

Fludarabine plus cyclophosphamide combination: a new standard for first-line therapy in chronic lymphocytic leukaemia



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A B S T R A C T

Phase III studies have demonstrated that the purine analogue fludarabine is an effective first-line agent in the primary treatment of B-cell chronic lymphocytic leukaemia (CLL) with superior efficacy to chlorambucil. However, although fludarabine improves responses, including an improvement in progression-free survival (PFS) in some studies, this remains sub-optimal. Thus, combination treatment with fludarabine has been considered. Both fludarabine and the alkylating agent cyclophosphamide are dose-dependently cytotoxic, and the extent of apoptosis when they are combined is more than the additive effect for each individual agent. Such increased apoptosis may be due to a synergistic effect between alkylation by cyclophosphamide and inhibition of DNA repair by fludarabine. Phase II studies in first-line CLL have shown that the efficacy of fludarabine plus cyclophosphamide (FC) is promising, with response rates often exceeding 90%. Data from Phase III studies have demonstrated that FC induces significantly higher response rates than fludarabine monotherapy across all patient age groups, including relatively young patients. PFS was also significantly longer with FC than with fludarabine monotherapy. Fludarabine is available in either intravenous or oral formulations and both appear to be similarly effective.

The rationale for fludarabine plus cyclophosphamide in chronic lymphocytic leukaemia

The purine analogue fludarabine is one of the most potent cytotoxic drugs currently available for the treatment of B-cell chronic lymphocytic leukaemia (CLL). Its cytotoxicity is due to its ability to induce apoptosis, and it is available in both intravenous and oral formulations.^{1,2} The bioavailability of oral fludarabine is approximately 55% of a dose via the intravenous route;³ systemic exposure following an oral dose of 40 mg/m² has been found to be equivalent to an IV dose of 25 mg/m². The oral formulation of fludarabine offers potential benefits over the IV form because it is

easy to administer, facilitates outpatient treatment and is more convenient for both healthcare practitioners and patients. In addition, similar efficacy to the IV form has been demonstrated.^{1,2} It is well tolerated in patients with previously untreated B-cell CLL, and its safety profile is similar to that of the IV formulation, with the exception of increased gastrointestinal toxicity, which is generally mild-to-moderate and usually does not require a modification of treatment. Quality of life (QOL) scores are not adversely affected by use of the oral formulation, and it may even be associated with improved emotional and insomnia scores.¹ However, these findings need to be interpreted with caution, as such improvements could also be due to the *response shift* phenomenon. For exam-

ple, a patient's impression that treatment is improving their condition may reduce anxiety, which could in turn reduce insomnia. The oral formulation is recommended by the UK National Institute of Clinical Excellence (NICE) over the intravenous form on the basis of better cost effectiveness (cost per course: UK£3000 vs. UK£5300); use of the intravenous form should be reserved for when the oral form is contraindicated.⁴

Superiority of fludarabine over chlorambucil for the primary treatment of CLL has been demonstrated in a phase III clinical trial.⁵ In this study, eligible patients with previously untreated CLL received 10- to 30-minute IV infusions of fludarabine 25 mg/m² on days 1–5 (n=179), oral chlorambucil 40 mg/m² on day 1 (193) or combination therapy with IV fludarabine 20 mg/m² on days 1–5 plus oral chlorambucil 20 mg/m² on day 1 (137), with all regimens repeated every 28 days. Patients with an additional response at each monthly evaluation continued to receive the assigned treatment for a maximum of 12 cycles. Fludarabine was associated with higher complete remission (CR) rates and longer duration of remission and progression-free survival (PFS) than chlorambucil. However, the improved PFS with first-line fludarabine at 25–32 months was still deemed suboptimal, particularly in younger patients.

Other phase III trials have demonstrated that fludarabine is superior to a combination of cyclophosphamide, adriamycin and prednisone for the treatment of CLL.^{6,7} When used as first-line therapy, fludarabine significantly increased the duration of remission, compared with the three-drug regimen, and was associated with significantly greater rates of CR and partial remission (PR) when used as second-line therapy. However, median overall survival was not increased by fludarabine in any of these phase III studies, but many patients who received fludarabine subsequently also

received other chemotherapeutic agents during the course of their disease confounding the interpretation of the survival time data. In addition, many patients randomized to alkylating agent therapy receive a purine analogue when they relapse further confounding the interpretation of the effect of fludarabine on overall survival.^{5,7}

Both fludarabine and mafosfamide (the active form of cyclophosphamide *in vitro*) are dose-dependently cytotoxic to cells from B-cell CLL. *In vitro* studies have demonstrated that the exposure of CLL cells to the combination of fludarabine plus mafosfamide results in an increased, synergistic cytotoxicity compared with either agent alone.^{8,9} When B-cell CLL cells were incubated for 48 hours with fludarabine and mafosfamide alone and in combination, the degree of cytotoxicity seen with the combination was significantly greater than the additive cytotoxicity of the two agents, indicating the presence of synergy. Notably, the addition of mafosfamide significantly increased fludarabine-induced apoptosis of CD19⁺ ($p=0.007$), but not CD3⁺, cells. A similar synergistic effect has been seen in another study in which fludarabine plus mafosfamide was associated with greater apoptosis than with the individual agents.⁹ The mechanism underlying this synergy appears to be that DNA repair mechanisms in CLL cells, initiated in response to cyclophosphamide exposure, appear to be inhibited by fludarabine.¹⁰

Efficacy and safety of fludarabine plus cyclophosphamide in chronic lymphocytic leukaemia

Data from clinical studies to date have generally found fludarabine combined with cyclophosphamide (FC) to be an effective and relatively well-tolerated regimen for the treatment of CLL. Data from phase II studies inves-

tigating the use of FC in CLL have indicated promising efficacy, with response rates ranging from 63.9 to 100%, and >90% in most studies for both previously untreated and pre-treated patients.¹¹⁻¹⁷

For example, in one such study, 36 CLL patients (median age 59 years) received a regimen of fludarabine 30 mg/m² plus cyclophosphamide 250 mg/m², both as a 30-minute IV infusion on days 1–3, with treatment cycles repeated every 28 days.¹³ Twenty-one patients had previously received 1–3 different treatments and 15 patients had received no prior therapy. Treatment responses according to the National Cancer Institute criteria were achieved in 29/32 (91%) evaluable patients, with CR in 5 patients and PR in 24. Grade 3 and 4 neutropenia and leucocytopenia were the most commonly reported adverse events (69% and 55% of patients, respectively). Anaemia and thrombocytopenia each occurred in only 17% of patients and other grade 3 and 4 adverse events, including allergy, disorientation, dysrhythmia, incontinence, phlebitis, and elevated bilirubin levels, occurred in <3% of patients; all low-grade adverse events were uncommon. No treatment-related deaths or grade 3 or 4 infections were reported.

In another study, 32 patients with newly diagnosed (47%) or relapsed/refractory (53%) CLL received six courses of fludarabine 30 mg/m² IV plus cyclophosphamide 300 mg/m² on days 1–3; relapsed/refractory patients had previously received ≤5 different chemotherapy regimens.¹⁶ CR was achieved in 32 (44%) patients and 16 (50%) achieved a PR. As expected, the CR rate was higher in previously untreated patients at 9/15 (60%), compared with 5/17 (29%) previously treated patients; however, the CR rate for previously treated patients with disease that is refractory to other therapies is relatively promising. Myelosuppression was the most frequent cause of toxicity, with 10/32 (31%) of patients experiencing

severe neutropenia (polymorphonuclear neutrophil count <0.5×10⁹/L). Bacterial infections were also common, being reported in 28% of patients, with 70% of these occurring in previously treated patients. After a median follow-up of 24 months (range 8–48), 20/32 (62%) patients remained alive and 14/32 (44%) were free from progression. Median overall survival and median time to progression were 35 and 25 months, respectively.

Front-line therapy with fludarabine plus cyclophosphamide

Data to date on the efficacy and safety of FC for front-line treatment of CLL indicate that this combination provides better overall response rates, PFS and treatment-free survival than fludarabine monotherapy. FC is associated with acceptable adverse events in these studies. One phase II study has evaluated the clinical and molecular response, toxicity and complications associated with the FC for front-line treatment of CLL.¹⁷ Patients, aged 43–74 years (mean: 60 years), with untreated CLL (n=26) received 3 days' treatment with IV fludarabine 25 mg/m² plus cyclophosphamide 300 mg/m² repeated every 28 days. Initially six cycles were planned, but this was decreased to four due to the high rate of haematological toxicity seen in the first patients to receive treatment. Among 20 evaluable patients, 15 (75%) achieved a CR and 3 (15%) achieved a PR (overall response rate of 90%). Disease progression after 21 months of follow-up was reported in only one patient, who had an initial PR. Less haematological toxicity was reported in the patients who received 4 rather than 6 cycles of therapy. Other toxic effects were not significantly affected by the number of cycles; however, they mainly occurred after the third course of treatment. The investigators concluded that four courses of treatment appeared to

be the most beneficial in terms of efficacy and tolerability.

A Phase III randomised study of FC versus fludarabine alone as front-line therapy in CLL has demonstrated the therapeutic benefits of this treatment combination.¹⁸ Patients in the combination treatment arm of the study received IV fludarabine 20 mg/m² on days 1–5 plus IV cyclophosphamide 600 mg/m² on day 1 followed by a course of filgrastim. Patients in the monotherapy arm received IV fludarabine 25 mg/m² on days 1–5. The median age of patients was 62 years (range 34–86). Patients received up to 6 cycles of therapy; 57% of patients received all 6 cycles. Preliminary response data available for 246 patients showed CR in 22.4% of patients in the combination treatment arm (n=125), compared with 5.8% of patients in the fludarabine monotherapy arm (n=121). PR rates were also greater among the combination therapy recipients than the monotherapy recipients (48.0 vs. 43.8%). The overall response rate was significantly greater among patients receiving combination therapy than those receiving monotherapy (70.0 vs. 49.6%; $p=0.001$). Preliminary estimates of the median PFS time were also significantly better for patients receiving FC than for those receiving monotherapy (41.0 vs. 17.7 months; $p<0.001$). Each treatment arm contained one patient who developed fatal infection secondary to grade 3 neutropenia. There was a trend for a greater incidence of severe adverse events with FC compared with fludarabine alone. The overall rates for non-haematological grade 4+ events and infections in the FC arm were both 17%, while the respective rates in the fludarabine monotherapy arm were 13 and 11%; the between-group differences were not statistically significant.

Combination chemotherapy with FC has also been compared with fludarabine monotherapy for first-line treatment of younger patients with CLL.¹⁹ In this Phase III study, 375 patients

(aged <66 years) with predominantly advanced CLL were randomly assigned to receive either monotherapy with IV fludarabine 25 mg/m² on days 1–5 or combination therapy with IV fludarabine 30 mg/m² plus IV cyclophosphamide 250 mg/m² on days 1–3. Both regimens were repeated every 28 days and administered for a maximum of 6 courses. The CR rate was significantly greater with combination therapy than monotherapy (24 vs. 7%; $p<0.001$), as was the overall response rate (94 vs. 83%; $p<0.001$). Combination therapy was also associated with significantly longer median PFS than monotherapy (48 vs. 20 months) and significantly longer treatment-free survival (37 vs. 25 months; $p<0.001$), although no improvement in median overall survival was detected (Figure 1). There was a significantly greater incidence of thrombocytopenia and leucocytopenia with combination therapy, compared with monotherapy, but the number of severe infections was not increased significantly. Similar results have recently been reported from the LRF CLL4 trial in the United Kingdom which included patients aged >70 years of age.

Fludarabine plus cyclophosphamide in combination with biological agents

Studies investigating FC plus rituximab for the treatment of patients with CLL who have had at least one line of prior treatment have reported complete and overall response rates of 28 and 72%, respectively, and an estimated median overall survival of 42 months.²⁰ In addition, the same group have reported their experience of FCR in 300 patients with previously untreated CLL with an overall response rate of 95% and 72% patients achieving a complete remission.²¹ These figures are greater than those for FC in patients with similar pre-treatment characteristics. Patients who have

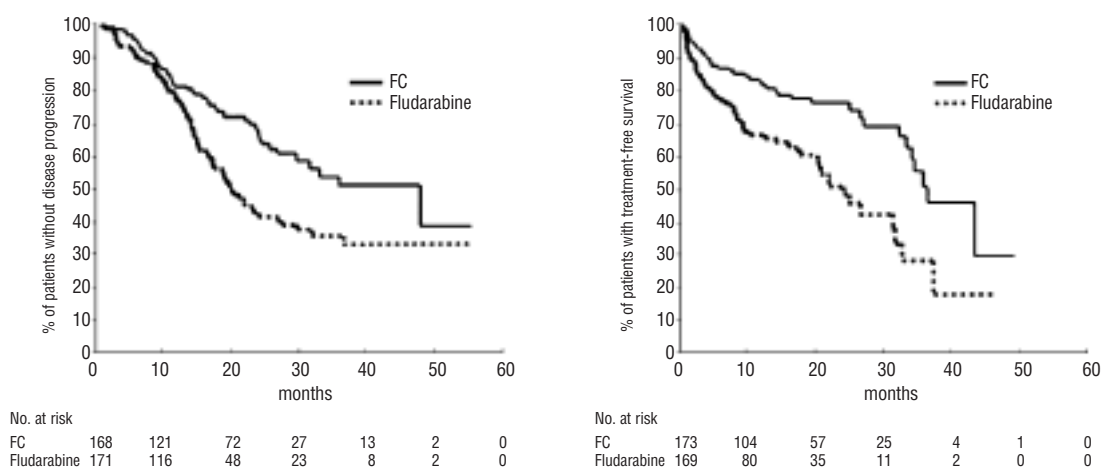


Figure 1: Median progression-free survival (PFS) and treatment-free survival in patients with chronic lymphocytic leukaemia (CLL) treated with fludarabine plus cyclophosphamide (FC) compared with fludarabine alone.¹⁹ Reproduced with permission from Eichhorst B, *et al.* Fludarabine plus cyclophosphamide versus fludarabine alone in first-line therapy of younger patients with chronic lymphocytic leukaemia. *Blood* 2006;107:885–91.

been treated with the three-drug regimen have also been able to receive more courses for therapy, which may, at least in part, contribute to the higher response rates. Initial data indicate that the three-agent combination is associated with a greater incidence of neutropenia and thrombocytopenia, although the incidence of infections does not appear to be increased. While these data indicate a potential superiority of the three-agent combination over the two-agent combination, randomized studies comparing the two regimens are ongoing.

A recent study has investigated the efficacy and safety of granulocyte-macrophage colony-stimulating factor (GM-CSF) therapy to reduce myelosuppression following a course of FC in patients with CLL or low-grade non-Hodgkin’s lymphoma.²² While there was no evidence of decreased incidence of febrile neutropenia associated with GM-CSF use, the study did produce the intriguing finding that CR and PR rates were greater in patients who received GM-CSF. The investigators concluded that further investigation into this unexpected finding is warranted.

A number of ongoing European clinical stud-

ies are currently investigating the combined use of FC plus alemtuzumab either alone or in comparison with FC or FC with rituximab in previously untreated patients with CLL. An Italian study is also investigating the use of FC plus alemtuzumab in relapsed CLL patients. Ongoing US-based clinical studies include the use of CFAR (combination of fludarabine, cyclophosphamide, alemtuzumab, and rituximab) both in previously untreated patients and relapsed/refractory patients. Data from all studies are eagerly anticipated.

Conclusions

In conclusion, currently available evidence indicates that first-line treatment with the combination of FC increases response rates and the treatment-free interval in patients with advanced CLL, irrespective of age or CLL genetic marker in three large randomized trials. While fludarabine chemotherapy on its own is still often an effective option and superior to chlorambucil, the overall response is sub-optimal. The use of the oral formulation of

fludarabine does not appear to be any less effective or safe than the IV form, and is more cost effective and convenient. The addition of monoclonal antibodies, such as rituximab, may potentiate the activity of FC but to date there are no randomized controlled studies supporting its use. Therefore, the FC combination can now be considered the gold-standard therapy for patients with CLL who require treatment and who have no significant co-morbidity.

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