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Inflammation is predictive of outcome in Waldenström macroglobulinemia treated by Bruton tyrosine kinase inhibitors: a multicentric real-life study

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Conflict-of-interest: None related to this manuscript

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Running title: Inflammation and BTK inhibitors in Waldenström

Key words: BTK inhibitors, Waldenström, inflammatory

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Waldenström macroglobulinemia (WM) is a chronic indolent mature B-cell lymphoma characterized by bone marrow infiltration of lymphoplasmacytic cells and a monoclonal immunoglobulin M. The most frequent somatic anomaly in WM is a gain of function mutation of \textit{MYD88} (\textit{MYD88}^{L265P}), present in 90% of WM at diagnosis leading to constitutive activation of NF-kB and JAK/STAT pathways, followed by 6q deletion (del6q, 30-55%) and \textit{CXCR4} gain-of-function mutations (30-40%). The therapy is based on chemo-immunotherapy (CIT) or BTK inhibitors (BTKi). The numerous prognostic scores, specific of WM, did not impact the therapeutic choice in clinical practice.

Based on WM and inflammatory disorder association, the prognosis impact of inflammation in WM during CIT was recently highlighted by two independent teams. In the first cohort, inflammatory syndrome (CRP $\geq$ 20 mg/L) was present in one-third of the patients. This inflammatory syndrome decreased during treatment but was associated with a shorter time-to-next-treatment (TTNT, 1.6 years versus 4.8 years, p<0.001). In the second cohort, inflammation (CRP > 5 mg/L) was associated with more frequent del6q and, more frequent need for treatment initiation, inflammation decrease during CIT and a trend towards poorer progression-free survival (PFS) and overall survival (OS).

Importantly, the outcome of inflammatory WM (iWM) was evaluated during CIT, whereas data about BTKi therapy and inflammation were lacking. Therefore, we performed a multicentric cohort to evaluate the impact of BTKi on iWM. In this real-life cohort, the inflammation positively impacts the prognosis of WM with BTKi.

The pooled cohort used in this study was based on published WM cohorts from Saint Louis (n=268) and Pitie-Salpetriere hospitals (n=270) with the addition of a Necker cohort hospital (n=110). \textit{MYD88}^{L265P} and \textit{CXCR4}^{S338X} mutations were evaluated by restriction-fragment-length polymorphism and allele-specific PCR or targeted-NGS respectively, as previously described.

iWM was defined by the presence of two CRP measures $\geq$ 20 mg/L without other causes to explain inflammatory syndrome (e.g. infection, inflammatory complication). We excluded patients without CRP measurement before treatment. The CIT cohort at second line used as control was extracted from the Saint-Louis cohort.

The response was assessed according to the IWWM-6. Patient data were obtained in conformity with the Declaration of Helsinki and registered by the Assistance-Publique-Hôpitaux-de-Paris data protection office.

OS was defined as the time from diagnosis to death from all causes. PFS was defined as the time from BTKi initiation and its discontinuation for any reason (progression or toxicity) or death. TTNT was defined as the time from BTKi or CIT initiation to disease progression requiring treatment or death from any cause. All quantitative variables were described using medians (quartiles), while qualitative...
variables were described by frequencies (percentage). Categorical and quantitative data were compared using Fisher’s exact test and t student test, respectively. Kaplan–Meier curves were plotted for survival, and data for the various groups were compared using the log-rank test. Maximally selected-rank statistics were used to select the best cut-off for CRP based on TTNT survival. Statistical analyses were obtained using R 4.0.4.

Among 648 WM patients from the pooled-cohort, 474 (73%) WM patients received CIT including 398 (84%) with multiple CRP measures before treatment (supplementary-Table1A). We confirmed the inferior outcome after CIT of iWM, defined by CRP ≥ 20 mg/L, based on TTNT at three levels (supplementary-Figure 1A) and maximally selected-rank statistics (supplementary-Figure 1B). CXC4R4 mutation was not associated with TTNT (HR1, 95%CI 0.65-1.6, p=0.96). iWM was associated with more del6q (49% versus 20%, p<0.001, supplementary-Figure 1C) and less CXC4R4 mutation than non-iWM (15% versus 34%, p=0.02, supplementary-Figure 1D).

Seventy-eight WM patients who received BTKi between 2015 and 2022 were included (Figure 1A). After one exclusion for lack of CRP measurement, 42 (54%) patients were classified as iWM as previously described (Figure 1B). Among iWM, the median CRP before BTKi initiation was 37 mg/L [IQR 26-60]. The median age at WM diagnosis was 65 years (IQR 56-73, Table 1). Median follow-up after BTKi initiation was 3.3 years (IQR 1.7-5.9). Thirty-one (40%) patients had full characterization of MYD88/CXC4R4/del6q. Ninety percent of the patients had MYD88 mutation. CXC4R4 mutation was less frequent in iWM than in non-iWM (17% [4/24] versus 50% [10/20], p=0.04). Del6q was twice more frequent in iWM than non-iWM without reaching statistical significance (58% [14/24] versus 33% [6/18], p=0.19). No difference was observed for characteristics at diagnosis, first-line choice or BTKi initiation between iWM and non-iWM. Among BTKi, most patients received Ibrutinib. Half of the patients received BTKi on 2nd line.

Concerning hematologic response, the overall response rate (ORR = partial response/ very good partial response/ complete response [CR]) was superior in iWM than non-iWM (82% versus 52%, p=0.02, figure 1C). Regarding the inflammation syndrome kinetic, all iWM patients who reached minimal response (MR) or better on BTKi had a nadir of CRP < 20mg/L (Figure 1D). Sixteen patients (43%) obtained normalization of CRP (< 5mg/L). In addition, 91% (34/37) obtained a 50% decrease or more in their CRP level. Among patients with B-symptoms, 82% (14/17) had regression during BTKi treatment.

Furthermore, iWM patients had better PFS than non-iWM upon BTKi treatment (Figure 2A, median: 4 years versus 2.4 years, p=0.0025). The leading cause of BTKi discontinuation was progression for non-iWM (n=11, 51%) and BTKi toxicity for iWM (n=8, 47%, Table 1). The cumulative incidence of progression was superior for non-iWM than iWM (4years: 43% versus 21%, p=0.05, Figure 2B). There was no difference in discontinuation due to BTKi toxicity between non-iWM and iWM (4 years versus 2.4 years, p=0.0025). The leading cause of BTKi discontinuation was progression for non-iWM (n=11, 51%) and BTKi toxicity for iWM (n=8, 47%, Table 1). The cumulative incidence of progression was superior for non-iWM than iWM (4years: 43% versus 21%, p=0.05, Figure 2B). There was no difference in discontinuation due to BTKi toxicity between non-iWM and iWM (4
years: 37% versus 34%, p=0.11). Also, the TTNT survival was superior for iWM than non-iWM (median: 4 versus 2.6 years, p=0.008, Figure 2C). TTNT survival and maximally selected-rank statistics confirmed the relevance of the 20 mg/L CRP cut-off (supplementary-Figure 2A-B). In univariate analysis, TTNT was associated positively with inflammatory syndrome (HR0.43, 95%CI 0.22-0.81, p=0.01), negatively with CXCR4 mutations (HR3.8, 95%CI 1.5-9.6, p=0.01) and platelets <100 G/L (HR2.38, 95%CI 1.02-5.55, p=0.044, Supplementary-Table 1B). Del6q was not associated with TTNT (HR1.3 95%CI 0.49-3.4, p=0.60). Multivariate analysis was not performed because of a low number of events (n=18). No difference was observed for OS (4 years: 75% versus 66%, p=0.15, Supplementary-Figure 2C).

To evaluate the impact of inflammation in the current recommendation of BTKi in 2nd line, TTNT survival analysis was performed with a focus on the 2nd line of treatment (CIT or BTKi) between iWM and non-iWM (Figure 2D, p=0.012). No difference was observed for demographic/disease characteristics between BTKi and CIT cohorts (data not shown). Among patients receiving CIT at 2nd line, most patients received alkylating agents +/- rituximab (55%) followed by chlorambucil (22%). iWM treated with BTKi (51% at 4 years) had better survival than BTKi treated non-IWM (22%), whereas 4 years survival in patients treated with CIT was 16% in iWM and 29% in non-iWM.

To the best of our knowledge, this is the first study evaluating inflammation and response to BTKi in WM. We validated a cut-off of 20mg/L of CRP for iWM definition and the association with poorer outcomes after CIT. However, we showed here that iWM with BTKi treatment had better hematological response and TTNT than non-iWM. In addition, the inflammatory syndrome decreased during the hematological response in BTKi-treated iWM. Several explanations could exist for these improved hematological response and survival. First, reduced inflammation via decreased proinflammatory cytokines after BTKi was described for SARS-COV-210, chronic graft-versus-host-disease11 and Schnitzler syndrome12. Second, BTK is expressed by malignant B cells13 but also by macrophages or monocytes14. We can hypothesize that decreased inflammation mediated by BTKi might be related to the action on tumoral cells15 and/or microenvironment14. Also, 6q chromosome contains an inhibitor of BTK (iBTK)3. Deletion of 6q, more frequent in iWM, could thus lead to BTK activation, corrected by BTKi treatment. CXCR4 mutation was less frequent in iWM than non-iWM (17% vs 50%) and could explain a part of differential prognosis to BTKi. Additional study about the inflammation origin in WM would be required to understand BTKi action in iWM. One limit of our study is the small sample size for genetic analysis that limits the evaluation of interaction between CXCR4 mutation, del6q and inflammation. CXCR4 especially with high clonality (>25%), is the main adverse factor during BTKi therapy in WM16,17. Related to the partial evaluation of CXCR4 mutation (52% of the cohort) without any clonality analysis, additional studies are necessary to evaluate CXCR4 mutation and inflammation prognosis role independently. Nevertheless, assessment of CRP could be easier, quicker and cheaper to perform than evaluation of CXCR4 mutational status and clonality.
analysis on bone marrow samples. Also, the retrospective design of our study is a limit, and we will need to confirm our findings in prospective large multicentric cohorts but also to reanalyze clinical trials of BTKi in WM in light of our results\textsuperscript{16}.

In summary, inflammation appears to have a positive impact on the clinical outcome of WM patients on BTKi therapy. Thus, this study supports the use of BTKi in patients with iWM. On the other hand, inflammation could represent a novel biomarker for predicting the effects of BTKi in WM patients that can be easily and quickly evaluated in prospective cohorts and clinical trials.
References


Figure legends

Figure 1. Inflammatory Waldenstrom macroglobulinemia (iWM) was associated with a higher response to BTK inhibitors (BTKi) than non-iWM.

(A) Flowchart of the study. Seventy-eight patients received BTKi for WM, including 42 (54%) with inflammatory syndrome (CRP $\geq$ 20 mg/L). (B) Histogram and density plot for CRP distribution at BTKi initiation with the cut-off 20 mg/L. Two peaks among patients were observed at 0-5 mg/L and at 20 mg/L. (C) Hematologic response based on IWWM-6 criteria between non-iWM and iWM patients. Green bar represents overall response rate (= partial response [PR] / very good partial response [VGPR] / complete response [CR] response), the yellow bar for minimal response (MR) and orange bar for progressive disease (PD) /stable disease (SD). (D) Inflammation evolution in iWM (n=37) during BTKi treatment. Orange lines show patients who had SD/PD. Green lines show patients who had MR/VGPR/PR/CR. For progressive disease/ stable disease patients (n=5) in iWM, two patients had persistent CRP $\geq$ 20 mg/L, but received less than 4 months of BTKi. Among patients with clinical signs (n=17), all patients had B symptoms regression except for two iWM (1 with hematologic stable disease and 1 with VGPR but high CRP level at 19 mg/L who had a progression at 9 months) and one non-iWM patient who developed DLBCL 3 months after BTKi introduction.

Figure 2. Inflammatory WM (iWM) had an improvement of time to next treatment during BTKi treatment than non-iWM.

(A) Progression-free survival (PFS) between non-iWM (blue) and iWM (red). (B) Cumulative incidence of the reason for BTKi discontinuation (progression in a straight line and toxicity in a dotted line) between non-iWM (blue) and iWM (red) (C) Time to next treatment (TTNT) after BTKi for all cohorts between non-iWM (blue) and iWM (red) (D) TTNT after the 2nd line of treatment (BTKi in a straight line and CIT in dotted line) in non-iWM (blue) and iWM (red).
Figure 1

A)

- WM from Necker (n=110)
  - n=22, 20%

- WM from Saint Louis (n=268)
  - n=34, 13%

- WM from Pitié (n=270)
  - n=22, 8%

WM patients who received BTKi (n=78, 13%): 76 Ibrutinib, 1 Acalabrutinib and 1 Zanubrutinib

Exclusion for absence of CRP measure before BTKi initiation (n=1)

- Non inflammatory WM (n=35, 46%)
- Inflammatory WM (n=42, 54%)

B)

Graph showing CRP at BTKi initiation (mg/L) with density distribution.

C)

- Non Inflammatory WM (n=33)
  - 51%
  - 15%
  - 33%

- Inflammatory WM (n=39)
  - 82%
  - 5%
  - 13%

p=0.02

D)

Graph showing changes in CRP (mg/L) with color-coded categories: PD/SD, MR, PR/VGPR/CR. Significant difference indicated (p<0.0001).
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**Co-before last authors
#Co-last authors
**Supplementary Table 1A. Description of the global pooled cohort of WM patients who received a treatment and with CRP measure**

<table>
<thead>
<tr>
<th>CRP (mg/L)</th>
<th>CRP &lt;5 (n=170)</th>
<th>CRP 5–20 (n=104)</th>
<th>CRP ≥20 (n=124)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men (n, %)</td>
<td>110 (65%)</td>
<td>60 (58%)</td>
<td>93 (75%)</td>
</tr>
<tr>
<td>Age at WM diagnosis (years, median, IQR)</td>
<td>67 [58; 76]</td>
<td>68 [58; 75]</td>
<td>66 [59; 76]</td>
</tr>
<tr>
<td>Age at first line treatment (years, median, IQR)</td>
<td>69 [60; 77]</td>
<td>72 [59; 78]</td>
<td>70 [61; 79]</td>
</tr>
<tr>
<td>MYD88 mutation (n, %, on 218 testing)</td>
<td>71 (84%)</td>
<td>54 (95%)</td>
<td>69 (91%)</td>
</tr>
<tr>
<td>CXCR4 mutation (n, %, on 159 testing)</td>
<td>21 (35%)</td>
<td>17 (36%)</td>
<td>8 (15%)</td>
</tr>
<tr>
<td>Del6q (n, %, on 205 testing)</td>
<td>8 (10%)</td>
<td>19 (31%)</td>
<td>33 (48%)</td>
</tr>
</tbody>
</table>

WM: Waldenström macroglobulinemia, IQR: interquartile

**Supplementary Table 1B. Univariate analysis for time to next treatment (TTNT)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI for HR)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>0.7 (0.35–1.4)</td>
<td>0.30</td>
</tr>
<tr>
<td>Age at WM diagnosis</td>
<td>1 (0.98–1.1)</td>
<td>0.32</td>
</tr>
<tr>
<td>Kappa (versus Lambda)</td>
<td>1.4 (0.44–4.7)</td>
<td>0.54</td>
</tr>
<tr>
<td>IMWW score Adverse (vs Low or Intermediate)</td>
<td>1.1 (0.4–3.2)</td>
<td>0.82</td>
</tr>
<tr>
<td>Age at WM diagnosis &gt; 65 years</td>
<td>1.3 (0.68–2.4)</td>
<td>0.46</td>
</tr>
<tr>
<td>Hemoglobin &lt; 11.5 g/dL</td>
<td>1.22 (0.41–3.5)</td>
<td>0.72</td>
</tr>
<tr>
<td><strong>Platelets &lt; 100 G/L</strong></td>
<td><strong>2.38 (1.02–5.55)</strong></td>
<td><strong>0.04</strong></td>
</tr>
<tr>
<td>β2-microglobulin &gt; 3 mg/L</td>
<td>1.6 (0.44–5.7)</td>
<td>0.48</td>
</tr>
<tr>
<td>Monoclonal IgM &gt; 70 g/L</td>
<td>0.76 (0.1–5.7)</td>
<td>0.79</td>
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<tr>
<td>LDH &gt; 250 UI/L</td>
<td>0.52 (0.23–1.2)</td>
<td>0.13</td>
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<tr>
<td>MYD88 mutation</td>
<td>0.48 (0.11–2.1)</td>
<td>0.33</td>
</tr>
<tr>
<td><strong>CXCR4 mutation</strong></td>
<td><strong>3.8 (1.5–9.6)</strong></td>
<td><strong>0.01</strong></td>
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<tr>
<td>Del6q</td>
<td>1.3 (0.49–3.4)</td>
<td>0.60</td>
</tr>
<tr>
<td>Line of WM treatment before BTKi</td>
<td>1.3 (0.97–1.8)</td>
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<tr>
<td>Age at BTKi initiation</td>
<td>1 (0.97–1)</td>
<td>0.9</td>
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<tr>
<td>Year of BTKi initiation</td>
<td>0.85 (0.7–1)</td>
<td>0.11</td>
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<tr>
<td><strong>Inflammatory (CRP ≥ 20 mg/L) at BTKi initiation</strong></td>
<td><strong>0.43 (0.22–0.81)</strong></td>
<td><strong>0.01</strong></td>
</tr>
</tbody>
</table>

BTKi: Bruton tyrosine kinase inhibitors, ISSWM: International prognosis Score System for Waldenström Macroglobulinemia, WM: Waldenström macroglobulinemia
Supplementary Figure 1. Global cohort analysis. (A) Time to next treatment (TTNT) survival curves at first line in the pooled cohort with 3 levels of CRP (0-5, 5-20 and 20 mg/L). Dotted line represents the median of TTNT survival. (B) Maximally selected rank statistics on pooled global cohort for TTNT at first line. Standardized log-rank statistics was performed on CRP level (continuous variable) at different cut-off. The dotted line (here at 22 mg/L of CRP) showed the best cut-off to separate the cohort into 2 groups of different survival (HR 4.9 for 22 mg/L). (C-D) Del6q (C) and CXCR4 (D) incidence among the global pooled cohort of WM patients separated in 3 groups based on the CRP level (CRP < 5 mg/L, CRP 5-20 mg/L, CRP ≥ 20 mg/L)
Supplementary Figure 2. BTK cohort analysis. (A) Time to next treatment (TTNT) survival curves after BTK treatment with 3 levels of CRP (0-5, 5-20 and 20 mg/L). Dotted line represents the median of TTNT survival. (B) Maximally selected rank statistics on BTKi cohort for TTNT. Standardized log-rank statistics was performed on CRP level (continuous variable) at different cut-off (C) Overall survival between inflammatory WM (red) and non-inflammatory WM (blue) after BTKi treatment.