant difference was found among the different treatment regimens used.

- 
- Being a small number of case series we could not prognosticate our patients and neither a Univariate nor a multivariate analysis of factors impacting survival was statistically possible
 - Only one patient transformed to acute myeloid leukemia and this has been previously reported separately .



Conclusion

- In summary we conclude that Waldenstrom is a rare disorder and should be treated with Chlorambucil or CVP, however novel therapeutic modalities need to be identified to improve survival in these patients