Risk-Adapted Therapy in Early-Stage Chronic Lymphocytic Leukemia

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Summary
Chronic lymphocytic leukemia (CLL) is the most common leukemia in adults and usually affects the elderly patient. More than 50% of CLL cases are diagnosed at an early disease stage, often as an incidental lymphocytosis found in a routine blood screen. For about 40 years, the classifications according to Binet or Rai have been the hands-on staging systems to stratify patients in daily clinical practice. An increasing molecular understanding of the disease and the identification of strong prognostic markers, such as genetic lesions in TP53, have urged clinical scientists to create new scoring systems that improve prognostic risk assessment and treatment allocation. Until today, studies on early treatment interventions in asymptomatic patients using single chemo- or combined chemoimmunotherapy have failed to demonstrate a survival benefit. However, improved risk stratification tools integrating molecular disease features and the availability of new targeted drugs with attractive efficacy and limited toxicity might open new possibilities to re-investigate early treatment in well-defined clinical settings in the future.

Introduction
Once diagnosed, the clinical course of chronic lymphocytic leukemia (CLL) is hard to predict, with some patients requiring no treatment for decades and others suffering early progression and an increased risk of premature death. The current ‘gold standard’ is to treat when the patient develops symptomatic disease with B symptoms, painful or anatomically relevant lymph nodes, bone marrow failure, or recurring infections [1, 2]. Modifications to this ‘watch & wait’ approach would require scientific evidence for an early treatment intervention to provide a major survival benefit to patients, particularly to those who are at the highest risk of premature death due to the disease. The concern of ‘overtreatment’ with harmful side effects at a disease stage when patients are usually asymptomatic with an excellent quality of life explains why scientists have been hesitant to perform studies in early-stage CLL. Hence, very few prospective or even randomized clinical trials on early treatment interventions have been performed to date. All of these studies used different strategies to stratify patients with an adverse prognosis (high-risk CLL) for treatment initiation. This review briefly summarizes recent efforts to develop standardized scoring tools for an advanced, uniform, and center-independent risk stratification in CLL, as well as previous and novel strategies for early treatment interventions investigated in clinical trials.

Risk Assessment in Early-Stage CLL

The first risk stratification systems in CLL were established by Jean-Jacques Binet and Kanti Rai 40 years ago [3, 4]. Both the Binet and Rai classifications are simply based on clinical examination and blood cell counts, and identify 3–5 prognostic patient subgroups with significantly different survival perspectives. However, the majority of patients are diagnosed at an early Binet or Rai stage where both classifications more or less capture a snapshot of the disease in its early clinical evolution. The inherent and individual risk of progression or premature death, mainly influenced by a variety of molecular characteristics, is not reflected in such clinical staging systems.

At the molecular level, the strongest prognostic markers consistently confirmed to be associated with adverse clinical prognosis
after chemo- or chemoimmunotherapy have been chromosomal deletions or mutations in the TP53 gene, located on chromosome 17p13 (del(17p)) [5–8].

There is a constantly growing variety of additional biological markers that have been identified to be prognostically relevant in CLL, i.e. the mutation status of the immunoglobulin heavy chain genes (IGHV), elevated levels of serum β2-microglobulin (B2M) or thymidine kinase (TK), and recurrent gene mutations, i.e. in NOTCH1, SF3B1, and others.

Recently published CLL scores integrate the most potent clinical and biological parameters into advanced classification systems which may help to estimate the patients’ long-term outcome by a small set of prognostic markers (table 1). Most of them are based on the performance of these parameters as independent covariates in multivariable regression models: A prognostic nomogram developed at the MD Anderson Cancer Center (MDACC) estimates the time to first treatment (TTFT) in patients with early-phase CLL [9]. This model incorporates traditional (number and size of involved lymph node sites, serum lactate dehydrogenase (LDH)) and genetic parameters (del(17p), del(11q), IGHV mutation status) as independent prognostic factors for TTFT. Patients are graded between 0 and 100 points for the level of each factor, and added total points provide a projection for the probability of a 2-year, 4-year, and median treatment-free survival. This nomogram is simple to use, but it is based on a test set of rather young patients (median age 59 years) followed at a single center and it has never been validated in an independent cohort. Further, TTFT is a relatively weak time-to-event parameter since it is influenced by the physician’s discretion to initiate therapy.

The German CLL Study Group (GCLLSG) recently followed another approach to categorize 4 patient subsets with differential overall survival (OS) according to the presence or absence of several clinical (age, sex, performance status) and laboratory markers (del(17p), del(11q), IGHV mutation status, serum B2M and TK; table 1) [10]. Patients receive 1–6 points for each of the 8 parameters, and the total sum of points defines patients with low (0–2

<table>
<thead>
<tr>
<th>Table 1. Novel risk stratification systems incorporating clinical and molecular prognostic factors</th>
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<tr>
<td><strong>MDACC prognostic nomogram</strong> [9]</td>
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<tr>
<td>Incorporated factors: Largest lymph node size in the neck, number of lymph node sites involved, LDH (IU/L/100), IGHV mutation status, del(11q) or del(17p) (between 0 and 100 points per each factor)</td>
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<tr>
<td>Median TTFT, months</td>
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<tr>
<td>=&lt; 42 points</td>
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<td>42–74 points</td>
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<td>54–75 points</td>
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<td>76–90 points</td>
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<td><strong>GCLLSG prognostic index</strong> [10]</td>
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<tr>
<td>Incorporated factors: sex, age, ECOG status, del(17p), del(11q), IGHV status, serum B2M, serum TK (between 1–6 points per each factor)</td>
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<tr>
<td>5-year overall (treatment-free survival) probability, %</td>
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<tr>
<td>0–2 (low risk)</td>
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<td>3–5 (intermediate risk)</td>
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<td>6–10 (high risk)</td>
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<td>11–14 (very high risk)</td>
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<td><strong>CLL IPI</strong> [11]</td>
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<tr>
<td>Incorporated factors: age, clinical stage, del(17p) and/or TP53 mutation, IGHV status, serum B2M (between 1–4 points per each factor)</td>
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<tr>
<td>5-year overall (treatment-free survival) probability, %</td>
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<tr>
<td>0–1 (low risk)</td>
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<td>2–3 (intermediate risk)</td>
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<tr>
<td>4–6 (high risk)</td>
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<tr>
<td>7–10 (very high risk)</td>
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*Treatment-free survival (time from parameter assessment (= date of baseline presentation/registration at center in original publication) to first treatment), obtained only from early-stage/watch & wait CLL patients.

Overall survival from the date of parameter assessment (= date of registration/randomization in original publication) obtained from CLL patients of all stages.

MDACC = MD Anderson Cancer Center, LDH = lactate dehydrogenase, TTFT = time to first treatment, GCLLSG = German CLL Study Group, ECOG = Eastern Cooperative Oncology Group, B2M = β2-microglobulin, TK = thymidine kinase, CLL = chronic lymphocytic leukemia, IPI = international prognostic index.
points), intermediate (3–5 points), high (6–10 points), or very high risk (11–14 points) of short OS. The model is applicable to all disease stages and demonstrated validity in an independent patient set. It also works for the prediction of TTFT. However, it incorporates many parameters, making it difficult to work with when not all factors are available for diagnostic testing. Based on the GCLLSG approach, a consortium of international investigators has recently presented an international version of a prognostic index for CLL (CLL-IPI; table 1) [11]. The index has been worked out from data of 3,742 previously untreated CLL patients at an early or advanced disease stage recruited in 8 phase III trials from Europe and the USA. The 5-factor prognostic index incorporates genetic factors (IGHV, del(17p), TP53 mutation status), clinical stage, age, and B2M into a 4-risk group scoring system, categorizing patients between a 23% and a 93% 5-year survival probability. The simpler nature of this score increases the likelihood to be more widely used as a stratification tool in- and outside of clinical trials and outside of academic settings in the future.

In clinical practice, most physicians probably adapt their risk assessment in CLL patients to the laboratory parameters available at their diagnostic facilities. It must be emphasized that none of the afore-mentioned biological markers or scoring systems has been adopted as a standard of care to determine treatment decisions at an early time point of the disease. Furthermore, the scores have been developed based on data from patients treated with chemo- or chemoimmunotherapy, and it remains to be seen whether they retain validity in patients treated with novel small-molecule inhibitors. At an early stage of CLL without any clinical treatment indication, in particular molecular testing should preferably be performed within clinical trials that apply modern stratification tools for prospective validation and for a systematic investigation of risk-tailored treatment strategies.

State of the Art – Watch and Wait

The rationale of a watch and wait approach in early-stage CLL is substantiated on a set of randomized trials from the late 1980s and 1990s which compared chlorambucil – the most commonly used cytotoxic agent at that time – versus deferred treatment [12]. The seminal studies were performed by the French Cooperative Group on CLL in more than 1,500 patients: While early treatment with the alkylator chlorambucil was able to slow down disease progression, it did not prolong survival in treated versus untreated Binet A patients followed for more than 6–11 years after randomization. The relatively high rate of epithelial neoplasms in the treatment group suggested a possibly oncogenic potential of chlorambucil in early-stage CLL [13, 14]. At the turn of the millennium, the purine analogue fludarabine demonstrated better efficacy as a single agent in advanced CLL when compared to chlorambucil, CAP (cyclophosphamide, doxorubicin, and prednisone), or CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) treatment [15–17]. The ability of fludarabine to induce more complete remissions (20% vs. 4%) and a prolonged remission duration (25 vs. 14 months) compared to chlorambucil made it the preferred first-line drug in physically fit/young CLL patients in need of therapy [17]. Although a clear survival advantage has never been demonstrated in advanced CLL, new hopes were raised that this agent alone or in combination might be beneficial for early-stage patients, at least in cases with adverse prognosis.

Risk-Adapted Early Treatment with Chemo- and Immunotherapy

Subsequent clinical studies implemented risk-adapted treatment approaches to identify patients who might benefit from immediate purine analogue-containing treatment: German investigators were the first to implement a systematic risk stratification system in a prospective phase III trial setting in order to identify early-stage CLL patients with an anticipated unfavorable outcome [18]. 4 risk parameters were assessed in a total of 710 patients: the bone marrow infiltration pattern (diffuse vs. nodal), elevated serum B2M or TK levels, and a lymphocyte doubling time of < 12 months. 189 patients with ≥ 2 of these 4 unfavorable parameters were identified as high-risk CLL and were randomized between early treatment with fludarabine versus clinical observation. According to the latest study update presented at the American Society of Hematology congress in 2013, cytotoxic therapy with fludarabine resulted in a significant benefit for progression-free (30 vs. 13 months) and treatment-free survival (74 vs. 41 months), when compared to the observation arm. However, a difference in OS was not found after a median follow-up of 8.5 years.

In 2008, randomized phase III data demonstrated that the addition of the anti-CD20 antibody rituximab to a fludarabine and cyclophosphamide (FC) backbone versus FC alone induces unprecedented rates of remission (overall response rate 90%, 44% complete responses), and – for the first time – prolonged long-term survival in previously untreated CLL in need of therapy (3-year survival 87% vs. 83%) [6]. Based on these data, FC plus rituximab (FCR) was approved for frontline therapy in advanced CLL by European Union (EU) and US authorities. Using a modified 4-parameter risk stratification system integrating genetic features, a randomized German-French cooperative phase III trial prospectively investigated the efficacy of 6 cycles of FCR in standard dosing in Binet A patients with high-risk disease. Patients were stratified according to the presence or absence of clinical and molecular markers (unmutated IGHV status, del(11q), del(17p), or trisomy(12)), a lymphocyte doubling time of < 12 months, or elevated serum TK levels). The presence of ≥ 2 of 4 risk features was required to assign a patient to the high-risk disease category. A first analysis of overall 840 recruited patients was presented at the American Society of Hematology congress in 2013 [19]: FCR substantially improved the event-free and progression-free survival (median not reached in 100 treated vs. 24.2 months in 101 observed patients) but failed to improve the OS in Binet A high-risk CLL patients after a median follow-up of 49 months. The main adverse events were hematotoxicity and infections (60% and 15%, respectively), whereby these rates were compa-
rable to what has been reported for combined chemoimmunotherapy in advanced-stage patients [6, 20]. An updated analysis with longer follow-up data is expected at the end of 2015.

A few phase II studies have investigated rather unconventional treatment approaches in early-stage CLL. The efficacy and safety of a chemo-free combination of 2 monoclonal antibodies, alemtuzumab (anti-CD52) and rituximab (anti-CD20), was tested in 30 Rai 0–II patients with at least 1 feature indicating high-risk disease (del(17p), del(11q), or unmutated IGHV in combination with ZAP70 or CD38 positivity) [21]. Treatment included a 31-day regimen with 3 times weekly subcutaneous alemtuzumab and weekly rituximab administrations. 90% of the patients responded to treatment; significant hematotoxicities and infections were each observed in approximately 17%. The median time from diagnosis to second-line therapy was reported to be 4.4 years in antibody-treated patients. However, with the market withdrawal of alemtuzumab for CLL, the treatment design does not have a realistic future. Another phase II experience was reported by investigators from the MDACC, testing 8 weeks of rituximab therapy (once weekly) in 34 asymptomatic Rai 0–II patients with elevated serum B2M [22]. The median time to progression was 23 months, the median time to subsequent treatment 43 months. An alternative treatment approach has recently been pursued by administering high doses of orally given green tea extract (polyphenon E and epigallocatechin gallate) in 42 asymptomatic Rai 0–II CLL patients [23]. During 6 months of therapy, up to 69% of the patients experienced reduced levels of peripheral blood lymphocytosis or lymphadenopathy. Sustained outcome data have not been reported. Other alternative treatment options include vitamin D and curcumin, which are part of ongoing phase II studies in early-phase CLL (registered at www.clinicaltrialsregister.eu or www.clinicaltrials.gov).

New Strategies for Early Treatment Involving New Substances

Recent advances in targeted drug development are about to substantially transform CLL therapy. A growing understanding of B cell receptor (BCR) signaling as a central stimulatory and survival pathway in CLL cells has led to the development of inhibitors that tackle enzymatic drivers of BCR effector signaling. Ibrutinib (PCI-32765) and idelalisib (CAL101/NS-1101) are inhibitors of kinases (Bruton’s tyrosine kinase (BTK) and phosphatidylinositol 3-kinase (PI3K), respectively) that are critical for the intracellular transmission of BCR signals for the activation of proliferation, differentiation, and migration [24]. They demonstrate remarkable remission rates as single agents in previously untreated and/or relapsed/refractory CLL, particularly in patients with adverse disease features, such as del(17p) [25–29]. A third class of promising new compounds in clinical development are BCL2 homology domain 3 (BH3) mimetics, small molecules that inhibit the anti-apoptotic molecule B cell lymphoma 2 (BCL2) and related family members. In general, the novel substances act more specifically on the malignant B cell compartment and cause less diffuse organ toxicity compared to chemotherapy. Common but manageable grade 3/4 adverse events after kinase inhibition are neutropenia (20–40%) and pneumonias (5–20%). Otherwise, patients mostly experience low-grade adverse events (about 30–50% of patients), i.e. diarrhea, fatigue, arthralgia, or signs of an inflammatory response. Another attractive aspect regarding the application of these novel drugs at an early disease stage is their oral availability (1–3 tablets/day), which results in less visiting and infusion hours for patients. Areas of concern are the potential overtreatment of patients with an otherwise indolent disease course, missing knowledge about long-term toxicities, and a possibly limited patient adherence to a daily intake of an oral drug. It is unclear if the novel agents, which are currently approved as a maintenance treatment until disease progression, can be simply discontinued in case of a deep molecular remission, i.e. minimal residual disease (MRD)-negative complete remission. A critical appraisal also needs to be made of the risk that an early application of the new substances in clinically inactive CLL might select for new escape mechanisms of resistance, as demonstrated by the appearance of BTK mutants found in a small subset of ibrutinib-treated patients [30]. Thus, the use of oral inhibitors in CLL cases without a clinical need of therapy should exclusively be limited to controlled clinical trials. Ibrutinib is currently being investigated in a placebo-controlled phase III study in early-stage high-risk CLL patients. The trial design incorporates the multivariable prognostic index developed by the GCLLSG, which defines 4 different risk groups of survival. Whereas low-risk patients are being observed (watch and wait), intermediate- to very-high-risk patients are randomized 1:1 to receive either treatment with ibrutinib at a daily dose of 420 mg or placebo [31]. First efficacy results are expected in 2016.

Conclusions

At an early stage of CLL without treatment indication, assessment of prognostic features – particularly on the molecular level – should only be performed within clinical trials that evaluate modern risk stratification systems. The evidence obtained from previous studies is the following: Although not necessarily more toxic compared to later treatments, the early administration of chemotherapeutic/ or immunotherapy defers progression and subsequent treatment events but fails to prolong OS in patients determined to have ‘high-risk’ CLL. Reasons for this might be the failure of these regimens to completely eradicate (‘cure’) CLL and the possibility of (sub)clonal selection, leading to a more aggressive disease behavior in subsequent (salvage) therapies. Therefore, watch & wait remains the current gold standard for the management of early-stage CLL. Novel oral small-molecule inhibitors have attractive efficacy and toxicity profiles. However, they also bear the risk to select for new mechanisms of resistance. Testing these targeted drugs in early-stage CLL is attractive for future clinical investigation, but will require a careful and comprehensive molecular characterization of patients and risk-tailored treatment designs to identify those substances best suitable for given patient subsets.
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