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Minimal residual disease following chemoimmunotherapy for patients with relapsed chronic lymphocytic leukemia

Andreas Engert
Holger Schultz
Thomas Elter

Klinik 1 für Innere Medizin,
Universität zu Köln,
Köln, Germany

Correspondence:
Andreas Engert,
Klinik 1 für Innere Medizin,
Universität zu Köln,
Neubau Ebene 01/B, R 202
Joseph-Stelzmann-Str. 9,
Köln D-50924,
Germany
Tel: +49.221.4785933/5966.
Fax: +49.221.4783778.
E-mail: a.engert@uni-koeln.de

The goal of therapy in patients with chronic lymphocytic leukemia (CLL) is, whenever feasible, to induce sustained long-term complete remissions (CR). However, in most instances, patients in CR relapse after varying periods of progression-free survival (PFS). A number of studies have shown that patients, in whom detectable residual disease has been eradicated, have a longer duration of PFS than those in whom residual disease remains after treatment,[1–4] especially when minimal residual disease (MRD) is measured using sensitive methods such as gated four-color flow cytometry (MRD Flow) or allele-specific oligonucleotide polymerase chain reaction (ASO-PCR).[5]

This article first reviews fludarabine-based chemotherapeutic regimens and immunotherapy with alemtuzumab. The rationale for the treatment of CLL with fludarabine plus alemtuzumab combination therapy is then discussed, followed by a review of the results obtained to date, particularly the capacity of this therapeutic approach to induce molecular remissions and long-lasting clinical responses.

Fludarabine-based treatment protocols

Fludarabine and fludarabine-based combination regimens are becoming widely used in the treatment of CLL because of their higher efficacy compared with *conventional* regimens such as chlorambucil-based protocols.[5,6]

In a study by Rai *et al.*,[6] fludarabine monotherapy was compared with chlorambucil alone, and with fludarabine plus chlorambucil combination therapy. The overall response rate (ORR) with fludarabine monotherapy was higher than that achieved with chlorambucil alone[6] (Table 1). Chlorambucil plus fludarabine yielded similar response rates compared with fludarabine alone, but this arm of the protocol was stopped due to a high level of toxicity. The durations of response and of PFS were also significantly longer in patients treated with fludarabine, the median PFS being 20 months and 14 months for fludarabine and chlorambucil, respectively.[6] Despite the improvements in ORR and PFS there was no difference in overall survival (OS) between the two monotherapies, even though fludarabine resulted in longer remissions than chlorambucil.[5,6]

Rai *et al.*[6] reported an ORR of 63%, which included a 20% CR rate with fludarabine monotherapy. Conversely, Eichhorst *et al.*[7] reported an ORR of 86%, which included a 9% CR rate with fludarabine monotherapy. Recently, Rossi *et al.*[8] have reported similar efficacies for monotherapy with an oral fludarabine preparation.

Combining fludarabine in combination with appropriate agents increases efficacy further. Fludarabine plus cyclophosphamide (FC) increased the ORR to 94% and the CR to 20% in first-line treatment of CLL.[7] These results are consistent with those previously reported by O'Brien *et al.*[9] for first-line FC therapy: 88% ORR with a 35% CR rate, and a median PFS in excess of 41 months. In addition, this latter study also yielded an ORR >80% in previously treated patients who were not fludarabine-refractory at the start of treatment. A similar PFS was recently reported by Flinn *et al.*,[10] with a modified FC protocol.

Fludarabine plus rituximab protocols

Fludarabine is a purine analog that is phosphorylated to the triphosphate, leading to inhibition of DNA synthesis, and cyclophosphamide is a DNA alkylating agent. It is reasonable to suppose that adding an antibody, specific for a CLL surface marker, might yield further improvements in response, as the mechanisms of action of the antibody would differ from those of the antimetabolites. Several studies[11,12] have examined the effect of combining fludarabine or FC with rituximab, a monoclonal antibody directed against the CD20 B-cell marker. The results, consistent with the above hypothesis, were encouraging and are included in the summaries shown in Table 1. Furthermore, a recent retrospective

Table 1. Response rates with various regimens for patients with untreated CLL.

*Protocol**	*N*	*ORR (%)*	*CR (%)*	*Authors (reference)*
F 25 mg/m^2, days 1–5 every 28 days	170	63	20	Rai *et al.*[6]
Chlorambucil 40 mg/m^2, once every 28 days	181	37	4	
F 25 mg/m^2, days 1–5 every 28 days	190	86	9	Eichhorst *et al.*[7]
F 30 mg/m^2+ C 250 mg/m^2, days 1–3 every 28 days	185	94	20	
F (oral) 40 mg/m^2, days 1–5 every 28 days	81	72	37[§]	Rossi *et al.*[8]
F 30 mg/m^2 + C 300 mg/m^2,[∝] days 1–3 every 4 to 6 weeks	34	88	35	O'Brien *et al.*[9#]
F 25 mg/m^2, days 1–5	121	50	6	Flinn *et al.*[10Δ]
F 20 mg/m^2, days 1–5 + C 600 mg/m^2, day 1	125	70	22	
F 25 mg/m^2, days 1–5 every 28 days	53	77	15	Byrd *et al.*[11¶]
F 25 mg/m^2, days 1–5 + R 375 mg/m^2, day 1	51	90	33	
F + C + R[ε] (Composite analysis, NCI response criteria)	224	95	71	Keating *et al.*[12]
R 375 mg/m^2, once/week for 4 weeks	43	58	9[ς]	Hainsworth *et al.*[13]
A 30 mg, 3 times per week sc up to 18 weeks	38	87	19	Lundin *et al.*[14]
F 25 mg/m^2, days 1–5 + R 375 mg/m^2, day 1	104	84	38	Byrd *et al.*[15]

**Monotherapy protocols shown in italics; §By IWCLL criteria, CR by NCI criteria was 12%; ∝Initial doses were higher prior to toxicity related reductions ; #First-line results; ΔCycle duration was not reported. 57% of patients received the maximum 6 cycles of therapy; ¶Results from the induction portion of the study; εProtocol not reported but see Keating et al.[16]; ςCR + unconfirmed CR. A = alemtuzumab; C = cyclophosphamide; CR = complete response rate; F = fludarabine; ORR overall response rate; R = rituximab.*

analysis indicated that fludarabine combined with rituximab results in greater PFS and OS than fludarabine alone, although the combination was associated with markedly higher levels of neutropenia.[15] Response rates for these protocols are shown in Table 1, together with the responses obtained with single-agent rituximab and alemtuzumab therapies. At the doses used, a greater proportion of the responses to alemtuzumab were CRs than in the case of rituximab therapy. Interestingly, rituximab therapy appears to induce a transient downmodulation of CD20 expression.[17] Furthermore, the level of circulating CD20 protein may have an inverse prognostic significance.[18]

Minimal residual disease

A CR should not be construed as the elimination of MRD. The majority of patients achieving a CR will eventually relapse due to the presence of MRD,[1] which may or may not be detectable, depending on the methodology used.[4] The assessment of MRD levels is discussed in more detail by Ritgen on page 5 of this supplement.

Magnac *et al.*[19] reported on a series of 12 patients in CR, nine following chemotherapy and three after autologous bone marrow transplantation (ABMT). Using consensus PCR, MRD was detectable in all but one of the chemotherapy patients and none of the ABMT patients. However, when the more sensitive ASO-PCR method was used, which is based on individual complementarity determining region-3 sequences, MRD was detectable in all patients with the sole exception of one of the ABMT patients. Of note, the one chemotherapy patient who was MRD-negative by consensus PCR, but MRD-positive by ASO-PCR, relapsed at 1 year. The clear inference to be drawn is that assessment of MRD status must include consideration of the method(s) used[4] and, furthermore, that when highly sensitive detection methods are employed, elimination of MRD by chemotherapy alone is rare. This is consistent with the conclusion of Brüggemann *et al.*[1] that patients in CR are nevertheless likely to have significant levels of MRD.

Alemtuzumab therapy

The above results notwithstanding, alemtuzumab appears to offer even greater potential than previous protocols for the eradication of MRD. Alemtuzumab is a humanized recombinant IgG1κ monoclonal antibody with human Fc and V region framework sequences. The complementarity determining regions (CDR) are derived from rodent (rat) gene sequences.[20] The antibody is specific for the CD52 cell-surface glycoprotein, which is found at densities of up to 5x10^5 binding sites per cell on the surface of normal and malignant B and T cells, as well as on natural killer (NK) cells, monocytes and macrophages. However, CD52 does not appear to be expressed by granulocytes, or myeloid or erythroid bone marrow cells. Furthermore,

treatment of bone marrow with the non-humanized parent campath-1 antibody did not delay engraftment following autologous transplantation in rhesus monkeys.[20] In addition, incubation with campath-1H did not affect the numbers of $CD34^+$ hematopoietic precursor cells or their growth in long-term bone marrow cultures.[20] Collectively, these results indicate that treatment with alemtuzumab should not affect hematopoietic recovery after transplantation, an important consideration for its therapeutic application.

In 1996, Osterborg *et al.*[21] reported the results of a pilot study using alemtuzumab as first-line treatment in nine patients with CLL. Three patients achieved a CR, and five a partial response (PR). Furthermore, malignant cells were cleared from the peripheral blood in all patients and from the marrow in seven patients. Response durations ranged from 8 to 24 months and, with the exception of one case of cytomegalovirus (CMV) pneumonitis, adverse events were mild. These results suggested that alemtuzumab might be a highly effective and well-tolerated treatment option for first-line use. In addition, the same group also reported that alemtuzumab had significant activity in patients who had relapsed disease following chemotherapy[22] or refractory disease. Subsequently, they reported the results of a first-line phase II trial with subcutaneous (s.c.) alemtuzumab in 41 patients with CLL.[14] An ORR of 87% and a CR rate of 19% were obtained in 38 evaluable patients. Infections were rare, although one patient suffered CMV reactivation. Twenty-one percent of the patients developed a transient grade 4 neutropenia. The median time to treatment failure (TTF) had not been reached after a median follow-up of 18 months.

Rai *et al.*[23] reported the results of a phase II pilot study in 24 patients with CLL whose disease had not responded to prior fludarabine chemotherapy regimens, or who had relapsed after a response duration of less than 6 months. Eight of the patients (33%) achieved a PR, although no CRs were attained. Nonetheless, prolonged response durations were obtained in responders. Ten patients developed major infections and the authors recommended that future alemtuzumab protocols should include prophylaxis against infections. It is, however, important to note that the incidence of infections in this trial could have been a consequence of the patients' characteristics rather than of alemtuzumab therapy per se. Fludarabine-refractory patients have a markedly higher rate of infection than those with fludarabine-sensitive disease (48% vs. 18%).[24] Furthermore, response status is the factor primarily responsible for reducing infectious morbidity and mortality. Thus, patients with heavily pretreated fludarabine-refractory CLL are considerably more likely than fludarabine-sensitive patients to experience rapid disease progression, bone marrow failure, immunosuppression, high infection rates and significant short-term mortality.[24] Set in this context, the ability of alemtuzumab to produce prolonged responses acquires correspondingly greater importance.

Based on the significant activity observed by Rai *et al.*[23] in pretreated poor-prognosis patients, a larger trial (CAM 211) was initiated.[25] Ninety-three patients were enrolled for this study; their median age was 66 years and 76% of them had advanced disease (Rai stage III/IV). Eligibility criteria included B-CLL with up to seven previous therapies, which must have included at least one alkylating agent regimen and failure with fludarabine (defined as failure to respond to at least one fludarabine regimen, disease progression while receiving fludarabine, or response duration of < 6 months following the last fludarabine treatment). The primary endpoint was ORR with safety as a secondary endpoint. Following an initial dose escalation period, patients were treated with intravenous (i.v.) alemtuzumab for 4–12 weeks, with response evaluations every 4 weeks. In the event of disease progression or a CR, treatment was discontinued, otherwise alemtuzumab therapy continued for up to 12 weeks.[24,25]

The ORR obtained in this trial was 33% with a 2% CR rate by National Cancer Institute sponsored Working Group (NCIWG) assessment.[25] However, an additional 7% of patients had clearance of B-CLL cells from all sites, but with persistent anemia or thrombocytopenia. The median response duration was 8.7 months (2.5–>22.6). The median time to progression (TTP) in the intent-to-treat (ITT) population was 4.7 months and 9.5 months in responders. Furthermore, there was a substantial reduction in disease in both the peripheral blood and the bone marrow, although MRD was not assessed. Overall, median survival was 16 months (32 months in responders), results that compare favorably with the 10-month median survival observed with other salvage regimens in fludarabine-refractory CLL.[26]

Anti-infective prophylaxis was employed in this trial and continued for at least 2 months after treatment cessation. Overall, 55% of patients developed an infection during the study. The most frequent opportunistic infection was CMV reactivation, which occurred in seven patients. Five of these cases resolved and the other two patients discontinued alemtuzumab treatment. The authors concluded that alemtuzumab was effective, and had an acceptable safety profile in treating high-risk patients with advanced disease.[25] The optimal management of alemtuzumab therapy in the treatment of CLL has been discussed in recent reviews.[24,27] Alemtuzumab has also been used as consolidation therapy following prior tumor reduction by chemotherapy.[28,29] Alemtuzumab consolidation thera-

Table 2. Dose comparison for FluCam compared with standard dosing.

Therapy	Schedule	Total intended dose
Fludarabine monotherapy	6 cycles @ 5x25 mg/m^2	750 mg/m^2
Alemtuzumab monotherapy	12 weeks @ 3x30 mg	1080 mg
FluCam:		
Fludarabine	4 cycles @ 3x30 mg/m^2	360 mg (48%)*
Alemtuzumab	4 cycles @ 3x30 mg	360 mg (33%)*

**Percent of corresponding standard monotherapy dose.*

py is reviewed in detail by O'Brien on page 18 of this supplement.

Rationale for fludarabine/alemtuzumab combination therapy

The above discussion underscores the availability of two different therapeutic approaches, each of which has significant efficacy as a first-line monotherapy. These observations provided compelling arguments for assessing the potential efficacy of fludarabine and alemtuzumab combination treatment: (i) these two agents have different mechanisms of action; (ii) there is, as yet, no standard therapy for patients with relapsed CLL; and (iii) the additive or synergistic effects of combining chemotherapeutic and immunotherapeutic modalities have been demonstrated in malignant lymphomas,[30,31] in addition to the rituximab studies cited above.

In a small but seminal pilot study, Kennedy *et al.*[32] selected 6 patients with fludarabine-refractory CLL, who had also failed to benefit from alemtuzumab monotherapy, and treated them with fludarabine and alemtuzumab in combination. Five of the 6 patients responded (1 CR, 4 PR) and 5 were alive at 12 months of follow-up, which compares favorably with an expected median survival of 10 months.[26] Furthermore, 2 of the patients became MRD-negative in the bone marrow, assessed using MRD flow. Hence, alemtuzumab, when combined with fludarabine, achieves significant responses, including immunophenotypic remissions, in patients in whom both fludarabine and alemtuzumab had failed as single agents. In light of these highly favorable results, and the apparent synergy between these agents, a phase II trial was conducted.

FluCam phase II study

Inclusion criteria for this study included relapsed or refractory CLL, at least one prior treatment regimen (no upper limit was set) and a World Health Organization (WHO)/Eastern Cooperative Oncology Group (ECOG) performance status 0–2. The primary endpoint was ORR, with response duration, toxicity and MRD as secondary endpoints.[33,34] The protocol was initiated with a dose escalation of alemtuzumab up to 30 mg over 3 days, followed by the FluCam schedule. Fludarabine was administered at 30 mg/m^2 on days 1–3, followed immediately on each day by a 2-hour infusion of 30 mg alemtuzumab. The cycle was repeated four times at 4-weekly intervals. Compared with the standard monotherapy regimens (fludarabine 6 cycles of 5 x 25 mg/m^2; alemtuzumab 12 weeks of 3 x 30 mg), the FluCam schedule has a markedly lower overall administered dose (Table 2). In addition, antimicrobial prophylaxis was administered throughout treatment duration and for at least 2 months afterwards.[33]

Thirty-four of 37 patients are evaluable to date. Their median age was 61 years (range 38–80 years), and the median number of prior treatment regimens was 2 (range 1–8). Seven of the 34 evaluable patients had autoimmune hemolytic anemia or thrombocytopenic purpura before the initiation of treatment. The ORR was 85%, which included 10 CR and 19 PR. Transient grade 3/4 hematologic toxicity was observed in patients with considerable bone marrow involvement, and one heavily pretreated patient who was refractory to both fludarabine and alemtuzumab died of fungal infection. Two patients experienced CMV reactivation, one of whom died from Escherichia coli sepsis. However, in general, side effects were mild and related only to the first 2 cycles of treatment.

There was impressive clearance of tumor cells from both the marrow and peripheral blood (Figure 1). Significantly, 15 of the 34 evaluable patients became MRD-negative in the peripheral blood, based on MRD Flow. Four of 6 patients evaluated also became MRD-negative in the bone marrow. Median TTF, to date, is 15.3 months.

These data show that the FluCam regimen is feasible, highly effective, and well tolerated in patients with

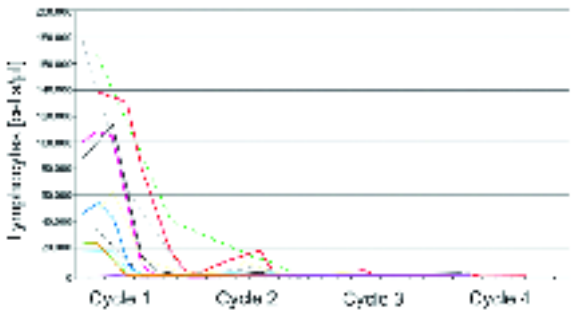

Figure 1. Peripheral blood lymphocyte counts vs. FluCam cycles.

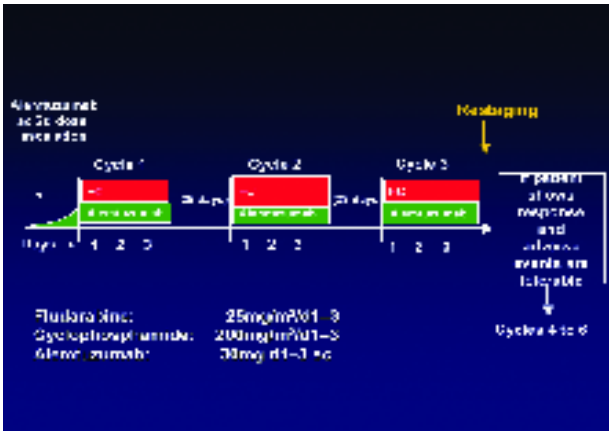

Figure 2. CLL2L protocol.

relapsed or refractory CLL. Furthermore, the results provide a solid rationale for proceeding to further studies.

Further studies

CLL2L study

Fludarabine/cyclophosphamide combination therapy has been shown to have a higher efficacy than fludarabine alone.[7] Hence, building on the above phase II study, cyclophosphamide has been added to the above FluCam regimen (FC-Cam), as shown in Figure 2.

Eligibility criteria for the CLL2L study are B-CLL in Binet stage C or A/B, relapsed or refractory disease after 2 prior regimens, adequate organ function, and any prior treatment with fludarabine or alemtuzumab at least 6 months earlier. In addition, as shown in Figure 2, alemtuzumab is administered subcutaneously in this study rather than intravenously. Other studies have indicated that the s.c. route of administration has equivalent efficacy to i.v. administration but with fewer side effects.[14] Unfortunately, no data are available from this study yet.

CAM 314 phase III trial

Following on from the encouraging results of the phase II FluCam trial described above, a phase III trial (CAM 314) has been initiated to compare the FluCam protocol with *standard* fludarabine monotherapy (four cycles of 25 mg/m^2 for 5 days). Inclusion criteria are relapsed or refractory B-CLL after only one prior regimen. Patients who previously responded to fludarabine or alemtuzumab are eligible provided the response lasted at least 12 months. Patients will be treated for 4 weeks and then restaged. At the time of writing, the study is still recruiting patients and no results are yet available.

Conclusions

These studies show that FluCam and FC-Cam regimens are highly effective and well tolerated in patients with previously treated CLL. Significantly, MRD-negative status can be obtained in both bone marrow and peripheral blood. Longer follow-ups are now needed to determine whether or not these MRD-negative remissions actually confer longer PFS and OS than those in patients who remain MRD positive. Lastly, a phase III trial is underway comparing FluCam with fludarabine monotherapy.

Collectively, these results indicate that the combination of these highly efficacious drugs, in either the FluCam or FC-Cam regimens, has the potential to yield significant response rates and highly durable remissions.

References

1. Bruggemann M, Pott C, Ritgen M, Kneba M. Significance of minimal residual disease in lymphoid malignancies. Acta Haematol 2004; 112:111-9.
2. Esteve J, Villamor N, Colomer D, Cervantes F, Campo E, Carreras E, et al. Stem cell transplantation for chronic lymphocytic leukemia: different outcome after autologous and allogeneic transplantation and correlation with minimal residual disease status. Leukemia 2001; 15:445-51.
3. Esteve J, Villamor N, Colomer D, Montserrat E. Different clinical value of minimal residual disease after autologous and allogeneic stem cell transplantation for chronic lymphocytic leukemia. Blood 2002; 99:1873-4.
4. Rawstron AC, Kennedy B, Evans PA, Davies FE, Richards SJ, Haynes AP, et al. Quantitation of minimal disease levels in chronic lymphocytic leukemia using a sensitive flow cytometric assay improves the prediction of outcome and can be used to optimize therapy. Blood 2001; 98:29-35.
5. Keating MJ, Chiorazzi N, Messmer B, Damle RN, Allen SL, Rai KR, et al. Biology and treatment of chronic lymphocytic leukemia. Hematology (Am Soc Hematol Educ Program) 2003; 153-75.
6. Rai KR, Peterson BL, Appelbaum FR, Kolitz J, Elias L, Shepherd L, et al. Fludarabine compared with chlorambucil as primary therapy for chronic lymphocytic leukemia. N Engl J Med 2000; 343: 1750-7.
7. Eichhorst BF, Busch R, Hopfinger G, Pasold R, Hensel M, Söling U, et al. Fludarabine plus cyclophosphamide (FC) induces higher remission rates and longer progression free survival (PFS) than fludarabine (F) alone in first line therapy of advanced chronic lymphocytic leukemia (CLL): results of a phase III study (CLL4 Protocol) of the German CLL Study Group (GCLLSG). Blood 2003; 102:72a.
8. Rossi JF, van Hoof A, de Boeck K, Johnson SA, Bron D, Foussard C, et al. Efficacy and safety of oral fludarabine phosphate in previously untreated patients with chronic lymphocytic leukemia. J Clin Oncol 2004; 22:1260-7.
9. O'Brien SM, Kantarjian HM, Cortes J, Beran M, Koller CA, Giles FJ, et al. Results of the fludarabine and cyclophosphamide combination regimen in chronic lymphocytic leukemia. J Clin Oncol 2001; 19:1414-20.
10. Flinn I, Kumm E, Grever M, Neuberg D, Dewald GW, Bennet JM, et al. Fludarabine and cyclophosphamide produces a higher complete response rate and more durable remissions than fludarabine in patients with previously untreated CLL: Intergroup trial E2997. Blood 2004; 104:139a.
11. Byrd JC, Peterson BL, Morrison VA, Park K, Jacobson R, Hoke E, et al. Randomized phase 2 study of fludarabine with concurrent versus sequential treatment with rituximab in symptomatic, untreated patients with B-cell chronic lymphocytic leukemia: results from Cancer and Leukemia Group B 9712 (CALGB 9712). Blood 2003; 101:6-14.

12. Keating MJ, O'Brien S, Lerner S, Wierda W, Kantarjian H. Chemoimmunotherapy with fludarabine (F), cyclophosphamide (C), and rituximab (R) improves complete response (CR), remission duration and survival as initial therapy of chronic lymphocytic leukemia (CLL). Proc Am Soc Clin Oncol 2004; 23:571.
13. Hainsworth JD, Litchy S, Barton JH, Houston GA, Hermann RC, Bradof JE, et al. Single-agent rituximab as first-line and maintenance treatment for patients with chronic lymphocytic leukemia or small lymphocytic leukemia: a phase II trial of the Minnie Pearl Cancer Research Network. J Clin Oncol 2003; 21:1746-51.
14. Lundin J, Kimby E, Bjorkholm M, Broliden PA, Celsing F, Hjalmar V, et al. Phase II trial of subcutaneous anti-CD52 monoclonal antibody alemtuzumab (campath-1H) as first-line treatment for patients with B-cell chronic lymphocytic leukemia (B-CLL). Blood 2002; 100:768-73.
15. Byrd JC, Rai K, Peterson BL, Appelbaum FR, Morrison VA, Kolitz JE, et al. Addition of rituximab to fludarabine may prolong progression-free survival and overall survival in patients with previously untreated chronic lymphocytic leukemia: an updated retrospective comparative analysis of CALGB 9712 and CALGB 9011. Blood 2005; 105:49-53.
16. Keating MJ, Manshouri T, O'Brien S, Wierda W, Kantarjian H, Lerner S, et al. A high proportion of true complete remission can be obtained with a fludarabine, cyclophosphamide, rituximab combination (FCR) in chronic lymphocytic leukemia. Proc Am Soc Clin Oncol 2003; 22:569.
17. Jilani I, O'Brien S, Manshuri T, Thomas DA, Thomazy VA, Imam M, et al. Transient down-modulation of CD20 by rituximab in patients with chronic lymphocytic leukemia. Blood 2003; 102:3514-20.
18. Manshouri T, Do K, Wang X, Giles FJ, O'Brien SM, Saffer H, et al. Circulating CD20 is detectable in the plasma of patients with chronic lymphocytic leukemia and is of prognostic significance. Blood 2003; 101:2507-13.
19. Magnac C, Sutton L, Cazin B, Laurent C, Binet JL, Merle-Beral H, et al. Detection of minimal residual disease in B chronic lymphocytic leukemia (CLL). Hematol Cell Ther 1999; 41:13-8.
20. Gilleece MH, Dexter TM. Effect of campath-1H antibody on human hematopoietic progenitors in vitro. Blood 1993; 82:807-12.
21. Osterborg A, Fassas AS, Anagnostopoulos A, Dyer MJ, Catovsky D, Mellstedt H. Humanized CD52 monoclonal antibody campath-1H as first-line treatment in chronic lymphocytic leukaemia. Br J Haematol 1996; 93:151-3.
22. Osterborg A, Dyer MJ, Bunjes D, Pangalis GA, Bastion Y, Catovsky D, et al. Phase II multicenter study of human CD52 antibody in previously treated chronic lymphocytic leukemia. European Study Group of CAMPATH-1H Treatment in Chronic Lymphocytic Leukemia. J Clin Oncol 1997; 15:1567-74.
23. Rai KR, Freter CE, Mercier RJ, Cooper MR, Mitchell BS, Stadtmauer EA, et al. Alemtuzumab in previously treated chronic lymphocytic leukemia patients who also had received fludarabine. J Clin Oncol 2002; 20:3891-7.
24. Keating M, Coutre S, Rai K, Osterborg A, Faderl S, Kennedy B, et al. Management guidelines for use of alemtuzumab in B-cell chronic lymphocytic leukemia. Clin Lymphoma 2004; 4:220-7.
25. Keating MJ, Flinn I, Jain V, Binet JL, Hillmen P, Byrd J, et al. Therapeutic role of alemtuzumab (campath-1H) in patients who have failed fludarabine: results of a large international study. Blood 2002; 99:3554-61.
26. Keating MJ, O'Brien S, Kontoyiannis D, Plunkett W, Koller C, Beran M, et al. Results of first salvage therapy for patients refractory to a fludarabine regimen in chronic lymphocytic leukemia. Leuk Lymphoma 2002; 43:1755-62.
27. Kennedy B, Hillmen P. Immunological effects and safe administration of alemtuzumab (MabCampath) in advanced B-CLL. Med Oncol 2002;19(Suppl):S49-S55.
28. O'Brien SM, Kantarjian HM, Thomas DA, Cortes J, Giles FJ, Wierda WG, et al. Alemtuzumab as treatment for residual disease after chemotherapy in patients with chronic lymphocytic leukemia. Cancer 2003; 98:2657-63.
29. Wendtner CM, Ritgen M, Schweighofer CD, Fingerle-Rowson G, Campe H, Jager G, et al. Consolidation with alemtuzumab in patients with chronic lymphocytic leukemia (CLL) in first remission - experience on safety and efficacy within a randomized multicenter phase III trial of the German CLL Study Group (GCLLSG). Leukemia 2004; 18:1093-101.
30. Coiffier B, Lepage E, Briere J, Herbrecht R, Tilly H, Bouabdallah R, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med 2002; 346:235-42.
31. Forstpointner R, Dreyling M, Repp R, Hermann S, Hanel A, Metzner B, et al. The addition of rituximab to a combination of fludarabine, cyclophosphamide, mitoxantrone (FCM) significantly increases the response rate and prolongs survival as compared with FCM alone in patients with relapsed and refractory follicular and mantle cell lymphomas: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. Blood 2004; 104:3064-71.
32. Kennedy B, Rawstron A, Carter C, Ryan M, Speed K, Lucas G, et al. Campath-1H and fludarabine in combination are highly active in refractory chronic lymphocytic leukemia. Blood 2002; 99:2245-7.
33. Elter T, Borchmann P, Reiser M, Schulz H, Staib P, Schinkoethe T, et al. Development of a new four-weekly schedule (FluCam) with concomitant application of campath-1H and fludarabine in patients with relapsed/refractory CLL. Proc Am Soc Clin Oncol 2003; 22:580.
34. Elter T, Borchmann P, Schulz H, Reiser M, Trelle S, Staib P, et al. Results of a phase II trial of a fludarabine with concomitant application of alemtuzumab in a four-weekly schedule (FluCam) in patients with relapsed CLL. Proc Am Soc Clin Oncol 2004; 22:603.