Management of chronic lymphocytic leukemia

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ABSTRACT

In the last decade, the management of chronic lymphocytic leukemia has undergone profound changes that have been driven by an improved understanding of the biology of the disease and the approval of several new drugs. Moreover, many novel drugs are currently under evaluation for rapid approval or have been approved by regulatory agencies, further broadening the available therapeutic armamentarium for patients with chronic lymphocytic leukemia. The use of novel biological and genetic parameters combined with a careful clinical evaluation allows us to dissect some of the heterogeneity of the disease and to distinguish patients with a very mild onset and course, who often will not need any treatment, from those with an intermediate prognosis and a third group with a very aggressive course (high-risk leukemia). On this background, it becomes increasingly challenging to select the right treatment strategy. In this paper, we describe our own approach to the management of different patients with chronic lymphocytic leukemia.

Introduction

The diagnosis of chronic lymphocytic leukemia (CLL) should be considered in the presence of an otherwise unexplained absolute or relative lymphocytosis. It requires a flow cytometric analysis to identify the characteristic phenotype of CLL cells consisting of the expression of CD5 and CD23 on $CD19^+/CD20^+$ B cells, with kappa or lambda light chain restriction or seemingly negative for both.

The diagnosis of CLL can only be established if the total number of B lymphocytes is above $50x10^9$/L.[1] With less than $50x10^9$/L B cells, the condition is called monoclonal B-cell lymphocytosis (MBL) if no palpable lymphadenopathy can be detected.[2] In the presence of enlarged nodes, a diagnosis of small lymphocytic lymphoma (SLL) is established. The management of SLL does not differ from that of CLL.

1. MBL and asymptomatic, early stage or intermediate stage disease: primum non nocere

Monoclonal B-cell lymphocytosis is a newly defined entity that should not be considered a disease. Depending on the number of monoclonal B lymphocytes, MBL carries a different risk of progression into clinically relevant CLL.[3] Cases with more than $5x10^9$/L monoclonal B cells have a risk of 1-2% per year to progress to CLL and to require therapy (clinical or high-count MBL).[4] Below $5x10^9$/L B cells, the risk appears to be rather limited.[5] For the latter condition, named low-count MBL, no particular follow up is recommended. For clinical MBL, a control of blood counts and a clinical examination is recommended every 6-12 months.[3]

Similarly, in the absence of symptoms, CLL patients with few or no enlarged lymph nodes (Rai stage 0-I or Binet stage A) should be followed by the principle *primum non nocere*.[1] At these stages, cytoreductive therapies were reported to have little if any beneficial effects.[6] Therefore, a wait and watch approach should be applied with regular clinical and laboratory follow up. According to the recently up-dated guidelines,[1] neither bone marrow biopsies nor computed tomography (CT) scans are recommended at these stages. Further therapeutic or diagnostic interventions are warranted, if the disease is symptomatic or rapidly progressing (*see below*).

The current recommendations are based on previous studies involving chemotherapeutics including only alkylators[6] with relevant, long-term side-effects such as immunosuppression, genotoxicity and secondary malignancies. Therefore, the application of these drugs was only indicated if the disease was more advanced or symptomatic. In the near future, with the steadily increasing number of non-chemotherapeutic agents, including monoclonal antibodies, immunomodulatory drugs and kinase inhibitors that show less side-effects, this concept will be challenged. Prospective protocols should test the pros and the cons of such an approach. On the one hand, an early intervention with these new agents might be able to prevent disease onset or development, thereby avoiding the progressive accumulation of dismal genetic alterations during disease progression. On the other hand, the early use of any treatment by itself might be potentially associated with the risk of inducing resistance mechanisms through the acquisition of genetic lesions, as recently shown during the prolonged use of kinase inhibitors (Stilgenbauer *et al.*, International Workshop on CLL (iwCLL), 2013). Methods such as next-generation sequencing may also help improve our ability to dissect further high-risk categories of CLL patients needing early interventions.

2. Advanced stage, active or symptomatic disease

At the present time, treatment should be applied if the disease is active (for a definition of active disease see the iwCLL

 doi:10.3324/haematol.2013.096107
Manuscript received on October 15, 2013. Manuscript accepted on April 23, 2014.
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guidelines[1]). In short, treatment should be applied in the presence of cytopenias (anemia and/or thrombocytopenia) due to bone marrow failure, or if bulky (>10 cm) or rapidly progressing lymphadenopathy occurs, or if a rapid increase (doubling within 6 months) of the lymphocyte counts or severe constitutional symptoms (night sweats, fever, weight loss, fatigue) occur.

A few comments might help to interpret these recommendations. First, it should be pointed out that the absolute lymphocyte count is not a criterion for initiation of treatment. Lymphocyte counts of even a few hundred thousand lymphocytes per μL cause no harm, and both patients and doctors should be reassured at this point. LDT should be evaluated only if the level of lymphocytes is above $30x10^9$/L, because values may fluctuate at lower levels with no clinical significance.[1] Moreover, it is important to remember that LDT is rarely an indication to initiate treatment. An isolated, rapid rise in lymphocyte count without any other symptom rarely occurs, and other reasons should be excluded (e.g. use of corticosteroids for unrelated causes). Similarly, severe constitutional symptoms are rarely the only criterion to start therapy and are often associated with other signs of the disease (cytopenia, lymphadenopathy).

3. Management of autoimmune cytopenias

Chronic lymphocytic leukemia is characterized by the potential appearance of autoimmune cytopenias (hemolytic anemia[7,8] in 7-10% of the cases and immune thrombocytopenia[7,9] in 2-5%). Neither situation signals progressive disease and, therefore, they do not justify the initiation of a cytoreductive treatment.[10] Accordingly, autoimmune cytopenias are often listed as exclusion criteria for enrollment in clinical trials. Indeed, both manifestations should initially be treated independently of the leukemia itself. Therefore, the presence of autoimmune cytopenias should be ruled out, in particular in cases of rapid onset of anemia or thrombocytopenia. In contrast, infiltration of the marrow by CLL cells is often leading gradually to anemia and/or thrombocytopenia. Anemia induced by marrow failure tends to precede thrombocytopenia. Isolated thrombocytopenia is usually of immune origin.[11-14]

Any case of anemia should be diagnosed carefully; other causes such as iron deficiency or vitamin deficiencies (folic acid and vitamin B12) should be excluded. The occurrence of autoimmune hemolytic anemia should be verified by the assessment of reticulocytes, direct antiglobin test, serum LDH, bilirubin, and haptoglobin. In the presence of thrombocytopenia, there is no laboratory test that can confirm an autoimmune origin, but a bone marrow biopsy should be performed.[15] Alternatively, the evaluation of response following steroid treatment might be used as a diagnostic test. Treatment with corticosteroids should be carried out for at least one week before evaluating platelet counts to assess response (or the lack of). Steroid treatment usually needs to be continued for at least three weeks followed by slow tapering.[16] In case of lack of response, or rapid loss of response, the most appropriate anti-leukemic therapy should be started (*see next chapter*).

4. Prognostic and predictive markers

Until recently, the decision to initiate treatment has been mostly based on clinical findings. Over the last 10-15 years several biological prognostic markers have been identified, starting from the immunoglobulin gene mutational analysis[17,18] to CD38[17], ZAP70,[19] CD49d[20] expression, and many others. Although they have some value in predicting clinical prognosis, with a high predictive value in larger populations of patients (up to 80% of correlation), they are insufficient to precisely determine the clinical fate of individual patients, as they all leave a rather wide (approximately 20%) margin of error.[21] Therefore, the use of these prognostic markers is not recommended at the time of diagnosis. Moreover, and more importantly, they should not be used to make treatment decisions in CLL patients.

The situation is different when a treatment is indicated. At this point, it is recommended to perform an evaluation of the *TP53* gene by assessing the presence of chromosome 17p deletion (*del(17p)*) and of *TP53* mutations, as both strongly correlate with chemorefractoriness and early relapse.[22] These tests should be performed as part of the decision-making process concerning both first-line and subsequent lines of treatment. In situations without treatment indication, these two analyses should only be performed with informed consent, since they will turn a 'watch and wait' strategy into a 'watch and worry' situation for the patient without any immediate therapeutic consequences. A number of patients carrying these abnormalities may indeed have a long, stable disease course,[23] and the *del(17p)* has been detected even in low-count MBL without sign of leukemia.[5] In addition, both del(17p) and the *TP53* gene mutations may appear during the course of the disease in both treated and untreated patients.[24] Therefore, they should be assessed prior to any treatment.

The very recent discovery of several new genes that carry point mutations in CLL, including *NOTCH1*[25,26], *SF3B1*[26] and *BIRC3*[27], has added more markers that seem to correlate with resistance to treatment and with transformation into Richter syndrome.[25-28] Interestingly, similarly to *TP53* abnormalities, these novel gene mutations can also be acquired during the course of the disease.

Before these new markers can be used in clinical routine, their value needs to be confirmed by prospective studies. In addition, reliable and reproducible detection methods need to be established.

How we treat CLL: selection of the optimal treatment

Given the increasing number of options available, the right choice of treatment of a CLL patient becomes a task that requires an appropriate use of the diagnostic tools, good clinical judgment and, equally important, physician's experience. At least the following parameters should be used when selecting a treatment for CLL:[29] 1) the clinical stage of the disease; 2) patient fitness; 3) the genetic risk of the leukemia; 4) the treatment situation (first- *vs.* second-line; response *vs.* non-response to the last treatment).

1. First-line treatment

As defined above, treatment should be initiated in a patient with advanced (Binet C, Rai III-IV) or active, symptomatic disease. In this situation, patients need to be evaluated for their physical condition and comorbidity. Based on this evaluation, we propose different treatment strategies (Table 1).

A. Patients with an impaired physical condition ("slow go"): these patients may be offered a mild chemotherapy regimen containing chlorambucil for symptom control, but

also dose-reduced fludarabine or bendamustine can be considered. Monotherapy with alkylating agents has served as initial, front-line therapy for CLL for several decades.[30] The advantages of chlorambucil are its low toxicity, low cost and convenience as an oral drug; the major disadvantages are its low complete response (CR) rate and some side-effects after extended use (prolonged cytopenia, myelodysplasia and secondary acute leukemia). Even today, this class of drugs remains an appropriate option in frail elderly or unfit patients.

Recent data from phase III trials suggest that chlorambucil in combination with an anti-CD20 antibody (rituximab, GA101, ofatumumab) seems to lead to a higher number of responses and complete remissions.[31-33] In particular, GA101 (obinutuzumab) seems to prolong progression-free survival and yield minimal residual disease (MRD) negative remissions in a significant fraction of patients, without an increase in clinically relevant hematologic toxicities or infections, though with the occurrence of manageable infusion reactions in almost 70% of the cases.[34] These results convinced the FDA to approve obinutuzumab for previously untreated CLL patients.

Due to its limited toxicity, the anti-CD20 monoclonal antibody rituximab is widely utilized as first-line therapy in unfit patients, especially in North America, though there is no such indication in Europe and the literature on its use in this setting is limited. Rituximab as a single agent is definitely much less efficient than in follicular lymphoma, unless very high doses are used.[35,36]

Among the three purine analogs used in CLL (fludarabine, pentostatin, and cladribine), fludarabine remains by far the best studied compound. Fludarabine monotherapy is now used less frequently, as it did not improve overall survival despite a higher number of CRs.[37-41] Dose-modified combination regimens such as FCR-Lite have been suggested to deliver the FCR combination therapy with a lower toxicity, but this combination still has to be tested in less fit patients.[42] Similarly, the use of pentostatin (PCR) instead of FCR was investigated to achieve a reduced toxicity, with promising results that still need to be validated in randomized trials.[43-45]

Bendamustine: bendamustine has also been compared to chlorambucil in a randomized trial. It produced improved responses, but also showed greater toxicity and no OS benefit.[46] Therefore, to date there is no evidence to support the use of this drug alone or in combination with rituximab as first-line treatment. It may be utilized as a salvage therapy in subsequent lines of therapy, especially in those patients who experience quick relapse or who do not respond to chlorambucil where the cost of a worse toxicity profile would be balanced by the need for a more effective approach in terms of expected responses.

B. Patients in good physical condition ("go go"): these patients are defined by a normal creatinine clearance and a low score on the Cumulative Illness Rating Scale (CIRS).[47] Patients should be offered chemoimmunotherapy. Following a large phase II trial conducted at the MD Anderson Cancer Center,[48] the results of the GCLLSG randomized trial CLL8[49] including 817 patients (median age 61 years) with good physical fitness comparing rituximab plus fludarabine/cyclophosphamide (FC) *versus* FC alone showed for the first time a survival advantage among fit CLL patients. Based on these results, FCR was recommended as a new standard for treatment of this subset of patients. A few questions, however, remain to be solved. First, some patients do not respond to or quickly relapse after FCR. Some of these patients carry *TP53* gene abnormalities. Therefore, *TP53* aberrations should be assessed before starting any therapy to direct these patients rapidly to alternative strategies.

Second, although no age limits were considered in the CLL8 study and no statistically significant differences were noted between individuals above and below 70 years of age in terms of response and/or toxicity, others have reported that FCR is less well tolerated in patients with advanced age over 70 years.[48] Accordingly, FCR treatment was more frequently associated with CTC grade 3 and 4 neutropenia (FCR 34%; FC 21%), and patients remain susceptible to infections up to two years after the end of therapy.[48] Therefore, FCR is not a treatment for all first-line patients, in particular among non-fit patients.

Finally, one has to consider that the survival advantage following FCR was observed with 6 complete treatment cycles; there is no evidence that stopping the treatment earlier, at CR or after 4 cycles, decreases toxicity or will give the same positive outcome.

Despite the great improvements achieved with FCR combination in the treatment of fit patients in first-line treatment, the associated toxicities may sometimes overcome the benefits in the individual patient. Thus, it is still advisable to carefully evaluate each case for the advantages and disadvantages inherent to the treatment, taking into consideration other possible alternatives, in particular for those with borderline fitness status, as other options may be preferable.

Table 1. First-line treatments for CLL patients.

Stage of disease		Non-progressive Binet A/B, Rai 0/I/II	Progressive disease/ Binet C/Rai III/IV			
Fitness status		Not applicable	Go go		Slow go	
TP53 abnormalities		Not applicable	No	Yes	No	Yes
Treatment	First choice	Wait and watch	FCR	FCR, AlDex, AlPred →alloSCT	CLB+/-anti-CD20-Mab (obinutuzumab*)	Alemtuzumab
	Others	Early intervention (Trials)	BR, trials	FA, CFAR, trials	BR, FCR-Lite, trials	Trials

*FCR: fludarabine + cyclophosphamide + rituximab; AlDex: alemtuzumab + dexamethasone; AlPred: alemtuzumab + prednisone; Allo-SCT: allogeneic stem cell transplantation; CLB: chlorambucil; BR: bendamustine + rituximab; FA: fludarabine + alemtuzumab; CFAR: FCR + alemtuzumab; *where available.*

Another possibility is the combination of bendamustine (90 mg/m^2 on Days 1 and 2) with rituximab. This was tested in first- and second-line therapy for CLL and compared favorably with the FCR regimen in that BR achieves similar response rates, but induces less neutropenia than FCR.[50,51] The results of the GCLLSG CLL10 protocol currently comparing BR to FCR as first-line treatment, show that fit CLL patients showed had a lower efficacy of BR with regard to CR and PFS, but a lower incidence of side-effects. This situation prevents us from giving any firm recommendation regarding the first-line therapy of CLL patients. However, physically very fit patients might benefit more from FCR than from BR, in particular if they show an IGHV mutated phenotype (*Fischer and Hallek, unpublished data, 2014*).

C. Patients with symptomatic disease and with del(17p) or TP53 mutations: these patients are known to carry a very dismal prognosis upon first progression, and there is no definitive data on the most efficacious first-line treatment. Even if responding, patients will eventually relapse. Therefore, these patients should be considered for alternative treatments within clinical trials whenever possible. Since the median time to progression for FCR in the CLL8 protocol was approximately two years in these high-risk patients, one can still use it as a de-bulking strategy during preparation for allogeneic stem cell transplantation. Patients may also be proposed an alemtuzumab-containing regimen as first-line treatment, taking into consideration, however, the fact that the duration of response is similar. In essence, there is currently no gold standard for the treatment of these high-risk patients.

The addition of alemtuzumab to chemotherapy may represent another possibility for treating high-risk CLL. Combinations of alemtuzumab with steroids are amongst the most potent therapies for this subset of patients, yielding response rates of 88% in previously untreated cases (all with *TP53* abnormalities), with 65% of cases achieving a complete response.[52] Unfortunately, the addition of cyclophosphamide to the combination is not a feasible option in this subset of patients as a recent phase III trial comparing the activity of alemtuzumab in association with FC (FCA) to FCR in first-line therapy was closed prematurely because of higher toxicity and excess mortality, due in particular to infections. Though patients with chromosome 17p deletion were excluded, the response rates of the FCA arm were also disappointing compared to FCR.[53]

Several variations have also been tested to further improve the efficacy of the FCR regimen without substantial improvements. FCR combined either with alemtuzumab (CFAR)[54] or with mitoxantrone[55] achieved a higher quality and number of responses, though at the expense of more frequent myelosuppression and infections.

2. Second-line treatment

Fortunately, treatment options for relapsed or refractory CLL have improved. There is, however, no standard approach that has been validated in clinical trials, and the most appropriate sequence of the available treatments still has to be established. Therefore, we propose our approach based on the 4 criteria proposed above (Table 2).

In general, the first-line treatment may be repeated if the duration of the first remission exceeds 24-36 months. In any second-line treatment decision after FCR, it is important to consider also the velocity of the relapse, patient fitness, and the side-effects of the previous therapy in order to decide on a re-treatment approach in the light of the potential additive toxicity of 6 subsequent cycles on bone marrow function and the occurrence of infections that might increase the risk of this regimen.

The choice becomes more difficult and more limited in treatment-refractory CLL, as defined by a lack of response or an early relapse within 2-3 years after chemoimmunotherapy combinations. This is particularly the case if these patients carry *TP53* abnormalities (i.e. *del(17p)* and/or *TP53* mutations). There is no satisfactory therapy for these patients at the moment and, of course, the initial regimen should not be repeated and should be stopped earlier in case of clear lack of response (Table 2).

Alemtuzumab alone or in combination[56,57]

The synergistic activity of fludarabine and alemtuzumab (FA) initially showed a high number of responses, including one CR, in 5 of 6 patients who were refractory to each agent alone.[58] In a phase II trial,[57] this combination has proven feasible, safe, and very effective with 83% overall response rate (ORR) including 30% CRs and negativity for MRD. In a phase III trial in patients with relapsed CLL, a regimen using fludarabine plus alemtuzumab (FA) was compared to fludarabine as a second-line therapy. FA

Table 2. Second-line treatment for CLL patients.

Response to first-line therapy		Late relapse (2-3 years)	Refractory or early relapse	
Fitness status		Not applicable	Go go	Slow go
Treatment	First choice	Repeat first line	Consider allo-sct	BR, HDMP+R, ofatumumab, alemtuzumab (if TP53 abnormal)
	Others	Change therapy if poorly tolerated, trials	HDMP+R, Aldex, Alpred, BR, FA, Trials (kinase inhibitors Bcl2 inhibitors CDK inhibitors Lenalidomide)	Trials (kinase inhibitors, Bcl2 inhibitors)

AlloSCT: allogeneic stem cell transplantation; BR: bendamustine + Rituximab; HDMP: high-dose methylprednisolone; R: rituximab; AlDex: alemtuzumab + dexamethasone; AlPred: alemtuzumab + prednisone; FA: fludarabine + alemtuzumab.

yielded clearly better response rates and an improved overall survival than fludarabine monotherapy.[59] Usually, the FA treatment is well tolerated if given intravenously.

Alemtuzumab has also been studied in combination with rituximab in refractory/relapsed CLL, producing an ORR of 52% (8% CR; 4% nodular PR, nPR; 40% PR).[60] The time to relapse was still unsatisfactory.

Anti-CD20 antibodies

Given the necessity of inducing apoptosis in a *TP53* independent fashion in this subset of patients, an effective approach is the use of high-dose methylprednisolone (HDMP) (1 g/m^2/d for 3-5 days) combined with rituximab (375 mg/m^2 weekly for 4 weeks).[61] This treatment was reported to achieve responses in 93% of the fludarabine-resistant patients, with one-third achieving CRs. The median time-to-progression (15 months) is similar to other salvage regimens including alemtuzumab with a very good tolerance and rare serious adverse events. Monitoring of blood glucose and blood pressure is recommended. Subsequent consolidation with alemtuzumab might be used to further improve the response though this has been attempted only in first-line treatment.[62]

In patients refractory to both fludarabine and alemtuzumab (double refractory), ofatumumab, a fully humanized antibody targeting a unique epitope of CD20 showed increased tumor cell killing *in vitro* due to greater CDC activity, an increased binding affinity to CD20 and prolonged dissociation rate (especially in cells expressing low levels of CD20).[63] The American FDA and the European EMA licensed ofatumumab as monotherapy based on an overall response rate of 51% in this double refractory group.[64] These promising results made ofatumumab a good candidate for combination first-line therapies with fludarabine and cyclophosphamide (BIFROST study). However, the results of the FCO (fludarabine, cyclophosphamide, ofatumumab) combination have been disappointing, characterized by a lower response rate and higher rate of neutropenias than FCR.[65] Several studies of combinations with ofatumumab are still ongoing, while recently the results of the combination with bendamustine (BendOfa) have been published, showing an interesting toxicity and efficacy profile.[66]

Allogeneic stem cell transplantation with curative intent

According to recent recommendations of an EBMT consensus group, physically fit patients with refractory CLL or with a *del(17p)/TP53* mutation should be offered an allogeneic transplantation, since their prognosis has remained extremely poor with conventional therapy.[67] This option should be discussed as early as the second line of therapy based on the fitness status of the patient and the availability of suitable donors. In addition, patients with refractory disease should be treated within clinical trials whenever possible with or without a transplantation option.

Novel drugs

For this category of patients, new drugs currently being explored in phase II and phase III clinical trials are raising great expectations, in particular the novel kinase inhibitors, including ibrutinib (BTK inhibitor) and idelalisib (GS1101; PI3K-delta inhibitor), the BCL2 antagonist GDC-0199 (ABT-199) and immunomodulators (IMiDs) such as lenalidomide (Table 3).

Results on clinical agents in refractory CLL patients have been published or presented in a preliminary form and are very encouraging, suggesting that we will see big changes in our armamentarium of CLL therapeutics over the next few months.[68,69] This optimism is supported by previous phase II studies of ibrutinib in refractory patients that showed a response in most patients with a PFS of more than two years,[70,71] receiving the Breakthrough Therapy Designation from the FDA. The phenomenon of increasing lymphocytosis in these kinase inhibitors is probably due to a compartment shift of CLL cells. To address this problem, most of these drugs are currently in combination with rituximab and/or bendamustine to resolve the lymphocytosis,[72,73] achieving a higher number of responses.[72] In this respect, a phase III study testing idelalisib in combination with rituximab *versus* rituximab plus placebo has been stopped early on the recommendation of the Data Safety Monitoring Board due to overwhelming efficacy in unfit, comorbid relapsed patients, with improved progression-free survival, response rate, and overall survival.[74]

The BCL2 inhibitor ABT-199, a 3rd-generation class of inhibitors, appears to be very promising based on the results obtained in an ongoing phase 1 clinical trial. In contrast to many of its predecessors (including obatoclax, vavitoclax) with a broader specificity, this compound showed an ORR of 85% (with 13% CR) in relapsed/refractory CLL patients, likely due to a more specific BCL2 targeting, with limited hematologic toxicity.[69] In contrast, the activity of this drug is characterized by a high incidence of tumor lysis syndrome (TLS) that has now been prevented by modifying the administration schedule with a lead-in dose followed by dose-escalation.

A look into the future

1. Novel agents on the horizon

As described earlier, the kinase inhibitors are currently being explored not only in the context of refractory disease, but also as first-line therapy both in young and elderly patients, thanks to their apparent mild toxicities, distinct from that of classic chemoimmunotherapy. Many other novel agents are also currently being explored. It is likely that some will help to achieve long-term control of CLL. This will only be achieved by a clever combination of the best available, non-toxic, synergistically acting drugs or therapeutic principles.

2. Eradicating minimal residual disease

The dramatic improvements in therapeutic strategies achieved by FCR and similar therapies have made molecular eradication an achievable goal also in CLL.

According to the guidelines, MRD negativity is defined by the presence of less than 1 leukemic cell per 10,000 leukocytes (10^{-4}) detected through allele-specific oligonucleotide quantitative PCR or flow cytometric techniques.[1]

Minimal residual disease status has been shown to be one of the most powerful predictors not only for PFS but also for OS. Its prognostic power is independent of treatment choice, being attainable with both monotherapy (e.g. alemtuzumab) or chemoimmunotherapy (FCR).[75] Based on this, the FDA is currently considering the possibility of using MRD assessment at three months after therapy as an early end point for the efficacy assessment of novel drugs within clinical trials.

Until now, MRD assessment has been recommended as a tool for clinical trials but not as routine practice. However, it is possible that this recommendation might change in the future, because MRD is a very potent and reliable end point to control the efficacy of the therapy. Due to the rapid evolution in this field, it is also foreseeable that Next Generation Sequencing techniques could become an additional way of detecting MRD in CLL.[76]

3. Maintenance or consolidation therapy

Given the increasing importance of achieving MRD there have been some attempts to use this parameter to improve outcome by consolidation or maintenance strategies. Improved PFS with alemtuzumab consolidation therapy was shown when compared to the observation arm (no progression *vs.* 24.7 months; P=0.036).[77] In a similar approach, an OR of 53% was achieved by an alemtuzumab consolidation therapy (39% at a 10 mg dose and 65% at a 30 mg dose; P=0.066)).[78] MRD was efficiently cleared from the bone marrow in most patients, with 38% of the patients achieving a molecular remission. Median time to disease progression had not yet been reached for patients who achieved MRD negativity, compared to 15 months for patients who still had residual disease after alemtuzumab consolidation treatment.[78] However, this approach may cause considerable myelotoxicity, lymphocytopenia, and sometimes life-threatening infections, in particular if conventional doses of alemtuzumab are administered within 3-6 months after the last chemotherapy in patients with a low tumor load.[79,80] Maintenance with rituximab after chemoimmunotherapy, though a reasonable option based on the results in other indolent lymphomas, has not been systematically explored and needs randomized studies before being considered for CLL. In the same direction, a trial by the GCLLSG is currently exploring the possibility of treating MRD-positive patients with consolidation with lenalidomide (CLLM1 protocol).

In conclusion, this is the most exciting time for clinical research on CLL, with more options than any time before in medical history and the potential to change the algorithm for the treatment of our patients. It is now more important than ever to include patients with CLL in clinical protocols, in particular those with high-risk features and/or with refractory disease. If we all make an effort, we are confident that CLL will be a different disease with an improved outcome in 5-10 years from now.

Acknowledgments

We wish to thank all patients and physicians participating in the studies of the German CLL Study Group and the Rete Ematologica Lombarda (REL) for their continuing support and excellent cooperation, and in general all patients agreeing to enroll in clinical trials, as this allows continuous improvement in care of their disease. This work is supported by the Deutsche Krebshilfe (German Cancer Aid), the Kompetenznetz Maligne Lymphome (Competence Network Malignant Lymphoma), Associazione Italiana per la Ricerca sul Cancro (AIRC) (Molecular Clinical Oncology Program 5xMille #9965), Milano, Italy; Ricerca Finalizzata 2010, Ministero della Salute, Roma, Italy.

Authorship and Disclosures

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

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