

M. Gobbi

Istituto di Ricerche  
Farmacologiche Mario Negri,  
Milano, Italy

## Cyclophosphamide in chronic lymphocytic leukemia first line: final results of Chronic Lymphocytic Leukemia 8 Study



The prognosis of patients with CLL (chronic lymphocytic leukemia) is extremely variable. The overall median survival is about 10 years, but besides patients whose disease has an indolent course and who have a survival no different from that of the general population, there are others who have a rapidly evolving and fatal course.<sup>1</sup>

Clinical staging (Rai *et al.* 1975 and Binet *et al.* 1981) at diagnosis remains the gold standard system for deciding when to treat a patient with CLL.<sup>2</sup>

Patients with low-risk or intermediate-risk disease at diagnosis, without evidence of symptoms or progression are currently not considered to have an indication for treatment outside a clinical trial.<sup>2</sup> The potential benefit, if any, of an early intervention therapy with antileukemic drugs, alone or in combination with monoclonal antibodies, requires further studies. Patients with intermediate stage and evidence of symptoms or progression and virtually all patients with advanced stage disease due to bone marrow infiltration require therapy.<sup>2</sup>

Standard treatment of CLL has evolved from the use of single alkylating agents with low response rates, particularly complete remission (CR) rates,<sup>3</sup> to fludarabine-based combination regimens, which have improved effi-

cacy. In particular, the combination fludarabine and cyclophosphamide (FC) is recognised as the most effective chemotherapy for inducing longer progression-free/treatment free periods. Clinical evidence from three large randomised trials have demonstrated that the combination of FC induce remissions in up to 95% of previously untreated CLL patients with high CR rates (25-40%) and long PFS (median 32-48 months), producing a substantial improvement compared with single-agent fludarabine.<sup>4-6</sup>

However also an highly effective regimen as FC capable of producing good results has not been able to cure advanced CLL. The development of new therapies which are able to eliminate minimal residual disease has high priority.

The efficacy of rituximab in CLL has been demonstrated in several phase II studies particularly in combination with cytotoxic drugs. The addition of rituximab to the fludarabine and cyclophosphamide (FC) combination went some way to fulfilling the clear medical need for improved treatments, markedly improving outcome in both first-line and relapsed setting in non-randomised studies conducted at the MD Anderson Cancer Center in Texas.<sup>7-8</sup>

In order to validate this concept,

randomised studies comparing R-FC with FC alone have been carried out, one in previously untreated patients (CLL-8)<sup>9</sup> and one in relapsed patients (REACH).<sup>10</sup> The pivotal study, CLL-8 was stopped early after review of interim efficacy due to the superior efficacy in favour of the R-FC arm compared with the FC arm: the first efficacy results of the trial presented at ASH 2008 based on the Intent to Treat (ITT) population definitively demonstrated that R-FC improved progression-free survival, the primary efficacy end-point, compared with FC alone. PFS was defined as the time between randomisation and the date of first documented disease progression (NCI 1996), relapse or death by any cause whichever came first. The CLL-8 trial of R-FC versus FC alone was first initiated by the German CLL Study Group (GCLLSG) in 2003. It was a randomised, multicentre, open label, comparative, parallel group, two arm Phase III study of R FC versus FC in patients with previously untreated CD20 positive CLL (according to the National Cancer Institute [NCI] criteria). Patients were randomly assigned to treatment groups through a central randomisation process using the following stratification factors: country and disease stage (Binet stage at pre therapeutic staging). Interim staging was performed after 3 cycles of therapy. All patients who showed at least a partial response after the first three cycles continued treatment according to the protocol up to 6 cycles of therapy. Patients who showed insufficient response (stable or progressive disease) after the first three cycles of treatment discontinued study treatment and were eligible to receive alternative treatment. However, all patients who prematurely discontinued trial treatment remained on the study and were followed for PD, new treatment received and survival. A total of 817 patients was recruited at 190 centres in 11 countries. The baseline characteristics of the recruited population are shown in Table 1.

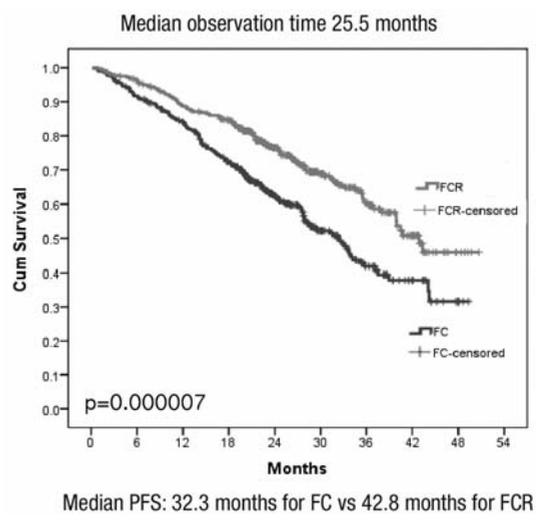
**Table 1.** Patients Intent to Treat population (n=817) of the CLL8 protocol.

	AFC (n=409)	FCR (n=408)
Female	105 (26%)	105 (26%)
Male	304 (74%)	303 (74%)
Median age	61 (range 36-81)	61 (36-80)
Binet A	22 (5.4%)	18 (4.4%)
Binet B	259 (63.6%)	263 (64.6%)
Binet C	126 (31%)	126 (31%)
B symptoms*	197 (48%)	167 (41%)
Median cumulative illness rating scale (CIRS)	1 (range 0-8)	1 (range 0-7)
Trisomy 12	14.4%	9.6%
Del(13q)	59.9%	53.7%
Del(11q23)	22.5%	26.7%
Del(17p13)	9.5%	7.0%

p<0.05

**Table 2.** Response to treatment.

	FC	FCR	p
CR	22.9%	44.5%	<0.01
CR <sub>v</sub>	5.1%	3.3%	0.22
CR <sub>i</sub>	1.9%	2.6%	0.52
nPR	4.9%	2.8%	0.15
PR	50.4%	39.6%	<0.01
SD	6.7%	3.9%	0.08
PD	8.1%	3.3%	<0.01



**Figure 1.** Progression free survival FCR versus FC.

The patient population in CLL-8 included mainly patients with symptomatic Binet stage B disease in need of therapy and Binet stage C disease (95%). The proportion of patients with Binet stage A disease in this study was low. The overall study population comprised more males than females (74% vs. 26%), with a median age of 61 years.

Demographics and disease characteristics assessed at baseline were well balanced between the two treatment arms.

In CLL-8, patients were to receive a total of 6 treatment cycles at intervals of 28 days.

The used dosing of rituximab in combination with chemotherapy in CLL was 500 mg/m<sup>2</sup>. Six cycles of therapy were planned, with a dose adjustment to 375 mg/m<sup>2</sup> for the first cycle only. The chosen regimen and doses used in this study were based on Phase II dose finding studies. Based on data from a dose escalation trial conducted by O'Brien and colleagues,<sup>11</sup> where increasing doses of rituximab monotherapy of up to 2250 mg/m<sup>2</sup> improved response rates in pre treated patients with CLL. The rationale behind starting with a decreased dose of rituximab (375 mg/m<sup>2</sup>) in cycle 1 followed by administration of 500 mg/m<sup>2</sup> in cycles 2-6 was based on the assumption that initially the high number of circulating malignant cells (characteristic of CLL) could increase the risk of severe infusion related reactions, whereas subsequently the relatively low CD20 expression on B cells in CLL, compared with most NHL B cells, could be expected to limit the effectiveness of rituximab at doses shown to be effective in NHL.<sup>12,13</sup>

Both the overall and complete response rates at the end of treatment were significantly increased for patients in the R-FC arm, with CR rates almost doubled.

At follow-up of 25.5 months, progression-free survival, the primary endpoint, was significantly longer in the R-FC arm (median 42.8 months versus 32.3 months,  $p=0.000007$ ).

The PFS benefit was most marked in patients with Binet stage A and B disease ( $p<0.000001$ ) than in stage C, where it did not reach statistical significance ( $p=0.44$ ).

Overall survival was improved for patients in the R-FC arm but the difference did not reach statistical significance (91% vs. 88% at 2 years,  $p=0.18$ ). When so few deaths have occurred, however, it is difficult to draw meaningful conclusions from the survival analysis, and longer follow-up is required.

CLL-8 has also shown a significant improvement in patients achieving minimal residual disease (MRD) eradication. MRD is considered a surrogate marker of overall survival.<sup>14</sup>

The safety data presented the only significant differences increased neutropenia and leucopenia in the R-FC arm: neutropenia 33.7% vs. 21%,  $p<0.0001$  and leucopenia 12.1% vs. 24%  $p<0.0001$ . There was no significant increase in infections between arms for the overall population. Given that many patients with CLL are elderly, they will also have a high degree of pre-existing co-morbidities. Therefore, many patients are unable to tolerate aggressive therapy which induces a consequent myelotoxicity and severe immunosuppression, and the use of chlorambucil in combination with rituximab is thus an attractive therapeutic option for such patients in view of the potentially increased activity compared to chlorambucil alone and the likely good tolerability profile. Data from two large Phase II studies in untreated patients with CLL evaluating the combination of rituximab and chlorambucil will be available in the future. The first of these two trials is a phase II, single arm study conducted by the CLL forum in the UK. The objective is to demonstrate safety and efficacy of the combination of rituximab and chlorambucil in previously untreated patients with CLL. Study treatment consists of chlorambucil (10 mg/m<sup>2</sup>/day p.o. days 1-7 every 28 days) given for a total of 6 cycles in combination

with rituximab (375 mg/m<sup>2</sup> in cycle 1, 500 mg/m<sup>2</sup> in cycles 2-6). Patients not achieving a CR will receive further treatment with chlorambucil single agent using the same schedule until CR or for a maximum of 12 cycles. The trial aims to recruit 100 patients.

The second study is multicenter, Phase II study of chlorambucil plus rituximab as induction therapy followed by randomisation to rituximab maintenance therapy versus observation. A total of 90 patients with previously untreated CD20<sup>+</sup> CLL with age >65 years or age 60-65 years and not suitable for fludarabine-based treatment will be recruited.

Induction Phase will consist of a maximum of 8 courses of therapy (2 courses of chlorambucil alone [8 mg/m<sup>2</sup> on days 1-7] followed by 6 courses of chlorambucil and rituximab [375 mg/m<sup>2</sup>/i.v. on day 1 in course 3; 500 mg/m<sup>2</sup>/i.v. on day 1 in courses 4-8] given every 28 days. Twelve weeks after the last dose of rituximab in the induction phase, patients with CR, CRi or PR will be randomised to receive 12 courses of rituximab maintenance treatment (375 mg/m<sup>2</sup>/i.v. every 8 weeks) or no further treatment. Primary objective of this study is to evaluate the response rate of rituximab in combination with chlorambucil at the end of the induction phase. Bendamustine is a chemotherapy drug that has a properties of both an alkylating agent and a purine analogue. A phase II trial of rituximab (500 mg/m<sup>2</sup>) plus bendamustine has been conducted in 62 evaluable patients with relapsed and refractory CLL. An overall response rate of 77.4% was achieved, with 14.5% of patients achieving a complete response. Taking the good tolerability profile of bendamustine into account, these data are promising. A phase III trial R-bendamustine versus R-chlorambucil in previously treated and untreated patients is being initiated.<sup>15</sup> The new rituximab-based combinations above mentioned show promising efficacy in CLL patients who may not tolerate FC.

## References

1. Montserrat E, Moreno C Chronic Lymphocytic leukemia: a short overview *Annals of Oncology* 2008;19:320-5.
2. Hallek M, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on chronic lymphocytic leukemia updating the National Cancer Institute Working Group 1996 Guidelines *Blood* 2008;111:5446-56.
3. Rai KR, Peterson BL, Appelbaum FR, et al. Fludarabine compared with chlorambucil as primary therapy for chronic lymphocytic leukemia. *N Engl J Med* 2000; 343:1750-7.
4. Eichhorst BF, Busch R, Hopfinger G, et al. Fludarabine plus cyclophosphamide versus fludarabine alone in first-line therapy of younger patients with chronic lymphocytic leukemia. *Blood* 2006;107:885-91.
5. Flinn IW, Neuberg DS, Grever MR, et al. Phase III trial of fludarabine plus cyclophosphamide compared with fludarabine for patients with previously untreated chronic lymphocytic leukemia: US Intergroup Trial E2997. *J Clin Oncol* 2007;25:793-8.
6. Catovsky D, et al. Assessment of fludarabine plus cyclophosphamide for patients with chronic lymphocytic leukemia (the LRF CLL-4 trial): a randomized controlled trial. *Lancet* 2007;370:230-9.
7. Tam C, O'Brien S, Wierda W, et al. Long term results of the fludarabine, cyclophosphamide and rituximab regimen as initial therapy of chronic lymphocytic leukaemia. *Blood* 2008;(2008):1-21.
8. Wierda W, et al. Chemoimmunotherapy with fludarabine, cyclophosphamide and rituximab for relapsed and refractory chronic lymphocytic leukemia. *J Clin Oncol* 2005; 23:4070-8.
9. Hallek M, et al. Chemoimmunotherapy with fludarabine (F), cyclophosphamide (C) and rituximab (R) FCR versus fludarabine and cyclophosphamide (FC) improves response rates and progression-free survival in previously untreated patients (pts) with advanced chronic lymphocytic leukemia (CLL). *Blood ASH meeting (abstract 385) Dec 2008.*
10. Robak et al. Rituximab, fludarabine and cyclophosphamide (R-FC) prolongs progression free survival in relapsed or refractory chronic lymphocytic leukemia (CLL) compared with FC alone: final results from the international randomized phase III REACH trial. *Blood ASH meeting (abstract LBA-1) Dec 2008*
11. O'Brien SM, Kantarjian H, Thomas DA, et al. Rituximab dose-escalation trial in chronic lymphocytic leukemia. *J Clin Oncol* 2001;19:2165-70.
12. Almasri, N.M. et al. Reduced expression of CD20 antigen as a characteristic marker for chronic lymphocytic leukemia. *American Journal of Haematology* 1992;40: 259-63.
13. Ginaldi L, et al. Levels of expression of CD19 and CD20 in chronic B cell leukaemias. *Journal of Clinical Pathology* 1999;51:364-69.
14. Bottcher S, et al. Quantitative MRD Assessments Predict Progression Free Survival in CLL Patients Treated with Fludarabine and Cyclophosphamide with or without Rituximab – a Prospective Analysis in 471 Patients from the Randomized GCLLSG CLL8 Trial *Blood ASH meeting (abstract 386) Dec 2008.*
15. Fisher K, et al. Bendamustine in combination with rituximab (BR) for patients with relapsed chronic lymphocytic leukemia (CLL): a multicentre phase II trial of the german Study Group (GCLLSG). *Blood ASH meeting (abstract 330) Dec 2008.*