

Authors

Sandhya Maddali¹, Sherif Seif¹, Xiaowen Sun², Lei Feng², Nkosi Dingani³, Keyur Patel³, Danielle Hammond⁴, Kelly Chien⁴, Lorenzo Gensini¹, Mahmoud Gaballa¹, Krina K. Patel¹, Oren Pasvolsky¹, J. Christine Ye¹, Sarvari Yellapragada¹, Donna M. Weber¹, Robert Z. Orlowski¹, Sheeba K. Thomas¹

¹ University of Texas MD Anderson Cancer Center, Department of Lymphoma and Myeloma, Houston, TX, United States, ² University of Texas MD Anderson Cancer Center, Department of Biostatistics, Houston, TX, United States, ³ University of Texas MD Anderson Cancer Center, Department of Hematopathology, Houston, TX, United States, ⁴ University of Texas MD Anderson Cancer Center, Department of Leukemia, Houston, TX, United States

Title

Impact of Clonal Hematopoiesis on Outcomes of Patients with Waldenström macroglobulinemia.

Introduction

Clonal hematopoiesis (CH) is a premalignant condition characterized by the presence of specific somatic mutations, and associated with an increased risk of leukemia, cardiovascular disease, and other inflammatory conditions. Around 75% of patients with CH have either *DNMT3A*, *TET2*, or *ASXL1* mutations. The prevalence of CH increases with age, occurring in $\geq 10\%$ of adults over 70. Next-generation sequencing (NGS) in patients with Waldenström macroglobulinemia (WM) can reveal mutations associated with CH. This study aimed to determine whether the presence of these CH-related mutations impacts presenting signs, symptoms, and overall survival (OS) in patients with WM.

Methods

We reviewed data from all patients (n=234) at our institution who were diagnosed with WM between 06/01/2001 and 12/20/2025, and who had a 162 NGS gene mutation panel performed on a bone marrow aspirate. CH positive status was defined by the presence of *DNMT3A*, *TET2*, or *ASXL1* mutations. OS was calculated from date of first NGS panel to date of last follow-up or death.

Results

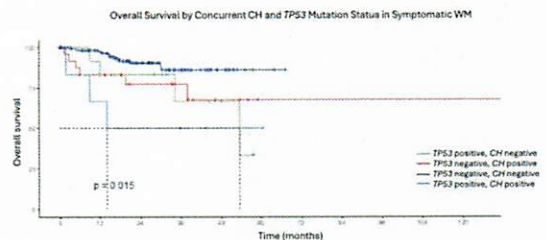
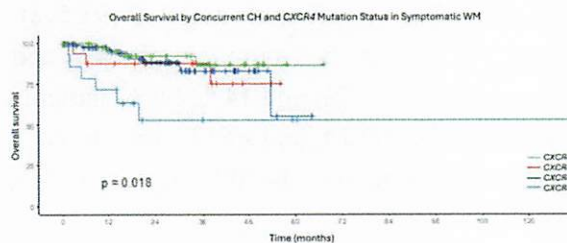
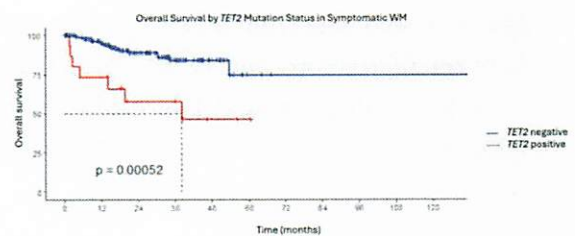
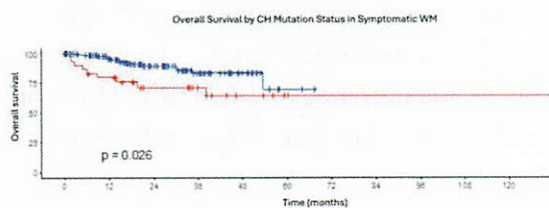
Median age at first NGS panel was 69 years (32-91); 146 (62.3%) were male and 219 (93.5%) identified as White/Caucasian. At time of NGS testing, 172 patients had symptomatic WM and 62 had smoldering disease. CH mutations were detected in 30 (17.4%) and 14 (22.6%) patients with symptomatic and smoldering WM respectively. *TET2*, *DNMT3A*, and *ASXL1* mutations were seen in 15 (8.7%), 11 (6.4%) and 6 (3.5%) patients with symptomatic WM, and 5 (8.1%), 9 (14.5%), and 1 (1.6%) patient(s) with smoldering WM.

Among those with symptomatic WM and CH, there was a higher incidence of cardiovascular disease ($p=0.04$) and chronic kidney disease ($p=0.02$), and a trend toward an increased incidence of osteoporosis ($p=0.08$). However, presenting features of WM did not differ between cohorts. Median total number of somatic mutations (excluding *MYD88* and *CXCR4*) on NGS panels was higher among patients with CH (3 vs 1, $p<.0001$). CH positivity was also associated with a shorter 2-year OS (72% vs 89%, $p=0.026$). This finding was driven by *TET2* positivity (2-year OS: 58% vs 89%, $p=0.0005$), as neither *ASXL1* nor *DNMT3A* independently impacted OS. Concurrent CH mutations with either *CXCR4* ($p=0.018$) or *TP53* ($p=0.015$) mutations had further negative prognostic impact. Of the 24 patients who died, reasons for death were WM/diffuse large B cell lymphoma (58.4%), non-hematologic malignancy (12.5%), infection (8.4%), small bowel obstruction (4.2%), and unknown causes (16.5%).

Within the smoldering cohort, CH positivity neither influenced time to development of symptomatic WM nor OS.

Conclusion

As observed in other malignancies (e.g. multiple myeloma, breast cancer), our findings suggest that CH, and more specifically *TET2* mutations, negatively impact OS in patients with symptomatic WM. Whether this negative prognostic impact is driven by WM, second malignancies, comorbid conditions, or a combination thereof, requires further investigation. Since chemotherapeutics commonly used in WM (e.g. alkylating agents) heighten the risk of developing leukemia, our results raise the question of whether CH/*TET2* status should be considered when selecting systemic therapy. These results warrant validation in a larger cohort of symptomatic WM patients.



Form record received

From International Workshop on Waldenstrom's Macroglobulinemia <pattersonkent@outlook.com>

Date Thu 30-Jul-26 5:39 PM

To Patterson, Christopher <Christopher_Patterson@DFCI.HARVARD.EDU>

External Email - Use Caution

Record saved to database with ID: 233

Form ID: 1

Form title: Abstract Submission

Form name: Abstract_Submission

Submitted at: 2026-07-30 17:37:54

Submitter IP: 206.127.182.161

User-ID: 0

Username: -

User full name: -

Submitter provider: Unknown

Submitter browser: Mozilla/5.0 (Macintosh; Intel Mac OS X 10_15_7) AppleWebKit/537.36 (KHTML, like Gecko) Chrome/150.0.0.0 Safari/537.36

Submitter operating system: mac

First Name: Sandhya

Last Name: Maddali

Email: svmadd26@dmu.edu

Phone Number (optional): 8326490135

Registration Type: Delegate in Training

Abstract Title: Impact of Clonal Hematopoiesis on Outcomes of Patients with Waldenström macroglobulinemia.

Select abstract file to attach:

/home/dkwolfpk2016/public_html/waldenstromsworkshop/media/breezingforms/uploads/clonalhematopoeisisinwmmaddali.pdf

Additional file (optional):

/home/dkwolfpk2016/public_html/waldenstromsworkshop/media/breezingforms/uploads/lossandhyamaddali.pdf

Please consider me for a YIA grant: YIA Grant Consideration

Conference: IWWM13