Treatment Outcome of Waldenstrom Macroglobulinemia: Experience from University hospital of Annaba

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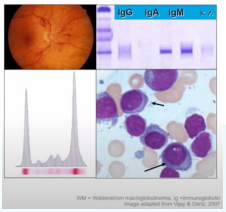

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Introduction

- Waldenström Macroglobulinemia (WM), also called "lymphoplasmacytic lymphoma"(LPL) is a rare B cell lymphoproliferative malignancy which accounts for 1.9% of all NHL.
- The disease was first described by Jan Gösta Waldenström in 1944, who reported an unusual presentation of lymphadenopathy, anemia, oronasal bleeding, elevated sedimentation (hyperviscosity) and IgM hypergammaglobulinemia
- It is a disease of the elderly, with a median age at diagnosis of 73 years.
- It has a well-defined immunophenotype, although exclusion of other low-grade lymphoproliferative disorders is required to confirm diagnosis.
- The clinical features of WM include a constellation of signs and symptoms related to infiltration of the bone marrow or other organs by the clonal cells, the production of the monoclonal immunoglobulin M (IgM) and its unique physicochemical and immunologic properties, as well as the production of cytokines that may cause various symptoms and complications.
- Recently, a somatic mutation of the MYD88 gene (L265P), found in 90% to 95% of patients with WM, shed new light on the biology of the disease
- There is no standard therapy for the treatment of symptomatic Waldenström's macroglobulinemia and no agents have been specifically approved for this disease, but initial treatment usually starts with the monoclonal anti-CD20 antibody rituximab, either alone or in combination with other agents, rather than chemotherapy alone.
- It is an indolent disease with a median survival ranging from 5 to 10 years or more.

Aim

- Analyze the clinical characteristics and treatment outcomes of patients diagnosed with WM in our department during these last years.

Methodology

- A retrospective study was conducted in our department from January 2020 to December 2023, including 14 patients with WM diagnosed during this period.
- The Second International Workshop on WM (IWWM-2) proposed diagnostic criteria were used to establish the diagnosis. Diagnostic work up including immunoglobulin assay, serum protein electrophoresis (SPE), immunofixation electrophoresis (IFE), bone marrow study, and Imaging studies were noted.

DIAGNOSIS / FEATURES	healthy	IgM-MGUS	IgM related disorders	aWM	WM
serum monoclonal IgM		✓	✓	✓	✓
BM infiltration				✓	✓
immunophenotype		✓	✓	✓	✓
symptoms			✓		✓

- International prognostic staging for WM (IPSS-WM) and revised IPSS-WM were used for staging

International Prognostic Scoring System for Waldenström's macroglobulinemia (adapted from Ref. [7]).

Adverse variable
Age > 65 years
Hemoglobin ≤ 11.5 g/dL
Platelets ≤ 100 × 10⁹/L
β2-microglobulin > 3 mg/L
S-monoclonal protein > 70 g/L

Risk	Score	5-Year survival
Low	≤ 1 adverse variable (except age)	87%
Intermediate	>2 adverse variables or age > 65	68%
High	>2 adverse variables	36%

	Points
Age <65	0
Age 66-75	1
Age > 75	2
B2microglobulin>4 mg/L	1
LDH > 250 IU/L	1
Serum albumin <3.5 gr/dl	1

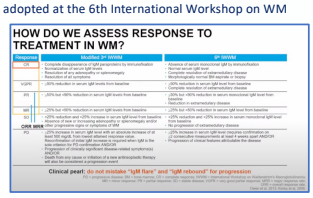
R-IPSS-WM

Stage	Score	% of patients
Very low	0	13%
Low	1	33.5%
Intermediate	2	25.5%
High	3	16%
Very high	4-5	12%

- All cases but three, were symptomatic and required therapy.

Clinical indications for initiation of therapy	Laboratory indications for initiation of therapy
Recurrent fever, night sweats, weight loss, fatigue	Hb ≤ 100 g/L Platelets <100×10⁹ /L
Hyperviscosity	IgM levels > 60 g/L
Lymphadenopathy - either symptomatic or bulky (≥ 5 cm in maximum diameter)	Amyloidosis-related to WM
Symptomatic hepatomegaly and/or splenomegaly	Autoimmune haemolytic anaemia and/or thrombocytopenia
Symptomatic organomegaly and/or organ or tissue infiltration	Symptomatic cold agglutinin anaemia
Peripheral neuropathy due to WM	Symptomatic cryoglobulinaemia

- The standard treatment for WM included systemic chemo-immunotherapy with the anti-CD 20 monoclonal antibody Rituximab and other chemotherapy drugs in varying combinations.
- Clinical response was classified as complete response (CR), Very Good Partial Response (VGPR), partial response (PR), stable disease (SD), and progressive disease (PD) based on response criteria adopted at the 6th International Workshop on WM



- The study outcomes were
  - Overall survival (OS): from date of diagnosis until date of last follow-up or death
  - Progression-free survival (PFS): calculated from the initiation of chemotherapy till disease progression or relapse.

Results

- **Baseline patients and disease characteristics** (are summarized in the table below)

Demographic Data

- A total of 14 cases of WM were enrolled in the study, ie. A mean of 3 cases per year
- At diagnosis the median age was 64 years (ranges 46-84), 43% of the cohort were > 65 years, with a male predominance (64%)
- 8 patients are known to have comorbidities including high blood pressure, diabetes, 4 pts experienced COVID-19,
- A history related to IgM-MGUS was noted in 9 patients

Clinical findings

- B-symptoms were frequent (10 pts)
- The most common complaints were organomegaly, hyperviscosity {(including headache, visual disturbances, neurologic symptoms (n=5), bleeding (n=4)} and renal failure (n=2)

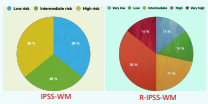
Biological features

- Bone marrow (BM) aspiration and biopsy showed infiltration by clonal lymphoplasmacytic cells/lymphoplasmacytic lymphoma (LPL). On immunohistochemical, the cells were CD20 & CD138 positive
- 4 patients had a diagnosis confirmation by flow cytometry
- Serum protein electrophoresis and immunofixation showed IgM-kappa (IgM-k) in 12 patients and IgM-lambda (IgM-λ) in 2 cases
- Quantitative IgM levels were elevated at diagnosis in all patients, and one patient with an IgM level of 192 g/L.
- None of these patients had evidence of hepatitis C virus infection.
- Among our patients, two tested positive for MYD88 mutation.

Baseline patient characteristics (n=14)	
Median age, years (ranges)	64 (46-84)
Gender ♂/♀	9/5
Mean time to first consultation, months	5 (1-9)
Lymphadenopathy +/- Splenomegaly	12 (86%)
Hyperviscosity	10 (71%)
Hb < 11,5 g/l	11 (78%)
Median Hb (ranges)	8,53 (2,05-11,2)
Platelets < 100 G/l	3 (21%)
Increased β2 µglobulinemia	6 (43%)
Elevated LDH > 250 UI/L	7 (50%)

Prognostic

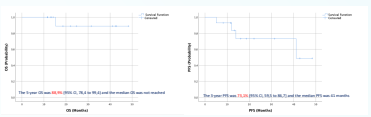
According to IPSS-WM and rIPSS-WM, the patients were classified as shown in the figure



- **Therapy and response**
  - No patient benefited from plasmapheresis due to its unavailability in our hospital.
  - Patients received different combination therapies : Chloraminophen +/- Rituximab, Dexamethasone, Rituximab and Cyclophosphamide (six 28-day cycles), Bortezomib and Bendamustine based-regimen were also used. All these combinations were safe and generally very well tolerated.
  - Of the 11 patients treated, the overall response rate was 73% with 3 patients achieved a complete response (CR), or a very good partial response (VGPR).
  - The median time to response was 4 months.
  - Five patients (45%), relapsed and received second line treatment comprising different chemotherapy protocols not previously used.

Treatment regimen	CBD	R/Chloraminophene	Chloraminophene	BR	EDR	No therapy
Number of patients	4	4	1	1	1	3
Response			ORR = 73%			
RC	1	0	0	0	0	
VGPR	0		0	1	1	
PR	2	3	0	0	0	
Stable disease	1	2	0	0	0	
Relapse/progression	1	1	1	0	0	2

- **Disease outcomes**
  - With a median follow-up of 44,66 months (95% CI, 37,88 to 51,44), One patient died.



Conclusion

- MW is a rare disease with an indolent course, only patients with symptoms require chemotherapy. The management of WM is heterogeneous, with limited access to molecular testing and modern therapies.
- Rituximab-based regimens represent the standard of care.
- Promising new molecules make it possible to improve the outcomes in this incurable disease
- Our study is limited by its retrospctive nature, however, outcomes were similar to those reported in the literature. The 3 year PFS was 73% and OS was 88%.

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