# Young Patients with Waldenstrom's Macroglobulinemia Fact Sheet

Waldenstrom's macroglobulinemia (WM) is a rare, indolent lymphoma that is typically diagnosed in older patients, with a median age at diagnosis of approximately 73 years. Young patients with WM form a smaller subgroup of patients with this malignancy.

Less than 10% of patients with WM are younger than 50 years, and 25% are younger than 60 years at diagnosis; thus, they have been often underrepresented in literature and clinical trials. Younger patients generally have better organ and functional reserve, or the ability to successfully return to their original physiological state after periods of stress, as compared to older patients, and thus can better tolerate therapy. Therefore, the disease and treatment course of WM is different in patients who are younger than in older patients, who often have a higher rate of comorbidities, or other health conditions, and are unable to tolerate more aggressive treatment regimens.

In addition to the lack of studies that have specifically assessed young patients with WM, much of the available data precedes the widespread use of Bruton's tyrosine kinase (BTK) inhibitors, which limits the conclusions that can be drawn in this modern era of treatment.

In this Fact Sheet, we summarize the current data and relevant information related to young patients with WM. The age cut-off in most studies defining younger WM is 50 years old, although this is an arbitrary definition.(Nelson et al. 2013; Kyle et al. 2012). For the purposes of this Fact Sheet, this is the definition we will use, unless otherwise designated.

## EPIDEMIOLOGY OF WM

- WM is a rare disorder with an incidence of approximately three per million people per year with 1,400 new cases diagnosed in the United States each year.
- Approximately 60% of patients are males.
- WM is much more common in the Caucasian population compared with other groups. Specifically, it is uncommon in Black populations, who make up approximately 5% of cases, and individuals from or with families from Mexico.
- First-degree family members of patients with WM have a higher-than-expected frequency of developing WM, although the absolute risk remains low. In one large database, the diagnosis of WM was 15.8-fold higher among first-degree relatives than among the general population.

## CLINICAL PRESENTATION IN YOUNG WM

- In a study of young WM (less than 55 years), most patients (70%) were asymptomatic at presentation. (Varettoni et al. 2020)

- However, young patients with WM who were symptomatic at the time of diagnosis tended to present with higher rates of enlarged lymph nodes (lymphadenopathy), enlarged spleen (splenomegaly), symptoms of hyperviscosity (increased thickness of blood), and serum IgM levels when compared to older patients. It is possible that, given their better organ and functional reserve, younger patients are better able to compensate for the physiologic stresses of early disease, thereby presenting later with more advanced features.(Piccirillo et al. 2008)
- The proportion of smoldering (asymptomatic) WM, the median time from diagnosis to initiation of first-line therapy, and the age-adjusted International Prognostic Scoring System for Waldenstrom Macroglobulinemia (IPSSWM score) at the time of therapy initiation were similar among older (greater than 65 years) and younger (less than 50 years) patients with WM.(Chohan et al. 2023) The IPSSWM is a prognostic tool used to estimate the probability of survival in patients with WM, and it takes into account several clinical and laboratory factors, such as age, hemoglobin levels, platelet counts, beta-2 microglobulin levels, and serum monoclonal protein levels.(Morel et al. 2009)
- Among patients with a documented family history, the incidence of familial WM was 13% in younger (less than 50 years) patients, which is statistically similar to the incidence of 9% in older patients (greater than 65 years). (Chohan et al. 2023)
- Assessing the disease severity/risk, most young patients were of very low or low risk (92%) of death using the revised IPSSWM score, and a smaller fraction were of intermediate risk (8%).(Varettoni et al. 2020) The revised IPSSWM takes into account age, beta-2 microglobulin, LDH, and albumin levels.(Kastritis et al. 2019)
- The prevalence of the MYD88 L265P mutation (90%) and CXCR4 mutations (44%) in young patients was similar to the expected prevalence in this disease and was no different when compared to older patients.(Babwah et al. 2019; Chohan et al. 2023)

**PROGNOSIS IN YOUNG WM**

- Overall, there are very few studies assessing the outcomes of the younger population with WM, and the available data are confusing because of potential overestimation of survival owing to the inclusion of patients with smoldering WM.(Pophali et al. 2019)
- The estimated survival of younger patients with WM is much longer than for older patients. In patients with symptomatic WM requiring treatment, one study showed that ten years after first-line treatment, 86% of patients younger than 45 years and 74% of those younger than 50 years were alive compared to 31% of the older patients (greater than 65 years). Overall, young WM patients have excellent prognosis with chemoimmunotherapy treatment regimens

(less than 2% patients were treated with BTK inhibitors in this study).(Babwah et al. 2019) (Chohan et al. 2023)

- Younger patients with WM (less than 50 years) had significantly longer overall survival (OS) compared to older patients (greater than 65 years), likely in the context of better functional reserve and fewer comorbidities.(Piccirillo et al. 2008) However, while only half of the deaths in the older WM group were WM-related, more than 90% of deaths in younger patients were WM-related.(Chohan et al. 2023)

## TREATMENT INITIATION IN YOUNG WM

- The majority of young patients with WM (less than 45 years) did not need treatment at the time of diagnosis but required treatment initiation at a median time of 2.5 years from diagnosis.(Babwah et al. 2019)

## UNIQUE TREATMENT CONSIDERATIONS FOR YOUNG WM

- Despite differences in outcomes, the optimal treatment strategy for younger patients is not well defined.
- In younger patients with a longer life expectancy ahead, it is vital to consider a long-term treatment strategy to maximize treatment-free intervals while minimizing the risk of persistent or late side effects from therapy. The simplest way of achieving these goals is by ensuring that treatment is only given when absolutely necessary (spacing/delaying treatments as much as possible). The management of WM in younger patients is a marathon, not a sprint.
- The depth of response achieved with treatment seems to correlate with improved survival.(Perera et al. 2021) While older patients, with a higher rate of comorbidities, may not tolerate more aggressive therapies (associated with a higher rate of deeper responses), younger patients might derive the most benefit from them. No studies have yet been done to explore this approach, and younger patients should work closely with their doctors to define the best treatment strategy for them.
- Younger patients are more likely to be candidates for autologous stem cell transplantation, and this treatment should not be automatically excluded. Preparation is important, and collection of stem cells should be part of the treatment plan early in the disease course. With novel and better therapies, stem cell transplantation is becoming a less relevant option, but it is better to be prepared for it with a stem cell collection than not to have this option available if ever needed.

- For such a unique group of patients with a rare disease, younger patients with WM should always consider an expert opinion regarding the management of their disease.

**LIVING WITH WM**

- Being a patient with WM means living and co-existing with this disease. At the time of diagnosis, younger patients with WM tend to have a different set of priorities in their lives, as compared to older patients, including work and professional careers, family demands and younger kids/older family members to care for, a less stable financial situation, etc.
- Every patient has a unique psychosocial situation that should not be overlooked. There may be concern about how the WM diagnosis affects the patient and the family. All these fears and worries are normal.
- If you are a younger patient, talking with a member of your health care team may help you deal with these fears and help connect you with support when available. If you feel emotionally overwhelmed after your WM diagnosis, tell your doctor. He or she can connect you with support services and may also offer you treatment choices for specific concerns or refer to you a mental health professional.
- In addition to your health care team, there are multiple support groups and organizations, for example, the International Waldenstrom's Macroglobulinemia Foundation (IWMF), the Leukemia & Lymphoma Society (LLS), the American Cancer Society, and the National Comprehensive Cancer Network (NCCN®), that provide resources and connections to other patients going through the same challenges.
- To live with WM, it is important to:
  - Stay active – Studies show that people who are active do better than those who spend much of the day in bed or in a chair. In a study of patients with lymphoma, those exercising at least 150 minutes per week did better with treatment and lived longer. Any activity, even five minutes, is better than nothing.
  - Eat a balanced diet – Eating a healthy diet with at least five daily servings of fruits and vegetables may help you keep your weight and energy. The amount of IgM protein in your blood is not affected by the amount of protein in your diet. There is no need to limit protein in your diet. It is not known if a certain diet can decrease the risk of lymphoma progressing or not responding to treatment.
  - Get enough rest – Get a good night's sleep and avoid fatigue during the day by resting or sleeping between activities. Most adults need seven to nine hours of sleep at night.
  - Find a "new normal" – After the diagnosis of WM, you may feel that your life has changed, and emotions like anxiety, depression, anger, and guilt are common. It is important to share how you feel as a way of coping with the diagnosis of cancer. Often patients find it

helpful sharing with relatives, friends, or other patients going through the same challenges. It is also important to share how you are feeling with your health care team, especially if these feelings are overwhelming to you. There is an IWMF support group for young patients with WM; contact the IWMF for more details on joining this group.

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## ABOUT THE IWMF

The International Waldenstrom's Macroglobulinemia Foundation (IWMF) is a patient-founded and volunteer-led, nonprofit 501(c)(3) organization with an important vision, "A World Without WM," and a mission to "Support and educate everyone affected by WM to improve patient outcomes while advancing the search for a cure."

More information about Waldenstrom's macroglobulinemia and the services and support offered by the IWMF and its affiliate organizations can be found on our website, www.iwmf.com.

The IWMF relies on donations to continue its mission, and we welcome your support. The Foundation maintains a Business Office at 6144 Clark Center Ave., Sarasota, FL 34238. The Office can be contacted by phone at 941-927-4963, by fax at 941-927-4467, or by email at info@iwmf.com.



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