Prognostication of chronic lymphocytic leukemia in the era of new agents

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The prognosis of chronic lymphocytic leukemia (CLL) is very heterogeneous. Therefore, a plethora of prognostic factors has been identified to allow a better prediction of the individual prognosis of a given patient. The clinical staging systems by Rai and Binet have been the backbone of clinical management for several decades. The advent of genetic and biochemical markers, as well as next-generation sequencing has provided several markers that can predict the prognosis of patients with CLL. Using this knowledge, several scores have been created to improve predicting overall survival and/or treatment-free survival. These prognostic scores were developed in the era of chemotherpay/chemoimmunotherapy. Therefore, they now need to be tested with novel agents. However, despite tremendously improved therapeutic options, CLL patients with *TP53* dysfunction or a complex karyotype remain at very high risk and seem to have a shorter (treatment-free) survival. The recently published international prognostic index (CLL IPI) incorporates most of these factors and provides a tool to analyze outcome in the modern era of targeted therapies.

Learning Objectives

- Know the relevant prognostic factors for predicting individual prognosis of CLL
- Know the different risk-adapted treatment options

The clinical staging systems for chronic lymphocytic leukemia (CLL) were developed 40 years ago.[1,2] Until now, both staging systems are the backbone of prognostication in clinical practice and trials. Moreover, the decision for treatment initiation is supported by these staging systems.[3] The greater insight into the genetic and molecular biology of CLL facilitated by the development of new techniques as next-generation sequencing (NGS) has led to identification of a variety of novel prognostic markers. These markers provide prognostic information that is complementary to the classical staging systems. In particular, cytogenetic and molecular genetic investigations of CLL cells have introduced more precise prognostic factors predicting time to treatment and overall survival.

This review gives an update of the most relevant prognostic factors and scoring systems in CLL and their role in the era of new targeted treatments in CLL. This review will also discuss time points for the evaluation of prognostic factors.

Prognostic factors and scoring systems in CLL

A plethora of different prognostic factors in CLL has been evaluated over recent decades. In addition, the prognostic value of these factors has been summarized and extensively discussed in >300 reviews. During the past 15 years, genetic markers are the focus of prognostication in CLL. Some of these genetic markers, such as the deletion of the short arm of chromosome 17 (del(17p)), which includes the locus of the tumor suppressor gene *TP53*, which can often be mutated,[4] can predict both a poor course of CLL and refractoriness to chemoimmunotherapy.[5,6] The mutational status of IGHV genes discriminates between more mature, genetically stable CLL and more immature, genetically unstable CLL.[7,8] Patients with unmutated IGHV genes have a more aggressive disease course and develop more frequently unfavorable genetic deletions or mutations than patients with mutated IGHV.[9] The expression of ZAP-70[10] and CD38[8] detected by immunophenotyping correlates with IGHV status, with some independent prognostic value.[11] Recently, the application of NGS has identified novel gene mutations or deletions, including *NOTCH1, SF3B1*, and *BIRC3*,[6,12-15] which seem to be associated with shorter survival.

However, compared with some of these genetic aberrations, some biological or clinical parameters, such as β_2-microglobulin, age, gender, or ECOG status,[16,17] seem relevant for prognostication, independent of cytogenetic or molecular genetic findings. In addition, as soon as patients require treatment, quality of response and remission duration should be considered as additive information for further prognosis.[18]

Because of the abundance of prognostic markers, several scoring systems have been created to introduce better prognostication of patients with CLL (Table 1). All scores share the problem of being

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Table 1. Overview on a selection of recently developed scores in CLL

	Wierda et al, 2007[16]	Wierda et al, 2011[19]	Haferlach et al, 2010[20]	Rossi et al, 2013[21]	Pflug et al, 2014[17]	CLL-IPI working group, 2016
Number of patients	1674	930	399	637	1948	3472
Application	All stages, previously untreated	Early stage only	Early stage only	All stages, previously untreated	All stages, previously untreated	All stages, previously untreated
Clinical implications	OS and TTT	TTT	oS and TTT	OS	OS	OS
Factors included	Age, β_2-M, ALC, Hb, gender, Rai stage, involved LNA	unmutated IGHV, diameter palpable LN, del(11q) or del(17p), involved LNA, LDH	Age, WBC, del(17p), unmutated IGHV, IGHV locus translocation, N cytogenetic aberrations	*TP53* del/mut, *BIRC3* del/mut, NOTCH1 mut, SF3B1 mut, del(11q), trisomy 12 normal genetics, del(13q)	age, gender, ECOG, thymidine kinase, β_2-M, unmutated IGHV, del(17p), del(11q)	*TP53* del/mut, unmutated IGHV, β_2-M, clinical stage, age
Validation	Concordance index	Internal	None	Internal	Internal and external	Internal and external
Definition of risk groups	Low	Prognostic nomogram	Favorable	Very low	Low	Low
	Intermediate		Intermediate	Low	Intermediate	Intermediate
	High		Unfavorable	Intermediate	High	High
				High	Very high	Very high

ALC, absolute lymphocyte count; β_2-M, beta$_2$-microglobulin; Hb, hemoglobin; LN, lymph node; LNA, lymph node areas; WBC, white blood cell count.

established before the introduction of kinase inhibitors or small molecules into the routine CLL therapy.

A study of 1674 previously untreated patients at the MD Anderson Cancer Center between 1981 and 2005 performed univariate and multivariate analysis for prognostic markers.[16] The prognostic nomogram developed on the basis of available prognostic factors included mostly clinical and traditional laboratory prognostic factors, whereas cytogenetic results were not included. Age, β_2-microglobulin, absolute lymphocyte count, hemoglobin, gender Rai stage, and involved lymph node areas were independent prognostic factors for overall survival.[16] A different model was introduced by the same group in 2011 based on data of 930 patients studied between 2004 and 2011.[19] At this point, prognostic factors included cytogenetic results detected by fluorescence in situ hybridization (FISH), as well as clinical and traditional laboratory parameters, and were evaluated for predicting time to first treatment. A formula weighting the independent prognostic factors of unmutated IGHV status, largest diameter of palpable lymph node, del(11q) or del(17p) by FISH, number of involved nodal sites, and lactate dehydrogenase level was applied.[19] The limitation of this data set is that data were collected from a single center and patients were relatively young (58 and 59 years, respectively).

Another model for predicting time to treatment and overall survival was evaluated using clinical and genetic data of 390 patients from different German centers.[20] Age, white blood cell count, del(17p), unmutated IGHV status, IGHV locus translocation, and number of cytogenetic aberrations were found to be independently prognostic for overall survival, whereas genetic parameters only (unmutated IGHV status, IGHV locus translocation, del(11q), and number of cytogenetic aberrations) were identified as independent prognostic markers for time to treatment.[20]

Rossi et al were the first to include single genetic abnormalities in a prognostic score.[21] One-thousand two-hundred seventy-four (1274) sample results of 637 previously untreated CLL patients were included. Four CLL subgroups were defined for prediction of overall survival: (1) TP53 and/or BIRC3 abnormalities with the poorest overall survival with a 10-year overall survival of 29% only, (2) intermediate-risk with NOTCH1 and/or SF3B1 and/or del(11q), (3) low-risk harboring trisomy 12 and/or normal genetics, and (4) very-low-risk group with del(13q) with 69% 10-year overall survival.[21] A Scandinavian group evaluating the prognosis of 364 patients with CLL included the same genetic markers in their analysis, but found a different weighting of genetic markers: NOTCH1 or SF3B1 mutation displayed a worse outcome compared with del(11q).[22]

Another score was developed in a cooperation between the German CLL Study Group (GCLLSG) and the Mayo Clinic in Rochester.[17] An analysis of 1948 patient data identified 3 clinical parameters (age, gender, ECOG score), 2 serum parameters (serum thymidine kinase, serum β_2-microglobulin), and 3 genetic parameters (unmutated IGHV status, del(17p), and del(11q)) as independent parameters for prognostication of overall survival. The score was developed by weighting the different prognostic parameters by factors I to IV, and also differentiated between 4 different prognostic subgroups.

Based on this approach, an international group of CLL investigators performed a meta-analysis using data from 8 prospective, controlled, randomized clinical trials.[23] Data sets of 3472 patients treated within phase 3 trials from France, Germany, the UK, the US, and Poland were included. In addition to an internal validation, 2 separate cohorts

(838 patients from the Mayo Clinic and 416 from a Scandinavian population–based cohort) were used for external validation. Five independent prognostic factors were identified: *TP53* deletion and/or mutation, IGHV mutational status, serum β_2-microglobulin, clinical stage, and age. Other than *TP53* disruption, recurrent genetic abnormalities (eg, of *NOTCH1*, *SF3B1*) failed to demonstrate independent prognostic information. Using a weighted grading of these independent factors, a prognostic index was derived separating 4 risk groups with significantly different overall survival at 5 years: low risk (93.2%), intermediate risk (79.3%), high risk (63.3%), and very high risk (23.3%).[23]

In summary, thus far, the majority of the developed scores in CLL detected TP53 aberrations, IGHV status, serum β_2-microglobulin, stage, and age as independent and most relevant prognostic markers. Because these prognostic scores were developed using data sets of patients treated with chemotherapy and/or chemoimmunotherapy, it remains to be determined whether they will hold their value when treating with kinase inhibitors and small molecules. To date, there is no prognostic model that has been developed on the basis of patient data receiving novel agents in relapse or even in frontline therapy. However, scoring systems, which predict time to therapy, are still valid in the era of novel therapies, whereas those predicting overall survival will undergo changes because of the better efficacy of targeted therapies, particularly in high-risk CLL. The possible change of the prognostic value of different markers, old and new, will be discussed in the next section.

Markers predicting the outcome of newer therapies

TP53 mutation/deletion

TP53 aberrations (including del(17p) and *TP53* mutations) are so far the most important prognostic factor in CLL. At frontline therapy, *TP53* aberrations can be detected in 10% of patients with CLL, at relapse in as much as 30%, and at refractoriness even in as much as 50%.[6,24,25] *TP53* is coding for a central regulator of the DNA damage response. Because of the impaired apoptosis induction by chemotherapy in *TP53* mutant or deleted CLL cells, these cells are rarely eradicated with chemoimmunotherapy. In addition, CLL cells harboring *TP53* aberrations frequently show an outgrowth at relapse after treatment.[26-28] All aforementioned scores, which included genetic results, defined very-high-risk CLL by detection of del(17p) and/or *TP53* mutation either alone or in combination with other unfavorable prognostic factors. Before the introduction of new agents, allogeneic stem cell transplantation was the only procedure to control very-high-risk CLL.[29] B-cell receptor (BCR) pathway inhibitors appear to overcome the chemotherapy resistance caused by *TP53* and improve the poor prognosis of this subgroup. Within several trials, the Bruton tyrosine kinase (Btk) inhibitor ibrutinib, administered alone or in combination with rituximab, has shown promising activity in pretreated and previously untreated patients with *TP53* aberrations.[30-32] Median progression-free survival (PFS) was not yet achieved in this very high-risk group in most studies and was 80% at 2 years.[32] Similar promising data, particularly in patients with del(17p) or *TP53* mutation, were obtained using the PI3K inhibitor idelalisib in combination with rituximab in relapsed CLL or in frontline.[33,34]

Though in historical comparison, BCR pathway inhibitors are more efficacious than chemoimmunotherapy or antibody alone, CLL harboring *TP53* aberrations is associated with shorter PFS during treatment with ibrutinib (median PFS, 28.1 months vs not reached, respectively) as well as shorter overall survival (at 30 months, 65% vs 83%, respectively).[35] Idelalisib, was previously approved for first-line therapy of patients with *TP53* aberrations in Europe only, but its administration in the first-line setting needs to be balanced against a relevant toxicity profile. Subgroup results of clinical trials evaluating idelalisib show that *TP53* aberrations do not discriminate for inferior PFS, but do for overall survival.[33,36] These results will have to be consolidated by longer follow-up.

The prognostic value of del(17p) or *TP53* mutation for treatment with the small-molecule and bcl2 inhibitor venetoclax is not yet clear. A phase 1/2 trial evaluating venetoclax monotherapy in 116 patients with relapsed and/or refractory CLL showed similar rates of complete responses (16% with vs 18% without del(del17p)), but a slightly lower overall response rate (71% vs 80%).[37] One-hundred seven patients with relapsed and/or refractory CLL, all carrying del(17p), showed a comparable PFS rate within a phase 2 trial using venetoclax (72% PFS at 12 months) as previously reported with ibrutinib.[32,35,38]

Taken together, results of phase 2 and 3 studies show that the prognostic impact of *TP53* aberrations is probably less prominent with BCR inhibitors and bcl2 inhibitors, but remains relevant because even with these p53-indepenent treatments, inferior efficacy and overall survival rates are demonstrated with these agents. Mechanisms resulting in inferior response duration and survival are very likely a result of the acquisition of coexpressing mutations in patients with CLL.[27,39,40]

Del(11q), ATM mutation, and BIRC3 mutation

Del(11q) can be detected in 10% to 20% of CLL patients before therapy. In the past, prognosis of CLL with del(11q) was poor,[5] but has significantly improved with the introduction of chemoimmunotherapy regimen, particularly the FCR regimen.[6,41] Although the combination of chlorambucil plus obinutuzumab also yielded very promising results in patients with del(11q), rituximab combined with bendamustine or chlorambucil appears to be less effective in patients with del(11q).[42,43] The results of the CLLIPI, which did not identify del(11q) as an independent prognostic marker, also indicate that chemoimmunotherapies resulting in significant eradication of the disease may overcome the poor prognosis of del(11q).[23]

However, not all patients are suitable for fludarabine, cyclophosphamide, and rituximab (FCR) or obinutuzumab-based treatment or may be pre-exposed to these treatments. BCR pathway inhibitors and bcl2-inhibitor have been demonstrated to be very effective in this subgroup of patients,[31,33,37] but longer follow-up showed also a slight inferiority in patients with del(11q) with regard to PFS (for ibrutinib, median PFS of 39 months for patients with del(11q), whereas median PFS was not reached in patients without del(11q) or del(17p)).[35]

The commonly deleted region of the long arm of chromosome 11 contains both genes, *ATM* and *BIRC3*. *ATM* mutations of the residual allele can be found 36% of patients,[44] *BIRC3* mutations in 5% of patients with del(11q).[45,46] Although *ATM* is encoding a kinase that is important for repair of double-strand breaks, *BIRC3* is a negative regulator of the alternative NF-κB pathway. The inactivation of the second *ATM* allele is associated with a poorer prognosis than del(11q) alone.[44] *BIRC3* mutation has been shown to be associated with shorter OS and poorer response to fludarabine.

However, the prognostic value of *ATM* aberrations, including del(11q) and additional ATM mutation, as well as BIRC3 mutation

in the era of new inhibitors, is not yet clear and needs to be validated more thoroughly with inclusive multivariate testing. Future studies will need to show whether substances attacking the NF-κB pathway are of particular efficacy in CLL harboring *BIRC3* mutation.

NOTCH1, SF3B1, and MYD88 mutations

The *NOTCH1* gene coding for transmembrane proteins is mutated in 4% to 11% of CLL patients and is frequently associated with trisomy 12.[6,12,13] Multivariate testing has demonstrated that NOTCH1 is an independent prognostic factor of poor prognosis[22]—at least in the era of chemoimmunotherapy. Patients carrying *NOTCH1* mutation appear to have a higher risk of Richter transformation. The comparison of FCR vs fludarabine and cyclophosphamide treatment within the CLL8 study showed no significant difference in PFS for patients with *NOTCH1* mutation,[6] indicating that the addition of a CD20 antibody is not increasing the efficacy of chemotherapy in this group of patients. A recently published paper showed that 87 CLL patients with *NOTCH1* mutation had a significantly lower CD20 expression on CLL cells compared with 605 CLL patients without *NOTCH1* mutation.[47] Analyses of response to BCR inhibitors or venetoclax in patients with *NOTCH1* mutations are not yet available, but *NOTCH1* mutation might become a predictive marker for response to chemoimmunotherapy and relevant for treatment decision in similar way as *TP53* aberrations.

SF3B1 is a component of the mRNA splicing machinery. Mutations encoding for SF3B1 are enriched in patients with unmutated IGHV and can be detected in 7% to 10% of patients with CLL.[12,48] So far the prognosis of patients with *SF3B1* mutation was associated with intermediate prognosis with chemoimmunotherapy in most studies,[6,48,49] but also showed a high-risk profile in others.[22] The prognostic impact of *SF3B1* also needs to be determined with the new agents.

Mutations of *TLR* / *MYD88*, which can be recurrently detected in different types of lymphoma, are detectable in 3% of unselected patients with CLL. A study evaluating the prognosis of 23 patients with CLL with *TLR*/*MYD88* mutation among 587 patients showed that, although time to treatment was similar for patients with or without *TLR*/*MYD88* mutation, overall survival of these patients was excellent.[50] However, there is a possible bias because these 23 patients were relatively young (median age, 47 years) and had a mutated IGHV status in 88%. In Waldenström lymphoma, patients with mutant *MYD88* have excellence response rates to ibrutinib.[51] Similar data for CLL are not yet available.

IGHV status

As outlined before, IGHV status has been shown to be an independent prognostic factor in different prognostic models for overall survival. BCR pathway inhibitors showed no difference between mutated and unmutated IGHV CLL for PFS so far, but longer follow-up will have to prove whether mutational status is still relevant as prognostic factor for treatment with novel agents. The bcl2 inhibitor venetoclax yielded a 76% overall response rate in unmutated IGHV vs 94% in mutated IGHV and 17% vs 24% complete responses.[37] Though excellent efficacy of new substances has been demonstrated in IGHV-mutated CLL, it is questionable whether new substances will be able to replace the FCR regimen for fit patients in frontline therapy.[52,53] More than 50% of fit patients treated with FCR are still in remission after long-term observation after FCR showing a possible curative potential of this regimen.[52,53] Therefore, IGHV status will probably remain a relevant predictive factor for response to chemoimmunotherapy and will also remain a prognostic marker for time to treatment.[54]

Complex karyotype

Three or more karyotype aberrations are defined as complex karyotype and are prognostically relevant as demonstrated in a model including 399 patients.[20] The impaired prognosis of patients with complex karyotype has also been demonstrated in a randomized trial in less fit patients receiving chemoimmunotherapy.[55] The prognostic value of complex karyotype for response duration of treatment with ibrutinib was demonstrated in a series of 56 patients with relapsed and/or refractory CLL.[40] Twenty-one patients had a complex karyotype, of whom 17 had a del(17p) as indicated by FISH. In multivariate analysis, only complex karyotype was associated with inferior event-free survival, whereas other markers as del(17) were not. Though the number of included patients is low, results show that complex karyotype is a possible predictive marker for ibrutinib therapy. However, these results have to be confirmed by larger phase 3 studies. For the PI3K inhibitor idelalisib or the bcl2 inhibitor venetoclax, similar data have not yet been obtained.

BCR pathway mutations

So far progression during treatment with BCR pathway inhibitors is an infrequent event, but the majority of the studies still have a relatively short follow-up period. During the administration of ibrutinib, drug-resistant mutations in the BCR pathway genes including the *BTK* binding site of ibrutinib or gain-of-function mutation in *PLCG* have been detected.[56] These mutations could not be detected before the start of ibrutinib therapy indicating that they occur under the selective pressure of the drug. Similarly, in patients who develop resistance to the bcl2 inhibitor venetoclax, mutations of bcl2 family proteins have been observed.[57]

Clinical prognostic factors and MRD

All scoring systems in CLL, including clinical parameters, detected age as an independent prognostic parameter.[16,17,19,20] Because CLL is a typical disease of the elderly, age is expected to maintain a prognostic value, even with the new agents, but the significance of this prognostic factor could be abandoned in the future. Although the intensity of administered chemoimmunotherapies is highly dependent on age and physical fitness, new oral treatments are mostly well tolerated also in old and less fit patients. However, because of drug interactions and a different side effect profile, specific comorbidities and comedication will possibly have a larger impact on overall survival in the future.

Minimal residual disease (MRD) negativity determined at the end of chemoimmunotherapy or immunotherapy is highly significant for the prognosis of PFS and OS.[58,59] So far, with a limited time of exposure, BCR pathway inhibitors do rarely result in MRD negativity and also complete responses are less frequently achieved (7% in relapsed/refractory CLL, 23% in previously untreated CLL after 3 years follow-up).[35] However, during treatment with BCR inhibitors, response quality as assessed by the IWCLL criteria does not seem to correlate with PFS.[60] In contrast, MRD negativity is achieved even in some heavily pretreated patients receiving monotherapy with the bcl2-inhibitor venetoclax.[37,38] BCR-pathway inhibitors or bcl2 inhibitor combined with CD20 antibodies or chemoimmunotherapy have been shown to induce MRD negativity in patients.[30,61] However, future studies need to determine whether MRD negativity remains a relevant prognostic factor during or after therapy with novel agents.

Clinical implications and outlook

Individual prognosis of CLL can be well determined at diagnosis and until treatment initiation, but varies during the course of the disease

Table 2. Time points of evaluation of prognostic factors (other than Rai/Binet stage and age)

	Initial diagnosis asymptomatic	Initial diagnosis symptomatic	Before start frontline therapy	Before start* relapse therapy
del(17p)/TP53 mutation	Yes†	Yes†	Yes‡	Yes‡
del(11q)	No	Yes†	Yes§	Yes§
IGHV	Yes†	Yes*	Yes*	—
Karyotype	No	Yes†	Yes¶	Yes¶
β_2-microglobulin	Yes†	Yes	Yes	—

*If not done before.
†If consequences (more/less intensive follow-up or early treatment; eg, within clinical studies) can be drawn.
‡Unless *TP53* mutation/deletion was already detected before.
§If patient would be suitable for FCR.
¶If patient can be considered for allogeneic transplantation or clinical study.

because of the acquisition of new genetic aberrations, which occur at least partially under the pressure of therapy.[27,39,56] Scoring systems developed in the era of chemoimmunotherapy define 3 to 4 risk groups (low, intermediate, high, and very high risk), providing additional prognostic information regarding overall survival compared with conventional clinical staging.[17,21] Although overall survival is currently undergoing significant changes with the novel agents, the evaluated and published scores thus far still hold the potential to support clinical patient management. Though comparisons of different scores regarding the prognostic impact have been performed,[62,63] it is difficult to define the optimal score for all centers internationally. As a practical approach, each center should consider using a score that includes prognostic factors that can be easily performed at the center and whose costs are covered by the national health care insurances.

Given the very good outcome of the very-low-risk or low-risk group (5-year overall survival, 93%), a watch-and-wait approach until symptomatic progression is appropriate, even in the era of new treatment approaches. For those asymptomatic low-risk patients, low-risk annual follow-up visits might be sufficient, given the expected long interval until treatment initiation.[54] Patients with intermediate-risk (5-year overall survival, 73%) should be seen more frequently. Particularly patients with high-risk or even very-high-risk (5-year overall survival, 23%-63%) should be followed intensively. If treatment is needed in high-risk CLL, these patients very likely do not benefit from conventional therapies and should undergo treatment with novel agents, if possible within clinical studies. So far, the previously evaluated scores might still be useful to differentiate between low-risk and high-risk CLL differentiating between those patients who still might benefit from conventional chemoimmunotherapy (eg, excellent outcome of CLL with mutated IGHV with FCR) vs those who will benefit from novel agents. However, scores might be modified during the next years. Novel, very likely molecular, markers will differentiate more precisely, particularly in the group of high-risk or very-high-risk CLL and will also predict response to therapy.

In summary, prognostic testing might be valuable at early stage, because of different follow-up strategies[54] and possibly earlier treatment initiation of very high-risk CLL within a clinical trial (Table 2). The possible consequence of the screening results on follow-up, therapy, and quality of life should be discussed with the patient before prognostic testing. Particularly in older and more comorbid patients, prognostic marker results may not result in any consequences until the patient becomes symptomatic. Hence the benefit of prognostic markers analysis in early-stage CLL of older and comorbid patients should be discussed individually. At the time of treatment initiation, comprehensive risk factor assessment including genetic markers, is generally recommended for all patients, because of therapeutic implications. Complex karyotype and multiple genetic mutations result in poor prognosis, even with novel agents. Therefore, these additional tests should be considered in patients fit enough for allogeneic stem cell transplantation and experimental protocols.

Together with the continuous development of novel therapies and treatment approaches, scoring systems and prognostication are expected to undergo dramatic changes during the next years. Altogether this holds the promise that a more individualized treatment approach on the basis of prognostic profiles will be possible.

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