IX. Chronic lymphocytic leukemia for the clinician

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Several new drugs have recently been approved for chronic lymphocytic leukemia (CLL) treatment (fludarabine, bendamustine as well as three monoclonal antibodies, alemtuzumab, rituximab and ofatumumab). Recent data show that chemoimmunotherapies composed of fludarabine and rituximab (with or without cyclophosphamide), or of fludarabine and alemtuzumab may improve overall survival when used as therapy for CLL patients. This review integrates this knowledge and proposes a treatment algorithm for patients with CLL.

chemotherapy

During the past decade it became apparent that the use of some combination therapies produced a superior efficacy than chlorambucil monotherapy, the former gold standard of chronic lymphocytic leukemia (CLL) therapy [1]. In particular, fludarabine has been evaluated in a variety of combination regimens. The most thoroughly studied combination chemotherapy for CLL is fludarabine plus cyclophosphamide (FC). It showed superior efficacy [higher response rates, longer progression-free survival (PFS) and overall survival (OS) for major subgroups in some trials] when compared with single-agent fludarabine [2, 3].

chemoimmunotherapy

The CALGB 9712 protocol combined rituximab with fludarabine in either a sequential or concurrent regimen in a randomized study. The long-term follow-up of 104 patients included in this trial was recently reported (median follow-up of 117 months) [4]. The median OS was 85 months, and 71% of patients were alive at 5 years. The median PFS was 42 months, and 27% were progression free at 5 years of follow-up suggesting an extended OS and PFS with fludarabine plus rituximab. Similarly, the combination of FC with rituximab (FCR) was investigated in a phase II trial on 300 patients with previously untreated CLL. FCR resulted in an overall response (OR) rate of 95%, with complete remission (CR) in 72%, nodular partial remission (nPR) in 10%, partial remission (PR) due to cytopenia in 7% and PR due to residual disease in 6% [5]. Six-year OS and failure-free survival were 77% and 51%, respectively. Median time to progression was 80 months.

In the CLL8 protocol of the German CLL Study Group (GCLLSG), 817 treatment-naïve, physically fit patients (aged 30–81 years) were randomly assigned to receive six courses of intravenous fludarabine (25 mg/m² per day) and cyclophosphamide (250 mg/m² per day) for the first 3 days of each 28-day treatment course with or without rituximab (375 mg/m² on day 0 of the first course, and 500 mg/m² on day 1 of the second to sixth courses) [6]. At 3 years after randomization, 65% of patients in the FCR group were free of progression compared with 45% in the FC group (P < 0.0001); 87% were alive compared with 83%, respectively [0.67 (0.48–0.92); P = 0.01]. FCR was more frequently associated with grade 3 and 4 neutropenia [136 (34%) of 404 compared with 83 (21%) of 396; P < 0.0001] and leukocytopenia [97 (24%) compared with 48 (12%); P < 0.0001]. Other side-effects, including severe infections, were not increased. There were 8 (2%) treatment-related deaths in the chemoimmunotherapy group compared with 10 (3%) in the chemotherapy group. These results suggest that the choice of FCR as first-line treatment prolongs OS of CLL patients.

Similar results were obtained in a trial comparing FCR with FC in second-line treatment of CLL (Table 1) [7].

The synergistic activity of fludarabine and alemtuzumab was initially suggested by the induction of responses, including one CR, in five of six patients who were refractory to each agent alone [8]. A combination of fludarabine and alemtuzumab (FA) was also investigated in a phase III trial that recently reported a significant improvement in PFS and OS for fludarabine plus alemtuzumab (FluCam) compared with single-agent fludarabine in patients of advanced (Rai III/IV) stage, previously treated CLL (Table 1) [9].

The combination of FC plus alemtuzumab (FCA) was studied by the GCLLSG in a phase II trial and by the French CLL study group and the Groupe Ouest-est d’Etudes des Leucemies Aigues et Autres Maladies du Sang (GOELAMS) in a phase III study. Increased toxicity of FCA compared with FCR was found, preventing the use of the FCA combination outside of clinical trials [10, 11].

Several variations on this theme have been studied in phase II trials, like dose-reduced FCR, bendamustine plus rituximab, the replacement of fludarabine by pentostatin in the FCR regimen, and the use of novel anti-CD20 antibodies in the FCR regimen. None of them has shown superior efficacy in a phase III trial so far. Some of these combinations are currently under investigation in phase III trials. A more detailed summary can be found in a recent review [3].
treatment algorithm for patients with CLL: what clinicians need to know

Tables 2 and 3 propose an algorithm for the therapy of CLL patients that considers four major points [12]:

(i) stage;
(ii) fitness of the patient;
(iii) genetic changes in CLL cells as determined by FISH;
(iv) response to the first treatment.

By using the assessment of these four points, the following recommendations can be given:

(i) Patients at early stage (Binet A and B, Rai 0–II) without symptoms usually do not require therapy. Early treatment is currently tested in clinical trials for patients at high risk.

(ii) In patients with advanced (Binet C, Rai III–IV) or active, symptomatic disease, treatment should be initiated as follows.

- For patients in good physical condition (‘go go’), as defined by a normal creatinine clearance and a low score at the ‘cumulative illness rating scale’ (CIRS) [13], an FCR combination therapy should be offered.
- Patients with relevant comorbidity (‘slow go’) may be treated with chlorambucil. Alternatives are bendamustine or a dose-reduced fludarabine-containing regimen to achieve symptom control.
- Patients with symptomatic disease and with del(17p) or p53 mutations respond poorly to fludarabine or FC, and show a response rate of ~50% to alemtuzumab monotherapy [14] or to FCR [6] but these responses usually have a short duration of a few months to 1.5 years. These patients should receive an allogeneic stem cell transplant within a clinical trial whenever possible [15].

(iii) For the selection of second-line treatment, the quality of the first response plays a major role:

- In physically fit patients with refractory disease or relapse within 24 months after a chemoimmunotherapy- or fludarabine-based combination therapy, the second remission should be used to proceed to an allogeneic stem cell transplant [15].

Table 1. Randomized trials comparing chemotherapy with chemoimmunotherapy or with chemotherapy plus targeted agents

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Reference</th>
<th>N</th>
<th>Age (median)</th>
<th>Advanced stage (%)</th>
<th>ANC, toxicity grade 3–4 (%)</th>
<th>CR (%)</th>
<th>OR (%)</th>
<th>PFS (months)</th>
</tr>
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<tbody>
<tr>
<td>First line</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FC</td>
<td>Hallek [6]</td>
<td>409</td>
<td>61</td>
<td>31</td>
<td>21</td>
<td>22</td>
<td>80</td>
<td>32.8</td>
</tr>
<tr>
<td>FCR</td>
<td>408</td>
<td>61</td>
<td></td>
<td>31</td>
<td>34</td>
<td>44</td>
<td>90</td>
<td>51.8</td>
</tr>
<tr>
<td>Second line</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>Engert [9]</td>
<td>167</td>
<td>60</td>
<td>37</td>
<td>60</td>
<td>16.4</td>
<td>67.9</td>
<td>29.6</td>
</tr>
<tr>
<td>FA</td>
<td>168</td>
<td>60</td>
<td></td>
<td>37</td>
<td>66</td>
<td>30.4</td>
<td>84.8</td>
<td>20.7</td>
</tr>
<tr>
<td>FC</td>
<td>O’Brien [16]</td>
<td>121</td>
<td>63</td>
<td>50</td>
<td>11²</td>
<td>3</td>
<td>45</td>
<td>9</td>
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<tr>
<td>FCO</td>
<td>120</td>
<td>63</td>
<td></td>
<td>45</td>
<td>7²</td>
<td>9</td>
<td>41</td>
<td>6</td>
</tr>
<tr>
<td>FC</td>
<td>Robak [7]</td>
<td>272</td>
<td>62</td>
<td>NA</td>
<td>40</td>
<td>13</td>
<td>58</td>
<td>21²</td>
</tr>
<tr>
<td>FCR</td>
<td>274</td>
<td>62</td>
<td></td>
<td>NA</td>
<td>42</td>
<td>24</td>
<td>70</td>
<td>31²</td>
</tr>
</tbody>
</table>

³Rai III–IV or Binet C.

⁴Only CTC grade 4.

⁵Time to treatment failure.

FC, fludarabine and cyclophosphamide; O, oblimersen; R, rituximab; ANC, absolute neutrophil count.

Table 2. Proposal of an algorithm for first-line therapy of CLL

<table>
<thead>
<tr>
<th>Stage</th>
<th>Fitness</th>
<th>del(17p)</th>
<th>p53mut</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binet A–B, Rai 0–II, inactive</td>
<td>Irrelevant</td>
<td>Irrelevant</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Active disease or Binet C or Rai III–IV</td>
<td>Go go</td>
<td>no</td>
<td>FCR</td>
<td></td>
</tr>
<tr>
<td>Slow go</td>
<td>yes</td>
<td>no</td>
<td>AlloSCT</td>
<td></td>
</tr>
<tr>
<td>Slow go</td>
<td>yes</td>
<td>yes</td>
<td>A, high-dose R or O</td>
<td></td>
</tr>
</tbody>
</table>

F, fludarabine; C, cyclophosphamide; A, alemtuzumab; R, rituximab; B, bendamustine; O, ofatumumab; AlloSCT, allogeneic stem cell transplantation.

Table 3. Proposal of an algorithm for second-line therapy of CLL

<table>
<thead>
<tr>
<th>Duration of remission</th>
<th>Fitness</th>
<th>del(17p)</th>
<th>p53mut</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;2 years</td>
<td>Irrelevant</td>
<td>Irrelevant</td>
<td>Repeat first-line therapy</td>
<td></td>
</tr>
<tr>
<td>≤2 years</td>
<td>Go go</td>
<td>Irrelevant</td>
<td>AlloSCT</td>
<td></td>
</tr>
<tr>
<td>Slow go</td>
<td>no</td>
<td>Change to alternative treatment (trials!)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>Change to A, high-dose R or O, lenalidomide (trials!)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Clb, chlorambucil; F, fludarabine; C, cyclophosphamide; A, alemtuzumab; R, rituximab; B, bendamustine; O, ofatumumab; AlloSCT, allogeneic stem cell transplantation.
In physically unfit patients with refractory disease or relapse within 24 months after a chemoimmunotherapy- or fludarabine-based combination therapy, the treatment strategy should be changed to an alternative regimen (e.g. from FCR to BR or alemtuzumab plus dexamethasone; from BR to FCR, etc.). It should be communicated to the patient that the prognosis in this group is usually poor. This group of patients is excellently suited for testing new, alternative treatment strategies, since it represents an unmet medical need.

In all patients experiencing a relapse later than 24 months after the first therapy, the first-line treatment can be repeated.

acknowledgements

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references

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