Annals of Oncology 22 (Supplement 4): iv54–iv56, 2011
doi:10.1093/annonc/mdr175

IX. Chronic lymphocytic leukemia for the clinician

M. Hallek

Department I of Internal Medicine, Center for Integrated Oncology Köln Bonn, Center of Excellence on 'Cellular Stress Responses in Aging-Associated Diseases', University of Cologne, Germany

Several new drugs have recently been approved for chronic lymphocytic leukemia (CLL) treatment (fludarabine, bendamustine as well as three monoclonal antibodies, alemtuzumab, rituximab and ofatumumab). Recent data show that chemoimmunotherapies composed of fludarabine and rituximab (with or without cyclophosphamide), or of fludarabine and alemtuzumab may improve overall survival when used as therapy for CLL patients. This review integrates this knowledge and proposes a treatment algorithm for patients with CLL.

chemotherapy

During the past decade it became apparent that the use of some combination therapies produced a superior efficacy than chlorambucil monotherapy, the former gold standard of chronic lymphocytic leukemia (CLL) therapy [1]. In particular, fludarabine has been evaluated in a variety of combination regimens. The most thoroughly studied combination chemotherapy for CLL is fludarabine plus cyclophosphamide (FC). It showed superior efficacy [higher response rates, longer progression-free survival (PFS) and overall survival (OS) for major subgroups in some trials] when compared with single-agent fludarabine [2, 3].

chemoimmunotherapy

The CALGB 9712 protocol combined rituximab with fludarabine in either a sequential or concurrent regimen in a randomized study. The long-term follow-up of 104 patients included in this trial was recently reported (median follow-up of 117 months) [4]. The median OS was 85 months, and 71% of patients were alive at 5 years. The median PFS was 42 months, and 27% were progression free at 5 years of follow-up suggesting an extended OS and PFS with fludarabine plus rituximab. Similarly, the combination of FC with rituximab (FCR) was investigated in a phase II trial on 300 patients with previously untreated CLL. FCR resulted in an overall response (OR) rate of 95%, with complete remission (CR) in 72%, nodular partial remission (nPR) in 10%, partial remission (PR) due to cytopenia in 7% and PR due to residual disease in 6% [5]. Six-year OS and failure-free survival were 77% and 51%, respectively. Median time to progression was 80 months.

In the CLL8 protocol of the German CLL Study Group (GCLLSG), 817 treatment-naive, physically fit patients (aged 30–81 years) were randomly assigned to receive six courses of intravenous fludarabine (25 mg/m^2 per day) and cyclophosphamide (250 mg/m^2 per day) for the first 3 days of each 28-day treatment course with or without rituximab (375 mg/m^2 on day 0 of the first course, and 500 mg/m^2 on day 1 of the second to sixth courses) [6]. At 3 years after randomization, 65% of patients in the FCR group were free of progression compared with 45% in the FC group ($P < 0.0001$); 87% were alive compared with 83%, respectively [0.67 (0.48–0.92); $P = 0.01$]. FCR was more frequently associated with grade 3 and 4 neutropenia [136 (34%) of 404 compared with 83 (21%) of 396; $P < 0.0001$] and leukocytopenia [97 (24%) compared with 48 (12%); $P < 0.0001$]. Other side-effects, including severe infections, were not increased. There were 8 (2%) treatment-related deaths in the chemoimmunotherapy group compared with 10 (3%) in the chemotherapy group. These results suggest that the choice of FCR as first-line treatment prolongs OS of CLL patients.

Similar results were obtained in a trial comparing FCR with FC in second-line treatment of CLL (Table 1) [7].

The synergistic activity of fludarabine and alemtuzumab was initially suggested by the induction of responses, including one CR, in five of six patients who were refractory to each agent alone [8]. A combination of fludarabine and alemtuzumab (FA) was also investigated in a phase III trial that recently reported a significant improvement in PFS and OS for fludarabine plus alemtuzumab (FluCam) compared with single-agent fludarabine in patients of advanced (Rai III/IV) stage, previously treated CLL (Table 1) [9].

The combination of FC plus alemtuzumab (FCA) was studied by the GCLLSG in a phase II trial and by the French CLL study group and the Groupe Ouest-est d'Etudes des Leucemies Aigues et Autres Maladies du Sang (GOELAMS) in a phase III study. Increased toxicity of FCA compared with FCR was found, preventing the use of the FCA combination outside of clinical trials [10, 11].

Several variations on this theme have been studied in phase II trials, like dose-reduced FCR, bendamustine plus rituximab, the replacement of fludarabine by pentostatin in the FCR regimen, and the use of novel anti-CD20 antibodies in the FCR regimen. None of them has shown superior efficacy in a phase III trial so far. Some of these combinations are currently under investigation in phase III trials. A more detailed summary can be found in a recent review [3].

Table 1. Randomized trials comparing chemotherapy with chemoimmunotherapy or with chemotherapy plus targeted agents

Regimen	Reference	*N*	Age (median)	Advanced stage (%)[a]	ANC, toxicity grade 3–4 (%)	CR (%)	OR (%)	PFS (months)
First line								
FC	Hallek [6]	409	61	31	21	22	80	32.8
FCR		408	61	31	34	44	90	51.8
Second line								
F	Engert [9]	167	60	37	60	16.4	67.9	29.6
FA		168	60	37	66	30.4	84.8	20.7
FC	O'Brien [16]	121	63	50	11[b]	3	45	9
FCO		120	63	45	7[b]	9	41	6
FC	Robak [7]	272	62	NA	40	13	58	21[c]
FCR		274	62	NA	42	24	70	31[c]

[a]Rai III–IV or Binet C.
[b]Only CTC grade 4.
[c]Time to treatment failure.
FC, fludarabine and cyclophosphamide; O, oblimersen; R, rituximab; ANC, absolute neutrophil count.

treatment algorithm for patients with CLL: what clinicians need to know

Tables 2 and 3 propose an algorithm for the therapy of CLL patients that considers four major points [12]:

(i) stage;
(ii) fitness of the patient;
(iii) genetic changes in CLL cells as determined by FISH;
(iv) response to the first treatment.

By using the assessment of these four points, the following recommendations can be given:

(i) Patients at early stage (Binet A and B, Rai 0–II) without symptoms usually do not require therapy. Early treatment is currently tested in clinical trials for patients at high risk.
(ii) In patients with advanced (Binet C, Rai III–IV) or active, symptomatic disease, treatment should be initiated as follows.

- For patients in good physical condition ('go go'), as defined by a normal creatinine clearance and a low score at the 'cumulative illness rating scale' (CIRS) [13], an FCR combination therapy should be offered.
- Patients with relevant comorbidity ('slow go') may be treated with chlorambucil. Alternatives are bendamustine or a dose-reduced fludarabine-containing regimen to achieve symptom control.
- Patients with symptomatic disease and with del(17p) or p53 mutations respond poorly to fludarabine or FC, and show a response rate of ~50% to alemtuzumab monotherapy [14] or to FCR [6] but these responses usually have a short duration of a few months to 1.5 years. These patients should receive an allogeneic stem cell transplant within a clinical trial whenever possible [15].

(iii) For the selection of second-line treatment, the quality of the first response plays a major role:

Table 2. Proposal of an algorithm for first-line therapy of CLL

Stage	Fitness	del(17p) p53mut	Therapy
Binet A–B, Rai 0–II, inactive	Irrelevant	Irrelevant	None
Active disease or Binet C or Rai III–IV	Go go	no	FCR
		yes	AlloSCT
	Slow go	no	CLB
		yes	A, high-dose R or O

F, fludarabine; C, cyclophosphamide; A, alemtuzumab; R, rituximab; B, bendamustine; O, ofatumumab; AlloSCT, allogeneic stem cell transplantation.

Table 3. Proposal of an algorithm for second-line therapy of CLL

Duration of remission	Fitness	del(17p) p53mut	Therapy
>2 years	Irrelevant	Irrelevant	Repeat first-line therapy
≤2 years	Go go	Irrelevant	AlloSCT
	Slow go	no	Change to alternative treatment (trials!)
		yes	Change to A, high-dose R or O, lenalidomide (trials!)

Clb, chlorambucil; F, fludarabine; C, cyclophosphamide; A, alemtuzumab; R, rituximab; B, bendamustine; O, ofatumumab; AlloSCT, allogeneic stem cell transplantation.

- In physically fit patients with refractory disease or relapse within 24 months after a chemoimmunotherapy- or fludarabine-based combination therapy, the second remission should be used to proceed to an allogeneic stem cell transplant [15].

- In physically unfit patients with refractory disease or relapse within 24 months after a chemoimmunotherapy- or fludarabine-based combination therapy, the treatment strategy should be changed to an alternative regimen (e.g. from FCR to BR or alemtuzumab plus dexamethasone; from BR to FCR, etc.). It should be communicated to the patient that the prognosis in this group is usually poor. This group of patients is excellently suited for testing new, alternative treatment strategies, since it represents an unmet medical need.
- In all patients experiencing a relapse later than 24 months after the first therapy, the first-line treatment can be repeated.

acknowledgements

I thank all patients and physicians participating in the studies of the German CLL Study Group for their continuing support and excellent cooperation. This work was supported by the Deutsche Krebshilfe (German Cancer Aid), and the Kompetenznetz Maligne Lymphome (Competence Network Malignant Lymphoma).

references

1. CLL trialists collaborative group. Chemotherapeutic options in chronic lymphocytic leukemia. J Natl Cancer Inst 1999; 91: 861–868.
2. Hallek M. State-of-the-art treatment of chronic lymphocytic leukemia. Hematology Am Soc Hematol Educ Program 2009: 440–449.
3. Hallek M, Pflug N. State of the art treatment of chronic lymphocytic leukaemia. Blood Rev 2011; 25: 1–9.
4. Woyach JA, Ruppert AS, Heerema NA et al. Chemoimmunotherapy with fludarabine and rituximab produces extended overall survival and progression-free survival in chronic lymphocytic leukemia: long-term follow-up of CALGB study 9712. J Clin Oncol 2011; 29: 1349–1355.
5. Tam CS, O'Brien S, Wierda W et al. Long-term results of the fludarabine, cyclophosphamide, and rituximab regimen as initial therapy of chronic lymphocytic leukemia. Blood 2008; 112: 975–980.
6. Hallek M, Fischer K, Fingerle-Rowson G et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. Lancet 2010; 376: 1164–1174.
7. Robak T, Dmoszynska A, Solal-Celigny P et al. Rituximab plus fludarabine and cyclophosphamide prolongs progression-free survival compared with fludarabine and cyclophosphamide alone in previously treated chronic lymphocytic leukemia. J Clin Oncol 2010; 28: 1756–1765.
8. Kennedy B, Rawstron A, Carter C et al. Campath-1H and fludarabine in combination are highly active in refractory chronic lymphocytic leukemia. Blood 2002; 99: 2245–2247.
9. Engert A, Gercheva L, Pilipenko G et al. Overall survival advantage and acceptable safety profile with fludarabine in combination with alemtuzumab (FluCam) in previously treated patients with advanced stage chronic lymphocytic leukemia. 2010 ASH Annual Meeting Abstracts. Blood 2010; 116(21): Abstract 919.
10. Elter T, James R, Stilgenbauer S et al. Chemoimmuno-therapy with fludarabine, cyclophosphamide and alemtuzumab (FC-Cam) in patients with relapsed or genetic high-risk CLL: final analysis of the CLL2L trial of the German CLL Study Group. 2009 ASH Annual Meeting Abstracts. Blood 2009; 114(22): Abstract 209.
11. Lepretre S, Aurran T, Mahe B et al. Immunochemotherapy with fludarabine (F), cyclophosphamide (C), and rituximab (R) (FCR) versus fludarabine (F), cyclophosphamide (C) and MabCampath (Cam) (FCCam) in previously untreated patients (pts) with advanced B-chronic lymphocytic leukemia (B-CLL): experience on safety and efficacy within a randomised multicenter Phase III Trial of the french Cooperative Group On CLL and WM (FCGCLL/MW) and the 'Groupe Ouest-Est d'Etudes Des Leucemies Aigues Et Autres Maladies Du sang' (GOELAMS): CLL2007FMP (for fit medically patients). 2009 ASH Annual Meeting Abstracts. Blood 2009; 114(22): Abstract 538.
12. Cramer P, Hallek M. Prognostic factors in chronic lymphocytic leukemia-what do we need to know? Nat Rev Clin Oncol 2011; 8: 38–47.
13. Extermann M, Overcash J, Lyman GH et al. Comorbidity and functional status are independent in older patients. J Clin Oncol 1998; 16: 1582–1587.
14. Stilgenbauer S, Dohner H. Campath-1H-induced complete remission of chronic lymphocytic leukemia despite p53 gene mutation and resistance to chemotherapy. N Engl J Med 2002; 347: 452–453.
15. Dreger P, Corradini P, Kimby E et al. Indications for allogeneic stem cell transplantation in chronic lymphocytic leukemia: the EBMT transplant consensus. Leukemia 2007; 21: 12–17.
16. O'Brien S, Moore JO, Boyd TE et al. Randomized phase III trial of fludarabine plus cyclophosphamide with or without oblimersen sodium (Bcl-2 antisense) in patients with relapsed or refractory chronic lymphocytic leukemia. J Clin Oncol 2007; 25: 1114–1120.