Appropriate use of bendamustine in first-line therapy of chronic lymphocytic leukemia. Recommendations from SIE, SIES, GITMO Group

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A B S T R A C T

By using the GRADE system we produced the following recommendations for the use of bendamustine in the first-line treatment of CLL: (1) bendamustine with rituximab is recommended in elderly fit patients potentially eligible to FCR; (2) Bendamustine alone is recommended in patients who are candidate to chlorambucil alone; (3) Rituximab–bendamustine is recommended in patients not eligible to FCR, but suitable to receive rituximab. Consensus-based recommendations addressed evidence-orphan issues concerning the use of bendamustine in genetically-defined high-risk patients and the appropriate dose of bendamustine as single agent or in association with rituximab.

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1. Introduction

Considerable progress has been made in the treatment of chronic lymphocytic leukemia (CLL) over the last decade [1]. The alkylating agent chlorambucil has been the mainstay treatment for B-CLL for over 50 years; however fludarabine was shown to significantly improve PFS in a Cochrane meta-analysis of randomized trials [2] and to prolong survival in a long-term observational study of a randomized trial [3], a finding not confirmed in another trial [4]. Further improvement was achieved by the combination fludarabine and cyclophosphamide [4] which attained a 20-month increase in progression-free survival (PFS) over fludarabine, that did not translate into survival advantage.

The adjunct of Rituximab to chemotherapy improved overall survival in patients reported by SEER [5]. Importantly, the adjunct of Rituximab to fludarabine achieved a significant reduction in mortality (HR = 0.58) [5], and this advantage was maintained irrespective of age in a retrospective analysis of 4 successive frontline CALGB trials [6].

The combination of rituximab fludarabine and cyclophosphamide (FCR) was shown to be superior to FC for all clinical endpoints including overall survival in young and/or fit patients and this chemioimmunotherapy regimen became the standard first-line therapy for CLL without comorbidities [1]. However, this frequent lymphoid clonal disease occurs at a median age over 70 years [7,8], and coexisting medical conditions make treatment tolerability a major issue in a substantial fraction of elderly patients.

in [9,10]. In these patients the efficacy of chlorambucil is significantly improved by the adjunct of rituximab, obinutuzumab and ofatumumab [11–13].

Bendamustine hydrochloride is a bifunctional alkylating agent incorporating a central ring system that is similar to that in purine analogs. Unlike alkylators, bendamustine primarily targets base excision repair and activates DNA-damage stress responses and apoptosis. Therefore, it is only partially cross-resistant with other alkylators. Due to its favorable toxicity profile, it has been tested alone and in combination with rituximab in refractory/relapsed indolent lymphoma, including CLL and, more recently, in treatment naïve patients [14–18].

The Guideline Committee of the Italian Society of Hematology reckoned that an unmet need for CLL was reached and deserved a prescriptive position for the community practice for the use of bendamustine in the first-line setting.

2. Methods

2.1. Guidelines development process

The Advisory Council (AC), composed of three members with expertise in clinical epidemiology, hematology and critical appraisal, oversaw the process. An Expert Panel (EP) was selected according to the conceptual framework elements of the NIH Consensus Development Program [19]. During a first meeting, the EP decided which clinical issues needed recommendations, and the AC checked which clinical queries might be addressed by a critical appraisal of evidence.

2.2. Producing and grading evidence-based recommendations

The EP chose the critical outcomes for each clinical query deserving evidence-based recommendations. Literature search was performed in February 2013 and limited to English-language publications edited after 2005. The search included proceedings 2011 through 2013 of the American Society of Hematology, the European Hematology Association and the International Conference on Malignant Lymphoma meetings. Even though the recommendations were issued on the basis of systematic review of literature published up to September 2013, analysis of data published since that date up to January 2014 was performed before publication of the present paper. According to GRADE methodology [20], the AC prepared “evidence tables” and “quality of evidence tables” (available by the corresponding author on request) for each critical appraisal. The EP received the critical appraisals and was asked to draft recommendations based on the benefit to risk profile of each compared intervention. Definite agreement of the recommendations and of their strength (weak or strong) was made through subsequent face-to-face meetings.

2.3. Producing consensus-based recommendations

The consensus methodology was applied for all the issues worth to be discussed but not addressable by a critical appraisal of evidence. During three consecutive consensus conferences, the issues were analyzed and discussed according to the nominal group technique [21].

3. Results

The following questions were raised by the panel as clinically relevant (Table 1):

1. Is bendamustine alone appropriate in patients candidate to first-line FCR? (Consensus based)

Preliminary considerations: Phase II studies [22] and randomized trials [23] reported that FCR first-line treatment in CLL patients induced complete response (CR) rates ranging from 44% to 70% and a median PFS ranging from 52 to 80 months (Table 2). Grade 3-4 neutopenia usually occurred in more than half of the patients and major infections in 2.6% of the patients.

Table 1: Key questions and recommendations for the use of bendamustine in previously untreated CLL.

<table>
<thead>
<tr>
<th>Questions</th>
<th>GRADE (critical outcomes)</th>
<th>Recommendation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Is bendamustine alone appropriate in patients candidate to first-line FCR?</td>
<td>No</td>
<td>In patients who are eligible to FCR, bendamustine alone is not recommended</td>
</tr>
<tr>
<td>2 Is bendamustine alone appropriate in patients potentially candidate to FCR but with contraindications or intolerance to Rituximab?</td>
<td>No</td>
<td>In patients who are candidates to FCR but with contraindications or intolerance to rituximab, bendamustine alone is a reasonable treatment</td>
</tr>
<tr>
<td>3 Should R-bendamustine be preferred to FCR in patients candidate to first-line FCR?</td>
<td>Yes (PFS, severe AE)</td>
<td>Based on its efficacy/safety profile R-bendamustine might be considered as an alternative to FCR in young and fit patients (level of evidence: low; strength of recommendation: do, weak) and should be recommended in the elderly (≥65) fit patient (level of evidence: low; strength of recommendation: do, strong)</td>
</tr>
<tr>
<td>4 Should bendamustine alone be preferred to chlorambucil in patients candidate to first-line chlorambucil alone?</td>
<td>Yes (PFS, severe AE)</td>
<td>Bendamustine plus rituximab is beneficial in CLL patients non eligible to FCR, but suitable to receive rituximab. (level of evidence: very low; strength of recommendation: strong)</td>
</tr>
<tr>
<td>5 Is R-bendamustine appropriate in patients not eligible to FCR?</td>
<td>Yes (PFS, severe AE)</td>
<td>Bendamustine with or without rituximab or bendamustine-containing regimens might not be useful options in patients with del 17p and or p53 mutation</td>
</tr>
<tr>
<td>6 Are bendamustine-containing regimens appropriate in patients with 17p- and/or p53 mutations?</td>
<td>No</td>
<td>Bendamustine and rituximab is recommended in patients with 11q- or IGHV unmutated who are not candidate to FCR</td>
</tr>
<tr>
<td>7 Are bendamustine-containing regimens appropriate in patients with 11q- or IGHV unmutated?</td>
<td>No</td>
<td>The recommended dose of bendamustine alone in untreated CLL patients less than 75 years old is 100 mg/sqm. The recommended dose of bendamustine in association with rituximab is 90 mg/sqm. The dose of bendamustine may be reduced in patients older than 75 years according to fitness and comorbidities</td>
</tr>
<tr>
<td>8 Which are the appropriate schedule and duration of bendamustine-based regimens</td>
<td>No</td>
<td>Antibiotic prophylaxis and the prophylactic use of IVIG can be considered on an individual basis. Occult HBV infection and HBV carriers should be given antiviral prophylaxis if bendamustine is associated with Rituximab. Bendamustine, alone or with rituximab, may be initiated in patients with ABHA or ITP unresponsive to steroids and therapy in patients with moderately impaired renal function, bendamustine alone or associated with rituximab can be administered. Since the use of bendamustine in patients with impaired renal function increases the risk of cytopenias, in this circumstance the dose should be reduced</td>
</tr>
<tr>
<td>9 How should infections and autoimmune cytopenias be managed and prevented during bendamustine therapy?</td>
<td>No</td>
<td>In patients with relatively impaired renal function, first-line therapy with bendamustine is associated with an increased risk of infections and autoimmune cytopenias</td>
</tr>
<tr>
<td>10 Should bendamustine therapy be modified in B-CLL patients with renal or hepatic comorbidities?</td>
<td>No</td>
<td>In patients with relatively impaired renal function, first-line therapy with bendamustine is associated with an increased risk of infections and autoimmune cytopenias</td>
</tr>
</tbody>
</table>

* See text for details.

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Table 2  
Efficacy and safety of bendamustine plus rituximab, FCR, chlorambucil and anti CD20 monoclonal antibodies in previously untreated CLL

<table>
<thead>
<tr>
<th>Regimen and reference</th>
<th>N. pts</th>
<th>Specific inclusion criteria</th>
<th>Age (median)</th>
<th>CR rate</th>
<th>PFS*</th>
<th>% Patients with grade 3–4 neutropenia</th>
<th>% Patients with grade 3–4 infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-bendamustine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fisher et al. [18]</td>
<td>117</td>
<td>WHO PS 0–2; CrCl &gt; 30 ml/min</td>
<td>64</td>
<td>23.1</td>
<td>33.8</td>
<td>19.7</td>
<td>7.7</td>
</tr>
<tr>
<td>Eichhorst et al. [27]</td>
<td>279</td>
<td>CIRS ≤ 6; CrCl &gt; 70 ml/min; No del(17p)</td>
<td>62</td>
<td>38.1</td>
<td>78.2**</td>
<td>56.8</td>
<td>25.4</td>
</tr>
<tr>
<td>FCR</td>
<td></td>
<td></td>
<td>58</td>
<td>70%</td>
<td>80</td>
<td>52**</td>
<td>2.6**</td>
</tr>
<tr>
<td>Eichhorst et al. [27]</td>
<td>284</td>
<td>CLL requiring therapy; Cr &lt; 2 mg/dL; Bil &lt; 2 mg/dL</td>
<td>62</td>
<td>47.4%</td>
<td>85.0**</td>
<td>81.7</td>
<td>39.0</td>
</tr>
<tr>
<td>Hallek et al. [23]</td>
<td>408</td>
<td>ECOG PS 0–1; CIRS ≤ 6; CrCl ≥ 70 ml/min</td>
<td>61</td>
<td>44%</td>
<td>51.8</td>
<td>34</td>
<td>25</td>
</tr>
<tr>
<td>Chlorambucil and anti CD20</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foà et al. [11]</td>
<td>85</td>
<td>&gt;65 or ineligible to fludarabine; CrCl ≥ 50 ml/min</td>
<td>70</td>
<td>16.5%</td>
<td>34.7</td>
<td>19.6%</td>
<td>1%</td>
</tr>
<tr>
<td>Hillmen et al. [36]</td>
<td>100</td>
<td>ineligible to fludarabine</td>
<td>70</td>
<td>10%</td>
<td>23.5</td>
<td>41%</td>
<td>7%</td>
</tr>
<tr>
<td>Goede et al. [12]</td>
<td>330</td>
<td>CIRS &gt; 6, CrCl 30–69 ml/min</td>
<td>73</td>
<td>7%</td>
<td>15.2</td>
<td>28%</td>
<td>6%</td>
</tr>
<tr>
<td>Goede et al. [12]</td>
<td>333</td>
<td>CIRS &gt; 6, CrCl 30–69 ml/min</td>
<td>74</td>
<td>20.7%</td>
<td>26.7</td>
<td>33%</td>
<td>6%</td>
</tr>
<tr>
<td>Hallek et al. [13]</td>
<td>447</td>
<td>ineligible to fludarabine</td>
<td>69</td>
<td>12%</td>
<td>22.4</td>
<td>26%</td>
<td>15%</td>
</tr>
</tbody>
</table>

*Median (months) unless otherwise specified; ** at 2 years; **** rituximab; **** obinutuzumab; ***** Ofatumumab; time to progression; % of cycles; Abbreviations: Cr: serum creatinine; CrCl: Creatinine clearance; DAT: direct antiglobulin test.

Table 3  
Efficacy and safety of bendamustine, chlorambucil and fludarabine plus cyclophosphamide in previously untreated CLL

<table>
<thead>
<tr>
<th>Regimen and reference</th>
<th>N. pts</th>
<th>Specific inclusion criteria</th>
<th>Age (median)</th>
<th>CR rate</th>
<th>PFS*</th>
<th>% Patients with grade 3–4 neutropenia</th>
<th>% Patients with grade 3–4 infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bendamustine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knauf et al. [16]</td>
<td>162</td>
<td>Age ≤ 75 yrs; WHO PS 0–2; CrCl ≥ 30 ml/min</td>
<td>63</td>
<td>31%</td>
<td>21.6</td>
<td>23</td>
<td>8</td>
</tr>
<tr>
<td>Chlorambucil</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knauf et al. [16]</td>
<td>157</td>
<td>Age ≤ 75 yrs; WHO PS 0–2; CrCl ≥ 30 ml/min</td>
<td>63.6</td>
<td>2%</td>
<td>8.3</td>
<td>10.6</td>
<td>3</td>
</tr>
<tr>
<td>Cavoovsky et al. [4]</td>
<td>387</td>
<td>All ages; Stage A-progressive, B, C</td>
<td>65</td>
<td>7%</td>
<td>20</td>
<td>28</td>
<td>25 (febrile episodes)</td>
</tr>
<tr>
<td>Goede et al. [12]</td>
<td>118</td>
<td>CIRS &gt; 6; CrCl 30–69 ml/min</td>
<td>72</td>
<td>0%</td>
<td>11.1 mo</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>FCR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eichhorst et al. [25]</td>
<td>180</td>
<td>Age 18–65; ECOG 0–2</td>
<td>58</td>
<td>23.8%</td>
<td>48 mo</td>
<td>55.5 (leukopenia)</td>
<td>69</td>
</tr>
<tr>
<td>Finn et al. [26]</td>
<td>141</td>
<td>Age ≥ 18 yrs; PS 0–2; CrCl ≥ 40 ml/min</td>
<td>61</td>
<td>23.4%</td>
<td>31.6</td>
<td>25**</td>
<td></td>
</tr>
<tr>
<td>Cavoovsky et al. [4]</td>
<td>196</td>
<td>All ages</td>
<td>65</td>
<td>38%</td>
<td>43</td>
<td>56</td>
<td>35 (febrile episodes)</td>
</tr>
<tr>
<td>Hallek et al. [23]</td>
<td>409</td>
<td>Age 30–81 yrs; ECOG PS 0–1; CIRS ≤ 6; CrCl ≥ 70 ml/min</td>
<td>61</td>
<td>22%</td>
<td>32.8</td>
<td>21</td>
<td>21</td>
</tr>
</tbody>
</table>

*Median (months) unless otherwise specified; **5% febrile neutropenia, 8% infection with neutropenia, 9% infection without neutropenia, 3% pneumonitis.

Courses and in up to 39% of the patients. Reported treatment-related death in the CLL8 trial was 2%.

Bendamustine alone was never tested in a head-to-head study vs FCR, however, the Panel deemed that first-line studies of bendamustine alone might be the evidence base for a consensus-based recommendation.

The efficacy of bendamustine alone (Table 3) was tested in a head to head comparison with chlorambucil in a randomized study of 319 patients [15,16] with median age 63 years, creatinine clearance ≥ 30 ml/min and advanced stage disease in 28% of the cases. Bendamustine (100 mg/m² days 1 and 2, without rituximab) attained a 31% CR rate the first-line setting and prolonged PFS (median 21.6 months) as compared with chlorambucil (median 8.3 months). Grade 3/4 neutropenia occurred in 23% of the patients and severe infection in 8% of the patients treated by bendamustine.

The Panel reckoned that the lower median age and better fitness of patients assigned to FCR might partially impair the indirect comparison with bendamustine, however, the inferior PFS reported by bendamustine was more relevant than the higher toxicity reported by FCR, therefore the Panel deemed that Bendamustine alone was not a favorable alternative to FCR.

Recommendations:

In patients who are eligible to FCR first-line therapy, bendamustine alone is not recommended.

2. Is bendamustine alone appropriate as first-line therapy in patients potentially candidate to FCR but with contraindications or intolerant to Rituximab? (Consensus-based)

Preliminary considerations:

Despite desensitization protocols, severe infusion reactions to Rituximab may occur, preventing its use in a minority of patients [24]. Furthermore rituximab cannot be administered safely in rare cases with hypersensitivity and anaphylactic reaction to humanized monoclonal antibodies or with coexisting medical conditions. The alternative treatments for the above patients are FC and bendamustine. Salient efficacy and tolerability data in trials using bendamustine and FC are shown in Table 3. No study directly compared bendamustine with FC, therefore the Panel indirectly compared bendamustine and FC single arms from randomized trials of bendamustine against chlorambucil [16,17] or FC against other regimens [4,23,25,26], as reported in Table 3. Bendamustine
was administered to patients with decreased renal function [16]: the trials testing FC enrolled different proportions of elderly patients, up to 30% in the UK trial [4] and different proportions of patients with renal failure, since creatinine clearance was allowed to be a low as 40 ml/min in the US Intergroup study [26], while it was over 70 ml/min in the other 3 studies. Nevertheless, the above studies reported similar 31% and 22–38% CR rates with bendamustine and FC, respectively, and a longer PFS (31.6–48 months) with FC than with bendamustine (21.6 months). Despite lower median age and better renal function in some of the FC trials compared to the bendamustine trial, infections were significantly more frequent in patients treated with FC (8–21%) than with bendamustine (8%). Also, febrile episodes and grade 3–4 neutropenia occurred at a higher rate with FC. Transient autoimmune hemolytic anemia occurred in 1.5% of the patients treated by bendamustine [16] and in 5% and 11% of the patients treated by fludarabine alone or FC in the UK trial [4]. Considering this indirect comparison of efficacy and safety, the Panel deemed that bendamustine could be considered a treatment option in this setting.

Recommendations:

In patients who are candidates to FCR but with contraindications or intolerance to rituximab, bendamustine alone is a reasonable treatment.


Preliminary considerations:

The Panel initially discussed this issue based uniquely on indirect comparisons between data from a phase II prospective study [18] and those from the randomized GCLLSG trial [23], bearing in mind that in the former study patients with higher median age (64 vs 61 years) were included and that creatinine levels <70 ml/min were not an exclusion criterion (Table 2). CR rate in 117 previously untreated CLL using bendamustine and rituximab was 23.1%, with 33.8 months median PFS after a median observation time of 27 months. Severe hematological toxicity was observed in 52.1% of the patients, neutropenia in 19.7% and severe infections in 7.7% of the patients, with 3.4% treatment-related mortality.

The GCLLSG CLL10 phase III trial (Eichhorst 2013 ASH) [27] recently reported the outcome of 564 patients without severe comorbidities or del(17p) and with a normal creatinine clearance randomly assigned to FCR or R-bendamustine (90 mg/m² days 1 and 2) (Table 3). Thirty percent of those assigned to FCR failed to receive the full 6 cycle program vs 20% of those assigned to R-bendamustine: this was in part due to the higher rate of severe neutropenia and severe infections, especially in the elderly (i.e. 65 years or more). Severe AE were more frequent in the FCR arm (91% vs 78%, p < 0.001) as were neutropenia (81.7% vs 56.8%, p < 0.001) and infections, especially in the elderly (FCR: 47.4% vs BR: 26.5%, p = 0.002). Treatment-related death were 3.5% vs 2.1% in the FCR arm and in the BR arm, respectively. At intention-to-treat analysis of efficacy, however, the balance between the two treatments was reversed: overall response rate was 98% in both arms, but CR rate was significantly higher in patients treated with FCR (47% vs 38%, p = 0.031), as was the case with two-year PFS (85% vs 78%, p = 0.041) and EFS (83% vs 76%, p = 0.037). These efficacy measures favoring FCR were enhanced in patients younger than 65 years (median PFS for R-bendamustine 38.5 months vs not reached for FCR; p = 0.016), whereas the advantage disappeared in the elderly subgroup where the median PFS at 2 years in the R-bendamustine arm was not reached as compared with 45.6 months in the FCR arm; p = 0.757.

In an unselected population prospectively enrolled in a German registry and assigned to one of the two above treatments according to the physician and patient judgment, those patients receiving R-bendamustine achieved similar CR rates and survival as FCR-treated ones despite their worse clinical conditions [28].

The Panel was aware of the limitations imposed by interim analysis and subgroup analysis of the GCLLSG trial, however, safety was judged to be much more relevant than efficacy in the setting of elderly patients, therefore the large safety advantage of R-bendamustine in this setting was judged to overcome the possible efficacy advantage of FCR. On converse, data from longer follow-up and confirmatory studies are awaited before a definite evidence-based recommendation can be made for young patients, since long-term PFS was judged to be the master outcome in this setting.

Recommendations:

Available data do not prompt a change in the current standard of care, i.e. FCR in the first-line therapy for fit, younger patients. Based on its efficacy/safety profile R-bendamustine might be considered as an alternative to FCR in young and fit patients (level of evidence: low; strength of recommendation: do, weak) and should be a recommended option in the elderly (>65) fit patient (level of evidence: low; strength of recommendation: do, strong)

4. Should bendamustine alone be preferred to chlorambucil in patients candidate to first-line chlorambucil alone? (Evidence-based. Critical outcomes: PFS, severe AE)

Comorbidity is the major driver of therapeutic decisions in a substantial fraction of patients with hematologic malignancies, including lymphoid malignancies [29] and single agent chlorambucil [30]. It is an option in unfit CLL patients unsuitable to receive rituximab. Direct randomized comparisons between bendamustine (100 mg/m² days 1 and 2 every 4 weeks) and chlorambucil (0.8 mg/kg days 1 and 15 every 4 weeks; a dosage corresponding to the 10 mg/m² day 1–7 used in the UK trial [4]), highlighted a better efficacy profile of the former, including a significant PFS prolongation by more than 12 months, with increased though manageable toxicity [16,17]. Time to next treatment, was over 20 months longer in the bendamustine arm. The incidence of grade 3–4 neutropenia (23% vs 11%), infections (8% vs 3%), skin reactions and the need for antiemics (36% vs 4%) was higher in bendamustine treated patients than in the chlorambucil arm. Even though more patients in the bendamustine arm (11% vs 3.2%) stopped treatment due to severe AE, no significant effect on the overall quality of life was reported [16]. In the long-term follow-up no statistically significant OS prolongation was observed in bendamustine-treated patients [17]. In a multiple-treatment meta-analysis bendamustine and R-fludarabine-based regimens [31] were found to achieve a similar PFS advantage (HR = 0.23) over chlorambucil.

The Panel judged that, among critical outcomes, safety has a priority over PFS in the setting of elderly patients. However, the significant PFS advantage of bendamustine vs chlorambucil, consistent with the very long time to next treatment, was considered to provide also an amelioration of patient quality of life. Therefore, the Panel judged that the benefit deriving from more prolonged disease control attained by bendamustine was superior to the disadvantage of in terms of toxicity.

Recommendations:

In patients who are conventionally candidate to chlorambucil alone, bendamustine alone is recommended (level of evidence: low; strength of recommendation: do, strong).

5. Is R-bendamustine appropriate in patients not eligible to FCR? (Evidence-based. Critical outcomes: PFS, severe AE)

Patients with comorbidities, poor performance status or with impaired renal function were excluded from fludarabine-based clinical trials or featured poor tolerance to FCR [22,23], whereas
they made up to 40% of those treated by bendamustine with or without rituximab [18,32]. A retrospective analysis of two electronic medical databases in the US analysed bendamustine safety in 379 B-CLL patients, half of which with a creatinine clearance lower than 60 ml/min, and found no increased toxicity for those without a severe renal impairment, i.e. creatinine clearance over 40 ml/min [33]. Subgroup analysis of the phase II R-Bendamustine trial, reported a higher rate of hematologic and non-hematologic toxicity in patients with impaired renal function, i.e. creatinine clearance between 40 and 70 ml/min, however the observed differences did not reach statistical significance, with the exception of anemia [18].

Fludarabine exposes patients to the risk of developing autoimmune hemolytic anemia (AIHA), the absolute risk being up to 8% and relative risk higher than 20% [34]. Contraindication to fludarabine was extended from those patients who developed AIHA after fludarabine exposure to fit patients with ongoing autoimmune hemolysis before exposure to fludarabine-based therapies [23]. To the contrary, some patients with active hemolysis were enrolled into trials using bendamustine with rituximab [18] and only occasional cases of autoimmune hemolytic anemia were reported using bendamustine as single agent [16].

R-bendamustine might compete with R-chlorambucil in the above reported setting and preliminary data from an ongoing randomized trial are available. The trial enrolled 85 untreated B-CLL patients not candidate to fludarabine-based treatments as a result of age or comorbidities and assigned them to either R-bendamustine (90 mg/m² up to 6 cycles) or R-Chlorambucil (10 mg/m² daily 1–7, up to 12 cycles): CR rate were 30% vs 13%, respectively, despite similar overall response rates and severe AE rates [35]. Since the above randomized trial included only a small subgroup of untreated patients and no PFS data have yet been reported, the Panel judged direct evidence insufficient to support an evidence-based recommendation.

Data from two trials testing chlorambucil and rituximab in the elderly patients unfit for fludarabine-based treatment (Table 2) showed a 10–16% CR rate with 24–34.7 months PFS [11,36]. The adjunct of rituximab or obinutuzumab to chlorambucil in patients with comorbidities precluding fludarabine-based treatment attained a 7% and 22% CR rate, respectively, with a 16.3 and 26.7 months median PFS. Notably, obinutuzumab in association with chlorambucil prolonged survival as compared with chlorambucil alone [12]. The adjunct of ofatumumab to chlorambucil attained a 12% CR rate with a 22.4 months median PFS (Table 3), these outcome measures being significantly better that those attained by chlorambucil alone [13].

Recommendations:
Bendamustine plus rituximab is beneficial in CLL patients non eligible to FCR, but suitable to receive rituximab (level of evidence: very low; strength of recommendation: do, strong) The panel also recognized that there are at the present time insufficient data to make a recommendation in favour either of bendamustine and rituximab or chlorambucil plus anti CD20 monoclonal antibodies in patients non eligible to FCR.

6. Are bendamustine-containing regimens an appropriate first-line therapy in high-risk patients (del 17p and/or p53 mutations)? (Consensus-based)

Preliminary considerations:
In B-CLL patients del 17p and/or p53 mutations are strongly associated with adverse outcomes and resistance to chemotherapy-based treatment: less than 10% achieve CR and PFS is shorter than 12 months [23]. Better results were obtained in this subset of high risk patients with Alemtuzumab plus high dose methylprednisone, which achieved a 65% CR rate, a PFS of 18.3 months and an OS of 38.9 months in previously untreated patients [37]. Grade 3–4 infections occurred in 35% of previously untreated patients; grade 3–4 hematologic toxicity and glucocorticoid-associated toxicity occurred in 67%, and 23% of patients respectively in the overall cohort, which included 56% previously treated patients.

Bendamustine might potentially be efficacious in these setting since its cytotoxic effect is related to both p53-dependent and p53-independent mechanisms [38]. However, when combined with rituximab, response in del(17p) patients was unsatisfactory: none of 8 del(17p) patients treated with bendamustine plus Rituximab achieved a CR, and only 3 achieved PR, with a 7.9 months median PFS [18]. The GCLLSG trial comparing R-bendamustine with FCR excluded from enrollment patients with del17p) therefore no comparative results from this subgroup can be expected from such a study [27]. The synergic in-vitro activity of bendamustine and cytarabine onto primary tumor cells from patients with del(17p) or p53 mutated [39] prompted testing rituximab–bendamustine–cytarabine regimens in the second-line setting: favorable response and PFS data were reported also in unfavorable cytogenetic risk patients, but multivariate analysis on a large set of patients showed that this could not be applied to patients with del(17p) [40,41]. Ongoing trials are testing this regimens in the first-line setting.

Recommendations:
Bendamustine with or without rituximab or bendamustine containing regimens might not be useful options in patients with del 17p and or p53 mutation.

7. Is bendamustine and rituximab appropriate in patients with 11q- or with IGHV unmutated? (Consensus-based)

Preliminary considerations:
No study was devoted to specific cytogenetic subsets of CLL, therefore, evidence was based on indirect comparisons between patients’ subgroups within clinical trials. Data on bendamustine were reported in the bendamustine plus rituximab trial [18]. Twenty patients with del(11q) were reported by the R-bendamustine phase II trial [17] and 80 in the FCR arm of Hallek trial [23]: 40% and 51%, respectively, achieved CR; median PFS was shorter than 3 years in the bendamustine trial, while 64% of the patients were progression free at 3 years in the FCR trial. The Panel judged that the difference in outcomes might have been influenced by different selection criteria in these studies, with more patients with unfavorable features having been included in the trial testing bendamustine and rituximab. In retrospective analyses and registries, the efficacy of bendamustine appeared to be independent of cytogenetic risk factors, with the exception of del(17p) [41]. Finally, the recent interim analysis of the GCLLSG CLL10 trial reported that del(11q) and IGHV status, as well as treatment (FCR vs R-bendamustine) were independent prognostic factors for PFS [27]. Three trials using FC reported a 15–38% CR rate in patients with 11q- [23,42,43] with a median PFS of 25.2 months [43] and a 32% PFS at 3 years [23]. In a trial using pentostatine and rituximab a 7.9 months median treatment free survival was reported [44], whereas no data for 11q-patients were provided in trials using fludarabine ad rituximab.

In 66 patients with unmutated IGHV gene bendamustine and rituximab attained a 27% CR rate, with 33.9 months median PFS [18]; in the CLL8 trial a 40% CR rate was reported in 196 unmutated IGHV patients, with 55% PFS at 3 years in the chemoinmunotherapy arm. In trials using FC those patients with unmutated IGHV gene attained a 18% CR rate with 35% PFS at 3 years in the CLL8 trial [23], and a 31.4 months median PFS in the U.S. trial [43].
Recommendations:
Bendamustine and rituximab is recommended in patients with 11q- or IGHV unmutated who are not candidate to FCR.

8. Which is the appropriate schedule and duration of bendamustine-based regimens for first-line CLL therapy? (Consensus-based)

Preliminary considerations:
Bendamustine as single agent was administered at a dose of 100 mg/m² on days 1–2 in a trial enrolling patients <75 years [16,17], 34% of whom required at least one 25% dose reduction. In a retrospective study analyzing real-world data on patients treated by bendamustine in first line dose reductions were reported in 67% of the patients >70 years [45]. R-bendamustine schedule included the administration of bendamustine at a dose of 90 mg/m² [18,27]. Dose reduction was necessary in about half of the patients, but over 90% of the planned dose was eventually administered [16–18].

Extra-hematologic toxicity was reported to be higher in patients over 70 years [18]. Doses as low as 75 mg/m² proved still effective and lower doses (50 mg/m²) were also used [15].

Recommendations:
The recommended dose of bendamustine alone in untreated CLL patients less than 75 years old is 100 mg/m² iv on days 1–2, every 4 weeks for 6 cycles. Increasing the dose of bendamustine alone in unresponsive patients is not recommended.

The recommended dose of bendamustine in association with rituximab as front-line therapy in CLL patients is 90 mg/m²qiv on days 1–2 every 4 weeks for 6 cycles. Increasing the dose of bendamustine alone in unresponsive patients is not recommended.

For patients aged older than 75 years, the dose of bendamustine alone or when associated with rituximab may be reduced according to the patient fitness and comorbidities.

Maintenance with bendamustine is not recommended after induction therapy with bendamustine alone or bendamustine plus rituximab.

Empirical combination of bendamustine with other myelosuppressive agents are strongly discouraged outside of clinical trial.

9. How should infections and autoimmunity cytopenias be managed and prevented during bendamustine therapy?

Preliminary considerations:
Infections remain a major cause of morbidity in CLL and account for up to 50% of CLL-related deaths [46]. Risk factors include age, advanced clinical stage, burden of comorbidities, hypogammaglobulinemia and previous infection history. No mandatory infection prophylaxis, polyvalent IV immunoglobulin replacement, or hemopoietic growth factor administration was prescribed in patients enrolled in bendamustine clinical trials [16,18]. In selected patients with grade 3–4 neutropenia, bacterial respiratory infec
tions prophylaxis was suggested [18] and G-CSF prophylaxis recommended according to ASCO guidelines [47]. Hypogammaglobulinemia occurs in substantial fraction of CLL patients. A systematic review and meta-analysis of randomized-controlled trials comparing prophylaxis with polyvalent IVIG in CLL was performed, showing a significant decrease in the occurrence of major infections, without survival advantage [48,49]. Based on these finding IVIG replacement therapy was only recommended on individual basis for selected CLL patients with hypogammaglobulinemia and/or recurrent infections [49].

Before starting chemoimmunotherapy patients should be screened for hepatitis B and C infections as well as for HIV infection and preemptive antiviral treatment was recommended in patients positive for HBsAg or HBCab [50].

Autoimmune complications, mainly autoimmune hemolytic anemia (AIHA) or immune thrombocytopenic purpura (ITP), occur in approximately 4–10% and 2–5% during the course of the disease, respectively [51]. Data on the incidence of AIHA or ITP following bendamustine with or without rituximab are limited, however the risk appears low [16,18]. Autoimmune complications were not considered as contraindications to the use of bendamustine upfront in those patients with progressive CLL or with active hemolysis uncontrolled by steroids [51].

Recommendations:
In patients candidate to bendamustine as first line therapy of CLL antibiotic prophylaxis and the prophylactic use of IVIG can be considered on an individual basis.

Patients with occult HBV infection and HBV carriers should be given antiviral prophylaxis if bendamustine is associated with Rituximab.

Patients with HCV infection should be treated jointly with a specialist.

Treatment with bendamustine, alone or with rituximab, may be initiated in CLL patients with an associated AIHA or ITP unresponsive to steroids.

10. Should bendamustine therapy be modified in B-CLL patients with renal of hepatic comorbidities? (Consensus-based)

Preliminary considerations:
Bendamustine undergoes extensive primary metabolism in the liver by the action of cytochrome p450 enzyme complex. However unmetabolized bendamustine accounts for about 45% of the total drug recovered in the urine [52]. Prospective studies excluded patients with severe renal impairment or high liver enzymes, therefore no prospective evidence is available for such patients. In clinical trials renal toxicity, including tumor lysis syndrome, was observed in less than 1.5% of the patients, and liver toxicity was only rarely reported [16,18,19,53,54].

Patients treated by bendamustine and rituximab [18] with a moderate renal impairment experienced a higher rate of anemia (p = 0.033), leucopenia (p = 0.057) non hematologic toxicity (p = 0.08) and infections (p = 0.097) than patients with a creatinine clearance greater than 70 ml/min [18].

Indeed, at a starting dose of 70 mg/m²/day, 7 patients with CLL and a chronic kidney disease (CLL related in 2) received bendamustine monotherapy with no worsening of the renal function [54].

Recommendations:
Bendamustine should not be used in patients in whom renal and hepatic functions are severely compromised.

In patients with moderately impaired renal function, and therefore not eligible for fludarabine containing regimens, bendamustine alone or associated with rituximab can be administered with adequate hydration, tumour lysis syndrome prophylaxis and careful monitoring of hematologic toxicity and renal and liver functions.

Because of an increased risk of cytopenias the dose of bendamustine should be reduced in patients with impaired renal function.

11. Which are the unset clinical needs for the appropriate use of bendamustine in first-line therapy of CLL?

The results of the CLL10 trial [27] comparing bendamustine and rituximab with the FCR combination showed greater efficacy and toxicity of the FCR combination. However the efficacy advantage was not maintained in elderly fit patients and, since the study was not powered to detect difference according to age the identification of the best regimen in elderly patients requires further study.

The results of two studies incorporating new anti CD20 monoclonal antibodies were recently reported. Obinutuzumab and chlorambucil achieved higher response rate and MRD negativity with statistically significant prolongation of PFS compared with
rituximab and chlorambucil in patients with comorbidities [12], while ofatumumab plus chlorambucil significantly prolonged PFS compared to chlorambucil alone in patients with CLL considered inappropriate for fludarabine-based therapy [55]. Inclusion criteria in trials assessing bendamustine and rituximab were partially overlapping with those adopted in these chlorambucil-based combinations and a direct comparison between these regimens is lacking. The efficacy of bendamustine should be tested in combination with these new CD20 monoclonal antibodies in the frontline setting. Results recently reported on the combination of bendamustine and ofatumumab in previously treated CLL patients are encouraging [56].

Ibrutinib, an inhibitor of BTK achieved a high overall response rate with impressive PFS in heavily pre-treated high-risk CLL [57] and proved to be well tolerated and effective in untreated patients as well [58]. Other key components of the BCR pathway, namely PI3K-δ, are also being targeted with novel therapies with promising results [59]. Bendamustine could represent an effective chemotherapeutic partner for these new drugs and indeed trials are ongoing that incorporated this agent are ongoing [60].

The recent application of whole genome sequencing identified clinically significant mutations in NOTCH1, SF3B1 and BIRC3 genes which represent adverse prognostic factors. NOTCH1 mutations were associated with a shorter time to first treatment and, interestingly they identified a subset of patients that may not benefit from adjunct of rituximab to FC [61] as well as from the adjunct of ofatumumab to chlorambucil [55]. These data suggest that gene mutations represent novel independent prognostic factors that may influence clinical practice and the efficacy of bendamustine-containing regimens in these genetic subsets of CLL is worth exploring.

4. Discussion

In this analysis we adopted the GRADE system to assess the quality of evidence, followed by an analysis of the benefit-risk balance and by a final judgment about the strength of recommendations on 3 key clinical queries, i.e. (i) the role of bendamustine and rituximab in patients eligible to FCR, (ii) the role of bendamustine and rituximab in those patients not eligible to FCR and, (iii) the role of bendamustine in patients eligible to chlorambucil alone.

Even though using the GRADE method the overall the quality of available clinical trials was low, mainly due to selection criteria (i.e. limitations in directness of evidence), methodological limitations (i.e. lack of blinding) and imprecision of results (i.e. interim analyses, unplanned subgroup analyses), a GRADE-based discussion based on the two previously specified critical outcomes, i.e. severe adverse events and PFS, allowed us to produce “strong” recommendations for 2 out of 3 key queries. We could thus define an appropriate use of bendamustine in those patients not candidate to receive FCR and in those patients candidate to chlorambucil alone: these patients may benefit from bendamustine which proved cost-effective [62] and showed a relatively favorable efficacy/toxicity balance. It is worth noting that these patients’ categories are frequently encountered in clinical practice and are under-represented in the majority of clinical trials, which usually adopt selective inclusion criteria. Chlorambucil with anti CD20 monoclonal antibodies may represent an alternative therapeutic approach in some of these patients.

Available data indicated that R-bendamustine in the young and/or fit patient was better tolerated and produced shorter PFS as compared with FCR [18,23,27]. The panel judged that these data do not prompt a change in the current standard of care, i.e. FCR first-line for fit, younger patients. Based on the considerations (i) that FCR improved PFS and not survival in patients >65 years and (ii) that in the elderly fit patient as well as in real-world patients R-bendamustine was better tolerated and as effective as FCR, the panel judged that R-bendamustine can be a recommended option in the elderly fit patient.

We also produced consensus based recommendations on other queries concerning the use of bendamustine containing regimens in high-risk genetic categories as well as on the role of bendamustine, its optimal dosage, the management of the most relevant frequent side effects. Even though no study directly assessed the key points raised by the panel, a careful analysis of data scattered in the literature allowed the panel to formulate recommendations for each relevant issue.

The therapeutic scenario in CLL is being rapidly modified by the introduction of effective BCR-targeted treatment which showed durable efficacy in the relapsed/refractory setting [57,59]. Their introduction in the front-line setting appeared to produce durable responses [58] and their possible combination with several monoclonal antibodies and chemotherapeutic agents, including bendamustine [60] may change treatment paradigm in the next years.

Conflict of interest statement

None.

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