



REVIEW

Management of symptomatic, untreated chronic lymphocytic leukemia

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KEYWORDS

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Summary Fludarabine-based regimens have become an increasingly popular first-line approach for symptomatic patients with chronic lymphocytic leukemia. Compared with chlorambucil, fludarabine alone or in combination with cyclophosphamide or rituximab yields higher response rates, higher complete remission rates, and more durable progression-free survival. Immunotherapy and chemoimmunotherapy also have the potential to increase the depth of remission as assessed by flow cytometry or molecular techniques. An overall survival advantage with any one particular regimen has not yet been demonstrated. Progress with fludarabine-based regimens, monoclonal antibodies, chemoimmunotherapy, and high-dose therapy for previously untreated patients is reviewed. Fluorescent *in situ* hybridization and immunoglobulin variable heavy-chain sequencing now permit more individualized risk assessment. Examples of possible treatment algorithms based on risk category are explored. How to tailor treatment based on these newer prognostic factors remains a central, as yet unanswered management question.

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Introduction

With the advent of purine analogs and more recently monoclonal antibodies, therapeutic options

have expanded for patients with previously untreated or relapsed chronic lymphocytic leukemia (CLL). Fludarabine is now commonly combined with alkylating agents, rituximab, or both with improvements in overall response rates, complete remission (CR) rates, and remission duration compared with alkylating agents. Single-agent monoclonal antibodies, chlorambucil, and alkylating agent-based combinations also have a role in selected patients. With the expansion of treatment

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choices has come the increasing ability to risk-stratify patients on the basis of the genetic features of the malignant cells. Patients who tend to have lower response rates and shorter survival can therefore be more readily identified, raising fundamental questions about how to optimize risk-adapted therapy. Herein we review the recent progress in managing symptomatic patients in the first-line setting.

Indications for treatment

The 1996 National Cancer Institute-sponsored Working Group guidelines (NCI-96 guidelines)¹ continue to be the mainstay for CLL diagnosis, response assessment, and treatment criteria. As with the low-grade non-Hodgkin's lymphomas, no survival advantage has been demonstrated to early treatment initiation in patients without signs or symptoms of progressive disease.^{2,3} As such, watchful waiting is the standard accepted approach to such patients.

The absolute lymphocyte count in and of itself is not usually an indication to treat, as leukostasis is rare even with markedly elevated counts.¹ Treatment indications include disease-related constitutional symptoms; massive or progressive lymphadenopathy or splenomegaly; rapid lymphocyte doubling time (anticipated doubling by 6 months, or >50% increase in 2 months); cytopenias due to progressive marrow failure; and autoimmune phenomena refractory to steroids.¹ Autoimmune phenomena are well-recognized in CLL, most commonly manifested as hemolytic anemia (10 to 26%) and autoimmune thrombocytopenia (2%).⁴ It is important to distinguish whether cytopenias are due to progressive disease burden in the bone marrow or to autoimmune destruction, as the management differs.

A question that arises in current clinical practice is whether there is an advantage to earlier treatment initiation in patients with particularly poor-risk features, as defined by cytogenetics (including fluorescent *in situ* hybridization) and immunoglobulin variable heavy-chain (IgVH) mutational status. A number of other prognostic factors have long been recognized, including older age, advanced stage at presentation, diffuse bone marrow infiltration, rapid lymphocyte doubling time (12 months), and elevated β_2 -microglobulin levels.⁵⁻⁷ However, it is relatively recently that risk-stratification of individual patients based on genetic features of the disease has become common clinical practice. As examined elsewhere, pa-

tients at particular risk are those with deletions of 17p; deletions of 11q22 (including the ATM gene); and unmutated IgVH status (for which ZAP-70 and CD38 expression are imperfect surrogates).⁸⁻¹¹ Such patients tend to have shorter time to initial therapy, more resistant disease, shorter remission duration, and/or inferior overall survival. Importantly, however, it is not yet known whether earlier initiation of treatment in asymptomatic poor-risk patients carries a survival advantage over observation. Randomized clinical trials designed to answer this question are in progress. Our recommendation is that, unless such an advantage is demonstrated, earlier treatment not be initiated solely on the basis of these adverse prognostic factors.

Alkylating agents

Alkylating agents such as chlorambucil and cyclophosphamide have historically constituted the first-line treatment for patients with advanced or symptomatic CLL. Chlorambucil with or without prednisone has been extensively studied, producing response rates of approximately 40 to 80% in previously untreated patients, although most of these remissions are partial.¹²⁻¹⁶ A number of randomized studies of chlorambucil versus alkylating agent-based combinations (CAP, CVP, CHOP) have been published with generally comparable outcomes between the arms.^{16,17}

Purine analogs as single agents

The purine analogs (most notably fludarabine and cladribine) have major activity in previously untreated as well as relapsed CLL. The introduction of purine analogs into CLL management produced a significant increase in overall and/or complete remission rates.^{14,18-20} Fludarabine as initial therapy produces response rates of approximately 63 to 80%, and CR rates of 20 to 40%.^{14,18-20} More recently, fludarabine has largely replaced chlorambucil and other alkylating agents as the standard first-line agent for CLL, at least in the United States. Studies of fludarabine have demonstrated superior responses and prolonged progression-free, although not yet overall, survival. Three randomized trials (Table 1) have demonstrated the greater efficacy of single-agent fludarabine over chlorambucil¹⁴ or CAP (cyclophosphamide, doxorubicin, prednisone).^{18,21} Fludarabine has comparable efficacy to CHOP (cyclophosphamide, doxorubicin,

Table 1 Completed phase III studies of fludarabine versus alkylating agents in previously untreated patients.

Reference	Study type	Cohort	Regimen	Number evaluable	RR	CR	Median response duration	OS	Median OS
Johnson et al 1996 ²¹	Multicenter phase III (French Cooperative Group on CLL)	Untreated, Binet B or C	F	52	71%	23%	NR at median 34 mo follow-up ^b	78% at 3 yrs ^e	NR at 34 mo median follow-up
			CAP	48	60%	17%	7 mo	63% at 3 yrs ^e	52 mo
Rai et al 2000 ¹⁴	Multicenter phase III (CALGB 9011)	Untreated, Rai III/IV or I/II with disease activity	F	170	63% ^f	20% ^f	25 mo ^f	55% at 5 yrs ^e	66 mo
			Chlorambucil	181	37%	4%	14 mo	45% at 5 yrs ^e	56 mo
			F + Chlorambucil ^a	123	75% ^f	24% ^f	—	—	—
Leporrier et al 2001 ¹⁸	Multicenter phase III (French Cooperative Group on CLL)	Untreated, Binet B or C, age ≤75 yrs	F	336	71% ^b	40% ^{b,c,d}	32 mo	58% at 5 yrs	69 mo at 70 mo median follow-up
			Modified CHOP ^g	351	71.5% ^b	30% ^{b,d}	29.5 mo	57% at 5 yrs	67 mo
			CAP	237	58%	15% ^d	28 mo	60% at 5 yrs	70 mo

CAP: cyclophosphamide, doxorubicin, prednisone; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; CR: complete remission; F: fludarabine; NR: not reached; OS: overall survival; RR: response rate.

^a Fludarabine + chlorambucil arm closed early due to excess toxicity.

^b Significantly higher than CAP.

^c Significantly higher than CHOP.

^d Bone marrow response was not evaluated in 140 pts; therefore the response is termed "clinical" rather than "complete" remission. Per NCI criteria of CR: F = 8%, CHOP = 9%, CAP = 2%.

^e Approximated from Kaplan-Meier curve.

^f Significantly higher than chlorambucil.

^g Vincristine 1 mg/m² and doxorubicin 25 mg/m² on day 1; cyclophosphamide 300 mg/m² p.o. and prednisone 40 mg/m² days 1 through 5.

vincristine, prednisone), with significantly increased CR rates but similar overall response rates and remission duration.¹⁸ In the randomized comparison of fludarabine, CAP, and modified CHOP,¹⁸ it is noteworthy that median remission duration and median overall survival were similar in all groups, although time to next therapy was interestingly longer in fludarabine arm. A phase III trial of fludarabine versus chlorambucil in elderly patients with previously untreated CLL is in progress.²²

Cladribine has been less extensively studied than fludarabine, but also has major activity in CLL. Completed randomized studies of fludarabine and cladribine have not been published, although the overall and complete response rates appear similar in phase II studies.^{23,24} A phase III comparison of cladribine, fludarabine, and chlorambucil as first-line therapy is ongoing.²⁵ Pentostatin is also active CLL, but studies of first-line treatment are limited.²⁶

Some unique toxicities of purine analogs warrant attention. More neutropenia, major infections, and herpesvirus infections have been observed with fludarabine than with chlorambucil.^{14,27} Fludarabine carries significant hematologic toxicity, most notably neutropenia,¹⁴ thrombocytopenia,¹⁴ and profound cellular immunosuppression manifested as a protracted lymphocytopenia. Absolute lymphocyte counts fall markedly within the first few cycles, typically less than 250 / μ L,^{28,29} and are slow to recover. This CD4+ and CD8+ lymphocytopenia lasts months and sometimes one or more years after therapy cessation, potentially heightening the risk of infections including atypical infections.²⁸ Anti-pneumocystis prophylaxis and anti-viral prophylaxis therefore seem prudent. Anti-pneumocystis prophylaxis should importantly be continued beyond chemotherapy completion, until the CD4+ lymphocyte count has recovered.

Concern has also been raised about the bone marrow toxicity of fludarabine, and that fludarabine may impair the ability to harvest adequate numbers of stem cells for autologous blood or marrow transplantation (BMT).^{30–32} Fludarabine treatment has been found to be an independent predictor of inadequate stem cell yield. This may particularly be true in patients who have been heavily pretreated and therefore have limited bone marrow reserve. A study of front-line FC (fludarabine, cyclophosphamide), however, also found poor mobilization rates.³² In contrast, other studies have demonstrated that, following fludarabine-based therapy, stem cells can be adequately collected in most patients^{29,33,34} and timely engraftment achieved.²⁹ Given these mixed results, it is advisable to protect hematopoietic re-

serve by limiting the amount of fludarabine exposure in potential candidates for autologous BMT.

Additionally, fludarabine may precipitate or exacerbate an autoimmune hemolytic anemia,^{4,35} which has been attributed to cellular immune dysregulation.³⁶ It therefore must be used with great caution in patients with previous autoimmune complications. Hemolytic anemia may also occur with other chemotherapies, and a baseline Coomb's test is advisable before starting any regimen.¹

Combinations of purine analogs and alkylating agents

The integration of purine analogs in CLL management has brought considerable progress. However, the lack of an overall survival advantage underscores the need to further improve the complete remission rates, as well as the depth of remission as assessed by flow cytometry or polymerase-chain reaction. Lack of an overall survival advantage may reflect the considerable disease burden that may be present even in patients with a bone marrow CR,²⁹ defined as <30% involvement by CLL morphologically.¹

In vitro and in vivo data have suggested that the combination of nucleoside analogs and DNA-damaging agents (such as alkylating agents) is synergistic.^{37,38} As such, a number of phase I or II trials have been published of FC as initial therapy of CLL and low-grade lymphomas.^{29,39–41} For patients with previously untreated CLL, the overall response rates have ranged from 88 to 100%, and the CR rates from 35 to 60%, in these studies.^{29,39,41} The FC regimen is generally well-tolerated. As with single-agent fludarabine, myelosuppression, lymphocytopenia, and infections are leading side effects. Although the results seemed promising, they do not permit definite conclusions about the relative efficacy of FC versus fludarabine alone.

Two randomized trials addressing this question, one by the German CLL Study Group (GCLLSG)⁴² and one by the Intergroup⁴³ (interim results), have recently been reported (Table 2). In both studies, FC produced significantly higher overall response rates, CR rates, and median progression-free survivals than fludarabine alone, without significantly increasing the major infection rate. It is noteworthy that the complete remission rates in the fludarabine arms of both studies are unusually low: 6 to 7%, compared with 20 to 40% in other randomized phase III trials. These CR rates are similar to those achieved with chlorambucil.¹⁴ In

Table 2 Prospective comparisons of FC versus F in previously untreated CLL.

Reference	Study type	Cohort	Regimen	N	OR	CR	PFS	Median PFS	OS
Eichhorst et al 2006 ⁴²	Multicenter phase III (GCLLSG)	Any stage, with disease activity; age ≤65	FC	180	94% ^c	24% ^c	50% at 3 yrs ^{a,c} 35% at 3 yrs ^a	48 mo ^c 20 mo	81% at 3 yrs 80% at 3 yrs
Finn et al 2004 ⁴³	Multicenter phase III (E2997) ^b	Any stage	FC F	141 137	70% ^c 50%	22% ^c 6%	— —	41 mo ^c 18 mo	— —

GCLLSG = German CLL Study Group; FC = fludarabine, cyclophosphamide; F = fludarabine; OR: overall response; CR: complete remission; PFS: progression-free survival.

^a Estimated from Kaplan-Meier curve. PFS defined from randomization to time of disease progression or death.

^b Interim data. 125 pts in FC arm and 121 pts in F arm evaluable for response.

^c Statistically significant difference.

addition to potential differences in patient characteristics, one explanation, at least in the GCLLSG study, is the use of response criteria more stringent than the traditional NCI-96 criteria used in most other studies. In addition to fulfillment of the NCI-96 criteria for CR, regression of adenopathy on computed tomography was required. In contrast, the NCI-96 criteria do not require radiographic confirmation of lymph node response, but rather are based largely on physical examination.¹

Also of note, as with studies of other chemotherapy combinations in CLL, overall survival was virtually the same with FC and fludarabine in the GCLLSG study.⁴² Survival data for the recently closed Intergroup study are pending. As such, despite the statistically significantly greater overall and complete remission rates, the superiority of FC to fludarabine remains a matter of debate.

It should be mentioned that analysis of the fludarabine plus chlorambucil arm of the CALGB 9011 trial raised concern over a potentially increased risk of therapy-related myelodysplasia and acute myeloid leukemia with this combination.⁴⁴ This has potential relevance for the long-term follow up of existing studies of FC combinations and for planning further studies of purine analog – alkylating agent combinations.

The substantial difference in CR rates between the phase II and phase III studies of FC underscore the importance of confirming promising results in larger randomized trials.⁴² It is also important to note the criteria used for CR, as well as differences in inclusion criteria. This is well illustrated by the “clinical remission” rates reported by the French Cooperative Group randomized study of fludarabine, CHOP, and CAP¹⁸ (Table 1), wherein bone marrow biopsy was not required for response assessment. The “clinical remission” rates of 40%, 30%, and 15% for the three arms, respectively, dropped to 8%, 9%, and 2% when NCI-96 criteria for CR were implemented.¹⁸ As major efforts continue in improving the depth of remission in CLL patients, the need has arisen for more stringent response criteria in order to better discriminate the effectiveness of the therapies.

Rituximab and chemoimmunotherapy

Rituximab has single-agent activity in CLL⁴⁵ and has the potential to enhance the chemotherapeutic effect without significantly compromising overall tolerability.⁴⁶ Rituximab, when given at conventional doses and schedule (i.e. 375 mg/m²

weekly) was initially observed to have minimal activity in relapsed or refractory CLL/SLL.^{47–49} Dim CD20 expression, rapid clearance of antibody (possibly due to the large intravascular tumor burden or soluble CD20), and lower plasma trough concentrations were implicated.^{47,50} In CLL/SLL patients, rituximab was also more frequently associated with significant, at times life-threatening, infusional reactions, thought to be cytokine-mediated.⁵¹

However, with modifications in schedule (100 mg “test dose” followed by thrice weekly dosing at 375 mg/m²), the activity of single-agent rituximab was augmented and the frequency of infusional reactions diminished.⁴⁵ This trial involved mainly patients with relapsed disease. Activity at standard dosing, with or without a “maintenance” schedule, also appears significant in previously untreated patients (Table 3); however CR’s are infrequent.^{52–54}

The benefit of rituximab seems to be most pronounced in combination with other chemotherapeutic agents (Tables 3 and 4), as exemplified by two recently published studies.^{45,46,55} In a randomized phase II study performed by Byrd and colleagues (CALGB 9712),⁴⁶ fludarabine with concurrent versus sequential rituximab was examined in previously untreated patients. The majority (60%) of the 104 patients had early stage (Rai stage I-II) disease. In the concurrent arm, most patients received rituximab 375 mg/m² on days 1 and 4 of the first cycle, then 375 mg/m² on day 1 of subsequent cycles for a total of 6 doses; the last 7 patients received “stepped-up” rituximab dosing, with marked reduction in the frequency of grade 3/4 infusional reactions. In the sequential arm, patients with at least stable disease to fludarabine received 4 weekly doses of rituximab at 375 mg/m². Significant clinical activity was observed in both arms (Table 3), with a generally favorable toxicity profile. Formal statistical comparison of the arms was not intended given the study design. The concurrent arm appeared particularly favorable, although this arm had a greater cumulative rituximab dose than the sequential arm. Patients who achieved only stable disease with fludarabine did not achieve partial or complete remissions to consolidative rituximab. Interestingly, response to FR was not predicted by several validated prognostic factors including age, stage, and β_2 -microglobulin level. As later discussed, newer prognostic features were importantly defined in the patients and were correlated prospectively with treatment outcome.⁵⁶

An Italian phase II study of fludarabine with sequential rituximab was also recently published⁵⁷

(Table 3), with a prospective assessment of outcome based on validated prognostic factors. Progression-free survival rates similar to CALGB 9712 were achieved. Unusually high CR rates of 78% (per NCI-96 criteria) were attained, probably due to virtually all patients having early stage disease.

One of the highest CR rates reported to date in the first-line setting was achieved with the M.D. Anderson regimen of FCR (fludarabine, cyclophosphamide, rituximab; Table 3).⁵⁵ Significantly, in addition to NCI-96 response criteria, flow cytometry was used to assess residual disease in the bone marrow. Bone marrow CR was stringently defined as having <1% CD5+, CD19+ cells and normalization of the kappa: lambda ratio. Rituximab was administered at full dose (375 mg/m²) on day 1 concurrently with FC, then escalated to 500 mg/m² in subsequent cycles. Dose reductions occurred in approximately 15% of patients, and persistent cytopenia was the leading cause of therapy discontinuation. CR rates of 70% were achieved, with most patients also having undetectable disease on bone marrow flow cytometry. Notably in this study, approximately two-thirds of the 224 patients had Rai stage 0-II disease, which may in part contribute to the higher-than-typical CR rates. The quality of the remissions is however encouraging.

The addition of rituximab to fludarabine-based therapy appears quite promising based on retrospective comparisons with fludarabine-based therapy alone (Table 4). Retrospective comparisons of FR versus F⁵⁸ and FCR versus FC⁵⁵ suggest significant improvements in CR rate, progression free survival, and also overall survival. Moreover, in both comparisons, the rates of infectious complications appeared similar with and without the addition of rituximab.^{55,58} No significant differences in the incidence of grade 3/4 neutropenia or thrombocytopenia were apparent with FCR versus FC.⁵⁵

There are obvious limitations to such retrospective comparisons and caution should be exercised when interpreting these results. Confirmation of these promising phase II data in larger randomized trials is needed. This is underscored by the experience with the FC regimen: the high CR rate (42%) in the E1997 phase II trial of FC⁵⁹ (similar to the phase II data with concurrent FR)⁴⁶ was not reproduced in the follow-up randomized E2997 trial (22% CR),⁴³ probably due to differences in patient selection. The importance of phase III studies of chemoimmunotherapy therefore cannot be over-emphasized, with inclusion of information about newer prognostic features such as cytogenetics and IgVH mutational status.⁵⁶ Given the promise of FR and FCR and the increased activity of ritux-

Table 3 Rituximab alone or in combination in previously untreated CLL or SLL.

Reference	Study type	Cohort	Regimen	N	OR	CR	PFS ^f	Median response duration
Hainsworth et al 2003 ⁵²	Multicenter phase II	CLL or SLL, any stage with disease activity	Rituximab induction and maintenance ^e	44	58% ^b	9%	62% at 1 yr, 49% at 2 yrs	19 mo at 20 mo median follow-up
Hainsworth et al 2002 ⁵³	Multicenter phase II	SLL, any stage ^c	Rituximab induction and maintenance ^e	24	46% initially, 70% after maintenance rituximab	—	56% at 2 yrs ^d	34 mo ^d
Schultz et al 2002 ⁸⁴	Multicenter phase II (GCLLSG)	Binet B or C	FR	20	85%	25%	—	—
Byrd et al 2003 ⁴⁶	Multicenter randomized phase II (CALGB 9712)	Rai III/IV or I/II with disease activity (60%)	F with concurrent R F with sequential R	51 53	90% 77%	47% 29%	70% at 2 yrs 70% at 2 yrs	NR at 23 mo NR at 23 mo
Del Poeta et al 2005 ⁵⁷	Phase II	Rai III/IV or 0-II with disease activity (95%)	F with sequential R ^h	60	93%	78%	68% at 3 yrs	—
Keating et al 2005 ⁵⁵	Single-center phase II	Rai stage III/IV or progressive 0-II (67%)	FCR	224	95%	70%	85% at 2 yrs ^d , 69% at 4 yrs	NR at 4 yrs ^a
Kay et al 2004 ⁷⁴	Multicenter phase II ^g	Previously untreated CLL	PCR	33	97%	33%	—	—

OR: overall response; CR: complete remission; PFS: progression-free survival; NR: not reached; FCR: fludarabine, cyclophosphamide, rituximab; PCR: pentostatin, cyclophosphamide, rituximab; GCLLSG: German CLL Study Group.

^a Median follow-up per communication with M. Keating.

^b Response rates at 6 weeks (after rituximab induction).

^c A minority of pts (3%) received prior radiation therapy.

^d Estimated from Kaplan-Meier curve.

^e Rituximab 375 mg/m² weekly for 4 weeks, repeated every 6 mo for 2 yrs if no progression.

^f PFS variably defined as time to disease progression/nonresponse, or time to disease progression/nonresponse or death.

^g Interim data.

^h Rituximab 375 mg/m² weekly for 4 weeks, in pts with at least stable disease after fludarabine.

Table 4 Retrospective comparisons of chemotherapy and chemoimmunotherapy in previously untreated patients.

Reference	Arm	N	OR	CR	PFS	TTF	OS
Byrd et al 2005 ⁵⁸	F-R ⁴⁶ (CALGB 9712)	104	84% ^a	38% ^a	67% at 2 yrs ^a	—	93% at 2 yrs ^a
	F ¹⁴ (CALGB 9011)	178	63%	20%	45% at 2 yrs	—	81% at 2 yrs
Keating et al 2005 ⁵⁵	FCR ⁵⁵	224	95%	70% ^a	—	Median NR ^a	Median NR ^a
	FC ³⁹	34	88%	35%	—	40+ mo median	73+ mo median

CR: complete remission; NR: not reached; OR: overall response; OS: overall survival; PFS: progression-free survival; TTF: time to treatment failure.

^a Statistically significant difference.

imab with thrice-weekly dosing,⁴⁵ a trial of fludarabine or FC with concurrent, thrice-weekly rituximab would also be of interest.

Alemtuzumab as initial therapy and consolidation

Few studies have been performed of alemtuzumab (Campath-1H) as front-line treatment of B-CLL (Table 5).⁶⁰ Response rates approaching 90% have been achieved, with durable remissions and promising CR rates particularly in the bone marrow compartment. As seen in the relapsed setting, alemtuzumab is more effective in purging the blood and bone marrow of leukemic cells than in reducing adenopathy. In fact, in the study by Lundin et al,⁶¹ all CR's in lymph nodes occurred in nodes <2 cm in diameter, and no responses occurred in nodes over 5 cm. Infusional reactions, which occur commonly after intravenous administration, are markedly reduced with subcutaneous administration.⁶¹ The relative efficacy of intravenous and subcutaneous alemtuzumab, as well as the optimal schedule, remain matters of debate.

The infectious complications of alemtuzumab are significant due to protracted lymphocytopenia, and CMV reactivation in particular is a well-recognized complication. Weekly monitoring of CMV titers is therefore indicated, and anti-bacterial and anti-viral prophylaxis frequently but not universally employed. Following subcutaneous administration of alemtuzumab in previously untreated patients, rapid and severe lymphocyte depletion has been described.⁶² After therapy cessation, absolute CD4+ and CD8+ lymphocyte counts often remain depressed for months, and median counts for all lymphoid subsets (B-cell, T-cell, and NK-cell) remain below 25% of baseline for over 9 months.⁶² As with purine analogs, continued vigilance for infectious complications is therefore indicated well after therapy completion.

Consolidative alemtuzumab following first-line therapy has also been investigated by a number of groups in an attempt to eradicate minimal residual disease (MRD).^{63–66} Molecular disease remission was achievable in at least half of previously untreated patients.^{65,66} However, infectious complications were prominent and led to the early cessation of a randomized phase III trial.⁶⁵ Of particular concern was the 53% CMV reactivation rate in one study.⁶⁶ Unless it becomes clear that the benefits of consolidative alemtuzumab outweigh the risks, we would advise against the use of consolidative alemtuzumab outside of a clinical trial.

Moving toward risk-adapted therapy

As the number of more effective first-line CLL regimens has grown, a central management question has remained largely unanswered: How should the choice of initial therapy be influenced by individual prognostic factors?

Standard-dose therapy

Although the prognostic power of genomic aberrations and mutational status in the leukemic cells is well defined, how to tailor therapy based on these prognostic factors is largely unknown. A p53 deletion in particular is associated with aggressive disease that tends to be resistant to a variety of drugs, including alkylating agents, purine analogs, and rituximab.^{8,67–69} In contrast, retrospective data suggest that alemtuzumab has clinical activity in patients with p53 mutations or deletions;⁷⁰ confirmation of these findings would be significant.

Prospective studies have recently begun to be published, examining the relationship between validated prognostic factors and outcomes to a particular regimen.^{56,57} This is exemplified by the CALGB 9712 study of FR,⁵⁶ in which 85% of patients had detailed assessment of interphase cytogenetics, p53

Table 5 Alemtuzumab as first-line therapy of CLL.

Reference	Study type	Cohort	Route	N	RR	CR	Bone marrow CR	Lymph node response	Response duration	Hematologic toxicities	CMV infection
Österborg et al 1996 ⁶⁰	Pilot	Previously untreated, any stage with disease activity	i.v. or s.c., for up to 18 weeks	9	89%	33%	78% CR (per NCI response criteria)	87.5% OR, 38% CR	8+ to 24+ mo; median NR	Protracted lymphocytopenia in all; otherwise no severe toxicities.	11%
Lundin et al 2002 ⁶¹	Multicenter phase II	Previously untreated, any stage with disease activity	s.c., for up to 18 weeks	41 ^a	87%	19%	45% CR (including flow cytometry)	87% OR, 29% CR ^b	8 to 44+ mo; median NR at 18+ mo	Protracted lymphocytopenia in all. Transient grade IV neutropenia in 21%; grade IV thrombocytopenia in 5%.	10%

CR: complete remission; CMV: cytomegalovirus; NR: not reached; OR: overall response.

^a 38 pts were evaluable for response.

^b Lymph node responses confined to nodes \leq 5 cm.

mutational analysis, and IgVH status. Despite the promise of chemoimmunotherapy, patients with poor-risk genetic features had significantly shorter progression-free and overall survival rates. Interestingly the few patients with p53 deletions all responded to FR, although these were partial remissions of relatively short duration. In contrast, patients with 11q deletions had over a 50% CR rate to FR, but the remission durations also tended to be relatively short.⁵⁶

Although only a limited number of such studies have been published, additional prospective evaluations are in progress^{71–75} and should provide further guidance in developing risk-adapted strategies.

High-dose therapy with BMT

A number of relatively recent findings in the transplant literature have relevance for developing risk-adapted strategies in CLL.

Autologous BMT, while potentially improving the durability of remissions, has not resulted in a plateau in survival curves in patients with CLL and is not considered curative.⁷⁶ Although prone to selection bias, some retrospective analyses of allogeneic BMT in CLL have suggested a plateau,⁷⁷ implying that allogeneic BMT is curative in a proportion of patients. Unusually high treatment-related mortality rates (exceeding 40%) have, however, been cited in some,⁷⁸ but not all,⁷⁶ studies of fully ablative allogeneic BMT in CLL. This may be due in part to a heightened risk of infectious complications, given the immunosuppression that accompanies CLL or some of its treatments. It may also be due in part to the large proportion of patients having chemoresistant disease prior to allogeneic BMT in some studies.⁷⁸

Patients with CLL are often not candidates for full transplants because of older age. Non-myeloablative allogeneic BMT has therefore become a major research focus^{77,79} and is increasingly becoming a preferred high-dose therapy modality for patients with CLL. The anti-tumor activity associated with donor lymphocyte infusion (DLI) or the development of graft-versus-host disease (GVHD) illustrates the existence of a graft-versus-leukemia (GVL) effect in CLL.^{76,77,80} In a small study of non-myeloablative BMT that prospectively risk-stratified patients,⁸⁰ eradication of minimal residual disease (as measured by quantitative PCR of the peripheral blood) occurred in most patients after DLI or the onset of chronic GVHD. Notably, this cohort was poor-risk by IgVH mutational status. MRD remained undetectable at median 25 month follow-up and was accompanied by continuous clinical

remission, demonstrating the potential for a GVL effect even in patients with poor-risk genetic features. Interestingly, in a parallel study of autologous BMT for patients with unmutated IgVH status, PCR negativity was less often achieved and was not durable.⁸⁰ Taken together, the potential GVL effect of allogeneic BMT might contribute more to tumor control than the intensity of the conditioning regimen.⁸⁰

Most of the studies of BMT in CLL were performed before the definition and widespread recognition of genetic risk categories. Some reanalyses have since been performed with attention mainly to Ig mutational status.^{76,81,82} For example, in a retrospective analysis, the presence of an unmutated IgVH gene retained prognostic significance after autologous BMT.⁸¹ Nevertheless, the outcomes appeared promising. Another retrospective, case-control study also suggested the possibility of a survival advantage to autologous BMT even in the group with an unmutated IgVH status.⁸²

Given the heterogeneous natural history of CLL and the selection bias inherent to retrospective studies, the role and optimal timing of BMT need to be prospectively reexamined in light of the newer prognostic factors. Experience at our institution⁸³ suggests that the benefit of allogeneic BMT is most pronounced when performed early in the disease course. In patients with poor-risk CLL and good performance status, we generally favor upfront high-dose therapy with BMT following first-line chemotherapy, with increasing preference for non-myeloablative rather than fully ablative conditioning regimens in the allogeneic setting.

A potential algorithm based on patient risk

An example of a potential algorithm for managing symptomatic, previously untreated patients based on risk category is provided in Table 6. This is based on avoiding more toxic therapies upfront in patients with good-risk disease, and considering more intensive approaches for patients with a poorer prognosis. We emphasize that these recommendations are largely not evidence-based; rather our intent is to provide one illustration of a possible risk-adapted approach given the data presently available. As discussed above, evidence in this regard is still largely lacking and no one regimen has been proven to be superior in terms of an overall survival advantage. Within each categories of good, intermediate, and poor-risk disease, it is also important to appreciate that clinical behavior is quite heter-

Table 6 One approach to the initial management of symptomatic CLL.

Risk category (interphase cytogenetics, IgVH mutational status, ZAP-70)	Examples of therapy
Low-risk	Rituximab Chlorambucil Fludarabine
Intermediate-risk	FR FC FCR
High-risk	FR FC FCR Alemtuzumab (17p deletion) BMT, myeloablative or non-myeloablative

BMT: blood or marrow transplantation; FC: fludarabine, cyclophosphamide; FR: fludarabine, rituximab; FCR: fludarabine, cyclophosphamide, rituximab; IgVH: immunoglobulin variable heavy-chain.

ogeneous. Furthermore, the definition of risk may change as new prognostic factors are identified or more effective treatments developed.

Conclusion

Considerable progress has been made in recent years in defining more active therapies for CLL patients, whether in the first-line or relapsed setting. The superiority of any one particular combination over fludarabine monotherapy remains a matter of debate. Additional prospective, randomized studies are needed with attention to key prognostic factors and to the quality of remissions achieved. The upfront benefits of combinations such as FC or FCR must be balanced against toxicity considerations (most notably hematologic) and the lack of a proven overall survival advantage. Also of central and timely importance are efforts to define appropriate initial therapy based on powerful prognostic factors such as cytogenetics and IgVH mutational status. This includes prospective comparisons of watchful waiting versus early intervention in asymptomatic patients who are particularly poor-risk, and further studies of chemotherapy combinations and high-dose therapy stratified by patient risk.

Practice points

- Differentiate autoimmune cytopenias from progressive CLL as treatment paradigms differ.
- Risk-stratify patients before treatment with interphase cytogenetics and IgVH mutational status (or ZAP-70).
- Follow NCI guidelines for indications for treatment, unless evidence becomes available that earlier treatment of asymptomatic poor-risk patients is preferable to watchful waiting.
- For most patients consider fludarabine alone or in combination as first-line therapy.
- Remain vigilant about the protracted risk of infectious complications after fludarabine and alemtuzumab.
- Limit fludarabine exposure in younger patients who are potential candidates for autologous BMT.

Research agenda

- Risk-adapted therapy.
- Prospective evaluation of chemoimmunotherapy versus chemotherapy alone.
- Optimizing the integration of monoclonal antibodies into first-line regimens.
- Minimizing infectious and other complications of therapy.
- Improving the safety and anti-tumor activity of allogeneic BMT.

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