First-line treatments for chronic lymphocytic leukemia: Analysis of 7 trials based on the restricted mean survival time

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Abstract. Objective: The purpose of this study was to assess the effectiveness of the newest first-line treatments for chronic lymphocytic leukemia (CLL), used alone or in combination, in comparison with standard treatments. Materials and methods: We selected 15 cohorts of patients published in 7 clinical trials. The restricted mean survival time (RMST) was used for analyzing survival curves, performing the comparisons and ranking the treatments based on their effectiveness. The endpoint was progression-free survival (PFS). Results: 15 patient cohorts receiving 11 different first-line treatments were studied. Overall, all of the newest treatments had a positive effect on PFS compared with the old standards. As compared with chlorambucil monotherapy, the improvement in PFS resulting from targeted therapies ranged from 5.4 to 7.3 months per patient. Excluding chlorambucil alone or combined with obinutuzumab, the remaining 11 targeted treatments showed nearly identical values of PFS. Numerically but not statistically, ibritinib plus venetoclax was associated with the longest PFS. Post-hoc pairwise comparisons were calculated to better interpret these results. Conclusion: Our results provided an updated overview of the efficacy of the newest first-line treatments for CLL. Our findings confirmed the good performance of RMST in this type of analyses.

What is known about this subject

- The standard first-line therapy in chronic lymphocytic leukemia (CLL) is historically represented by chlorambucil in combination with anti-CD20 monoclonal antibodies for older patients or those with coexisting conditions.
- Bendamustine with rituximab is indicated for cases aged > 65 without comorbidity.
- Chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab is indicated for younger patients (< 65) in good health.

What this study adds

- Our study assessed the effectiveness of the newest first-line treatments for CLL, used alone or in combination, in comparison with standard treatments.
- We evaluated 15 cohorts of patients published in 7 clinical trials. The restricted mean survival time (RMST) was used for analyzing progression-free survival.
- Our study was conducted as a narrative review, integrated with a ranking analysis based on the RMST. This simplified approach is an alternative to network meta-analysis when the geometry of the analysis implies a high total number of indirect and direct comparisons.

Introduction

In patients with chronic lymphocytic leukemia (CLL), the expected survival is generally quite long, even in the absence of any treatment [1]. However, a number of trials have shown that effective treatments can significantly prolong survival or progression-free survival (PFS). In particular, the standard first-line therapy in CLL is historically represented by chlorambucil in combination with anti-CD20 monoclonal antibodies for older patients or those with coexisting conditions. Bendamustine with rituximab is indicated for cases aged > 65 without comorbidity. Chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab is indicated for younger patients (< 65) in good health.
In the last few years, numerous new agents (the so-called targeted therapies) have been developed that can be used alone or in combination. These new agents include inhibitors of the B-cell receptor signaling pathway, two Bruton’s tyrosine kinase inhibitors (ibrutinib and acalabrutinib), and venetoclax, an inhibitor of B-cell lymphoma 2 (BCL2) protein, unique in its mechanism of action.

The restricted mean survival time (RMST) is increasingly being used for analyzing survival curves and can be considered a new standard for conducting comparative analyses [2, 3, 4, 5, 7, 8]. Unlike the hazard ratio (HR), which is the standard parameter of conventional meta-analyses and network meta-analyses (NMAs), the RMST is easier to understand, is more strictly related to the outcome expected in the individual patient, and, in general, is characterized by numerous other advantages [2, 3, 4, 5, 6, 7, 8, 9, 10]. For example, it does not require to be mandatorily evaluated within a comparison versus another treatment; it is expressed in months per patient like the median, but does not share the limit that the median has of being not computable under numerous circumstances. For all of these methodological considerations, we make reference, anyhow, to the papers mentioned above [2, 3, 4, 5, 6, 7, 8, 9, 10].

In the present analysis, we assessed the survival data published in 7 recent trials focused on first-line treatments for CLL [11, 12, 13, 14, 15, 16, 17]. From this clinical material, we generated our results in terms of comparative effectiveness on the basis of RMST.

Materials and methods

Patients

The following 15 cohorts were included in our analysis:

- Trial RESONATE-2 published by Burger et al. (2015) [11]: ibrutinib (cohort LL-C1A) vs. chlorambucil (cohort LL-C1B);
- Trial ELEVATE TN published by Sharman et al. (2020) [12]: acalabrutinib + obinutuzumab (cohort LL-C2A) vs. acalabrutinib (cohort LL-C2B) vs. chlorambucil + obinutuzumab (cohort LL-C2C);
- Trial iLLUMINATE published by Moreno et al. (2019) [13]: ibrutinib + obinutuzumab (cohort LL-C3A) vs. chlorambucil + obinutuzumab (LLC3B);
- Trial by Shanafelt et al. (2019) [14]: ibrutinib + rituximab (cohort LL-C4A) vs. chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab (cohort LL-C4B);
- Trial by Woyach et al. (2018) [15]: ibrutinib + rituximab (cohort LL-C5A) vs. ibrutinib (cohort LL-C5B) vs. bendamustine + rituximab (cohort LL-C5C);
- Trial by Jain et al. (2019) [16]: ibrutinib + venetoclax (cohort LL-C6A);
- Trial by Fischer et al. (2019) [17]: venetoclax + obinutuzumab (cohort LL-C7A) vs. chlorambucil + obinutuzumab (cohort LL-C7B).

All Kaplan-Meier curves examined in our analysis represent PFS.

Statistical analysis and estimation of RMST

The values of RMST (with 95% confidential intervals (CIs)) were determined from each of these 15 time-to-event curves using the survRM2 package according to the R platform [18]. In our procedure, we first retrieved the published graphs of PFS curves, and for each curve we analyzed the survival percentage-vs.-time data points with a digitizer (WebPlotDigitizer https://automeris.io/WebPlotDigitizer). Each survival curve was truncated (“restricted”) at the last time point in the follow-up (the so-called “milestone” or t*). Thereafter, to calculate RMST with its 95% CI, we employed the “survRM2” statistical package in the R platform [18] which is the method most widely used for this purpose. This package requires that the graphs of the Kaplan-Meier curve are converted into an individual patient data population (taking into account the size of the population and the number of events). We performed this conversion using a method of curve reconstruction originally described in 2000 [19].

To determine whether the difference between two RMSTs was statistically significant, we simply compared the confidence intervals for those groups. If those intervals overlap, the difference between groups is not statistically significant. If there is no over-
RMST in chronic lymphocytic leukemia

lap, the difference is significant [20]. While this visual method of assessing the overlap is easy to perform, it is known to be slightly too conservative; however, a conservative approach can be adequate in the context of multiple simultaneous comparisons. In assessing specific pairwise comparisons, the p-value was calculated for the difference between the two RMSTs and their 95% CIs, as previously described [21]; no adjustment was made for the presence of multiple simultaneous pairwise comparisons. The threshold for statistical significance was set at \( p = 0.05 \) (two tailed).

### Ranking of the treatments according to RMST values

In our analysis, a \( t^* \) of 24 months was employed for calculating the RMST for each of the 15 cohorts. The value of \( t^* \) was set at 24 months because this was the longest length of follow-up reached by all included trials. The 15 cohorts were ranked according to the respective values of RMST in descending order.

### Results

A total of 15 separate procedures of curve fitting analyses were performed. These fitted curves allowed for the estimation of the values of AUC (i.e., RMST) along with their respective 95% CI (Table 1). In our analysis, the rankings in effectiveness were those described in Figure 1.

As shown in Figure 1, the treatments ranked at the first 8 positions had very similar values of RMST. The difference between

<table>
<thead>
<tr>
<th>Data set</th>
<th>Cohort</th>
<th>( t^* ) (mos)</th>
<th>Length of follow-up (mos)</th>
<th>No. of patients</th>
<th>Treatment</th>
<th>RMST (mos) with 95% confidence interval</th>
<th>Gain (mos)</th>
<th>Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) ibrutinib (cohort LLC1A) vs. chlorambucil (cohort LLC1B)(^{11})</td>
<td>LLC1A 24</td>
<td>24</td>
<td>136</td>
<td>Ibrutinib</td>
<td>22.5 (95% CI: 21.4 – 23.7)</td>
<td>6.3</td>
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<td></td>
<td>LLC1B 24</td>
<td>24</td>
<td>133</td>
<td>Chlorambucil</td>
<td>16.2 (95% CI: 14.6 – 17.8)</td>
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<td>2) acalabrutinib + obinutuzumab (cohort LLC2A) vs.</td>
<td>LLC2A 24</td>
<td>39</td>
<td>179</td>
<td>Acalabrutinib +</td>
<td>23.0 (95% CI: 22.4 – 23.6)</td>
<td>4.9 (max – min)</td>
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<td>LLC2B 24</td>
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<td>LLC2C 39</td>
<td>177</td>
<td></td>
<td>Chlorambucil +</td>
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<td>3) ibrutinib + obinutuzumab (cohort LLC3A) vs.</td>
<td>LLC3A 24</td>
<td>35</td>
<td>113</td>
<td>Ibrutinib +</td>
<td>21.6 (95% CI: 20.5 – 22.6)</td>
<td>3.2</td>
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<td>chlorambucil +</td>
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<td></td>
<td>LLC3B 35</td>
<td>116</td>
<td></td>
<td>Chlorambucil +</td>
<td>18.4 (95% CI: 17.3 – 19.4)</td>
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<td>4) ibrutinib + rituximab (cohort LLC4A) vs.</td>
<td>LLC4A 24</td>
<td>51</td>
<td>354</td>
<td>Ibrutinib +</td>
<td>23.4 (95% CI: 23.1 – 23.7)</td>
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<td>LLC4B 47</td>
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<td>Fludarabine,</td>
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<td>5) ibrutinib + rituximab (cohort LLC5A) vs.</td>
<td>LLC5A 24</td>
<td>52</td>
<td>170</td>
<td>Ibrutinib +</td>
<td>22.4 (95% CI: 21.6 – 23.2)</td>
<td>0.8 (max – min)</td>
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<td>LLC5B 52</td>
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<td>Ibrutinib</td>
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<td>Bendamustine +</td>
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<td>6) ibrutinib + venetoclax (cohort LLC6A)(^{16})</td>
<td>LLC6A 24</td>
<td>27</td>
<td>80</td>
<td>Ibrutinib +</td>
<td>23.5 (95% CI: 22.7 – 24.2)</td>
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<td>7) venetoclax + obinutuzumab (cohort LLC7A) vs.</td>
<td>LLC7A 24</td>
<td>35</td>
<td>216</td>
<td>Venetoclax +</td>
<td>22.2 (95% CI: 21.4 – 23.2)</td>
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<td>LLC7B 36</td>
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RMST = restricted mean survival time; mos = months; \( t^* \) = milestone; NA = not applicable.
ibrutinib + venetoclax (that ranked 1st with a RMST of 23.5 months) and ibrutinib + obinutuzumab (that ranked 10th with a RMST of 21.6 months) was less than 2 months. On the other hand, chlorambucil used alone was the treatment with the worst outcome (RMST = 16.2 months; 15th rank).

In comparison with chlorambucil monotherapy, the best 8 treatments (characterized by an RMST > 22 months) determined a gain in PFS of nearly 6 months per patient. Actually, this finding is clinically relevant particularly if one takes into account that the milestone of our analysis was set at only 24 months.

Numerous pairwise differences in RMST reached statistical significance (Figure 2) in line with the results of individual clinical trials. In our view, however, the best key for interpreting these results is more clinical than statistical and, in this context, the main finding is that old treatments based on chlorambucil alone or in combination are inferior to the treatments based on more recent agents (alone or in combination) that no longer include chlorambucil.

Anyhow, the treatment with venetoclax + ibrutinib showed the best value of PFS (RMST, 23.5 months), numerically but not statistically. Interestingly, in the direct comparison between ibrutinib vs. chlorambucil the gain in PFS was 6.3 months, which is a remarkable result. The other direct comparisons between a new agent vs. chlorambucil (alone or in combination) ranged from 1.2 to 4.9 months (Table 1).
Discussion

In this paper, we report the results of a survival analysis on new targeted therapies in chronic lymphocytic leukemia based on the estimation of RMST (with PFS as primary endpoint).

Our analysis, focused on previously untreated CLL patients, confirms that the addition of anti-CD20 monoclonal antibody to chlorambucil improves outcomes compared to chlorambucil alone. More importantly, our findings suggest very promising results in terms of improvement in PFS with the new targeted therapies. In particular, the inhibitor of B-cell lymphoma 2 protein (venetoclax) and inhibitors of Bruton’s tyrosine kinase (ibrutinib and acalabrutinib), used alone or in combination, can provide a clinically relevant advantage in PFS particularly in older patients or those with coexisting conditions. Last, from a methodological point of view, the RMST avoids the biases related to the different lengths of follow-up of included trials as other studies have already demonstrated [1, 2, 3, 4, 5, 6, 7, 8, 9].

The method adopted in this paper to review the available evidence deserves some comment. Our study was conducted as a narrative review, integrated with a ranking analysis based on the RMST. This simplified approach is an alternative to network meta-analysis [21] when the geometry of the analysis implies a high total number of indirect and direct comparisons. In a network meta-analysis comparing N treatments, a total of N(N-1)/2 comparisons need to be carried out irrespective of whether they are direct or indirect comparisons. For example, when N is 10 (as in the present case), 45 comparisons are needed. Examples are available from the literature in which a network meta-analysis has generated hundreds of pairwise comparisons [22]. Recent research has been conducted to simplify the presentation of the results of a network meta-analysis when the number of pairwise comparisons is high [23, 24]. The analytical approach experience presented herein belongs to this line of methodological research.

In conclusion, our experience has confirmed the excellent performance of the RMST in generating results that possess a high informative value. The simplicity of the RMST approach makes these analyses quite similar to a narrative overview focused on the comparative effectiveness of the available treatments.

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Conflict of interest

None.

References

Bartoli, Ferracane, Trippoli, and Messori

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