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## First-line therapy of chronic lymphocytic leukemia: when and how to treat



Chronic lymphocytic leukemia (CLL) shows a remarkable clinical heterogeneity: there are some patients with smouldering disease who may not have an altered survival due to CLL, and patients who will certainly have shorter expected survival owing to their progressive disease. In the last decade, impressive progress has been achieved in biological characterization of CLL, allowing better understanding of the pathophysiology of the disease and identification of biological features relevant to prognostic stratification. In the same time period, new therapeutic options, including auto and allotransplantation procedures, monoclonal antibodies (Mab) and new drugs have become available, in addition to alkylating agents and purine analogs.

Recent evidence from clinical trials supports that:

- high remission rates can be achieved in CLL
- the quality of response to first-line therapy is associated with response duration
- the first regimen a patient receives provides the best chance to achieve a complete remission (CR).

Thus, the choice of front-line therapy is very important in CLL and these established results represent the basis for optimization of front-line treatment.

Fludarabine is the most active single agent in the treatment of CLL. In patients requiring therapy according to the NCIWG guidelines,<sup>1</sup> randomized trials that compared single-agent fludarabine with chlorambucil or alkylator-based combinations<sup>2–4</sup> showed better response rates, PFS and quality of life for patients given fludarabine. On the basis of preclinical evidence of synergy,<sup>5</sup> combinations of fludarabine with alkylating agents have been evaluated in previously treated<sup>6</sup> patients in phase II trials. The suggestion that combination improves clinical outcomes, prompted researchers to launch randomized studies comparing fludarabine plus cyclophosphamide (FC) to fludarabine alone as first-line treatment in patients with symptomatic/progressive CLL. Recently, results have been published from three large trials:<sup>4,7–8</sup> although doses and schedules are *not super imposable*, all these studies report significantly superior response rates (overall response rates from 74% to 94%, CR rates from 23 to 39%) and longer PFS in patients receiving combination therapy (Table 1). In some phase II studies mitoxantrone has been substituted for CTX or the two compounds have been used in a 3-drug combination,<sup>9</sup> with comparable results to FC. In addition to the i.v. formulation, an oral fludarabine formula-

**Table 1. Results from randomized phase III clinical trials comparing single-agent fludarabine to fludarabine plus cyclophosphamide (Results updated at EHA 2007 Meeting).**

<i>Trial (Reference)</i>	<i>Regimen</i>	<i>ORR%</i>	<i>CR%</i>	<i>PFS Median (mos)</i>	<i>OS</i>
Flinn, 2007 (Intergroup E2997) <sup>8</sup>	FC	74.3	23.4	31.6	At 2 yrs 80%
	F	59.5	4.6	19.2	80%
Eichhorst, 2006 (GCLLSG CC4) <sup>7</sup>	FC	94.5	23.8	62	At 3 yrs 80%
	F	82.9	6.7	24	80%
Catovsky, 2007 (UK LRF CLL4) <sup>4</sup>	FC	94	39	43	At 5 yrs 54%
	F	80	15	23	52%
	CLB	72	7	20	59%

*F: Fludarabine; C: Cyclophosphamide; CLB: Chlorambucil.*

tion is available. Bioavailability of oral fludarabine is 60% and a dose of 40 mg/SQ p.o are equivalent to 25 mg/SQ i.v. Fludarabine and cyclophosphamide oral combination has been already tested in CLL showing good tolerability (mild-to-moderate gastrointestinal adverse events not requiring treatment withdrawal) and comparable efficacy to i.v. combination.<sup>4,10</sup> Oral therapy can be given on an outpatient basis avoiding hospitalization and associated treatment costs.

From previously mentioned clinical trials, two important findings should be underlined: 1) quality of response is relevant to outcome: patients achieving CR fare better than patients in partial response and patients who do not respond to therapy have the shortest time to progression and survival;<sup>7,11</sup> 2) despite better response rates and longer PFS with the combination, none of the three randomised trials<sup>4,7-8</sup> nor a meta-analysis<sup>4</sup> could demonstrate a benefit on OS compared to single-agent fludarabine. Interpretation of this finding is difficult: all studies reflect early follow up and progressive patients were allowed to cross over or receive salvage therapy, so that response to second-line therapy would impact the ability to appreciate a survival advantage. Moreover, it

can not be excluded that the combination regimen selects for resistant clones, unresponsive to salvage therapy.

The introduction of monoclonal antibodies into the therapeutic arena of CLL has revolutionized the possibility of effective treatment of this condition. Pilot data suggested that addition of the monoclonal antibody rituximab to fludarabine<sup>12</sup> and to fludarabine-based combinations may further improve patients' outcome.<sup>13</sup> At MDACC in a phase II non randomized trial the FCR regimen (fludarabine, cyclophosphamide, rituximab) yielded impressive results with ORR of 95%, CR rate of 70% and DFS of 69% projected at 4 yrs<sup>14</sup> in previously untreated patients. In addition, for the first time, a trend to prolonged OS was demonstrated for patients receiving FCR in comparison with historical control patients given fludarabine alone or FC.<sup>15</sup> To confirm these data, results from two ongoing randomized trials are awaited: the CLL8 GCLLSG trial comparing FC to FCR as first-line therapy in patients with no comorbidity and progressive CLL, and the CLL6 UK NCRI study in which a double randomization is scheduled: FC ± mitoxantrone ± rituximab in progressive CLL patients without co-morbidity.

Two other purine analogs, cladribine and pentostatine, also have activity as single agent and have been combined with cyclophosphamide and/or rituximab. The PCR regimen (pentostatine, cyclophosphamide and rituximab) has shown comparable efficacy with respect to fludarabine-based regimens and good tolerance.<sup>16</sup>

Another monoclonal antibody, anti CD52 alemtuzumab, has relevant activity in CLL. Alemtuzumab has been administered as single-agent first line treatment<sup>17</sup> and in combination with fludarabine as second-line therapy<sup>18</sup> The CAM307 trial, a randomized phase III study comparing alemtuzumab with chlorambucil as front-line therapy for patients with progressive B-cell CLL proved that alemtuzumab was superior to chlorambucil for response (ORR 83% vs. 55% ; CR 24% vs. 2% ) and PFS; risk of progression or death was 42% less with alemtuzumab versus chlorambucil ( $p=0.0001$ ).<sup>19</sup> In addition, minimal residual disease (MRD) negativity was observed in 26% (9/34) of CR's in the alemtuzumab arm while none were observed in the chlorambucil arm. Side effects were manageable and predictable: cytopenia, febrile neutropenia and symptomatic infections were comparable in the 2 treatment arms. As expected, CMV reactivation/infection were more frequent with a lemtuzumab. The subcutaneous administration markedly reduces the occurrence of infusional reactions while preserving activity.

Based on the feasibility and efficacy of the association of MoAbs to fludarabine-based regimens, a randomized trial by the French Cooperative Group on CLL (French CLL207) comparing FC associated with rituximab or with s.c. alemtuzumab in medically fit patients >18 yrs with untreated stage C/B disease is planned to begin in 2007, with the aim of defining which of the two MoAbs is more effective in improving FC results.

At present time, the association of fludara-

bine with CTX represents the gold standard of treatment for advanced CLL. In the future, immuno-chemotherapy could become the treatment of choice in CLL patients requiring treatment. The benefit on outcome of combinations and of immuno-chemotherapy, however, is counterbalanced by a global increase in toxicity due to immunosuppression and myelotoxicity. Thus, in patients receiving combination chemotherapy or immuno-chemotherapy an adequate supportive care is important. The following procedures are highly recommended:

- Prophylaxis of tumor lysis syndrome;
- Prophylaxis of *Pneumocystis Carinii* pneumonia: TMP-SMX 1cp x 3 /wk;
- Prophylaxis of *Varicella Zoster* virus: Valacyclovir 1 g/d until T4 cells >200/10<sup>9</sup>/L;
- Irradiation of blood products;
- Administration of G-CSF and EPO;
- Immunoglobulins for hypogammaglobulinemia <4 g/L and infections;
- Antiemetics with oral FC;
- Attention to the occurrence of autoimmune cytopenias (autoimmune hemolytic anemia and pure red cell aplasia).

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#### Concepts to be considered for a modern approach to front-line treatment of CLL

Recent knowledge on the biology of CLL, the identification of biologic markers with prognostic significance and the efficacy results of fludarabine-based regimens and immuno-chemotherapy, have made therapeutic decision in CLL more rationale and somewhat more complex at the same time.

In the future a number of issues will be relevant to design the optimal management of CLL

- change in the definition of remission;
- eradication of minimal residual disease;
- establishment of a biologically-based prognostic stratification and possible design of a

new scoring system;

- formulation of a risk-adapted therapeutic algorithm;
- early and aggressive therapeutic approach for young patients with poor prognostic features;
- the therapeutic choice in elderly patient, taking into account biologic age and co-morbidity;
- innovative treatment strategies.

Since 1996 CR has been assessed by the NCI WG criteria,<sup>1</sup> based on physical examination, blood counts and morphologic examination of bone marrow. Recently, the evidence of residual disease on CT scan or ultrasound examination has questioned the definition of clinical complete remission.<sup>7</sup> Moreover, sensitive test to evaluate residual disease on bone marrow have become available, especially four-color flow cytometry and real-time quantitative polymerase chain reaction (PCR) for the IgHV gene. Residual disease can be demonstrated by these tests in about 60% of patients achieving CR according to NCI WG criteria. In phase II non randomized studies, patients who have no residual disease by these methods have a longer remission duration and survival.<sup>20-22</sup> Therefore, a revision of criteria for CR is needed, taking into account imaging procedures and flow cytometry or PCR data to assess MRD. In addition, investigators should focus on improving the quality of response by achieving a negative status for residual disease in the bone marrow, that may translate into improved outcome. Chemo-immunotherapy and consolidation approaches with monoclonal antibodies are showing the greatest promise in targeting MRD, and several ongoing trials are evaluating different schedules of alemtuzumab or rituximab as consolidation in patients with positive MRD following chemotherapy.

The evolution of management in CLL is towards a risk-adapted approach, in which decision about time of starting therapy and

treatment selection will be based on biologic prognostic markers. Still currently, the decision on starting treatment is according to the NCI WG guidelines.<sup>1,2-25</sup> Patients with advanced stage usually require treatment at presentation, while in early stage treatment initiation is based on demonstration of active and progressive disease. Although the staging systems play a critical role in determining the natural course of the disease, they do not predict for the likelihood of progression especially among early-phase patients. In the past decade, various new biologic markers have been identified as having prognostic relevance on different outcome end-points. Presence of del17p by FISH analysis is uniformly recognized as the most important independent unfavorable parameter. Patients with del17p lack p53 function and are resistant to treatment with standard antileukemia drugs, such as alkylators and purine analogs,<sup>26,27</sup> and rituximab.<sup>28</sup> Given the highly unfavorable impact on response rate and survival, del17p has been recognized as an indication to allotransplant in young patients early during the course of the disease.<sup>29</sup> Also IgVH unmutated status, ZAP70 cytoplasmic expression, del11q, and CD38 expression have been associated with unfavorable outcome, although their prognostic value on different treatment end points is not consistent between different trials.<sup>27</sup>

For the near future, investigators' tasks will be: 1) to define which markers should be used to identify high risk patients and to refine a biologically-based prognostic stratification; 2) to establish whether biologically-defined high risk patients actually benefit from early treatment intervention independently of currently accepted guidelines; and 3) to design treatment regimens in which selection of drugs depends on the biologic profile of the disease.

Clinical prospective trials are ongoing to address these important issues, although employing somewhat different sets of prog-

**Table 2. First-line treatment based on biological risk stratification. Ongoing clinical trials.**

<i>Trial</i>	<i>Patients' selection according to NCI WG criteria and age</i>	<i>Identification of high risk patients according to biological markers</i>	<i>Regimen</i>
LLC0405 GIMEMA Phase II Risk-adapted  1 <sup>st</sup> line	Advanced stage and/ or progressive disease Age <60yrs	<ul style="list-style-type: none"> <li>• Del17p or p53 mutations</li> <li>• Del11q and unmutated IgVH</li> <li>• unmutated IgVH</li> <li>±trisomy12±ZAP70±CD38</li> </ul>	Fludarabine + Alemtuzumab
HOVON 68 Phase III, Randomized  1 <sup>st</sup> line	Symptomatic stage A, B or C Age 18-75	<ul style="list-style-type: none"> <li>• unmutated IgVH</li> <li>±del17p, del11, trisomy12</li> </ul>	Oral FC vs. Oral FC + Risk-adapted s.c. concomitant Alemtuzumab
CLL7 GCLLSG Phase III, Randomized Early, risk-adapted  1 <sup>st</sup> line	Stage A, stage B NOT progressive	Risk factors: <ul style="list-style-type: none"> <li>• Del11q,</li> <li>• Del17p,</li> <li>• unmutated IgVH,</li> <li>• STK&gt;10U/L,</li> <li>• LDT&lt;12mos</li> </ul>	<2 risk factors: W&W ≥2 risk factors: W&W vs FCR
CLL06 UK NCRI phase II Risk-adapted  1 <sup>st</sup> line	Age >18yrs	<ul style="list-style-type: none"> <li>• Del17p</li> </ul>	High-dose methylprednisolone + Alemtuzumab
CLL20 GCLLSG Phase II Risk-adapted  1 <sup>st</sup> or 2 <sup>nd</sup> line	-----	<ul style="list-style-type: none"> <li>• Del17p</li> </ul>	Alemtuzumab + Dexamethasone

FC: Fludarabine plus Cyclophosphamide; FCR: Fludarabine, Cyclophosphamide and Rituximab

nostic markers to select the high risk subgroup and different combinations of drugs and/or MoAbs (Table 2). In patients with del17p/p53 mutations (5–10% of patients at diagnosis) currently available combinations yield very unsatisfactory results,<sup>4,27</sup> and different strategies, bypassing p53-mediated apoptosis, are warranted. Alemtuzumab induces cell death through a p53 independent mechanism and has shown activity in patients with del17p refractory to fludarabine.<sup>30-31</sup> Thus, there is an agreement that patients with abnormalities in the

p53 pathway should receive investigational therapies including alemtuzumab as first-line treatment (Table 2).

It should be reminded, however, that the use of the new biologic markers as the basis for deciding whether and how to treat appears premature, except in the context of prospective clinical trials appositely designed. Until such evidence becomes available, in common practice treatment-related decisions should continue to be based on the NCI WG guidelines.

In planning new treatments attention should

be paid in avoiding toxicity that places patients at significantly increased risk for morbidity and mortality. This issue is particularly relevant dealing with elderly patient. In the community, the median age of CLL patients is around 70 years, whereas the elderly are underrepresented in clinical trials. This limits the ability to generalize results from trials to typical patients encountered in general practice. Age is a major factor in determining ability to tolerate chemotherapy, primarily because older patients tend to have co-morbidities. Co-morbidity is associated with higher risk of death from both CLL-related and CLL-unrelated causes, although the mechanisms of this interference are not well understood. As it has come out from German CLL4 and CLL5 trials,<sup>32</sup> multiple and severe co-morbidity are both independent predictors of survival in patients with advanced stage CLL, and are superior to calendar age per se in predicting survival. Indeed, trial including physically fit patients of all ages<sup>4,8</sup> suggest that the FC combination can be tolerated by selected patients aged over 70 yrs with a very good performance status and might be superior to mono-chemotherapy. Thus, also in elderly patients treatment selection should be aimed at going

beyond symptom palliation to induce the best possible and sustained remissions while minimizing toxicities. After a comprehensive assessment of co-morbid conditions, selection could be between fludarabine-based combinations at full or reduced dose and mono-chemotherapy with fludarabine or chlorambucyl. In patients >75 years or in case of severe co-morbid conditions, low dose single-agent chemotherapy or supportive care only are advisable, in order to pursue the control of symptoms.

The therapeutic approach in CLL has changed from that of palliation to an optimized risk-and fitness-adapted treatment, with the goal of eliminating residual disease and preserving a good quality of life. Ongoing investigations continue to develop more effective regimens as well as new agents with different mechanisms of action and targets. Compounds such as flavoperidol,<sup>33</sup> oblimersen,<sup>34</sup> anti CD23 monoclonal antibody lumiliximab,<sup>35</sup> lenalidomide<sup>36</sup> and small molecules such as 17-AAG<sup>37</sup> have been already assessed in pretreated patients with encouraging results and will be included in a future multi-modal therapeutic approach.

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