Kokilavani S et al /J. Pharm. Sci. & Res. Vol. 15(8), 2023, 1210-1212

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

A Review on Waldenstrom Macroglobulinemia

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Abstract:
Waldenstrom macroglobulinemia is the rarest type of blood cancer. It was first described by Jan.G.Waldendenstrom in 1944, who describes Waldenstrom macroglobulinemia as an unusual presence of lymphadenopathy bleeding, anemia, hepatosplenomegaly, cytopenias, hyperviscosity syndrome, elevated sedimentation rate, hypergammaglobulinemia. It is also called lymphoplasmacytic lymphoma. The symptoms are mainly associated with bone marrow infiltration. The common symptoms are fatigue and anemia. The first-line therapy includes alkylating agents, rituximab, and nucleoside analogs. Studies on chemotherapy to treat WM are still ongoing. Here in this review article, we will discuss the symptoms, diagnosis, epidemiology, pathogenesis, and disease management.

Key Words: Waldenstrom macroglobulinemia, symptoms, diagnosis, epidemiology, pathogenesis

INTRODUCTION:

Waldenstrom macroglobulinemia is a proliferative disorder. It is also a type of Non-Hodgkin's lymphoma. A low-grade, chronic, lymph proliferative, clonal disorder of B-Lymphocytes. It is described by elevated immunoglobulin M (Ig M) levels in the bone marrow. The causes of this disease are not known. It begins with the abnormal proliferation of WBCs. It is an incurable disease although it is treatable but needs long-term treatment. It has symptoms related to infiltration of lymphoplasmacytic lymphoma in the bone marrow also associated with hypersecretion of Immunoglobulin M monoclonal protein belonging to the Non-Hodgkin B-Lymphoma category.

Symptoms:

- Weakness
- Fatigue due to anemia
- Emaciation
- Lymphadenopathy (Enlarged lymph nodes).
- Splenomegaly (Enlarged spleen).
- Abdominal distension
- Diarrhea
- Malaise
- Fever (pyrexia)
- Numbness in the hands or feet.
- Bleeding from nose or gums
- Nostalgia (Bone pain)
- Night Diaphoresis
- Skin itchiness

The symptoms of hyperviscosity:

Hyperviscosity occurs due to elevated IgM levels in the blood. Since the IgM are larger molecules they make the blood to become thick or viscous. The symptoms accompanied by it are,

- Vision problem
- Confusion
- Dizziness
- Fatigue
- Dyspnea (Shortness of breath)

Diagnosis:

Waldenstrom Macroglobulinemia is a rare type of blood cell cancer that occurs in the bone marrow. This Lymphoplasmacytic lymphoma can be diagnosed by the following tests,

1. Blood test
2. Bone marrow biopsy
3. Imaging testing

1. Blood test:

Waldenstrom macroglobulinemia is a cancer that produces abnormal levels of IgM. The cause for the production of abnormal IgM is not known.

IgM is the first antibody produced by our body to fight against the invaded pathogens. The Waldenstrom macroglobulinemia is characterized by elevated levels of IgM in the blood. So, detecting the levels of IgM in the blood helps to diagnose Waldenstrom macroglobulinemia.

2. Bone marrow biopsy:

The bone marrow biopsy is the most accurate way of diagnosing Lymphoplasmacytic lymphoma. The bone marrow is the soft tissue present at the center of the bones in which the body's blood cells are produced. The bone marrow biopsy is done by extracting the sample of bone marrow from the hip bone with the help of a needle. Then these samples are examined under the microscope for the presence of cancer cells. If the test shows a positive result as the sample contains cancer cells, then advanced laboratory analysis is performed to study in detail the cancer cells, and their genetic mutations of the gene MYD88 are also studied.

* Presence of high levels of IgM in the blood and the >10% of clonal lymphoplasmacytic cells in the bone marrow confirms the test.

3. Imaging test:

By using CT (computerized tomography) scans, X-rays, and PET scans (positron emission tomography), cancer can be diagnosed which are spread all over the body. The imaging studies of the chest, abdomen, and pelvis look for an enlarged spleen or lymph node which are the characteristics of Lymphoplasmacytic lymphoma.

EPIDEMIOLOGY:

The patient with Waldenstrom macroglobulinemia (WM), has common symptoms of fatigue-associated normocytic anemia. In the reported cases of death in patients over 65 years old diagnosed with cancer, it was observed that the death is not due to cancer. Research says that patient with WM under age 70 has a survival period of about 7 years above 14% of patients with WM has clonal hematopoiesis. 70-year-old patients had a median survival over 10 years with WM. 70-79 year old patients existence 7 years and those people 80 years older have approximately 4 years of persistence.

Whites had more risk of WM compared to blacks (4.1/million years – 1.8 /million years). The viability of WM is enhanced. The SEER database (surveillance, epidemiology, and results) explains cancer demography's details. SEER index restrained 5784 patients with WM. Intermediate from 1991 to 2000 and 2001 to 2010 ameliorate from 6 to 8 years, respectively. Deaths armies from 2001 to 2010 were lower from WM-related and non-related causes. The danger/risk ratios of death of patients 20 years older are less compared to less than 50 years.

MANAGEMENT:

Systemic chemotherapy to reduce tumor mass:

- Rituximab cyclophosphamide/ dexamethasone.
- Proteasome inhibition.
- Bendamustine.
- BTK inhibitors.

1. Rituximab cyclophosphamide:

- The management of WM extensively used or accessible treatment is Rituximab cyclophosphamide.
- It produces plover long-term toxicity and a non-myeloid suppressive treatment profile.
- After all, the use of Rituximab alone leads to poor medical therapy.
- It results from less than 55% compared to combination therapy.

2. Rituximab cyclophosphamide Dexamethasone (RCD):

- The response rate of Rituximab cyclophosphamide Dexamethasone (RCD) had reported 83% compared to single therapy of Rituximab cyclophosphamide (55%).
- The Rituximab treatment performed for treating WM causes minimal toxicity because this combination of cyclophosphamide and Dexamethasone**.**
- The combinations of three drugs are alternative regimens used to cure or prevent WM.
- Rituximab – Bendamustine regimen newly used for the treatment of WM leads to a reduced rate of non-hematologic adverse events.

3. BTK inhibitors: (Ibrutinib, zanubrutinib, acalabrutinib)

- It was about 63 WM patients receiving (420mg) of BTK inhibitor Ibrutinib. The response rate was 73% inclusion of minor response of 90.5%.
- The adverse time for the response was about 4 weeks.
- Diarrhea, atrial fibrillation, and bleeding are the major non-hematological toxicities.
- Apart from clinical trials 80 WM patients had reported treating Ibrutinib therapy, and 91% of the overall response rate was achieved.
- Acalabrutinib is a more potent and selectable one for WM compared to Ibrutinib due to its short half-life and rapid absorption.

Pathogenesis:

The pathogenesis of Waldenstrom macroglobulinemia (WM) also known as lymphoplasmacytic lymphoma is not yet well understood. But studies reported that it may be arisen due to differences in B lymphocytes that play a major role in the maintenance of humoral immunity. It is mainly due to an increase in IgM paraprotein secretion which may further lead to hyperviscosity syndrome due to the proliferation of RBCs, WBCs, and Blood proteins, and infiltration of tissues with lymphoplasmacytic cells. The variations and mutations in the genetic information of the individual are one of the reasons for the development of WM in an individual. More than 90% of the patients who have been diagnosed with WM have been found with a mutated gene MYD88 gene (l265p) which plays a vital role in protein synthesis which are responsible for generating signals to the immune cells. The mutated gene activates an enzyme known as Bruton Tyrosine Kinase (BTK) which generates signals by toll-like receptors which in turn activates transcription factors (NF-kB) responsible for the development and proliferation of both normal & neoplastic B cells inhibiting apoptosis (destruction of unwanted cells). The somatic point mutation of the MYD88 gene also leads to a change in the amino acid of protein by substituting leucine with proline at position 265(MYD88 l265p) which further results in the hyperactivation of proteins which leads to the proliferation of neoplastic cells. Patients with WM have also been found with mutant C-X-C chemokine receptor type -4 (CXCR4) gene which is a G- protein-coupled receptor essential for the synthesis of reception proteins which is involved in maintaining the life span of cells in CNS and for the release of cytokines. Cytogenetic abnormalities (abnormalities in chromosomes) such as deletion of the long arm of chromosomes; trisomy; monosomy; del (6q); t(9:14);(p13:q32), deletion of the short arm of the chromosome have also been found in patients with WM. WM cell migration and adhesion were shown to be inhibited by CXCR4 inhibitors and Gi protein inhibitor treatments. The majority of cases of WM are of sporadic origin similarly familial WM have also been expressed. The risk of fatality has been increased in familial WM compared to sporadic.

FUTURE PROSPECTIVE :

Investigation on clinical trials performed has been in process for the development of a combination of drugs of chemotherapeutic agents with other targeted agents. Investigations have been carried out for the use of monoclonal antibodies, proteasome inhibitors, immunomodulatory agents, BTK inhibitors & histone deacetylase inhibitors by performing phase-2 clinical trials. Studies reported that patients given a combination

of rituximab cyclophosphamide dexamethasone RCd had minimal toxic effects in patients with WM. Investigations have been targeted toward the use of immunomodulatory agents. Physicians in the cancer institute at US named Dana Farber Cancer Institute have been conducting a phase 2 clinical trial with Loncastuximab tesirine & Bexucabtagene autoleucel which is an antibody-drug conjugate targeting the treatment of WM. These investigations have been looking for an effective and optimistic response in patients. Studies about stem cell transplantation reported that it can be used only when the use of chemotherapy and other treatment have been ineffective or exhausted. Stem cell transplantation is not yet an effective treatment for Waldenstrom macroglobulinemia.

CONCLUSION:

The review is about Waldenstrom macroglobulinemia, a rarest blood cancer management, pathogenesis, and epidemiology. Here, we conclude that Waldenstrom macroglobulinemia is not curable but possible only if treated before the rise of symptoms. From the reported cases, the death is not due to cancer. The study results that WM is more possible in mutant genes which play a major role in protein synthesis for generating signals to the immune cells.

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