Past, present and future role of chlorambucil in the treatment of chronic lymphocytic leukemia

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Abstract
For many decades, chlorambucil was the standard of care for chronic lymphocytic leukemia (CLL), but meanwhile has been replaced by purine analog-based chemoimmunotherapy. Monotherapy with the alkylator only retained significance in the treatment of older patients unfit for standard treatment. After successful phase II studies, recent phase III trials established combinations of chlorambucil with anti-CD20 antibodies such as rituximab, ofatumumab and obinutuzumab as a valuable treatment option for these patients. Today, chlorambucil therefore should be used as a chemotherapy backbone for antibody-based chemoimmunotherapy in this patient population rather than as monotherapy. Starting from the past role of chlorambucil in CLL treatment, we here review the most recent efforts to elaborate chlorambucil-based chemoimmunotherapy in CLL and discuss clinically relevant questions that arise from this approach.

Keywords: Chronic lymphocytic leukemia, chemotherapy, immunotherapy

Introduction
Chlorambucil (4-[bis(2-chlorethyl)amino]benzenebutanoic acid; Figure 1) is a bifunctional alkylating agent of the nitrogen mustard type [1]. Since its introduction as a chemotherapeutic drug, chlorambucil has been used for treating non-Hodgkin lymphoma, Hodgkin disease, Waldenström macroglobulinemia and polycythemia vera [2,3]. For more than 40 years, treatment with chlorambucil was the standard of care in chronic lymphocytic leukemia (CLL) [4–6]. Recent decades have seen significant advances in the treatment of CLL, beginning with the introduction of purine analogs such as fludarabine, which increased response rates [7,8]. Addition of the monoclonal anti-CD20 antibody rituximab to fludarabine/cyclophosphamide chemotherapy resulted in prolonged overall survival (OS) in previously untreated patients and improved progression-free survival (PFS) in relapsed patients [9–11]. Other agents such as bendamustine and alemtuzumab became available [12,13]. Most recently, drugs targeting the B-cell receptor signaling pathway or the apoptosis machinery demonstrated therapeutic benefit in CLL [14–17].

With the changing treatment landscape, chlorambucil played a smaller role in CLL therapy, particularly for younger and physically fit patients who normally are able to tolerate aggressive treatment. However, very recent approaches combined chlorambucil with anti-CD20 antibodies. Such chlorambucil-based chemoimmunotherapy was shown to significantly improve the outcome of older and less fit patients with CLL [18,19]; thereby providing a therapeutic competitor to other treatment strategies currently explored in this large patient population.

Important new questions arise from this finding. Optimal dosing and duration of chlorambucil treatment, when used as a chemotherapy backbone, have not yet been determined, and it is under debate which conclusions can be drawn from the chlorambucil trials published to date. It is also not clear whether optimal dosing of the alkylator is different for each type of anti-CD20 antibody used for chlorambucil-based chemoimmunotherapy. Further improvement of such combination treatment thus remains important. This review therefore outlines the past use of chlorambucil in CLL and discusses present as well as future strategies of chlorambucil-based therapy of CLL.

Pharmacodynamics and pharmacokinetics of chlorambucil in chronic lymphocytic leukemia
Chlorambucil can bind to a variety of cellular structures. Its main antitumor activity appears to be through crosslinking DNA, thus preventing replication and inducing apoptosis [20,21]. Reversible bone marrow suppression is the most
common side effect [7,8,13]. Gastrointestinal side effects occur less frequently. Other side effects such as allergy and skin reactions [22–26], pneumonia and pulmonary toxicity [27–29], mood alterations [30] and seizures [31] are less common, but have been reported. Secondary neoplasias have also been associated with long-term chlorambucil use [32,33].

Chlorambucil is readily absorbed through the gastrointestinal tract and is thus available as an oral formulation [34]. The drug appears to enter cells by simple diffusion, with predictable pharmacokinetics and low inter- and intrapatient variability [20,35]. It is metabolized in the liver, and 20–60% is excreted within 24 h of administration. Excretion of chlorambucil appears to be independent from kidney function, which allows its use in older patients with renal impairment [36].

Figure 1. Chemical structure of chlorambucil (4-[bis(2-chlorethyl) amino]benzenebutanoic acid).

Monotherapy with chlorambucil in chronic lymphocytic leukemia

It is more than 50 years since chlorambucil was first recognized and reported to be active in CLL [4–6]. The first clinical trials with chlorambucil in CLL explored different dosing schedules and combinations with corticosteroids [37–39]. Numbers of enrolled patients were generally low, and study populations were heterogeneous with regard to disease stage and prior treatment. Overall response rates of 30–60% were reported, with no significant benefit from the addition of steroids and similar efficacy between daily and intermittent dosing. Treatment toxicity was not uniformly assessed or reported in these trials, but approximate rates for moderate to severe myelosuppression and infections were 10–20% and 30%, respectively. In early-stage asymptomatic CLL, treatment with chlorambucil was found to have no benefit or even produced a detrimental effect on survival, compared to watch and wait until disease progression [40–43]. Subsequent clinical trials in advanced-stage and symptomatic CLL compared chlorambucil monotherapy with combination regimens not containing purine analogs [42,44–49]. These included cyclophosphamide, vincristine, prednisolone (COP) and cyclophosphamide, vincristine, adriamycin, prednisolone (CHOP). No survival advantage for these polychemotherapy regimens was found, and chlorambucil remained the standard of care in CLL. Consensus criteria for the assessment of treatment response or toxicity [50,51] did not yet exist when these trials were conducted. Therefore, efficacy and safety results are difficult to compare between these and newer studies. Overall response to chlorambucil was observed in 60–90% of treated patients, and was not inferior to that with COP or CHOP. In those trials reporting safety data, myelosuppression and infections were not significantly different between treatment arms.

More recent comparative trials [7,8,12,13,52,53] have demonstrated superiority of agents such as fludarabine with or without cyclophosphamide, cladribine, alemtuzumab and bendamustine over chlorambucil with regard to response rate and PFS, but have failed to improve OS in CLL (Table I). In the majority of these studies, toxicity was generally milder with chlorambucil than with the comparator treatment [54]. However, rates of infections mostly were not significantly different, and neutropenia rates sometimes were similar for treatment with chlorambucil or purine analog. Overall response rates, complete response rates and PFS for chlorambucil treatment ranged between 31 and 72%, 0 and 12%, and 8 and 20 months, respectively. Grade 3–4 neutropenias and infections were observed in 4–28% and 0–13% of the patients treated with chlorambucil.

In virtually all of these trials, the patients’ median age was around 60–65 years. Results of one randomized trial were more specific to older patients (German CLL5 study) [55], and suggested that fludarabine has no advantage over chlorambucil in terms of PFS or OS in these patients. PFS in this trial was 18 months with chlorambucil and 19 months with fludarabine treatment. Although statistically insignificant, OS appeared longer with chlorambucil (64 months) compared to fludarabine treatment (46 months). Subgroup analyses of other trials comparing fludarabine, alemtuzumab or bendamustine with chlorambucil also failed to provide conclusive evidence that these drugs are superior to the alkylation with regard to PFS or OS in patients of advanced age [12,56,57]. A randomized trial comparing chlorambucil with the immunomodulating drug lenalidomide in older patients with CLL was recently halted due to an increased mortality in the lenalidomide arm. Advantages of agents such as fludarabine, alemtuzumab, bendamustine and others over chlorambucil found in younger patients thus may not necessarily apply for the elderly. The observed lack of benefit from these drugs (relative to chlorambucil) in this patient group is not well understood and cannot be entirely explained by their specific toxicity profiles, which were found to be moderately but not dramatically different and sometimes even similar to chlorambucil [8,53,55]. More early withdrawals from purine analog compared to chlorambucil treatment were assumed to cause the lack of benefit. However, in the German CLL5 study in older patients, treatment withdrawals actually occurred more frequently with chlorambucil than with fludarabine and were caused by both adverse events and disease progression [55]. Whether limited eligibility to salvage therapies and higher rates of secondary cancers created the lack of benefit from the above-listed drugs in elderly patients remains to be proven.

Chlorambucil is available as 2 mg tablets [34]. The dosing and duration of chlorambucil monotherapy has varied widely in “historical” (i.e. published before 2000) and recent trials (i.e. published since 2000, Table I). Overall, intermittent dosing was more frequently used than daily dosing of chlorambucil. The following schedules were applied in a Spanish PETHEMA (Programa para el Tratamiento de Hemopatías Malignas), the Danish CLL-2, the British CLL1, an Eastern Cooperative Oncology Group and a French Cooperative Group study: 0.4 mg/kg per body weight monthly [44], 10 mg/m²/day for 5 days every 4 weeks [45], 20 mg/m²/day for 3 days every 4 weeks [42], 30 mg/m² every 2 weeks [315x78]
Table I. Phase III comparative studies of chlorambucil monotherapy in previously untreated patients with CLL (published since 2000).

<table>
<thead>
<tr>
<th>Trial</th>
<th>CLB regimen</th>
<th>CLB dose (per cycle*)</th>
<th>n</th>
<th>Median age (years)</th>
<th>ORR (%)</th>
<th>CRR (%)</th>
<th>PFS OS</th>
<th>Neutropenia (%)</th>
<th>Infections (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLB vs. F vs. FC (UK CLL4) [8]</td>
<td>10 mg/m² on days 1-7, q28 days max. 12 cycles</td>
<td>129 mg</td>
<td>387/194/196</td>
<td>65/64/65</td>
<td>72/60/65</td>
<td>38/11/38</td>
<td>10/10/136 % (at 5 years)</td>
<td>64/54/52 % (at 5 years)</td>
<td>129/112/115 % (at 5 years)</td>
</tr>
<tr>
<td>CLB vs. F vs. Cd [53]</td>
<td>10 mg/m² on days 1-10, q28 days 6 cycles</td>
<td>184 mg</td>
<td>77/74/72</td>
<td>63/64/64</td>
<td>62/70/75</td>
<td>6/5/8</td>
<td>9/10/25 months (median)</td>
<td>91/82/96 months (median)</td>
<td></td>
</tr>
<tr>
<td>CLB vs. Cd [52]</td>
<td>12 mg/m² on days 1-7, q28 days 6 cycles</td>
<td>155 mg</td>
<td>103/126</td>
<td>62/61</td>
<td>57/87</td>
<td>12/47</td>
<td>18/21 months (median)</td>
<td>82/78/78 % (at 2 years)</td>
<td></td>
</tr>
<tr>
<td>CLB vs. F (CALGB) [7]</td>
<td>40 mg/m² on day 1, q28 days max. 12 cycles</td>
<td>74 mg</td>
<td>193/179</td>
<td>62/64</td>
<td>37/63</td>
<td>4/20</td>
<td>14/20 months (median)</td>
<td>56/66 months (median)</td>
<td></td>
</tr>
<tr>
<td>CLB vs. A (CAM307) [12]</td>
<td>40 mg/m² on day 1, q28 days max. 12 cycles</td>
<td>74 mg</td>
<td>148/149</td>
<td>60/59</td>
<td>55/83</td>
<td>2/24</td>
<td>12/15 months (median)</td>
<td>84/84 % (at 2 years)</td>
<td></td>
</tr>
<tr>
<td>CLB vs. F (GCLLSG CLL5) [55]</td>
<td>0.4-0.8 mg/kg on days 1 + 15, q28 days max. 12 cycles</td>
<td>70 mg</td>
<td>100/93</td>
<td>70/71</td>
<td>51/72</td>
<td>0/7</td>
<td>18/19 months (median)</td>
<td>64/46 months (median)</td>
<td></td>
</tr>
<tr>
<td>CLB vs. BENDA [13]</td>
<td>0.8 mg/kg on days 1 + 15, q28 days 6 cycles</td>
<td>112 mg</td>
<td>157/162</td>
<td>66/63</td>
<td>31/68</td>
<td>2/31</td>
<td>8/22 months (median)</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>

CLL, chronic lymphocytic leukemia; CLB, chlorambucil; F, fludarabine; C, cyclophosphamide; Cd, cladribine; BENDA, bendamustine; A, alemtuzumab; ORR, overall response rate; CRR, complete response rate; PFS, progression-free survival; OS, overall survival; NR, not reported; CMV, cytomegalovirus.

*Total CLB dose per cycle calculated for a patient of 70 kg body weight and 170 cm body height.
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doses) [55,53]. It should also be noted that the differences in response and PFS between the chlorambucil arms of all of these trials might not only result from different dosing and duration of chlorambucil treatment but also from differences in study populations and methodology of response evaluation. The latter underwent fundamental changes by the implementation and further updating of consented response criteria [50,51] and by the growing availability of imaging technology used for response assessment. Finally, even though chlorambucil did not compare unfavorably with other treatments with respect to tolerability (even at 70 mg/m² per cycle), higher doses of chlorambucil when combined with other agents might result in greater toxicity. Moreover, increasing the dose of chlorambucil within such combination treatments may not always contribute to greater efficacy. Optimal dosing of chlorambucil within combination treatments therefore is difficult to conclude from previous studies exploring chlorambucil monotherapy.

**Combination therapy with chlorambucil in chronic lymphocytic leukemia**

With the aim to improve treatment efficacy, combinations of chlorambucil with other chemotherapeutic agents such as fludarabine, pentostatin, cladribine or epirubicin were explored [7,42,58,59]. No benefit from these combined treatments was found, however. Toxicity was unacceptably high in some of these studies; the treatment arm of chlorambucil plus fludarabine in the Intergroup study [7] had to be discontinued due to high toxicity, for example.

Given the later success of purine analog and antibody-containing chemoimmunotherapy in the treatment of younger and fit patients with CLL, the potential for chlorambucil-based chemoimmunotherapy to offer an active treatment particularly for older and less fit patients has been explored. It has been increasingly recognized that in such patients CLL remains the major medical problem and cause of an unfavorable outcome [60–62]. The treatment goal for those patients is thus changing from largely palliative to active antitumor activity. The rationale to use chlorambucil instead of purine analogs as the chemotherapy backbone was built on the milder toxicity reported for chlorambucil monotherapy in several (although not all) prior trials [54] and the lack of observed superiority of purine analogs and other drugs over chlorambucil in older and less fit patients [12,55,57]. Two phase II studies of rituximab plus chlorambucil in older patients have been reported (Table II). In a British study, a chlorambucil dose of 10 mg/m²/day on days 1–7 for 6–12 monthly cycles was used [63]. In an Italian study the dose was 8 mg/m²/day on days 1–7 for up to eight cycles [64]. Both of these studies reported encouraging response rates of approximately 80%, with some complete remissions and promising PFS results (2–3 years). For the British trial, a retrospective comparison of chlorambucil plus rituximab with chlorambucil monotherapy suggested higher efficacy of the combination treatment. In the Italian trial, the combination treatment was followed by rituximab maintenance, which in part may explain the remarkably long PFS observed in this study (35 months). Toxicity was well manageable in both trials, although myelotoxicity was more frequent than one would expect from chlorambucil monotherapy. Results comparable to those of these two larger phase II studies also were reported from a small series of 27 patients treated with chlorambucil (1.0 mg/kg monthly, eight cycles) plus rituximab [65].

There are two published phase III trials investigating chlorambucil-based chemoimmunotherapy in CLL (Table III). Both trials explored combinations of chlorambucil with novel anti-CD20 antibodies in previously untreated patients. The COMPLEMENT-I study was a randomized trial comparing the type 1 anti-CD20 antibody ofatumumab plus chlorambucil with chlorambucil alone in previously untreated patients “considered inappropriate for fludarabine-based therapy” [18]. Chlorambucil was dosed at 10 mg/m²/day for 7 days (maximum 12 cycles). The median duration of treatment in both treatment arms was six cycles. While PFS was significantly longer for the combination treatment compared with chlorambucil monotherapy (22 vs. 13 months), there was no significant difference in OS between the two arms of this trial. A limitation of this trial is that there was no comparison of ofatumumab plus chlorambucil with rituximab plus chlorambucil, a combination which has been demonstrated to be safe and efficacious in such patients [63,64]. The CLL11 study in 781 patients with CLL and comorbidities (cumulative illness rating scale [CIRS] score >6 and/or creatinine clearance <70 mL/min) investigated obinutuzumab plus chlorambucil vs. rituximab plus chlorambucil monotherapy suggested higher efficacy of the combination compared with chlorambucil plus rituximab suggested higher efficacy of the combination. In the Italian trial, the combination treatment was followed by rituximab maintenance, which in part may explain the remarkably long PFS observed in this study (35 months). Toxicity was well manageable in both trials, although myelotoxicity was more frequent than one would expect from chlorambucil monotherapy. Results comparable to those of these two larger phase II studies also were reported from a small series of 27 patients treated with chlorambucil (1.0 mg/kg monthly, eight cycles) plus rituximab [65].

<table>
<thead>
<tr>
<th>Reference</th>
<th>CLB regimen</th>
<th>CLB dose (per cycle*)</th>
<th>n</th>
<th>Median age (years)</th>
<th>ORR (%)</th>
<th>CRR (%)</th>
<th>PFS (months)</th>
<th>OS</th>
<th>Grade 3/4 adverse events (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-CLB (Hillmen et al.) [63]</td>
<td>10 mg/m² on days 1-7, q28 days 6-12 cycles</td>
<td>129 mg</td>
<td>100</td>
<td>70</td>
<td>84</td>
<td>10</td>
<td>24 months (median)</td>
<td>NR</td>
<td>41</td>
</tr>
<tr>
<td>R-CLB (Foa et al.) [64]</td>
<td>8 mg/m² on days 1-7, q28 days 8 cycles</td>
<td>103 mg</td>
<td>85</td>
<td>70</td>
<td>82</td>
<td>10</td>
<td>35 months (median)</td>
<td>NR</td>
<td>19</td>
</tr>
<tr>
<td>R-CLB (Laurenti et al.) [65]</td>
<td>1 mg/kg, q28 days 8 cycles</td>
<td>74 mg</td>
<td>27</td>
<td>72</td>
<td>74</td>
<td>26</td>
<td>29 months (median)</td>
<td>NR</td>
<td>19</td>
</tr>
</tbody>
</table>

CLL, chronic lymphocytic leukemia; CLB, chlorambucil; R, rituximab; ORR, overall response rate; CRR, complete response rate; PFS, progression-free survival; OS, overall survival; NR, not reported or reached.

*Total CLB dose per cycle calculated for a patient of 70 kg body weight and 170 cm body height.
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Table III. Phase III comparative studies of chlorambucil-based chemoimmunotherapy in previously untreated patients with CLL.

<table>
<thead>
<tr>
<th>CLB dose (per cycle)</th>
<th>Median age (years)</th>
<th>Efficacy</th>
<th>Grade 3/4 adverse events (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>ORR (%)</td>
<td>CRR (%)</td>
</tr>
<tr>
<td>CLB vs. R-CLB vs. G-CLB</td>
<td></td>
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<tr>
<td>(CLL11) [19]</td>
<td>0.5 mg/kg on days 1-15, q28 days 6 cycles 15</td>
<td>70 mg 118/330/333</td>
<td>72/73/74</td>
</tr>
<tr>
<td></td>
<td>6 cycles</td>
<td>70 mg 118/330/333</td>
<td>72/73/74</td>
</tr>
<tr>
<td></td>
<td>16/28/33</td>
<td>14/11/12</td>
<td>14/12/9</td>
</tr>
<tr>
<td>CLB vs. O-CLB</td>
<td>10 mg/m² on days 1–7, q28 days max. 12 cycles</td>
<td>129 mg</td>
<td>226/221</td>
</tr>
<tr>
<td>(COMPLEMENT-1) [18]</td>
<td></td>
<td>70 mg 118/330/333</td>
<td>72/73/74</td>
</tr>
<tr>
<td></td>
<td>6 cycles</td>
<td>70 mg 118/330/333</td>
<td>72/73/74</td>
</tr>
<tr>
<td></td>
<td>16/28/33</td>
<td>14/11/12</td>
<td>14/12/9</td>
</tr>
</tbody>
</table>

CL, chronic lymphocytic; CLB, chlorambucil; R, rituximab; G, obinutuzumab (GA101); O, ofatumumab; ORR, overall response rate; CRR, complete response rate; PFS, progression-free survival; OS, overall survival; NS, no statistically significant difference.

*Total CLB dose per cycle calculated for a patient of 70 kg body weight and 170 cm body height.

Dosing schedule of chlorambucil (0.5 mg/kg day 1 and day 15 every 4 weeks for up to six cycles) was based on the median chlorambucil dose successfully used in the German CLL5 trial (chlorambucil vs. fludarabine) with regard to PFS and OS [55]. The median duration of treatment was six cycles for all three treatment arms. Combination of chlorambucil with obinutuzumab or rituximab resulted in prolonged PFS compared with chlorambucil monotherapy (27 vs. 11 months and 16 vs. 11 months, respectively). In combination with chlorambucil, the type 2 anti-CD20 antibody obinutuzumab was superior to the type 1 anti-CD20 antibody rituximab with regard to PFS and complete and molecular responses. Importantly, addition of obinutuzumab to chlorambucil not just improved PFS, but also resulted in longer OS than treatment with chlorambucil alone.

Differences in methodology of data processing, enrolled patient populations and dosing of the study drugs are significant limitations for an intertrial comparison between the COMPLEMENT-1 and the CLL11 study. Interestingly however, although different schedules for the dosing and duration of chlorambucil treatment were used in these trials (higher dose in the COMPLEMENT-1, lower dose in the CLL11 study), PFS as well as complete response rates for patients treated with chlorambucil monotherapy were rather similar (13 and 11 months, 1% and 0%, respectively), whereas overall response rates differed between the trials (69% vs. 31%). Dosing of the alkylator in these trials thus may have had some impact on overall response to chlorambucil treatment, but seemingly not on complete response and PFS. Furthermore, PFS results reported for chlorambucil monotherapy in two earlier trials using similar dosing schedules (LRF CLL4, CLL5) [8,55] were reproduced neither in the COMPLEMENT-1 nor in the CLL11 study. This suggests that in addition to the dosing of chlorambucil, characteristics of study populations as well as changing methodology of response assessment must be taken into account when attempting to explain differences in outcome between these and previous trials. Clearly, the currently available data from the COMPLEMENT-1 and CLL11 studies do not allow full assessment of the impact of dosing and duration of chlorambucil treatment when combined with an anti-CD20 antibody. Most complete responses and longest PFS were observed with obinutuzumab in combination with lower-dosed chlorambucil (27 months), followed by ofatumumab in combination with higher-dosed chlorambucil (22 months). In both studies, combination of the antibody with chlorambucil added toxicity to the treatment, mainly neutropenia at fairly comparable rates, and infusion-related reactions, which appear to be most frequent with obinutuzumab (20%) and more frequent with ofatumumab (10%) than with rituximab (4%). It is therefore possible that optimal dosing of chlorambucil within combined treatments will depend on the anti-CD20 antibody selected as combination partner.

Besides the COMPLEMENT-1 and CLL11 studies, there are several ongoing trials investigating chlorambucil-based chemoimmunotherapy in elderly patients with CLL who are ineligible for fludarabine treatment. The MaBle study (NCT01056510) compares rituximab plus chlorambucil with rituximab plus bendamustine. The RIAltO study (NCT01678430) compares ofatumumab plus chlorambucil...
with ofatumumab plus bendamustine. A trial conducted in Russia (NCT01283386) explores rituximab plus chlorambucil vs. rituximab plus dose-reduced fludarabine/cyclophosphamide. In all of these trials, chlorambucil is dosed at 10 mg/m²/day for 7 days of each cycle, but with different treatment durations. To date, only preliminary results have been released [68,69]. Combinations of chlorambucil with novel agents other than anti-CD20 antibodies are rarely explored. A small study that evaluated chlorambucil in combination with the small molecule inhibitor imatinib in 11 patients with relapsed CLL has been conducted using chlorambucil at a dose of 8 mg/m²/day for 5 days of each cycle [70]. The treatment was well tolerated and showed evidence of clinical efficacy. A phase I/II study (NCT01403246) of lenalidomide plus chlorambucil (dose not yet reported; days 1–8 every month for 6 months, then lenalidomide maintenance) in elderly patients began in 2011.

Conclusions and perspective

The trial evidence reviewed above suggests that chlorambucil should no longer be used as monotherapy in CLL, but has significant value as a chemotherapy backbone when combined with anti-CD20 antibodies in older and less fit patients with CLL. Such chlorambucil-based chemoimmunotherapy represents a safe and efficacious treatment for these patients. Relative to chlorambucil monotherapy, clinical outcome is improved regardless of the anti-CD20 antibody added to chlorambucil. However, only the type 2 antibody obinutuzumab has demonstrated a survival benefit in this patient population to date. Neither previous studies that explored chlorambucil monotherapy nor recent trials that demonstrated superiority of chlorambucil plus anti-CD20 antibody over chlorambucil alone [18,19] allow definitive conclusions on the optimal dosing of the alkylator when given in combination treatments. It remains unknown whether higher doses and a longer duration of chlorambucil therapy would add significant net-benefit, i.e. increased efficacy but not toxicity to such treatment. Currently available data are not in support of this, but the pitfalls of intertrial comparisons prohibit final conclusions. Whether optimal chlorambucil dosing depends on the type of anti-CD20 antibody used as the combination partner (i.e. obinutuzumab, ofatumumab or rituximab) is an open question, too.

The future role of chlorambucil in CLL is difficult to estimate. A currently addressed question is whether chlorambucil-based chemoimmunotherapy in older and less fit patients could be further refined by replacing the alkylator by other, less-toxic but more efficacious agents, including non-chemotherapeutic drugs such as inhibitors of the B-cell receptor signaling pathway or inducers of the apoptosis machinery. Results from first studies investigating the combination of a B cell receptor inhibitor with rituximab in elderly patients were promising [16,71], and several randomized trials exploring “chemotherapy-free” treatments in these patients are now planned. Until such treatments will have become firmly established, chlorambucil-based chemoimmunotherapy stays a valuable treatment option and a reasonable comparator in randomized trials in this patient population.

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at www.informahealthcare.com/lal.

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