

Review / Revisão

## State of the art in the treatment of CLL

### *“Estado da arte” no tratamento da leucemia linfocítica crônica*

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*Chronic lymphocytic leukemia (CLL) is the most common form of leukemia in adults in the Western world and predominantly affects the elderly. Although CLL remains incurable with standard treatments, important progress in treatment, which classically is given only when the disease has become symptomatic, has been made in recent years. The diagnosis of CLL does not necessarily convey the necessity of treatment. However, treatment has classically been indicated in symptomatic or progressive disease according to criteria defined by stage of disease. Treatment of CLL has been markedly improved by highly effective new drugs and drug combinations. Rev. Bras. Hematol. Hemoter. 2009;31(Supl. 2):51-56.*

**Key words:** *Chronic lymphocytic leukaemia; chemotherapy; rituxumab.*

### Introduction

Until the late 1980s, only chlorambucil- and cyclophosphamide – containing regimens had shown relatively good activity in CLL but rarely led to complete remissions.<sup>1,2</sup> The purine analog fludarabine emerged rapidly as the standard second-line treatment in CLL in the 1990s and recently has also become an established first-line treatment option in CLL. Its use in monotherapy or combination therapy has resulted in higher response and event-free survival, but increased overall survival has been difficult to document, partly because of subsequently administered additional therapies.<sup>3</sup> Newer therapeutic approaches include autologous and allogeneic stem cell transplantation (the latter being potentially curative but limited in use by high treatment-associated morbidity and mortality),<sup>4</sup> and antibodies, such as rituximab and alemtuzumab.<sup>5,6,7</sup> Improvements in supportive care, including better use of prophylactic antibiotics and antiviral medications, may have contributed to the improvements seen in survival, especially among older patients.

### Evolution of the treatment

For almost forty years since its introduction in the 1950s, chlorambucil was the mainstay in the treatment of patients with chronic lymphocytic leukemia (CLL). While this resulted

in the palliation of symptoms, it had only a modest impact, if any, on survival. The lack of truly effective therapies, coupled with the notion that in most instances the disease has an indolent course, led to a nihilistic and detrimental approach towards the management of CLL. In the 1970s, Rai and Binet independently developed simple and reproducible prognostic systems allowing patients with CLL to be classified into different risk groups, making it clear that in some instances the prognosis of patients with CLL is extremely poor. Shortly afterwards, more effective therapies for CLL, in particular purine analogs, became available. This revived interest in CLL, and made it possible to design clinical trials based on the individual risk of each patient.

Studies carried out in the 1970s demonstrated that, for patients in early-stage CLL, chlorambucil administered immediately after diagnosis did not yield better results than treatment with the same agent upon disease progression, and that patients in advanced stage combination chemotherapy regimens used at that time (i.e., cyclophosphamide-vincristine-prednisone [COP]; cyclophosphamide-doxorubicin-prednisone [CAP]; cyclophosphamide-doxorubicin-vincristine-prednisone [CHOP]) produced higher response rates than alkylating agents but not longer survival. It was also found that fludarabine produced not only higher response rates but also a longer disease-free progression than chlorambucil, a first real advance in the treatment of CLL. More recently, treatment

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of CLL has switched to chemotherapy regimens built around purine analogs, chiefly fludarabine. Purine analogs, and in particular fludarabine, are the most active chemotherapeutic agents in CLL and form the base for most of the effective combination therapies. In particular, the combination fludarabine and cyclophosphamide (FC) is recognized as the most effective chemotherapy for inducing longer progression-free/treatment free periods. The results of three large trials that overall randomized more than 900 patients between fludarabine and fludarabine plus cyclophosphamide have recently been reported.<sup>8,9,10</sup> All three trials showed a significant improvement in complete response rate for the fludarabine plus cyclophosphamide combination; over double that of fludarabine monotherapy. In addition, fludarabine plus cyclophosphamide doubled the progression-free survival rate compared to that achieved with fludarabine monotherapy; even so, a highly effective regimen as FC capable of producing good results has not been able to cure advanced CLL. In the LRF CLL4 trial there was no upper age limit and 30% of the patients recruited were over 70 years of age. It was somewhat surprising that even in patients over 70 years old there was no significant increase in treatment-related toxicity or mortality. In addition, the benefit in response rates for the combined regimen of fludarabine plus cyclophosphamide was seen in all age groups. There was, however, no improvement in overall survival, which is probably due to a cross-over from fludarabine to fludarabine plus cyclophosphamide at progression. However in the LRF CLL4 trial there was extensive quality of life assessment which showed that patients who achieved a complete or nodular partial remission had a significantly better quality of life over the next two years. It was hypothesized that patients treated with fludarabine plus cyclophosphamide will also experience improved quality of life.

Therefore, the combination of fludarabine plus cyclophosphamide is now considered the gold standard for the initial treatment of CLL, even for elderly patients without co-existing morbidities. The combination of FC induces 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>9,11,12</sup>

Recently Bosch et al. reported on the results of adding mitoxantrone to fludarabine and cyclophosphamide (FCM) in relapsed, refractory<sup>13</sup> and untreated patients.<sup>14</sup> FCM produced high overall response rates with 78% of previously treated patients achieving a complete or partial remission. FCM also appeared to be effective in previously untreated patients with CLL, since 55% achieved a complete remission and, in a minority of patients with CLL, MRD was below the level of detection by highly sensitive techniques. In fact the only patients who were refractory to FCM were eight patients with deletion of the short arm of chromosome 17 (p53 deleted). The development of new therapies which are

able to eliminate minimal residual disease then became one of the most important targets and assumed high priority. The logical approach was to combine rituximab with the most effective front-line therapy for CLL, namely fludarabine plus cyclophosphamide. 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 by markedly improving outcomes in both first-line and relapsed settings in non-randomized studies conducted at the MD Anderson Cancer Center in Texas.<sup>7,15</sup>

This combination (FCR) was recently reported to produce extremely high response rates in a group of 300 previously untreated patients, with an impressive overall response rate of 95% and 72% of patients achieving a complete remission by NCI response criteria. In addition, this series of patients in whom detectable disease was eradicated according to sensitive PCR-based assays, had a very small chance (<10%) of progression at 5 years follow-up. In line with the above, the Cancer and Leukemia Group B (CALGB) conducted a phase II study (CALGB 9712) to determine the efficacy, safety, and optimal administration schedule of rituximab with fludarabine in previously untreated patients with CLL; rituximab was given either after fludarabine or concurrently. The overall response rate with the concurrent regimen was 90% (47% complete response [CR]) compared with 77% (28% CR) in the sequential arm, the conclusion being that rituximab administered concurrently was quite effective at inducing CR and that it appeared to be superior to fludarabine (an agent with which only around a 20% CR rate is obtained) and sequential fludarabine followed by rituximab. It should be noted however, that patients allocated in the sequential arm received less rituximab (4 doses) than those in whom rituximab was given concurrently (10-11 doses). Because of this, the optimum schedule for rituximab cannot be considered as having been definitively settled.

In order to validate this combination, randomized studies comparing FCR with FC alone have been carried out, one in previously untreated patients (CLL-8)<sup>16</sup> and one in relapsed patients (REACH).<sup>17</sup> The pivotal study, CLL-8 was topped early after review of interim efficacy due to the superior efficacy in favor of the FCR arm. The first efficacy results of the trial presented at ASH 2008 based on the intent to treat population definitively demonstrated that FCR improved progression-free survival, the primary efficacy endpoint. PFS was defined as the time between randomization and the date of first documented disease progression (NCI 1996), relapse or death by any cause, whichever came first. The CLL-8 trial was first initiated by the German CLL Study Group (GCLLSG) in 2003. It was a randomized, multicentre, open label, comparative, parallel

group, two arm phase III study in patients with previously untreated CD20+ CLL (according to the NCI criteria). Patients were randomly assigned to treatment groups through a central randomization 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 of 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 in the study and were followed for PD, new treatment received and survival. A total of 817 patients were recruited at 190 centers in 11 countries. Both the overall and complete response rates at the end of treatment were significantly increased for patients in the FCR arm, with CR rates almost doubled.

At follow-up of 25.5 months, progression-free survival, the primary endpoint, was significantly longer in the FCR 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 FCR 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 a longer follow-up is required.

Moreover CLL-8 also showed a significant improvement in patients achieving minimal residual disease (MRD) eradication. MRD is considered a surrogate marker of overall survival.<sup>18</sup> In short, the fludarabine, cyclophosphamide, and rituximab (FCR) combination therapy produces the largest proportion of complete responses (CRs) ever reported in CLL and, even more importantly, patients treated with this regimen have better outcomes, based on historical comparisons, than similar patients treated with fludarabine or fludarabine and cyclophosphamide or mitoxantrone. In addition, the relationship between the quality of the response and clinical outcome was confirmed. Furthermore, patients achieving CR with no detectable minimal residual disease (MRD) – albeit not studied by the technique currently considered preferable – do much better than the rest, thus confirming that, whenever possible, obtaining MRD negative status is a desirable treatment endpoint in CLL.<sup>2</sup> Notably, FCR abrogates the poor prognostic significance of classic variables, which indicates that it actually changes the natural history of CLL, the best that can be said of any new therapy for neoplastic disorders. On the downside, there

are manageable toxicities, the poor response of patients with chromosome 17 abnormalities, the risk of secondary myelodysplasia, and the fact that all patients are eventually projected to relapse.

Based on this report, should FCR be considered the new gold standard for CLL therapy? It is still difficult to answer this question: initial data from two large phase II studies in untreated patients with CLL evaluating different combinations of rituximab have been recently presented: the first of these two trials is a phase II, single arm study conducted by the CLL forum in the UK (UK CLL207). The objective is to demonstrate safety and efficacy of the combination of rituximab and chlorambucil in previously untreated patients with CLL: study treatment consists in 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 and 500 mg/m<sup>2</sup> in cycles 2-6). Patients not achieving CR will receive further treatment with chlorambucil as a 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 a multicentre, phase II study of chlorambucil plus rituximab as induction therapy followed by randomization to rituximab maintenance therapy vs. observation. A total of 90 patients with previously untreated CD20+ CLL with ages > 65 years or age 60-65 years and not suitable for fludarabine-based treatments will be recruited (ML21445 Roche).

Induction phase will consist in 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 and 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 in CR, CRi or PR will be randomized to receive 12 courses of rituximab maintenance treatment (375 mg/m<sup>2</sup> i.v. every 8 weeks) or no further treatment. The primary objective of this study was to evaluate the response rate of rituximab in combination with chlorambucil at the end of the induction phase.

The currently used response criteria in CLL were published in 1996 prior to the advent of purine analogs, monoclonal antibodies and stem cell transplantation as conventional therapies in CLL.<sup>19</sup> A patient with complete remission was defined as one in whom the clinical examination was normal with an essentially normal blood count and a morphologically normal bone marrow. These criteria have proven to be extremely useful to allow comparisons between the results of trials from the various collaborative groups. However, it is now clear that there can be as many as 2% CLL cells in the marrow of a patient who is in an NCI complete remission. This has driven the development of techniques that can detect extremely low levels of CLL. The two most used sensitive approaches are molecular techniques: allele-

specific oligonucleotide polymerase chain reaction (ASO-PCR) directed against the immunoglobulin gene of the CLL clone, and multi-parameter, four-color flow cytometry (MRD flow).<sup>20</sup> Both of these techniques detect a single CLL cell in 10000 leukocytes or more. ASO-PCR is slightly more sensitive than MRD flow but has several disadvantages which make flow cytometry more likely to become the standard approach. In all the series that have been reported, whether treated with combination chemotherapy, chemoimmunotherapy, monoclonal antibody-based therapy or stem cell transplantation, patients who achieve a negative MRD status have better progression-free and overall survival. However in all of these series the aim of therapy was to try to eradicate MRD and therefore they do not prove beyond doubt that MRD is critical (the patients achieving MRD negativity may have had a biologically better risk and, therefore, could have had a better survival, regardless of therapy, than their more resistant counterparts). Therefore the next series of clinical trials will address, in a randomized fashion, whether attempting to eradicate MRD is an important endpoint of therapy.

In recent years, chemoimmunotherapies that combine cytotoxic agents and monoclonal antibodies have been studied intensively for the treatment of B-cell chronic lymphocytic leukemia (CLL). Of particular interest are fludarabine-based combination regimens such as FluCam (fludarabine and alemtuzumab), FCR (fludarabine, cyclophosphamide, and rituximab), and FCCam (fludarabine, cyclophosphamide, and alemtuzumab). Alemtuzumab (Campath®), a humanized anti-CD52 monoclonal antibody, is currently approved in the United States as first-line, single-agent treatment of CLL and in the European Union as first-line treatment of CLL when fludarabine combination chemotherapy is not appropriate. When administered in the standard dosing schedule [30 mg intravenously (IV) 3 times a week (TIW) for up to 12 weeks], alemtuzumab demonstrated an overall response rate (ORR) of 33%-50% in fludarabine-refractory patients [complete response (CR) rate, 0-4%] 5-7 and 83%-87% (CR rate, 19%-24%) in previously untreated patients. Moreover, it is important to note that at this time, only limited data are available on the pharmacokinetics (PK) of alemtuzumab, and the approved dosing schedule of alemtuzumab monotherapy was developed empirically in the absence of detailed PK studies. Alemtuzumab is approved for fludarabine-refractory CLL: Rituximab (Rituxan® or MabThera®) has also been used, both alone and in combination, in large numbers of patients with CLL. Rituximab, used as a single agent at the conventional dose of 375 mg/m<sup>2</sup>/weekly for 4 weeks, has little efficacy in relapsed or refractory CLL since only partial remissions occur in a minority of patients and these remissions only persist for a few months. The partial remission rate increases as the dose of rituximab increases, but again complete remissions are not achieved and the doses used are extremely high (up to 2250

mg/m<sup>2</sup>). Conventional doses of rituximab have also been reported to give higher response rates in untreated CLL (up to 50% of patients) but still very few complete remissions and these responses are not durable. Therefore rituximab has no proven role as a single agent but will probably find its role in combination with chemotherapy.

In contrast, alemtuzumab is effective as a single agent in refractory and untreated CLL. The response rates to alemtuzumab, used as a single agent, in relapsed, refractory CLL range between 33% and 50% with up to 25% of patients achieving complete remissions.<sup>6,21</sup> The most important predictor of response to alemtuzumab is the presence or absence of significant lymphadenopathy. Patients with massive lymphadenopathy have a very low response rate and in those patients a more effective strategy is to try to control the lymphadenopathy prior to alemtuzumab therapy. Two recently reported phase II trials of subcutaneous alemtuzumab in fludarabine-refractory CLL suggest that the drug has a similar efficacy when given subcutaneously, but has a much improved toxicity profile when administered by this route. A phase II trial of subcutaneous alemtuzumab in previously untreated CLL was reported by Lundin *et al.*<sup>22</sup> in 2002, with response rates being in excess of 80% with a reasonable toxicity profile. This led to the CAM307 trial in which 297 previously untreated patients with CLL were randomized to receive either chlorambucil or intravenous alemtuzumab. Somewhat surprisingly the toxicity to alemtuzumab was not significantly greater than that in the chlorambucil arm of the trial. In fact there was little difference in treatment-related toxicity between the two arms. The higher overall and complete response rates for alemtuzumab were significantly higher than those in response to chlorambucil. In the Italian GIMEMA study CLL0405, CLL patients are treated according to risk factors with FluCam + Auto vs. FC x 4/6 cycles if low risk. Until now, 90 patients have been enrolled and the study is still ongoing.

Treatment of patients refractory to these treatments is particularly challenging and should be decided only upon a careful evaluation of the disease, patient characteristics, and prognostic factors. Refractory disease should be clearly separated from relapsing disease. The only curative therapy for patients with CLL, including those with refractory disease, is allogeneic stem cell transplantation. However, the use of allogeneic transplantation is limited because of the advanced age of most patients and the high transplant-related mortality (TRM). Transplants with non-myeloablative regimens may reduce TRM and allow more patients to receive transplants more safely, especially those patients in whom an allogeneic transplantation is not feasible or in whom it is deemed inappropriate. Finally, to investigate mechanisms to overcome resistance to therapy in CLL and to identify patients that might benefit from early, intensive therapies (e.g., based on biological markers) constitute a challenge that still needs active investigation.



## Conclusions

Many questions are still unanswered in spite of the enormous and continuing progress achieved in CLL therapy. Among these: is FCR necessary for all patients? Should FCR be given as up-front therapy or could it be part of a more conservative, sequential therapy? Can FCR toxicity be reduced? What is a patient's fate once progression occurs? Is retreatment safe? Given that all patients eventually relapse, should some kind of maintenance therapy be considered? How should lessons from this study be applied to the predominantly elderly or physically unfit population of patients with CLL?

All in all, however, it is easy to predict that FCR will become an important new gold standard for CLL therapy. Treatment of patients with CLL is rapidly evolving, and we can surely expect dramatic improvements in the management of this common form of leukemia based on its biological and clinical diversity, most likely not with a single, unique gold standard therapy, but different and individualized treatment approaches.

There are a number of novel agents that are now being developed in CLL. These include flavopiridol which, despite disappointing results following the initial clinical studies, appears to be potentially very effective with a modified dose schedule. Recently both thalidomide and lenalidomide have been reported to have activity in CLL and are being developed for use in the disease. Bcl-2 is upregulated in the vast majority of patients with CLL and this has led to the use of Bcl-2 antisense in initial studies in CLL. A variety of new monoclonal antibodies to pre-existing and novel targets are now being studied in CLL.

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## Resumo

*A leucemia linfóide crônica (LLC) é a mais frequente leucemia dos adultos no mundo ocidental e acomete principalmente pacientes idosos. Embora esta doença continue incurável, progressos importantes no tratamento, habitualmente, apenas dado a pacientes sintomáticos, têm sido obtidos nas últimas décadas. O diagnóstico de LLC não obrigatoriamente exige terapia. Entretanto, tratamento tem sido classicamente indicado em pacientes sintomáticos ou com doença progressiva de acordo com os critérios definidos pelo NCI. A resposta terapêutica tem sido marcadamente melhor com novas drogas e combinações altamente eficientes. O autor faz aqui uma breve revisão do assunto. Rev. Bras. Hematol. Hemoter. 2009; 31 (Supl. 2):51-56.*

**Palavras-chave:** Leucemia linfocítica crônica; quimioterapia; rituximabe.

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