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Waldenstrom Macroglobulinemia: A Brief Review to the Therapeutic Approach

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ABSTRACT

Waldenström Macroglobulinemia (WM) is a low grade lymphoproliferative disorder with bone marrow involvement, adenopathy and hepato/splenomegaly. It is a chronic disease but recently discoveries and advancement in pathogenesis made possible to improve drugs' armamentarium available for therapy and thus, clinical outcome.

Keywords: Waldenstrom macroglobulinemia, Therapeutic, Lymphoproliferative disorder, Adenopathy, Hepato/splenomegaly

INTRODUCTION

WM is a rare B-cell lymphoproliferative neoplasm characterized by an infiltration of IgM-producing lymphoplasmacytic lymphocytes into the bone marrow with an incidence, in Europe, of 7.3 per million men per year and 4.2 per million women per year [1].

Moreover, WM accounts for 1 to 2% of all hematological malignancies appearing to be more common in older patients with a median age at diagnosis of 60-70 years old and in Caucasians rather than in Africans, with an overall survival (OS) of 74 months [2].

CLINICAL PRESENTATION

WM is an indolent disease whose signs and symptoms can be various and heterogeneous. Since diagnosis, most patients are asymptomatic for years, without needing any treatment until progression.

Main symptoms related to the disease, basically depend on lymphoplasmacytic infiltration and IgM-paraprotein.

On the one hand, patients usually present with fatigue, B-symptoms such as weight loss, night sweats or fever, lymphadenopathies and/or hepato/splenomegaly (up to 20-30%), as well as with cytopenia due to bone marrow infiltration [2].

On the other hand, high levels of IgM-paraprotein may result in systemic amyloidosis due to the deposition into organs, cryoglobulinemia, cold agglutinin anemia and hyperviscosity syndrome: a clinical situation which presents with visual disturbances, neurologic and cardiovascular disorders, more likely to manifest with IgM>4 g/dL [3].

At last, 20-25% of WM patients develop anti myelin-associated-glycoprotein antibody (anti-MAG) at the base of peripheral polineuropathy [4].

Diagnosis and prognosis

Diagnostic pathway which leads to detect WM patients must exclude, first of all, other IgM-producing lymphoproliferative neoplasms. In WM, it is mandatory to perform bone marrow examination demonstrating at least 10% of lymphoplasmacytic lymphocytes and the presence of IgM monoclonal gammopathy. On the basis of absence or presence of signs and symptoms, the disease is qualified as smoldering or symptomatic WM, respectively.

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Despite some exceptions, immunophenotypic pattern in WM, is comparable to a mature B-cell profile expressing CD19, CD20, CD22, CD79a, s/cyIgM and negative for CD5, CD10, CD23, CD103 [4].

Further studies described recurrent mutations of Myeloid differentiation primary response 88 (MyD88) and CX-Chemochine Receptor 4 (CXCR4) with different biological features, response to treatment and prognosis [5].

MyD88 is an adaptive protein which activates NF-kB pathway after stimulation of Toll-like receptors and receptors for IL1 and IL18.

Thus, MyD88 mutations cause an increased survival and decreased apoptosis in neoplastic cells. It is present in >90% of WM and the most frequent is L265P mutation [6].

In literature, the impact of status mutation on the clinical history of the disease appears to be controversial. Treon et al. [7] showed a 10 year overall survival of 73% vs. 90% in MyD88 wild-type vs. MyD88 L265P. On the contrary, more recently, Mayo clinic group found no difference about survival and prognosis in WM independently from MyD88 mutation status [8].

CXCR4 is a chemochine receptor implicated in migration and adhesion of blood cells into the bone marrow. Activating mutations of CXCR4 are present up to 30% of WM patients, causing a major medullary involvement with cytopenia, higher level of IgM paraprotein and less adenopathy [5].

The above mentioned mutated patients were characterized by MyD88 L265P mutation in almost the whole group and despite a more aggressive presentation of the disease at the onset and a shorter progression of smoldering to symptomatic WM, overall survival was not impacted [9].

A standardized scoring system for WM has been made: the International prognostic scoring system for Waldenström Macroglobulinemia (IPSSWM) assessing prognosis based on 5 variables: age>65, hemoglobin<11.5 g/dL, platelets<100.000/mm^3, ß2 microglobulin>3 mg/L, IgM>70 g/L.

The 5 year OS ranged from 87% in the low risk group (one variable except of age) to 36% in the high-risk group (>3 variables) [10].

TREATMENT

Considering the indolent nature of the disease, treatment may not be necessary for years until clinical progression or symptomatic disease and thus “watch and wait” seems to be the recommended approach. Rather, the treatment choice is influenced by the presentation of the disease, age of onset, patients’ comorbidities and previous treatment [11]. Response evaluation was based on Consensus Panel Recommendations from the Second International Workshop on Waldenstrom’s Macroglobulinemia [12].

Rituximab represents the basis of WM treatment. Monotherapy is about 4 weekly administrations at a dose of 375 mg/m^2 with an ORR ranging from 25% to 40%, increased to 65% with an extended course of 4 weekly administrations after 8 weeks [13]. Beyond response rate, Rituximab is very well tolerated but attention need to be paid in case of high level of IgM paraprotein because of IgM flare (an increase >25% above baseline of IgM level) which could exacerbate paraprotein related symptoms. In this setting, patients must undergo cytoreduction with alkylating agent or plasmapheresis which could reduce IgM related hyperviscosity by 20-30% with a single course [14].

Combination chemotherapy proved to be more efficient to reduce the burden of the disease and thus signs and symptoms affecting patients. In a multicentric retrospective study, the association of dexamethasone, cyclophosphamide and rituximab achieved an overall response rate (ORR) of 83%; 2 years progression free survival (PFS) of 90% and a minimal toxicity of grade 3 or 4 (9%) [15].

An experience of the French group with association of Bendamustine and Rituximab found no difference of OS in WM independently from the status mutation of CXCR4 and MyD88 with 2 years OS and PFS of 97% and 87%, respectively. [16].

In elderly unfit patients, a valid alternative that does not affect efficacy is the association of Chlorambucil and Rituximab. With an ORR of 80%, it overlaps the results of DRC regimen at the price of a minimal toxicity of grade 1-2 [17].

The combination of Bortezomib associated regimen obtained an ORR of 96% in naive patients, with 83% of major response rate even if it might be possible the premature interruption of administration because of the worsening of neuropathy [18].

In the modern era of upcoming new drugs, Ibrutinib acquired relevance considering the high prevalence of MyD88 L265P mutation associated with an increased survival of neoplastic cells via BTK pathway. At the dose of 420 mg/die in monotherapy, Ibrutinib produced an OR of >90% in previously treated patients [19]. This advantage is lost if CXCR4 mutation is present which confers a resistance to the therapy though with a major ORR if MyD88 mutation is present [20].

The iNNOVATE study evaluated the association of Ibrutinib + Rituximab vs. Placebo + Rituximab both in naive and relapsed patients. The 30 months-PFS was 82% vs. 28% respectively with a 30 months OS of 94% vs. 92%. Major responses were obtained in patients with MyD 88 L265P mutation despite the mutation status of CXCR4. Surprisingly in the placebo-Rituximab group, a higher rate of responses were identified in patients with CXCR4 mutation, highlighting again how the prognosis is not affected in this subset of patients but the response to ibrutinib [21].

In a future scenario, BCL2 inhibitors will be a part of the drugs inventory available to treat WM. In preclinical studies, Venetoclax proved to be an inducer of apoptosis and enhancer of BTK inhibitors activity independently from the status mutation of CXCR4, thus overcoming ibrutinib resistance which may be related to increased BCL-2 levels [22,23].

Several studies evaluated stem cell transplantation (SCT) in WM, both in relapsed/refractory patients and in patients gaining response after 1st line treatment.

Regarding autologous SCT, data available agree on the efficacy and feasibility as a first line therapy after debulking treatment with 5 years OS of 63% and very minimal transplant related mortality (TRM) and a longer time to next treatment [24-27].

As far as allogeneic SCT, despite the reduced conditioning regimen, a better management of GVHD and the proved GVWM effect might make it more attractive, it remains reserved to a very little group of relapsed/refractory WM patients with poor prognosis since the higher TRM, until 30% [24].

CONCLUSION

Recent advancement on WM pathogenesis made possible the chance to increase drugs' arsenal available for therapy. Accordingly, new therapies such as BTK-inhibitors proved to be effective in WM and nowadays, several studies and trials are ongoing about combination regimens disclosing the future scenario of BCL2 inhibitors and AKT inhibitors which might put on the background stem cell transplantation.

REFERENCES

1. Christian B, Shalal S, Efstathios K (2018) Treatment and outcome patterns in European patients with Waldenström's macroglobulinaemia: A large, observational, retrospective chart review. Lancet Hematol 5: e299-309.
2. Thuyan T (2013) Waldenstrom's macroglobulinemia: A review of laboratory findings and clinical aspects. Lab Med 44: e19-e21.
3. Oza A, Rajkumar SV (2015) Waldenstrom macroglobulinemia: Prognosis and management. Blood Cancer J 5: e394.
4. Seongseok Y, Ariel, Onyemaechi O (2017) Waldenström macroglobulinemia: Review of pathogenesis and management. Clin Lymphoma Myeloma Leuk 17: 252-262.
5. Marine B, Laurence S, Stéphanie P (2019) How recent advances in biology of Waldenström's macroglobulinemia may affect therapy strategy? Curr Oncol Rep 21: 27.
6. Treon SP (2015) How I treat Waldenström macroglobulinemia? Blood 126: 721-732.
7. Treon SP, Joshua G, Lian X (2018) MYD88 wild-type Waldenstrom macroglobulinaemia: Differential diagnosis, risk of histological transformation and overall survival. Br J Hematol 2018: 374-380.
8. Abeykoon J, Paludo J, King R (2018) Impact of MYD88 mutation status in Waldenström macroglobulinemia. Am J Hematol 93: 187-194.
9. Treon SP, Cao Y, Xu L (2014) Somatic mutations in MYD88 and CXCR4 are determinants of clinical presentation and overall survival in Waldenstrom macroglobulinemia. Blood J 123: 2791-2796.
10. Dimopoulos MA, Kastritis E, Delimpassi S (2008) The international prognostic scoring system for Waldenström's macroglobulinemia is applicable in patients treated with rituximab-based regimens. Hematologica 93: 1420-1422.
11. Leblond V, Kastritis E, Advani R (2016) Treatment recommendations for Waldenström macroglobulinemia. Eighth International Workshop on WM. Blood 04-711234.
12. Weber D, Treon SP, Emmanouilides C (2003) Uniform response criteria in Waldenstrom's macroglobulinemia: Consensus panel recommendations from the Second International Workshop on Waldenstrom's Macroglobulinemia. Semin Oncol 30: 127-131.
13. Kapoor P, Ansell SM, Fonseca R (2017) Diagnosis and management of Waldenström macroglobulinemia mayo stratification of macroglobulinemia and risk-adapted therapy (mSMART) guidelines 2016. JAMA Oncol 3: 1257-1265.
14. Stone MJ (2013) Role of plasmapheresis in Waldenström's macroglobulinemia. Clin Lymphoma Myeloma Leukemia 13: 238-240.
15. Dimopoulos MA, Anagnostopoulos A, Kyrtsonis MC (2007) Primary treatment of Waldenström macroglobulinemia with dexamethasone, rituximab and cyclophosphamide. J Clin Oncol 25: 3344-3349.
16. Laribi K, Poulain S, Willems L (2018) Bendamustine plus rituximab in newly-diagnosed Waldenström macroglobulinemia patients. A study on behalf of the French Innovative Leukaemia Organization (FILO). Br J Hematol, pp: 1-3.
17. Innocenti I (2018) Chlorambucil plus rituximab as front-line therapy for elderly patients with comorbidities affected by Waldenstrom macroglobulinemia: A single center experience. J Blood Lymph 8: 193.
18. Treon SP, Ioakimidis L, Soumerai JD (2009) Primary therapy of Waldenström macroglobulinemia with

bortezomib, dexamethasone and rituximab: WMCTG clinical trial 05-180. J Clin Oncol 27: 3830-3835.

19. Treon SP, Gustine J, Meid K (2017) Ibrutinib is highly active as first line therapy in symptomatic Waldenstrom's macroglobulinemia. Blood 130: 2767.
20. Treon SP, Tsakmaklis N, Meid K (2016) Mutated MYD88 zygosity and CXCR4 mutation status are important determinants of ibrutinib response and progression free survival in Waldenstrom's macroglobulinemia. Blood 128: 2984.
21. Dimopoulos MA, Tedeschi A, Trotman J (2018) Phase 3 trial of ibrutinib plus rituximab in Waldenström's macroglobulinemia. N Engl J Med 378: 2399-2410.
22. Paulus A, Akhtar S, Yousaf H (2017) Waldenstrom macroglobulinemia cells devoid of BTKC481S or CXCR4WHIM-like mutations acquire resistance to ibrutinib through upregulation of Bcl-2 and AKT resulting in vulnerability towards venetoclax or MK2206 treatment. Blood Cancer J 7: e565.
23. Magierowicz M (2018) Working toward a genomic prognostic classification of Waldenstro¨ m macroglobulinemia C-X-C chemokine receptor type 4 mutation and beyond. Hematol Oncol Clin N 32: 753-763.
24. Chakraborty R (2016) The role of stem cell transplantation in Waldenström's macroglobulinemia. Best Pract Res Clin Hematol 29: 229-240.
25. Kyriakou C, Canals C, Sibon D (2010) High-dose therapy and autologous stem-cell transplantation in Waldenstrom macroglobulinemia: The Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. J Clin Oncol 28: 2227-2232.
26. Bachanova V (2012) Hematopoietic cell transplantation for Waldenström macroglobulinemia. Bone Marrow Transpl 47: 330-336.
27. Kyriakou C, Boumendil A, Finel H (2014) Autologous stem cell transplantation (ASCT) for the treatment of patients with Waldenstrom's macroglobulinemia/lymphoplasmacytic lymphoma (WM/LPL). A risk factor analysis by the European Society for Blood and Marrow Transplantation (EBMT) Lymphoma Working Party. Blood 124: 678.