Partial response or better at six months is prognostic of superior progression-free survival in Waldenström macroglobulinemia patients treated with ibrutinib

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Summary

Ibrutinib is associated with durable responses in patients with Waldenström macroglobulinemia (WM). We hypothesized that response depth is predictive of progression-free survival (PFS) in WM patients treated with ibrutinib. Using landmark analyses, we evaluated response depth in two cohorts of WM patients treated with ibrutinib monotherapy. The learning cohort was composed of 93 participants from two clinical trials, and the validation cohort of 190 consecutive patients treated off clinical trial. Rates of partial response (PR) or better at six months in learning and validation cohorts were 64% and 71% respectively (P = 0.29). In the learning cohort, three-year PFS rates for patients who attained PR or better at six months versus not were 81% and 57% respectively (P = 0.009). In the validation cohort, three-year PFS rates for patients who attained PR or better at six months versus not were 83% and 54% respectively (P = 0.008). In multivariate analyses, attaining PR or better at six months was associated with superior PFS in the learning [hazard ratio (HR) 0.38; P = 0.01] and validation cohorts (HR 0.18; P = 0.004). Attaining PR at six months on ibrutinib emerges as an intermediate outcome of interest and should be validated as surrogate for PFS in clinical trials evaluating Bruton tyrosine kinase inhibitors in WM.

Keywords: Waldenström macroglobulinemia, Ibrutinib, response.

The oral Bruton tyrosine kinase (BTK) inhibitor ibrutinib is approved in Europe and the United States (USA) for the treatment of patients with symptomatic Waldenström macroglobulinemia (WM). The approval was based on the results of a prospective phase II study in which 63 previously treated patients with WM were treated with ibrutinib monotherapy, with an overall response rate (ORR) of 91%, a major response [partial response (PR) or better] rate of 73% and a five-year progression-free survival (PFS) of 54%.1 In two other prospective studies in previously untreated patients or those refractory to rituximab therapy similar response rates were seen, with an 18-month PFS rate in previously
untreated versus rituximab-refractory of 92% vs. 86% respectively.\textsuperscript{2,3} WM is an indolent malignancy, and with the use of effective therapies, PFS can be substantially prolonged, thereby requiring protracted patient follow-up in randomized controlled clinical trials.

Prior studies have suggested that depth of response correlates with PFS in WM patients treated with chemoinmunotherapy.\textsuperscript{4,6} However, it is unclear if depth of response can be used as a surrogate for PFS in patients with WM treated with ibrutinib monotherapy. This analysis is timely, as the recently published open-label, randomized phase III ASPEN study comparing zanubrutinib and ibrutinib, has the proportion of patients achieving very good partial response (VGPR) or better as the primary end-point.\textsuperscript{7}

We hypothesized that the depth of response at a specific time point following treatment initiation is predictive of PFS in patients with WM treated with ibrutinib. We tested our hypothesis by evaluating two separate cohorts (learning and validation) of WM patients treated with ibrutinib monotherapy using a landmark analysis.

**Patient and methods**

**Patient selection**

The patients who participated in two prospective clinical trials (NCT01614821 and NCT02604511) at Dana-Farber Cancer Institute (DFCI), Memorial Sloan Kettering Cancer Center and Stanford Cancer Center composed the learning cohort. The validation cohort was composed of consecutive WM patients treated with ibrutinib monotherapy off clinical trial at DFCI and Mayo Clinic. All patients provided consent to having their data collected for research, and met clinicopathological criteria for a diagnosis of WM requiring treatment based on guidelines from the 2nd International Workshop on WM (IWWM-2).\textsuperscript{8,9} Patients with central nervous system involvement by WM were excluded from the study.

**Data collection**

Pertinent clinicopathological data were collected at the time of ibrutinib therapy initiation. Categorical responses were assessed based on modified IWWM-6 criteria,\textsuperscript{10} in which assessment of extramedullary disease was not required for attainment of a minor response (MR, 25–50% decrease in serum IgM from baseline), PR (50–90% decrease in serum IgM from baseline), VGPR (>90% decrease in serum IgM from baseline, or normalization of serum IgM levels with persistence of a detectable IgM monoclonal paraprotein in serum protein electrophoresis) but was mandated for attainment of complete response (CR; normalization of serum IgM level and serum protein electrophoresis and complete resolution of extramedullary disease as well as bone marrow involvement). This modification to IWWM-6 response criteria is widely used for clinical trial design. We evaluated two depths of response: attainment of PR or better, and VGPR or better. As the depth of response to ibrutinib monotherapy is time-dependent, with rates of response increasing over time, we chose two response assessment time points, at six (±1 month, in the validation cohort) and 12 months (±2 months, in the validation cohort) from treatment initiation. At DFCI and for patients from clinical trials, MYD88 and CXCR4 mutational status was assessed in CD19-selected bone marrow samples using allele-specific polymerase chain reaction (AS-PCR) for MYD88 L265P and nonsense CXCR4 mutations. Frameshift CXCR4 mutations were assessed by Sanger sequencing, MYD88 and CXCR4 mutational detection techniques have been previously reported.\textsuperscript{11–14} At Mayo Clinic, MYD88 mutational status was assessed by the amplification-refractory mutation system (ARMS), a variant of AS-PCR. DNA is extracted using the Qiagen DNeasy kit (Qiagen, Valencia, CA, USA) from archived unsorted bone marrow aspirate sample pellets fixed in methanol + acetic acid. A single-tube multiplex ARMS is performed using primers situated in exon 5 of MYD88 (NM_002468.4), including one primer specifically targeting the L265P alteration. Reaction products are analyzed using capillary electrophoresis (QIAxcel, Qiagen). MYD88 wild-type control amplification yields a PCR product of 141 base pairs (bp), and if present, an additional specific 72-bp product denotes the L265P mutation. CXCR4 mutational testing was not performed in Mayo Clinic patients.

**Statistical analysis**

Patients’ characteristics and response rates are presented using descriptive statistics. Differences between categorical variables were assessed using the chi-squared test or the Fisher exact test, based on the number of observations. Depending on the time of the landmark analyses, PFS was estimated starting at the six-month mark (for patients with response assessment at six months) and starting at the 12-month mark (for patients with response assessment at 12 months). Survival curves were generated using the Kaplan–Meier method for incomplete observations and compared using the log-rank test. Since we performed four separate landmark analyses evaluating two depths of response (PR or better, and VGPR or better) at two different time points (six and 12 months), $P < 0.0125$ was considered statistically significant ($P < 0.05$ divided by 4, to adjust for multiplicity). We then fitted univariate and multivariate Cox proportional-hazard regression models for PFS at each landmark. Outcomes are reported using hazard ratio (HR) with 95% confidence interval (CI). Differences in overall survival or survival after first treatment initiation were not assessed due to a small number of deaths in this cohort (n = 37; 13%) at the time of this report. Calculations were obtained using STATA 15 (StataCorp, College Station, TX, USA).
Results

Patients’ characteristics

Ninety-three and 190 patients comprised the learning and validation cohorts respectively. The distribution of patients’ characteristics as well as differences between groups are shown in Table I. In the validation versus learning cohort, there was a statistically lower proportion of male patients (62% vs. 74%, \( P = 0.04 \)), and bone marrow involvement \( \geq 50\% \) (48% vs. 68%; \( P = 0.003 \)) and a trend towards a higher proportion of previously untreated patients (78% vs. 68%; \( P = 0.07 \)) respectively. There were no statistical differences between cohorts in the proportion of patients age \( > 65 \) years, haemoglobin level \( \leq 115 \) g/l, platelet count \( \leq 100 \) K/\( \mu l \), serum \( \beta 2 \)-microglobulin \( \leq 3 \) mg/l, serum IgM level \( > 7000 \) mg/dl, IPSSWM distribution, \( MYD88 \) and \( CXCR4 \) mutational status. \( CXCR4 \) mutational status data were not available in one patient from the learning and 83 patients from the validation cohorts.

Response to ibrutinib therapy

Categorical response rates at six and 12 months in patients from the learning and validation cohorts are shown in Table I. In the validation versus learning cohort, there was a statistically lower proportion of male patients (62% vs. 74%, \( P = 0.04 \)), and bone marrow involvement \( \geq 50\% \) (48% vs. 68%; \( P = 0.003 \)) and a trend towards a higher proportion of previously untreated patients (78% vs. 68%; \( P = 0.07 \)) respectively. There were no statistical differences between cohorts in the proportion of patients age \( > 65 \) years, haemoglobin level \( \leq 115 \) g/l, platelet count \( \leq 100 \) K/\( \mu l \), serum \( \beta 2 \)-microglobulin \( \leq 3 \) mg/l, serum IgM level \( > 7000 \) mg/dl, IPSSWM distribution, \( MYD88 \) and \( CXCR4 \) mutational status. \( CXCR4 \) mutational status data were not available in one patient from the learning and 83 patients from the validation cohorts.

Table I. Baseline characteristics of Waldenström macroglobulinaemia patients treated with ibrutinib from the learning and validation cohorts.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Learning cohort (n = 93)</th>
<th>Validation cohort (n = 190)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ( &gt; 65 ) years</td>
<td>50 (54%)</td>
<td>116 (61%)</td>
<td>0.24</td>
</tr>
<tr>
<td>Male sex</td>
<td>69 (74%)</td>
<td>118 (62%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Haemoglobin level ( \leq 11.5 ) g/dl</td>
<td>66 (71%)</td>
<td>131/179 (73%)</td>
<td>0.70</td>
</tr>
<tr>
<td>Platelet count ( \leq 100 ) K/( \mu l )</td>
<td>9 (10%)</td>
<td>23/176 (13%)</td>
<td>0.41</td>
</tr>
<tr>
<td>Serum ( \beta 2 )-microglobulin ( &gt; 3 ) mg/l</td>
<td>65/91 (71%)</td>
<td>77/124 (62%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Serum IgM level ( &gt; 7000 ) mg/dl</td>
<td>6 (5%)</td>
<td>10/189 (5%)</td>
<td>0.98</td>
</tr>
<tr>
<td>Bone marrow involvement ( \geq 50% )</td>
<td>63 (68%)</td>
<td>78/161 (48%)</td>
<td>0.003</td>
</tr>
<tr>
<td>IPSSWM</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Low risk</td>
<td>20/91 (22%)</td>
<td>30/134 (22%)</td>
<td>0.54</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>34/91 (38%)</td>
<td>41/134 (31%)</td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>37/91 (41%)</td>
<td>63/134 (47%)</td>
<td></td>
</tr>
<tr>
<td>( MYD88 ) L265P mutation present</td>
<td>89 (96%)</td>
<td>137/146 (94%)</td>
<td>0.54</td>
</tr>
<tr>
<td>( CXCR4 ) mutation present</td>
<td>36/92 (39%)</td>
<td>42/107 (39%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Previously treated</td>
<td>63 (68%)</td>
<td>148 (78%)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

IPSSWM, International Prognostic Scoring System for Waldenström macroglobulinaemia.

At 12 months, data on response were available in 76 patients (82%) from the learning cohort and in 126 patients (66%) from the validation cohort. In the learning cohort, 16 patients were not evaluable for response as follow-up time was shorter than 12 months, leaving one patient (1%) with missing data. In the validation cohort, 54 patients were not evaluable for response due to follow-up time shorter than 12 months, leaving 10 patients (8%) with missing data. The rates of PR or better at 12 months in the learning and validation cohorts were 74% (56/76) and 81% (102/126), respectively (\( P = 0.23 \)), and the rates of VGPR or better were 20% (15/76) and 25% (31/126) respectively (\( P = 0.42 \)). There was one patient in the validation cohort who attained CR.

Landmark analyses at six months

The median follow-up times for the learning cohort was 40 months (95% CI 38–49 months) while it was 31 months (95% CI 28–34 months) for the validation cohort (\( P < 0.001 \)).

In the learning cohort, the three-year PFS rate starting at the six-month mark was 72% (95% CI 60–81%; Fig 1A). For patients who attained PR or better at six months versus not, the three-year PFS rate starting at the six-month mark was 81% (95% CI 67–89%) vs. 57% (95% CI 35–74%) respectively (\( P = 0.009 \), Fig 1B). For patients who attained VGPR or better versus not at six months, the three-year PFS rate was 88% (95% CI 39–98%) vs. 70% (95% CI 58–80%) respectively (\( P = 0.25 \), Fig 1C).

In the validation cohort, the three-year PFS rate starting at the six-month mark was 76% (95% CI 66–84%; Fig 1D). For patients who attained PR or better at six months versus not, the three-year PFS rate starting at the six-month mark was 83% (95% CI 71–90%) vs. 54% (95% CI 32–71%) respectively (\( P = 0.02 \), Fig 1E).
patients who attained PR or better at 12 months was 69% (95% CI 26–75% (95% CI 58–62) respectively (P = 0.08, Fig 1E). For patients who attained VGPR or better versus not at six months, the three-year PFS rate starting at the six-month mark was 84% (95% CI 43–97 vs. 73% (95% CI 61–82%) respectively (P = 0.08, Fig 1F).

Landmark analyses at 12 months

In the learning cohort, the three-year PFS rate starting at the 12-month mark was 71% (95% CI 57–81%; Fig 2A). For patients who attained PR or better at 12 months versus not, the three-year PFS rate starting at the 12-month mark was 75% (95% CI 58–86%) vs. 62% (95% CI 35–80%) respectively (P = 0.08, Fig 2B). For patients who attained VGPR or better versus not at 12 months, the three-year PFS rate starting at the 12-month mark was 69% (95% CI 26–91%) vs. 72% (95% CI 57–82%) respectively (P = 0.99, Fig 2C).

In the validation cohort, the three-year PFS rate starting at the 12-month mark was 71% (95% CI 57–81%; Fig 2D). For patients who attained PR or better at 12 months vs. not, the three-year PFS was 76% (95% CI 58–86%) vs. 56% (95% CI 27–77%), respectively (P = 0.02, Fig 2E), and therefore did not meet the pre-defined study criteria for statistical significance. For patients who attained VGPR or better at 12 months vs. not, the three-year PFS rate starting at the 12-month was 56% (95% CI 27–77%) vs. 75% (95% CI 62–84%) respectively (P = 0.42, Fig 2F).

Univariate and multivariate analysis

We fitted univariate models to identify predictive factors for PFS starting at the six-month mark in the learning and validation cohorts separately. These models are shown in Table III.

In the learning cohort, attaining a major response at six months was associated with better PFS (HR 0.37, 95% CI 0.17–0.80; P = 0.01), while serum IgM ≥ 7000 mg/dl (HR 4.65, 95% CI 1.36–16.0; P = 0.01) and CXCR4 mutations (HR 2.47, 95% CI 1.13–5.39; P = 0.02) were associated with worse PFS. No other variables were associated with either a better or worse PFS. In a multivariate model including attaining PR or better at six months and CXCR4 mutations, attaining a major response at six months was an independent prognostic factor of adverse PFS (HR 0.38, 95% CI 0.15–0.84; P = 0.01). None of these variables violated the proportionality assumption (P = 0.85 and P = 0.78 respectively). The interaction term between PR or better at six months and CXCR4 mutations was not significant (P = 0.38).

In the validation cohort, attaining PR or better at six months was associated with better PFS (HR 0.38, 95% CI 0.18–0.80; P = 0.01), while platelet count ≤ 100 K/µl (HR 4.73, 95% CI 1.94–11.5; P = 0.001) and CXCR4 mutations (HR 3.01, 95% CI 1.09–8.30; P = 0.03) were associated with worse PFS. No other variables were associated with either a better or worse PFS. In a multivariate model including attaining PR or better at six months, platelet count ≤ 100 K/µl and CXCR4 mutations, attaining PR or better at six months was an independent prognostic factor for better PFS (HR 0.18, 95% CI 0.05–0.58; P = 0.004). None of these variables violated the proportionality assumption (P = 0.55, P = 71 and P = 0.39 respectively). The interaction term between PR or better at six months and CXCR4 mutations was not significant (P = 0.97).

Discussion

Ibrutinib is the only drug formally approved for the treatment of patients with symptomatic WM in the USA and Europe, and a number of prospective and retrospective studies have shown ibrutinib monotherapy to be safe, effective and able to induce durable responses in treatment-naive as well previously treated patients with WM.\(^1\)-\(^3\),\(^15\),\(^16\) Data, however, are limited regarding prognostic factors for PFS on ibrutinib therapy. Furthermore, the association between depth of response to and PFS on ibrutinib has not been previously evaluated.

To the best of our knowledge, this is the first study evaluating the prognostic value of depth of response on PFS in
patients with WM treated with ibrutinib monotherapy. All the patients in the validation cohort were treated at academic institutions with experience in WM. Using a landmark analysis, we evaluated two depths of response, PR or better and VGPR or better, at two different time points, six and 12 months. The only combination of depth and timing of response that met our predetermined criteria, and therefore the only factor prognostic of a superior PFS in both the learning and the validation cohorts, was attaining PR or better at six months. As the median follow-up time for the learning cohort was 40 months and for the validation cohort was 31 months, we presented PFS rates at three years. The

Fig 1. Kaplan–Meier progression-free survival (PFS) curves starting at the six-month mark in Waldenström macroglobulinaemia patients. Learning cohort: (A) PFS, (B) PFS according to attaining partial response (PR) at six months or not, and (C) PFS according to attaining very good partial response (VGPR) at six months or not. Validation cohort: (D) PFS, (E) PFS according to attaining PR at six months or not, and (F) PFS according to attaining VGPR at six months or not. CI, confidence interval. [Colour figure can be viewed at wileyonlinelibrary.com]
three-year PFS rates for attaining PR or better versus not in the learning cohort were 81% and 57%, respectively, while in the validation cohort the three-year PFS rates for attaining PR or better versus not were 83% and 54% respectively.

The baseline characteristics between our learning and validation cohorts were relatively similar, with higher proportion of men and bone marrow involvement $\geq 50\%$ in the validation cohort with no other differences. The patients included had a
PR at Six Months is Prognostic in WM on ibrutinib

Table III. Univariate Cox proportional-hazard regression models for progression-free survival in the learning and validation cohorts.

<table>
<thead>
<tr>
<th></th>
<th>Learning cohort</th>
<th>Validation cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Age &gt;65 years</td>
<td>1.36 (0.63–2.96)</td>
<td>0.43</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.02 (0.41–2.56)</td>
<td>0.96</td>
</tr>
<tr>
<td>Haemoglobin level ≤115 g/l</td>
<td>1.03 (0.45–2.38)</td>
<td>0.94</td>
</tr>
<tr>
<td>Platelet count ≤100 K/μl</td>
<td>2.76 (0.82–9.26)</td>
<td>0.10</td>
</tr>
<tr>
<td>Serum β2-microglobulin ≥3 mg/l</td>
<td>0.53 (0.24–1.20)</td>
<td>0.13</td>
</tr>
<tr>
<td>Serum IgM level &gt;7000 mg/dl</td>
<td>4.65 (1.36–16.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>Bone marrow involvement ≥50%</td>
<td>0.49 (0.23–1.06)</td>
<td>0.07</td>
</tr>
<tr>
<td>High versus low IPSSWM</td>
<td>1.45 (0.52–4.02)</td>
<td>0.47</td>
</tr>
<tr>
<td>Intermediate versus low IPSSWM</td>
<td>0.87 (0.30–2.51)</td>
<td>0.80</td>
</tr>
<tr>
<td>MYD88 L265P mutation present</td>
<td>0.20 (0.03–1.58)</td>
<td>0.13</td>
</tr>
<tr>
<td>CXCR4 mutation present</td>
<td>2.47 (1.13–5.39)</td>
<td>0.02</td>
</tr>
<tr>
<td>Previously treated</td>
<td>1.65 (0.60–4.52)</td>
<td>0.33</td>
</tr>
<tr>
<td>PR or better at 6 months</td>
<td>0.37 (0.17–0.80)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

IPSSWM, International Prognostic Scoring System for Waldenström macroglobulinaemia; PR, partial response; HR, hazard ratio; CI, confidence interval; UTC, unable to calculate.

Bold values denote statistically significant.

similar distribution to WM patients in the general population, with more than half of the patients being older than 65 years and an approximate 2-to-1 male predominance.17–19 The laboratory values for serum haemoglobin, β2-microglobulin and IgM levels as well as platelet counts were consistent with previous retrospective and prospective studies.4,5,15 Consistently, the proportion of patients deemed to be of low, intermediate and high risk based on the International Prognostic Scoring System for Waldenström macroglobulinaemia (IPSSWM) was similar to the seminal report by Morel and colleagues.20 Finally, the distribution of the genomic alterations in MYD88 and CXCR4 are consistent with prior reports from our research group and others.11,16,21–23 Overall, we believe the characteristics of the patients reported in the present study are representative of the WM population, which would make our results generalizable.

We also assessed univariate and multivariate Cox proportional-hazard regression models to better understand the independent impact of attaining PR or better at six months on PFS. As data on prognostic factors in WM patients on ibrutinib therapy are limited, we constructed the statistical models by evaluating clinically relevant factors such as age, serum IgM levels and haemoglobin levels, among others. Attaining PR or better at six months was an independent favourable prognostic factor for PFS in both the learning and validation cohorts, associated with a 60–80% lower risk of progression and/or death than in patients who did not attain PR or better at six months.

We believe our findings of impact of attaining PR or better at six months are of clinical relevance and could help practitioners counselling patients and family members, and more importantly, serve as a surrogate for PFS in clinical trial design evaluating BTK inhibitors. The covalent, irreversible BTK inhibitors acalabrutinib, zanubrutinib and tirabrutinib are undergoing clinical development in WM, and have shown encouraging safety and efficacy data.24–26 The results of the randomized ASPEN study have been recently published.7 In this open-label study, 201 WM patients were randomized to receive zanubrutinib or ibrutinib. The main objective of the study was to show superiority in VGPR rates of zanubrutinib over ibrutinib. In this regard, the study did not meet its end-point, as zanubrutinib and ibrutinib were associated with VGPR rates of 28% and 19%, respectively, and were not statistically different. Rates of PR or better were comparable at 77% and 78%, and with a median follow-up of 18 months, the 18-month PFS rates were also similar at 85% and 84% respectively.

The presence of CXCR4 mutations emerged as an adverse prognostic factor for PFS in WM patients treated with ibrutinib monotherapy. We had previously reported an adverse impact of CXCR4 mutations in depth of response and PFS in WM patients treated with ibrutinib monotherapy.1,3,16,27 However, not all CXCR4 mutations appear to weigh equally on outcome, as there is mounting evidence that nonsense CXCR4 mutations, especially with a clonality higher than 25%, might have a more adverse impact on outcomes to ibrutinib than frameshift CXCR4 mutations.16,28 These findings support the development of therapeutic strategies targeting CXCR4, as one avenue for clinical research in patients with WM. Prospective clinical trials evaluating the combination of ibrutinib and the anti-CXCR4 monoclonal antibody ulocumab (NCT03225716) and ibrutinib and the CXCR4-targeting small molecule mavrobxofax (NCT04274738) are under way in WM patients who harbour a CXCR4 mutation. Akin to chronic lymphocytic leukaemia, BTK C481S mutations have shown to confer resistance to irreversible, covalent
BTK inhibitors in patients with WM.\textsuperscript{29,30} A new generation of reversible, non-covalent BTK inhibitors that do not interact with the C481 loci, such as vecabrutinib (NCT03037645), LOXO-305 (NCT03740529) and ARQ513 (NCT03162536), are also being evaluated in clinical trials.

Our study has limitations. First, the total sample size of 283 patients could be considered small, when compared to other malignancies. However, WM is a rare disease with an incidence of 1500 new cases per year in the USA. Taking this aspect into account, our cohort is the largest reporting clinical experience in WM patients on ibrutinib. Second, there were missing data on response in the validation and in the learning cohort. Yet, the rates of missing data were low, at 1% in the learning cohort and less than 10% in the validation cohort. Despite the difference in missing response data, the rates of response at six and 12 months were not statistically different between the learning and validation cohorts. Data on serum IgM levels (as well as median serum IgM levels) were consistent with and representative of the general population of patients with WM.

We should note that the purpose of our study was to identify a predictive marker of PFS in WM patients that could be later validated as a surrogate marker in clinical trials. Our purpose was not to identify a timepoint in which ibrutinib therapy should be modified, and therefore not attaining PR or better at six months on ibrutinib monotherapy should not be factored into the decision of discontinuing or changing ibrutinib therapy in patients with WM. We conclude that attaining PR or better at six months on ibrutinib monotherapy was associated with better PFS and should be validated as a surrogate end-point for PFS in clinical trials evaluating BTK inhibitors in WM patients.

Acknowledgements

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Author contributions

JJC designed the study and performed the analysis. JJC, JPA, JNG, SZ and KM collected patients’ data. MD, MLG, AK, CJ, XI, MM, NT, RK, LX, GY and ZRH performed molecular testing in patients’ samples. JJC, JA, SZ, CAF, RHA, MLP, SMA, MAG, PK and SPT took care of patients. JJC and PK drafted the initial manuscript. All the authors critically reviewed and approved the final manuscript.

Conflicts of interests

JJC received honoraria and/or research funding from Abbvie, Beigene, Janssen, Kymera, Millennium, Pharmacycics and TG Therapeutics. RHA received research funding from Janssen and Pharmacycics. MLP received honoraria and/or research funding from Celgene, Kite, Merck, Novartis and Pharmacycics. SMA received research funding from Affirmed, Al Therapeutics, Bristol Myers Squibb, Pfizer, Regeneron, Seattle Genetics and Trillium. MAG received honoraria and/or research funding from Abbvie, Aplylam, Amgen, Annexon, Appellis, Celgene, Ionis/Akcea, Janssen, Johnson & Johnson, Pharmacycics, Prothena, Teva and Spectrum. PK received research funding from Amgen, Celgene and Takeda Pharmaceuticals. SPT received research funding and/or consulting fees from Bristol Myers Squibb, Janssen and Pharmacycics. All the other authors have no conflict of interests to disclose.

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Partial response or better at 6 months is prognostic of superior progression-free survival in patients with Waldenström macroglobulinaemia treated with ibrutinib

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The B-cell receptor and Bruton tyrosine kinase (BTK) play a fundamental role in the proliferation of B-cell neoplasia such as Waldenström macroglobulinaemia (WM). In WM, ibrutinib, a first-generation BTK inhibitor (BTK-i) has obtained high rates of response and progression-free survival (PFS), both in untreated and rituximab-refractory disease. A Phase II trial of 63 patients with relapsed/refractory (R/R) WM demonstrated an overall response rate (ORR) of 91% and a 2-year PFS of 69.1%. Similar results were observed in treatment-naïve patients, with an ORR of 100% and 18-month PFS of 92%. Based on these data, ibrutinib has been approved for symptomatic WM.

Waldenström macroglobulinaemia is an indolent non-Hodgkin lymphoma that usually responds well to treatment with long survival. Due to its natural history, it is particularly difficult to find early predictors for survival outcomes in WM. In the era of chemo-immunotherapy, several studies have identified a correlation between depth of response and long-term survival. Attainment of at least a partial response (PR) or a very good PR (VGPR) was associated with better PFS in patients treated with rituximab-based regimens. However, with BTK-i this has not been investigated yet. In this scenario, the identification of factors that may predict poor responders would help clinicians to better tailor treatment and is worthy of investigation.

In this issue of the British Journal of Haematology, Castillo et al. investigated whether different depth of response to treatment at defined time-points could be a predictor of PFS in patients with WM treated with ibrutinib. A learning cohort and a validation cohort of 93 patients from clinical trials and 190 patients off trial respectively, were tested. Major response at 6 months, considered as PR or better (≥PR) was shown to correlate with higher rates of 3-year PFS in both cohorts [hazard ratio (HR) 0.38 and 0.18 for the learning and validation cohorts respectively].

According to the results of this study, attaining a ≥PR after 6 months of exposure to ibrutinib was a good predictor of treatment efficacy and may be considered as a surrogate of prolonged PFS.

Treatment with ibrutinib in WM is characterised by prolonged survival rates, with the median PFS >5 years for patients carrying a myeloid differentiation primary response gene 88 (MYD88) mutation and lacking C-X-C motif chemokine receptor 4 (CXCR4) mutations. Thus, evaluating the advantages of adding new drugs to ibrutinib or comparing new agents with ibrutinib in Phase III trials is difficult, as they would require very prolonged follow-up to show any differences. As Castillo et al. state in their study, attaining a ≥PR at 6 months could be considered as a surrogate end-point for PFS in clinical trials evaluating ibrutinib or other BTK-i in the WM setting, making the results available in a shorter observation time.

The design of the Castillo et al. study considered two depths of response: attainment of ≥PR and ≥VGPR, and two response assessment time-points of 6 and 12 months from treatment initiation. Interestingly, comparing patients with ≥VGPR at 6 months versus others, no significant differences in PFS were observed. Moreover, neither a ≥PR nor ≥VGPR assessed at 12 months correlated with a benefit in terms of 3-year PFS. These results are intriguing and difficult to interpret. When rituximab-based treatments are used, the achievement of at least a VGPR is desirable to aspire to a durable effect. However, based on the results of the present study in the treatment of WM with ibrutinib, the speed of the achievement of a good response, that is at least a PR, might affect more favourably the long-term outcome than the depth of the response, but this remains a speculation that requires more data.

When univariate and multivariate analyses have been fitted, aside for not attaining a 6-month ≥PR, only the presence of CXCR4 mutations were associated with worse PFS in both the learning and validation cohorts (HR 2.47 and 3.01 respectively). These data confirm the high correlation...
between CXCR4 recurrent mutations, which have been detected in 30–40% of WM, and poor response to treatments and highlights the need for improved treatments in this setting. Nevertheless, other patients' characteristics such as a low platelet count and an elevated serum immunoglobulin M level (>70 g/l) correlated with poorer PFS in the validation and learning cohorts respectively, also bone marrow involvement of ≥50% and high International Prognostic Scoring System for WM (IPSSWM) showed a trend for lower PFS rates. These elements are worth mentioning and could be reconsidered as potential ab initio predictors of BTK-i refractoriness in future studies.

This study is well designed and represents the first report investigating the correlation between the depth of response to ibrutinib and PFS in WM, and identifying an intermediate response assessment time-point as predictive for long-term treatment efficacy. The population under investigation is relatively large, considering the rarity of WM disease, and the presence of a validation cohort empowers the value of the results.

There are some limitations worth mentioning including the retrospective nature of the study and a certain rate of data missing. Moreover, patients' characteristics in the two cohorts are well balanced, although 30% of patients in the validation cohort were not assessed for CXCR4 mutational status. It is noticeable that a considerable higher 6-month VGPR rate was observed in the validation cohort (19% vs. 9%); this difference might be at least be partially explained by less stringent criteria adopted for response assessment in the off-trial setting, and should be taken into account in the overall evaluation of the study.

Some questions remain open and could be worthy of further investigation. Besides CXCR4 mutational status, can we find other ab initio patient or disease characteristics predictive for BTK-i resistance, that is a <PR at 6 months? Could 6-month attainment of a ≥PR be a factor robust enough to be adopted in the future as a criterion to modify therapy for patients with an intermediate unsatisfactory response to BTK-i? At the moment in clinical practice, due to the lack of prospective data in this poor responder subgroup and the paucity of well-defined alternative treatments, ibrutinib treatment should not be discontinued on the basis of an early time-point response assessment. Nevertheless, several new treatment options are under investigation for WM that could be useful in these poor-responder patients. Several trials are ongoing, combining ibrutinib and other agents such as the anti-CD38 monoclonal antibody daratumumab (NCT03679624), proteasome inhibitors ixazomib (NCT03506373) and bortezomib (NCT03620903), along with anti-CXCR4 agents (NCT03225716) (NCT04274738); or using different new generation and more potent BTK-i such as vecabrutinib (NCT03037645), LOXO-305 (NCT03740529), ARQ-351 (NCT03162536) and tirabrutinib (NCT02457559, NCT02457598). Idelalisib has been found to be effective in R/R WM and its activity in combination with obinutuzumab (NCT02962401) and the novel phosphatidylinositol-3 kinase (PI3K) inhibitor umbralisib (NCT03364231) are being studied. The B-cell lymphoma-2 (BCL-2) inhibitor venetoclax has shown promising results in a Phase I trial, preliminary data from a Phase II trial demonstrated efficacy even in patients previously exposed to BTK-i and a combination of ibrutinib plus venetoclax is under investigation (NCT04273139). In this extended panorama of new potential treatment strategies for WM, the utility of an early end-point during ibrutinib treatment such as the 6-month ≥PR may have an important role for the design of clinical trials and possibly in clinical practice in the future. Further investigations to corroborate these data are warranted.

References