Clonal hematopoiesis is associated with increased risk of progression of asymptomatic Waldenström Macroglobulinemia


18th International Myeloma Workshop
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Disclosure Information

• I have no financial relationships to disclose.
Clonal Hematopoiesis of Indeterminate Potential (CHIP)

Clonal hematopoiesis (CH) and hematological malignancies

Multiple Myeloma (MM) at time of ASCT

Non-Hodgkin lymphoma (NHL) at time of ASCT


Indolent NHL characterized by immunoglobulin-M (IgM) secreting lymphoplasmacytic cells and hallmark mutations in genes involved in B-cell signaling, including \textit{MYD88} and \textit{CXCR4}

Symptomatic patients are managed by cytotoxic chemotherapy, proteasome inhibitors, Bruton tyrosine kinase (BTK) inhibitors and anti-CD20 antibodies

Genomic profiling is of importance in treatment selection

Many patients present with precursor stages IgM MGUS and smoldering WM and do not require treatment at time of diagnosis

Study Aims and Objectives

1. To investigate the frequency of CH in Waldenström Macroglobulinemia

2. To study the association of CH mutations with clinical outcome in WM patients
Study Workflow

602 WM patients at DFCI

Clinical data collection Oct 2014 – Febr 2020

Genetic profiling of PB or BM by NGS\(^1\) (n=587), coverage ~1500X

Clonal dynamics over median of 2.3 years (n=104)

Clinical association with median follow-up 5.6 years

CH detection at VAF >2%

Thirteen patients (3%) had a coincident diagnosis of MDS or AML and one had ALL at the time of NGS; these 14 patients were excluded from further analysis

CH was defined by the presence of somatic mutations in DNMT3A, TET2 or ASXL1 (CH-DTA)

## Study Cohort Baseline Characteristics (n=587)

<table>
<thead>
<tr>
<th></th>
<th>Asymptomatic WM (n=147)</th>
<th>Symptomatic WM (n=440)</th>
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</thead>
<tbody>
<tr>
<td>Age at NGS</td>
<td>66 (40-89)</td>
<td>68 (33-93)</td>
</tr>
<tr>
<td><em>Median (range)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>69 (47%)</td>
<td>161 (37%)</td>
</tr>
<tr>
<td>Male</td>
<td>78 (53%)</td>
<td>279 (63%)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MGUS</td>
<td>31 (21%)</td>
<td>-</td>
</tr>
<tr>
<td>SWM</td>
<td>116 (79%)</td>
<td>-</td>
</tr>
<tr>
<td>WM</td>
<td>-</td>
<td>440 (100%)</td>
</tr>
<tr>
<td>BM involvement at NGS</td>
<td>20 (0.3-95%)</td>
<td>50 (0-95)</td>
</tr>
<tr>
<td><em>Median (range)</em></td>
<td></td>
<td></td>
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<tr>
<td>Cytotoxic therapy pre-NGS</td>
<td>0 (0%)</td>
<td>141 (32%)</td>
</tr>
<tr>
<td>IgM at NGS</td>
<td>1228 (134-7554)</td>
<td>1706 (15-8310)</td>
</tr>
<tr>
<td><em>Median (range)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MYD88 mutation (PCR)</td>
<td>113 (77%)</td>
<td>369 (84%)</td>
</tr>
</tbody>
</table>
CH-DTA is present in at least 14% of WM patients

Asymptomatic WM
CH frequency: IgM MGUS: 13%; SWM: 14%

Symptomatic WM
CH frequency: 14%
CH-DTA is not associated with inferior OS

Median follow-up from diagnosis and NGS assay of 6.7 (95% CI: 6.1-7.6) and 2.5 (95% CI: 2.2-2.8) years
Asymptomatic WM patients with CH-DTA have an increased risk of progression
Clonal dynamics of WM-related mutations and CH-DTA mutations in response to therapy
Summary

CH is present in at least 14% of patients with WM.

Patients with CH are more likely to progress from IgM MGUS or smoldering WM to symptomatic WM.

No indication for changes in clinical management for WM patients with coexistent CH.

Further work is needed to determine how the presence of CH might promote progression to WM and whether it can be incorporated into risk stratification models.
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Increased risk of MDS and AML is well documented in WM and CH is associated with increased myeloid malignancy risk. We performed an exploratory analysis of patients with both WM and a myeloid malignancy.

Fourteen patients had a concurrent myeloid malignancy at the time of NGS, developing at a median of 7.9 years from WM diagnosis, 13 of which were MDS (87%). During follow-up, 1 additional patient with SF3B1 and SRSF2 mutations developed MDS after receiving bendamustine and rituximab.
Detection of mutated CXCR4 and MYD88 by diagnostic NGS in WM

Recent studies have shown CXCR4 and MYD88 detection is impaired by NGS in WM

- **Previous literature**: 90-95% MYD88; 40% CXCR4.
- Based upon studies using AS-PCR on CD19-selected BM to maximize sensitivity.

- **Our cohort** showed lower detection levels of MYD88 and CXCR4 by NGS, see below table:

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<tr>
<td>Mutation MYD88</td>
<td>51 (34.7%)</td>
<td>200 (45.5%)</td>
</tr>
<tr>
<td>Mutation CXCR4</td>
<td>14 (9.5%)</td>
<td>75 (17%)</td>
</tr>
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- **Gustine et al.**: 40% vs 15% when comparing AS-PCR on CD19 selected BM vs NGS on unselected BM (n=107, WM); 63% false-negatives.
- **Kofides et al.**: 66% of MYD88 mutations detected by AS-PCR on CD19-selected BM by NGS on unselected BM.

- Sensitivity of CXCR4 and MYD88 mutations was impacted by bone marrow involvement (patchy BM and/pr hemodilution).
- In our cohort no indication CH-DTA detection was influenced by BM involvement (biopsy or aspirate).

Was the presence of MYD88 L265P (or absence) associated with CH-related mutations?