

**FLUDARABINE PLUS CYCLOPHOSPHAMIDE VERSUS
FLUDARABINE ALONE
IN FIRST LINE THERAPY OF YOUNGER PATIENTS WITH CHRONIC
LYMPHOCYTIC LEUKEMIA**

Short title for running head:

FC versus fludarabine in first line therapy of CLL

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Editorial Note:

Barbara Eichhorst supervised and monitored the trial, made the analysis and wrote the report. Raymonde Busch made the analysis of the trial. Georg Hopfinger, Rita Pasold, Manfred Hensel, Cordelia Steinbrecher, Siegfried Siehl, Ulrich Jäger, Manuela Bergmann and Clemens Wendtner were responsible for patient accrual, monitoring and management of the clinical data at their referring center. Stephan Stilgenbauer and Hartmut Döhner were responsible for the genetic analysis. Carmen Schweighofer monitored the study. Günter Brittinger and Berthold Emmerich contributed to the design of the study. Michael Hallek designed und supervised the

trial and wrote the report. All authors critically contributed to the final preparation of the article.

ABSTRACT

The combination chemotherapy with fludarabine plus cyclophosphamide (FC) was compared to the standard regimen of fludarabine monotherapy in first line treatment of younger patients with chronic lymphocytic leukemia (CLL). Between 1999 and 2003 a total of 375 patients with predominantly advanced CLL younger than 66 years were randomized to receive either fludarabine (25 mg/m² for 5 days intravenously, repeated every 28 days) or FC combination therapy (fludarabine 30 mg/m² plus cyclophosphamide 250 mg/m² both for 3 days intravenously, repeated every 28 days). Both regimens were administered to a maximum of 6 courses. The FC combination chemotherapy resulted in a significantly higher complete remission rate (24%) and overall response rate (94%) compared to fludarabine alone (7% and 83%; $P < .001$ and $P = .001$). The FC treatment also resulted in a longer median progression-free survival (48 versus 20 months; $P = .001$), and a longer treatment-free survival (37 versus 25 months; $P < .001$). So far, no difference in the median overall survival could be observed. FC caused significantly more thrombocytopenia and leukocytopenia, but did not increase the number of severe infections. In summary first line treatment with FC increases the response rates and the treatment-free interval in young patients with advanced CLL.

INTRODUCTION

The purine analogues cladribine and fludarabine are the most potent cytotoxic drugs currently available for the treatment of B-cell chronic lymphocytic leukemia (CLL).

Three phase III studies have shown that fludarabine is superior to chlorambucil and to a combination of cyclophosphamide, adriamycin and prednisone (CAP) regarding the number of complete remissions and the duration of remission in first and second line treatment of CLL¹⁻³. However, none of these studies could demonstrate a benefit on median overall survival so far. Moreover, the relatively short progression-free survival of 25 to 32 months after a first line treatment with fludarabine is still unsatisfactory, especially for younger patients^{2,3}.

In vitro data showed that the exposure of CLL cells to fludarabine and cyclophosphamide resulted in an increased, synergistic cytotoxicity^{4,5}. The DNA repair mechanisms in CLL cells, which are initiated in response to cyclophosphamide exposition, are inhibited by fludarabine⁶. This observation was later translated into clinical trials. Results of phase II studies evaluating the combination of fludarabine plus cyclophosphamide (FC) showed very promising efficacy with response rates of more than 90% in previously untreated and pretreated patients⁷⁻¹¹.

In 1999 the German CLL Study Group (GCLLSG) initiated a prospective multicentre phase III trial, comparing fludarabine alone with the combination FC in first line therapy of CLL patients below the age of 66 years. Here, we report the results on the efficacy and safety of the two regimens.

METHODS

Criteria for eligibility

The diagnosis of CLL was based on the criteria established by the National Cancer Institute (NCI)-Sponsored Working Group 1996¹². The stage of the disease was assessed according to the Binet and Rai classification^{13,14} and the requirement of treatment according to the NCI criteria¹². Patients were eligible in Binet stage C and stage B, if they had rapid disease progression or symptoms by enlarged lymph nodes and organs or if they had severe B-symptoms. Patients in Binet stage A were included, if they suffered from B-symptoms. All patients with an age between 18 and 65 years without previous treatment of CLL were allowed to enter the trial. Patients needed to have a life expectancy of more than 6 months and an Eastern Cooperative Oncology Group performance status of 0, 1 or 2. Patients were excluded, if they had severe organ dysfunction, concomitant or previous other neoplasms or an autoimmune hemolytic anemia or thrombocytopenia.

The protocol has been approved by the institutional review board of the University of Munich. All patients had signed an informed-consent form before inclusion in the trial.

Randomization and treatment schedule

The randomization was performed by the Institute of Medical Statistics and Epidemiology, Technical University, Munich, Germany. Patients were randomly assigned to receive either fludarabine alone with a dose of 25 mg/m², administered intravenously daily over 30 minutes for 5 days, or fludarabine, dosed with 30 mg/m², administered intravenously daily over 30 minutes for 3 days, plus cyclophosphamide, dosed with 250 mg/m², administered intravenously daily over 30 minutes for 3 days. Both regimens were repeated every 28 days; a maximum of 6 courses was

administered in each arm. A routine antibiotic or antiviral prophylaxis or administration of growth factors was not performed.

Treatment was stopped, if a life threatening side effect occurred. Patients, who had stable or progressive disease after 3 courses of treatment, were stopped on treatment within this study. No cross-over was planned in case of non-response.

Response assessment

After every course of therapy patients were evaluated by clinical examination and blood count. After 3 and 6 courses of chemotherapy response assessment by clinical examination, blood count, serum chemistry, ultrasound examination or computed tomography (CT) and bone marrow biopsy for confirmation of complete response was performed. Patients who still had signs of toxicity after 3 courses of treatment were reassessed 3 months later. During follow-up response was assessed every three months by clinical examination, blood count and – if clinically indicated - ultrasound examination.

The clinical response was defined according to the guidelines of the NCI-sponsored workshop¹². Complete remission was defined as normal physical examination, disappearance of all symptoms and normal blood count, defined as lymphocytes less than $4 \times 10^9/L$, neutrophils more than $1.5 \times 10^9/L$, platelets more than $100 \times 10^9/L$, hemoglobin (untransfused) more than 110 g/L, as well as bone marrow lymphocyte percentage less than 30% in aspiration and biopsy. Moreover we evaluated complete remission with imaging diagnostics (CR with imaging), which had to be negative for any lymph node enlargement (enlargement was defined more than 1 cm¹²), splenomegaly (defined more than 12 cm diameter in length) or hepatomegaly (more than 1cm below costal arch or more than 14 cm medioclavicular). Unconfirmed complete remission (uCR) was defined as complete remission in a patient, for whom

a bone marrow biopsy was missing for confirmation of complete response¹². Partial remission was defined as 50% reduction of all measurable disease manifestations in physical and imaging examination and more than 50% improvement of all abnormal blood counts. Progressive disease was defined as at least 50% enlargement of lymph nodes, splenomegaly or hepatomegaly, appearance of new lymph nodes or more than 50% increase of circulating lymphocytes, as well as transformation into a more aggressive histology. Patients who neither fulfilled the criteria for partial remission nor for progressive disease were classified as stable disease.

Dose modifications

Toxic effects of the treatment were evaluated according to the Common Toxicity Criteria (CTC 1.0). Patients, who developed either CTC grade 3 infections or a neutrophil count of less than $1 \times 10^9/L$ or thrombocytopenia between $20 \times 10^9/L$ and $50 \times 10^9/L$ with concurrent bleeding complications received a dose reduced regimen to 75% for the next course. Patients, who had neutrophil counts of less than $.5 \times 10^9/L$ or thrombocytopenia of less than $20 \times 10^9/L$, received a 50% dose reduction for the next treatment cycle.

Statistical analysis

The study was initiated in July 1999, and recruitment was stopped in July 2003. A total of 375 patients were enrolled. Statistical analysis was performed on an intent-to-treat basis including the eligible patients. The analysis presented here was based on the data collected by 7th of December 2004.

Time to event was estimated using the Kaplan-Meier method and treatment comparison was tested with the log-rank test. Overall survival was calculated from the randomization time point to death, progression-free survival from randomization

to the time of disease progression or death. Treatment-free survival was measured from the end of therapy to the time point of second line treatment or death. Response rates were calculated for all patients with at least one cycle of therapy. Treatment arms were compared by the chi-square test. Myelotoxicity was also assessed according to the NCI-sponsored Workshop guidelines¹². All statistical tests were two-sided. Statistical significance was defined as p values less than 5%. The analysis was performed with SPSS V12.0.

RESULTS

Baseline characteristics of patients

375 patients were randomized within this study. 13 patients had to be excluded due to a violation of inclusion criteria (4 patients due to wrong diagnosis, 3 because of missing consent forms and 6 because of concomitant disease). 182 patients were randomized to receive fludarabine alone, 180 to receive FC. Eleven patients were lost for follow up. Survival data were available in 351 patients, response data in 328 patients and toxicity data in 346 patients.

When comparing patients in the two treatment arms, there was no significant difference regarding the main clinical features and risk categories (Table 1). A median number of 6 courses were administered in both treatment arms: 70.7% versus 64.0% of the patients completed 6 courses in the fludarabine and FC arm, respectively. The major reasons for an earlier treatment withdrawal in 51 patients from the fludarabine arm were non-response (33%), autoimmune hemolysis (23%) and toxicity (14%) including infections, myelotoxicity or skin reactions. FC therapy was stopped earlier in 63 patients because of toxicity (30%), partial or complete response (13%) or non-response (9%).

Response to treatment

Response data were available in 164 patients from each treatment arm. The FC treatment induced more complete remissions than the fludarabine treatment ($P < .001$) and a higher rate of overall responses ($P = .001$) (Table 2). We also assessed the complete response rates with imaging as defined by blood count, bone marrow biopsy and negative imaging techniques. FC resulted in a complete remission rate with imaging of 16.5% versus 4.9% with fludarabine alone ($P = .001$). When including the number of unconfirmed complete remissions (uCR), the FC regimen yielded an uCR rate of 36.0%, as compared to 18.3% for fludarabine ($P < .001$). The superiority of the FC treatment was most prominent for Binet stage C patients, resulting in a 96.2% overall response rate with 13.2% complete remissions compared to 76.8% overall response with fludarabine and without any complete response (Table 2). An univariate analysis showed, that gender, age, elevated serum thymidine kinase (s-TK) levels above 10 U/L and elevated serum β_2 -microglobulin levels (cut off level at 3.5 mg/dl) did not have any impact on response rates (data not shown).

Overall survival

The median time of follow-up was 22 months. There was no significant difference in overall survival between the two treatment arms, with a three year survival rate of 80.7 % in the fludarabine arm and 80.3 % in the FC arm (figure 1a). Interestingly, there was also no difference in overall survival between the two treatment modalities within the different Binet stages, nor between the three Binet stages indicating that the median observation time was too short to analyze overall survival.

Importantly, the overall survival of patients who did not respond to FC chemotherapy was shorter (30 months) than for patients without response to fludarabine (median not reached) or responders to FC or fludarabine (Figure 1b) ($P = .006$). Interestingly,

5 out of 8 patients with non-response to FC had a 17p deletion before treatment by fluorescence in situ hybridization (FISH). Six of 7 patients had unmutated immunoglobulin heavy-chain variable-region genes. In contrast, all patients who had achieved a complete remission with imaging are presently alive.

Fifteen of 20 deaths in the FC arm were CLL-associated versus 9 of 17 deaths in the fludarabine arm ($P = .51$). Three patients in each treatment arm developed secondary aggressive lymphoma (overall incidence rate 1.7%). Deaths due to Richter's syndrome were documented in three fludarabine-treated patients, and one FC treated patient died. In total, five therapy associated deaths occurred.

Progression-free survival and treatment-free survival

The median progression-free survival was significantly longer in the FC arm (48 months versus 20 months; $P = .001$) (Figure 2). FC treatment was also superior to fludarabine alone with regard to the progression-free survival in Binet B patients (17 months versus 45 months; $P = .001$). However, in Binet stages A and C the progression-free survival was not different in both arms. 76 pts with s-TK levels of ≤ 10 U/L, were compared to 190 patients with s-TK levels > 10 U/L. Median progression-free survival was 27 months for patients with elevated s-TK levels, and was not reached in patients with low levels ($P = .09$). No significant difference in progression-free survival was assessed in patients with elevated versus low serum β_2 -microglobulin levels (cut off level of 3.5 mg/dl). Progression-free survival was similar in patients with 60 years or older compared to patients younger than 59 years as well as in male and female patients.

FC treatment resulted in a significantly longer treatment-free survival time (37 months) compared to fludarabine (25 months) (Figure 3).

Response to second line treatment

32 FC and 59 fludarabine treated patients received relapse treatment. Response data were available in 23 and 54 patients, respectively. The overall response rate to second line treatment was 69.6% in the primarily FC treated group and 73.6% in the fludarabine treated group ($P = .72$).

Six of 9 patients without response to FC, received relapse treatment immediately afterwards. Four of them did not respond to relapse treatment as well, in the two remaining patients data on response to second line treatment were not available.

Toxicity

Data on toxicities were available from 173 patients in each treatment arm. Treatment-related mortality was recorded in five patients (1.4%). Two patients died of treatment-related side effects in the FC arm (one of severe autoimmune haemolytic anemia and thrombocytopenia, one of tumor lysis syndrome), 3 in the fludarabine arm (one patient of pneumonia with sepsis, one of a cerebral bleeding due to thrombocytopenia and one of autoimmune hemolytic anemia). Myelotoxicity was the major side effect in both arms. Both mild (CTC grade 1 and 2) and severe (CTC grade 3 and 4) myelotoxicity and in particular leukocytopenia were significantly more frequent in the FC arm (Table 3). When evaluating treatment-related anemia and thrombocytopenia according to the NCI criteria, severe thrombocytopenia (grade 3 and 4, indicating a more than 50% decrease of platelet counts), was also significantly more frequent in the FC arm (Table 3). The rate of severe infections as well as the incidence of opportunistic infections was similar in both treatment arms. In each treatment arm one case of fungal pneumonia occurred, in the FC arm one additional case of gastrointestinal tuberculosis was observed. Furthermore gastrointestinal side

effects such as nausea, vomiting, mucositis and gastritis were more common in the FC arm.

Autoimmune hemolytic anemias (AIHA) tended to occur more frequently in the fludarabine arm, but the difference was not statistically significant (7.7% versus 2.8%; $P = .06$). There was no significant difference in AIHA of CTC grades 3 and 4. At study entry the Coombs test was positive in 7.0% versus 6.8% of the patients in the fludarabine and FC arm, respectively. 31% of the patients received immunosuppressive agents for treatment of their AIHA and in 37% no specific treatment was necessary. There was no correlation between an initially positive Coombs test and the subsequent occurrence of AIHA: only two of nineteen patients (11%), who were initially Coombs positive developed an AIHA during treatment with fludarabine or FC, as compared to 13 of 262 who were initially Coombs negative (5%).

DISCUSSION

The results of this multicentre phase III trial show that a combination therapy consisting of fludarabine plus cyclophosphamide is more efficacious when compared to fludarabine monotherapy in the first line therapy of CLL. FC treatment improved the overall response rate, the complete remission rate, the progression-free survival time and treatment-free survival time.

Preliminary results of an Intergroup trial comparing FC with fludarabine alone showed similar results on the superiority of FC¹⁵. However, the overall response rates in this Intergroup trial were lower compared to our study, which might be due to a higher proportion of elderly patients or the inclusion of a higher proportion of high risk patients¹⁵.

It is noteworthy that in this study the rate of true complete remissions was lower in both treatment arms than in some studies published previously. Complete remission rates of 20% to 40% were reported for fludarabine used as first line therapy in two phase III trials^{2,3}. In our study, the complete remission rate was only 7% in the fludarabine arm. Similarly, higher complete remission rates of 35% to 49% were reported for FC if used as first line therapy^{7,9,11} compared to 24% complete remissions in our study. One explanation for this difference is that more advanced Binet stage C patients were included in our study (40% versus 33%) in comparison to the study of the French Cooperative Group on CLL². In addition, the French Cooperative Group trial did not use bone marrow biopsy to confirm a complete response². Similar results regarding the response rates with fludarabine or FC were observed by the recently presented Intergroup trial¹⁵. These differences in response rates between the phase II and phase III trials underscore the need of phase III trials, and of a systematic evaluation of complete and partial remissions.

We also assessed the complete remission rate including imaging procedures as CT scan and ultrasound examination which were performed during the final staging in all patients in this study. Especially with the FC treatment the complete remission rate was significantly lower when imaging procedures were used (16% versus 24% and 5% versus 7%). In the 1996 NCI response criteria the role of imaging diagnostic is not clearly defined. These criteria state that “absence of lymphadenopathy by physical examination and appropriate radiographic techniques” is needed for confirmation of complete remission¹². Our results support the need for a revision of these criteria with regard to modern imaging procedures by showing that the response rates vary considerably when using CT or ultrasound imaging.

Patients in Binet stage C benefited more from the FC regimen than from fludarabine monotherapy. In Binet stage C, no complete remission was achieved by fludarabine treatment alone. This is in agreement with the Intergroup trial, where a lower complete response rate of 14% in high risk versus 25% in intermediate risk CLL patients has been reported for fludarabine treatment ³.

In 5 out of 9 patients who did not respond to FC a 17p deletion was observed, which predicts a poor prognosis and resistance to treatment in CLL ¹⁶⁻¹⁸. In the future, alternative treatment strategies are needed (alemtuzumab, allogeneic stem cell transplantation). A cytogenetic analysis of all patients of the CLL4 protocol will show, if response to therapy can be determined by FISH.

The FC treatment resulted in a progression-free survival time of 48 months. Similar results on progression-free survival have been reported previously ^{11,15}. The difference in time to progression between the two treatment arms was 28 months. It remains to be seen, how the two-year progression-free survival rate of 67% obtained with the FC regimen compares to combinations consisting of fludarabine with the antibody rituximab, for which similar progression-free survival rates have been reported ¹⁹.

The fact that the progression-free survival for FC and fludarabine was not different for patients in Binet stage A can be explained by the small size of the group of patients, which reduced statistical power. The lack of difference in the progression-free survival in Binet stage C patients might be explained by the short observation period, since only 48 of 115 patients (42%) in Binet stage C had progressive disease or died so far.

So far, no difference between fludarabine alone and FC was observed with regard to overall survival. The median observation time of 22 months was too short to validate a survival difference between fludarabine alone and FC treatment. Similarly none of

the previously published phase III trials was able to show a significant survival advantage for any of the first line therapies^{2,3}. Because the recurring nature of indolent lymphomas routinely requires subsequent therapies, which modify the clinical course of the disease, an overall survival benefit by a more effective first line treatment strategy is often difficult to prove.

Relapse treatment options in CLL patients range from chlorambucil to allogeneic stem cell transplantation. The inconsistency in relapse strategies is one of the explanations for the lack of survival benefit after FC therapy. Therefore, future trials should contain specific advice for second and third line treatment strategies in CLL patients if possible. Moreover and more importantly, a longer median observation times is needed to determine a survival benefit for any first line regimen.

A third reason for the missing survival benefit in the FC arm might be an impaired response to second or third line treatment. No difference in overall response to second line therapy was observed between the two treatment arms in this trial. But we cannot exclude at the present time that FC treatment selects for more resistant cell clones. In this study no blood samples for cytogenetic aberration in follow up were obtained. Therefore, one can only speculate whether FC induces additional genetic aberrations in CLL.

An overall incidence rate of 1.7% of secondary aggressive lymphomas was observed in this trial. Previously published studies reported incidence rates of 3% to 12% Richter's transformation²⁰⁻²². Treatment with fludarabine is accused to have a major impact on an increased incidence of transformations of up to 12% in CLL due to its immunosuppressive effects²². The rate of Richter's transformation in our trial was relatively low, probably related to the short observation period. However, no difference in the rate of secondary aggressive lymphomas was observed between the two treatment arms.

The FC combination caused more side effects, in particular myelotoxicity. In spite of the higher rate of severe leukocytopenia in the FC arm, the incidence of severe infections was similar in both treatment arms. A possible explanation is that the FC dose was more frequently reduced or delayed than fludarabine. Compared to other studies^{9,11} the incidence of infections in patients treated with FC within this trial was relatively low. However, a lower dose of cyclophosphamide was used in this trial, and the patients included in this trial were younger than in previous phase II trials using FC^{11,15}.

Another important side effect of fludarabine is the occurrence of autoimmune cytopenias which are sometimes severe or even lethal. There was a trend for a higher incidence of AIHA in general in the fludarabine arm, which might be related to the lower dose of fludarabine within the FC regimen or to some protective effects of cyclophosphamide. Similar results have been reported by the UK CLL study group²³.

In summary, the FC combination yields significantly higher response rates and a longer progression-free survival and treatment-free survival than fludarabine alone. With regard to the progression-free survival and the treatment-free survival this phase III study shows the largest difference of two treatment regimens, which has ever been reported in CLL. The FC therapy can be given with acceptable side effects. The GCLLSG will therefore use FC as standard first line therapy in CLL patients who are physically fit. It remains to be seen whether this regimen allows to prolong the overall survival time of patients with advanced CLL.

Conflict of interest statement

We declare that we have no conflict of interests.

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Zittau: M. Schulze.

Characteristics	Fludarabine n = 182	FC n = 180
Age (years)	59 (43 – 65)	58 (42 – 64)
Age group (%)		
30 – 39 years	3.8	2.8
40 – 49 years	12.6	16.7
50 – 59 years	39.6	41.1
60 – 65 years	44.0	39.4
Binet stage (%)		
A	11.2	7.4
B	53.6	57.6
C	35.2	35.0
Rai Stage (%)		
0 (low risk)	2.4	3.1
I or II (intermediate risk)	56.6	58.2
III or IV (high risk)	41.0	38.7
Male sex (%)	70.4	75.0
ECOG* performance status (%)		
0	52.6	53.9
1	45.0	42.5
2	2.4	3.6
Leukocyte count (10 ⁹ /L)	70.4 (9.1 – 270.0)	65.8 (7.9 – 294.1)
Hemoglobin (g/L)	127 (83 – 159)	132 (76 – 158)
Thrombocyte count (10 ⁹ /L)	148 (58 – 281)	145 (52 – 292)
Thymidinkinase (U/L)	18.5 (4.5 – 80.8)	18.4 (5.0 – 72.5)
β ₂ microglobuline (mg/L)	3.2 (1.5 – 6.6)	3.2 (1.2 – 5.9)

Table 1: Baseline characteristics of the eligible patients according to treatment.

Median values are given for continuous variables (5th – 95th percentiles);

percentages are given for categorical values.

* Eastern Cooperative Oncology Group

	Fludarabine	FC	P
	n = 164	n = 164	
Number of patients (%)			
All patients			
CR	11 (6.7)	39 (23.8)	< .001
CR with imaging	8 (4.9)	27 (16.5)	.001
CR + uCR	30 (18.3)	58 (35.4)	< .001
Partial response	128 (78.0)	128 (78.0)	1.0
Overall response	136 (82.9)	155 (94.5)	.001
Non-response	28 (17.1)	9 (5.5)	.001
Binet stage A			
CR	4 (21.1)	6 (46.2)	.24
Overall response	17 (89.5)	12 (92.3)	.79
Binet stage B			
CR	7 (7.9)	25 (25.5)	.001
Overall response	76 (85.4)	92 (93.9)	.05
Binet stage C			
CR	0 (0)	8 (15.1)	.002
Overall response	43 (76.8)	51 (96.2)	.003

Table 2: NCI criteria defined response rates according to treatment arms

Complete response (CR) was defined according to the NCI criteria as normal physical examination, normal blood count, less than 30% lymphocytes in bone marrow biopsy. Complete response with imaging diagnostics (CR with imaging) was defined as CR and aspiration plus a normal CT scan or ultrasound examination. Finally, unconfirmed complete response (uCR) was defined as CR, irrespective of the bone marrow biopsy result. Non-response was defined as stable disease or progression.

Figure 1a

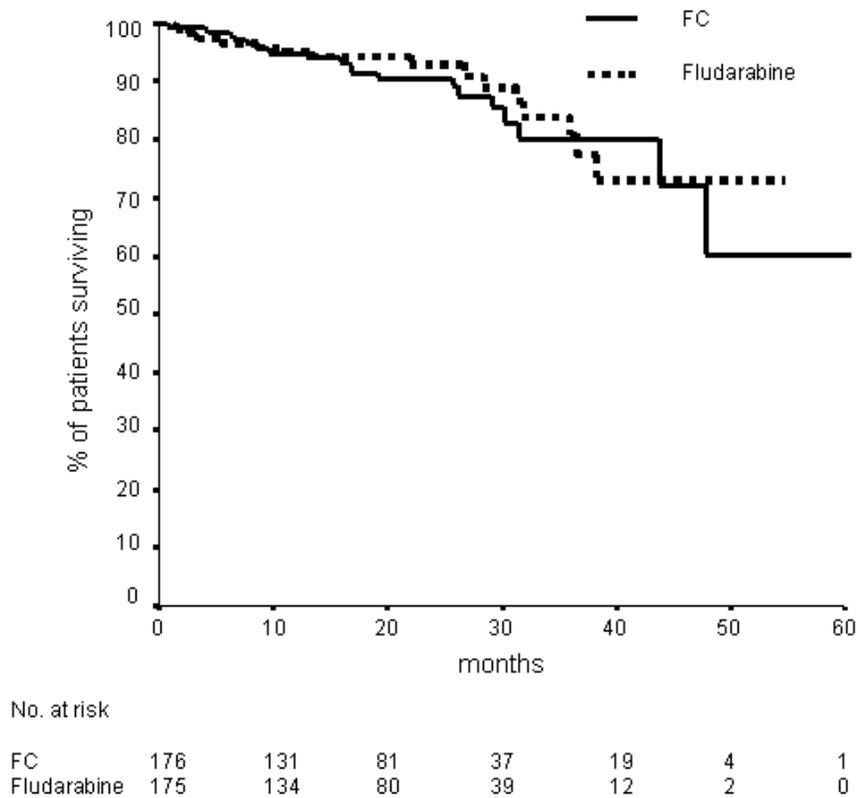


Figure 1 a: Overall survival according to randomization

175 patients assigned to fludarabine and 176 patients assigned to FC were evaluable for overall survival. 17 patients treated with fludarabine and 20 patients treated with FC died ($P = .74$). The median overall survival has not been reached in both arms.

Figure 1 b

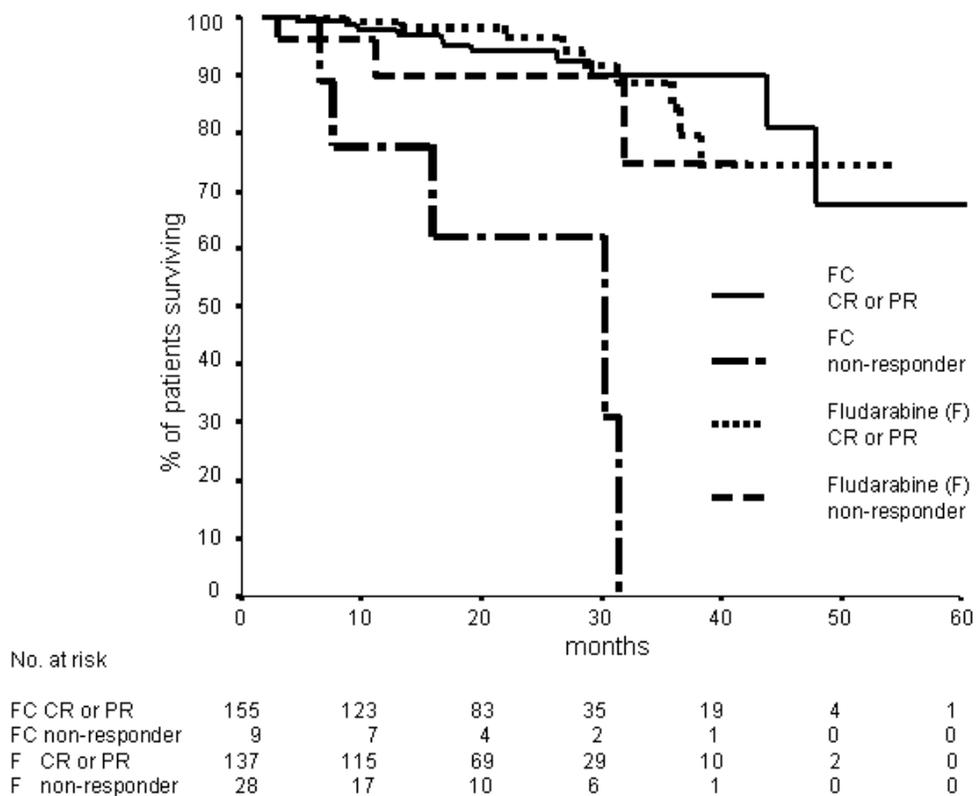


Figure 1 b: Overall survival according to randomization and response

164 patients assigned to fludarabine and 164 patients assigned to FC were evaluable for overall survival and response. Of the 28 patients without response to fludarabine therapy (stable disease or progressive disease) three have died. In the FC group 9 patients had no response, 5 among these had died ($P = .006$). The median overall survival in the FC non responder group was 30 months; in the fludarabine arm it has not yet been reached.

Figure 2

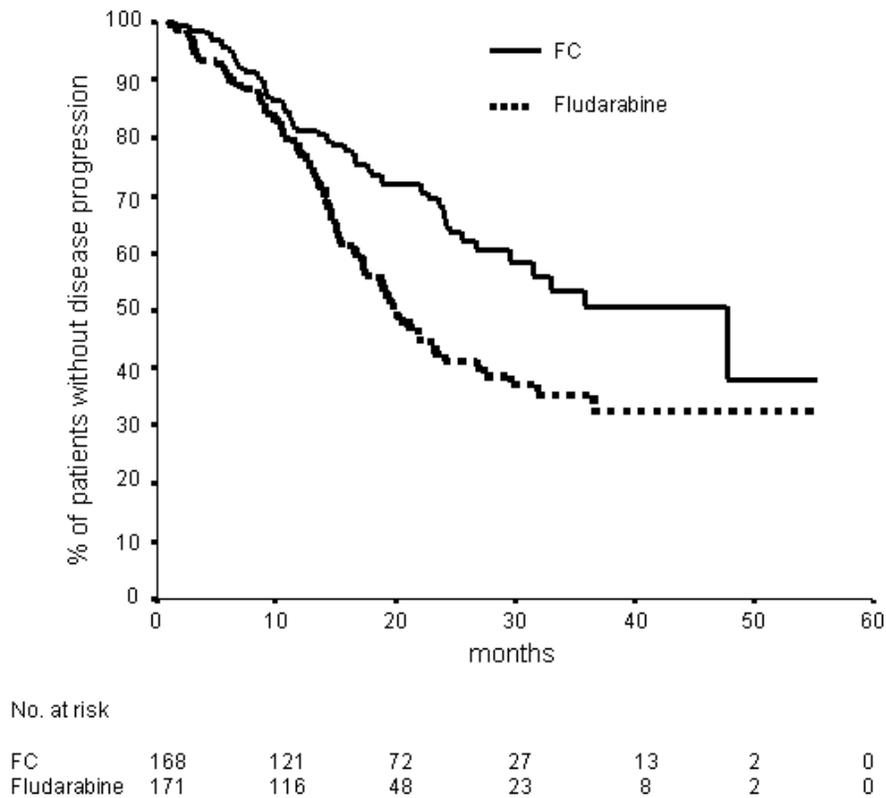


Figure 2: Progression-free survival according to randomization

79 of 171 patients (46.2%) treated with fludarabine had a progressive disease according to the NCI criteria compared to 53 of 168 patients (31.5%) treated with FC, in whom disease progressed. Median progression-free survival was 20 months in the monotherapy arm versus 48 months in the combination therapy arm ($P = .001$).

Figure 3

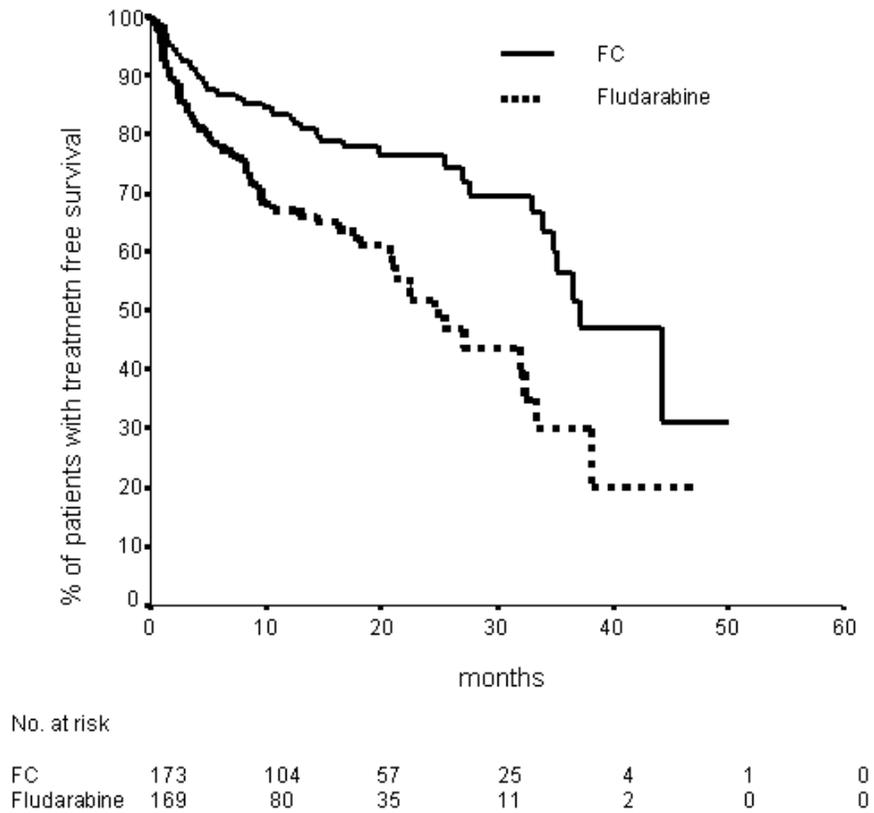


Figure 3: Treatment-free survival according to randomization

64 of 170 patients (37.6%) treated with fludarabine versus 41 of 175 patients (23.4%) treated with FC received a second-line treatment or died. Median treatment-free survival time was 25 versus 37 months ($P < .001$).

	Fludarabine n = 173	FC n = 173	P
CTC grade 3 and 4			
All grade 3 and 4	54.0	72.6	.001
toxicities			
Myelotoxicity	39.3	64.2	.001
Leukocytopenia	26.0	55.5	< .001
Anemia	11.6	8.1	.28
AIHA	3.8	2.2	.37
Thrombocytopenia	12.7	15.6	.44
Infection	8.7	8.7	1.0
Gastrointestinal side	1.7	5.8	.05
effects			
NCI grade 3 and 4			
Anemia	5.2	2.4	.17
Thrombocytopenia	23.3	34.9	.02

Table 3: Percent of patients with at least one grade 3 or 4 side effect classified by the CTC criteria and the NCI criteria according to randomization group

AIHA = Autoimmune hemolytic anemia

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Fludarabine plus cyclophosphamide versus fludarabine alone in first line therapy of younger patients with chronic lymphocytic leukemia

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