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CHRONIC LYMPHOCYTIC LEUKEMIAS (N JAIN, SECTION EDITOR)

Relevance of Prognostic Factors in the Era of Targeted Therapies in CLL

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Abstract

Purpose of Review Clinicians continue to utilize prognostic biomarkers, such as expression of CD38 and ZAP-70, *IGHV* mutational status, cytogenetic abnormalities, and genomic aberrations in *TP53*, to guide prognosis and treatment of patients with CLL. These biomarkers have been validated with standard chemoimmunotherapy. Here, we discuss whether these biomarkers maintain their prognostic significance in the era of targeted therapy.

Recent Findings Multiple phase 3 clinical trials have now proven improved efficacy of targeted therapy over traditional chemoimmunotherapy. We now have ample prospective data using targeted therapy to critically evaluate whether prior prognostic biomarkers remain relevant.

Summary High-risk features do not have the same magnitude of effect on clinical outcomes in the era of targeted therapy when compared to chemoimmunotherapy. Aberrations in *TP53* continue to predict inferior outcomes. More research is needed to determine what features confer poor prognosis when targeted therapy is used to treat CLL.

Keywords CLL · Chronic lymphocytic leukemia · Biomarkers · Prognosis · Targeted therapy

Introduction

Clinicians use prognostic and predictive biomarkers to guide treatment decisions for patients with chronic lymphocytic leukemia (CLL). The updated International Workshop on CLL guidelines suggest testing for the B cell receptor (BCR) immunoglobulin heavy chain variable region gene (*IGHV*) mutational status, presence of deletions in the long arm of chromosome 11 (del(11q)) and in the short arm of chromosome 17 (del(17p)), *TP53* gene mutations, and to consider testing for complex karyotype (CK) as defined by ≥ 3 chromosomal abnormalities by conventional cytogenetics as a baseline evaluation of CLL [1]. Along with ZAP-70 protein expression and gene methylation, earlier studies have shown these biomarkers to have negative predictive implications for patients with CLL treated with chemoimmunotherapy (CIT) [2–7]. Furthermore, specific genetic mutations such as *SF3B1* and *NOTCH1* detected by next-generation sequencing (NGS) may also be predictive in CIT-treated patients [8•, 9–11].

Since 2013, the Food and Drug Administration (FDA) has approved 4 novel agents for the treatment of CLL. These include the Bruton tyrosine kinase (BTK) inhibitor ibrutinib, the phosphoinositide 3-kinase (PI3K) inhibitors idelalisib and duvelisib, and the BCL-2 inhibitor venetoclax. Furthermore, many additional novel agents (e.g., BTK inhibitors acalabrutinib and zanubrutinib) have entered registrational studies. With the advent of these therapies, patients with CLL have expanding therapeutic options, with multiple phase 3 clinical trials now demonstrating superior clinical efficacy, including survival, of targeted therapy over CIT [12–14, 15••, 16–22]. A key group of patients that have benefited from the use of targeted therapy are those with certain genetic abnormalities that predict poor responses to CIT, which include

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del(11q), del(17p), and mutations in *TP53* [7]. This begs the question of whether the conventional prognostic and predictive markers are still relevant in the era of targeted therapy. Herein, we review the data evaluating the use of conventional biomarkers in the setting of patients treated with novel therapeutics for CLL. We have focused our summary on the best available evidence, including phase 3 trial data along with pooled analyses of phase 1/2 clinical trials.

Ibrutinib

Elucidation of the role of BCR signaling, specifically BTK, in CLL cell survival has arguably made the greatest impact in the way we treat CLL. This led to the introduction of the BTK inhibitors (i.e., ibrutinib), paving the way for the rapid development of targeted therapies [23, 24]. Ibrutinib was first approved by the FDA for the treatment of relapsed/refractory (R/R) CLL in 2013 following the positive results of the RESONATE trial, a randomized phase 3 clinical trial which compared ibrutinib to single-agent ofatumumab in patients with R/R CLL [17]. Prognostic data has been reported after a 5-year follow-up utilizing a multivariate cox proportional hazards regression analysis [25]. The following factors were analyzed: age, Rai stage, ECOG performance status, del(11q), del(17p), β2-microglobulin, and disease refractory to purine analogues. Gene mutations and CK were not available and thus not included in the analysis. No significant prognostic factors were identified when analyzing the ibrutinib arm of the study. When examining progression-free survival (PFS) for patients treated with ibrutinib, the 18-month PFS was similar when accounting for all baseline genetic factors (*IGHV*, del(17p), del(11q), CK, or mutations in *NOTCH1*, *BIRC3*, and *ATM*). Of note, there was a trend towards a shorter PFS among patients with *SF3B1* mutations [25]. Subsequently, a pooled data analysis from both RESONATE and PCYC-1102 was reported [26]. PCYC-1102 was a phase 1b/2 single-arm trial where patients were treated with ibrutinib as a single agent in both the R/R and TN settings [27]. In this pooled analysis, complete response (CR) rates were higher among patients who had no prior treatment, or those who had no bulky disease (lymph node ≥ 5 cm). Del(11q), del(17p), and *IGHV* mutational status again were not statistically significant prognostic factors [26].

In RESONATE-2, patients with TN CLL were randomized to treatment with ibrutinib or chlorambucil. Patients with del(17p) were excluded from this phase 3 trial. PFS was improved for all subgroups treated with ibrutinib, including del(11q) and unmutated *IGHV* (U-*IGHV*). Interestingly, 18-month PFS was identical for patients with U-*IGHV* and mutated *IGHV* (M-*IGHV*) treated with ibrutinib (89%), again highlighting the biologically distinct effect of BTK inhibition compared with CIT in CLL [16].

Concurrent with RESONATE-2, the HELIOS trial focused on combining ibrutinib with traditional CIT. This phase 3 trial randomized patients with R/R CLL to bendamustine and rituximab (BR) combined with ibrutinib or placebo [18]. Like RESONATE-2, this trial excluded patients with del(17p). Subgroup analyses demonstrated that patients who had del(11q), high ZAP-70 expression, or U-*IGHV* had superior PFS when treated with ibrutinib plus BR compared to placebo plus BR [18]. A recently published pooled analysis of RESONATE, RESONATE-2, and HELIOS conducted a multivariate cox proportional hazards regression analysis for PFS and overall survival (OS). The following risk factors were included: *IGHV*, del(11q), trisomy 12, and CK. Among ibrutinib-treated patients without del(17p), no association was detected between U-*IGHV*, del(11q), trisomy 12 and CK, and the above survival outcomes [28]. In the RESONATE-17 phase 2 clinical trial, which explored the use of ibrutinib for R/R patients with del(17p), overall response rates for patients with an additional del(11q) appeared to be similar to patients without a del(11q) (82.6% absent versus 87% present) [29]; however, the impact of del(11q) on PFS and OS was not analyzed in this study. These data suggest that the presence of del(11q) may not affect outcomes when patients are treated with ibrutinib, contrary to CIT.

Three large phase 3 studies comparing novel therapies to CIT were presented at the 2018 American Society of Hematology (ASH) annual meeting and further solidified the position of ibrutinib in therapy of TN CLL [15••, 20, 21]. In cooperative group study (Alliance), patients with TN CLL were randomized to ibrutinib versus ibrutinib combined with rituximab (IR) versus BR in patients who were TN and were aged 65 years or older [15••]. After a median follow-up of 38 months, patients treated with ibrutinib had a 2-year PFS benefit when compared to those who received BR (87% versus 74% respectively), and this benefit was maintained across all high-risk subgroups. The authors performed a primary analysis utilizing a multivariate cox proportional hazards regression analysis to look at the following factors: age, sex, Rai stage, performance status, β2-microglobulin, LDH, splenomegaly, high-risk FISH (del(17p) or del(11q)), *TP53* mutational status, CK, and ZAP-70 methylation status. *IGHV* mutational status was not included, as it was not tested for routinely. In this analysis, only presence of the *TP53* mutations retained statistical significance as a negative predictive biomarker regardless of treatment arm with a HR of 2.16 ($p = 0.005$). In a secondary analysis, del(17p) was found to be a statistically significant independent negative biomarker among the ibrutinib-treated patients with a HR of 2.20 ($p = 0.01$). Meanwhile, neither CK nor del(11q) had a negative influence on PFS [15••]. This data is interesting, in

that it continues to show that *TP53* mutation, and del(17p), continue to be prognostic for patients receiving ibrutinib.

In the iLLUMINATE trial, TN patients with CLL who were > 65 years of age or < 65 with coexisting comorbidities and/or *TP53* aberrations were randomized to ibrutinib and obinutuzumab (IO) versus chlorambucil and obinutuzumab (CO). Patients who received IO had an improved PFS across all subgroups including del(11q), del(17p), *TP53* mutated, and U-*IGHV* [20]. Longer follow-up is needed to help validate the prognostic markers within this trial, as median PFS was not reached at the time of the current publication, including in patients with traditional high-risk markers. The last clinical trial to mention from ASH 2018 was E1912, which randomized TN patients to IR versus fludarabine, cyclophosphamide, and rituximab (FCR) [21]. Patient with del(17p) were excluded from this clinical trial. IR was found to be superior to FCR for all subgroups including patients with del(11q), and U-*IGHV* [21].

As many of these trials have long-term follow-up reported, subsequent analyses have been pursued. In one of the longest published follow-ups, investigators analyzed both TN and R/R patients who had been treated with single-agent ibrutinib on the phase 1/2 PCYC-1102/1103 trials [30]. We will focus on the R/R patients ($N = 101$) as there were only 31 patients analyzed in the TN group. In a multivariate cox proportional hazards regression analysis, del(17p) and higher number of prior therapies were the only independent factors associated with a decreased OS in R/R patients with CLL (HR of 2.44 and 6.03, respectively). Although statistically significant in a univariate analysis, bulky disease (lymph node ≥ 5 cm) and CK were not found to be significant [30]. At MD Anderson Cancer Center, investigators analyzed 88 patients with R/R CLL treated with ibrutinib-based therapies from 2010 to 2013. Here, they discovered that fludarabine-refractoriness and CK were the only statistically significant prognostic variables associated with a lower OS (HR of 6.9 and 5.9 respectively), while del(17p) was not associated with a decreased OS [31]. In another analysis, 230 patients with R/R CLL with del(17p) were analyzed from the PCYC-1102/1103, RESONATE, and RESONATE-17 clinical trials. In this combined cohort, after a median follow-up of 28 months, estimated 30-month PFS and OS were 57% and 69% respectively. Lactate dehydrogenase level and bulky disease (lymph node ≥ 5 cm) were the only prognostic markers that showed a difference in PFS and OS among these traditionally high-risk patients ($p < 0.05$) [32]. The authors did not comment on the co-occurrence of del(11q) in this analysis.

While disease-intrinsic biomarkers seem to have reduced value in the era of ibrutinib, the characteristics of a host remain critical. A recent study demonstrated that patients with CLL who have comorbidities have shorter PFS and OS when treated with ibrutinib, and are more likely to discontinue the drug [33].

Looking at this data in its entirety, it is clear that ibrutinib has improved efficacy as compared to CIT among patients with all high-risk features. Furthermore, the prognostic value of traditional disease biomarkers may be of less value when ibrutinib is used. While the data is somewhat contradictory, there is a strong suggestion that *TP53* aberrations (del(17p), mutated *TP53*) retain their negative prognostic impact in patients treated with ibrutinib in both the R/R and TN settings. On the other hand, this begs the question of optimal therapy for patients with M-*IGHV*, where FCR has a curative potential, including whether BTK inhibition may continue to improve long-term outcomes in this common patient subgroup [34, 35]. In this context, a combination of ibrutinib with fludarabine, cyclophosphamide, and obinutuzumab is being investigated in TN patients who have M-*IGHV* and no *TP53* mutation. In this highly selected patient population, the early data is very promising. Investigation of additional biomarkers, i.e., del(11q), ZAP70, and NGS analysis, would be of value [36].

It will be important to know whether this knowledge, gained in clinical trials of ibrutinib, will be applicable to second-generation BTK inhibitors, which are now actively being studied in CLL [37, 38]. As time goes on, and these patients continue to be evaluated, we will be better able to determine the prognostic value of these biomarkers in patients treated with ibrutinib with both TN and R/R disease.

Idelalisib and Duvelisib

The PI3K inhibitors were first introduced into clinical practice following the approval of idelalisib, in treatment of R/R CLL in 2014. This approval came on the heels of the first multicenter randomized phase 3 trial comparing idelalisib with rituximab versus rituximab with placebo in patients with R/R CLL. Patients treated with idelalisib saw a benefit in their PFS across all subgroups, including U-*IGHV* status, del(17p), and mutations in *TP53* gene [13]. In a post hoc analysis of 185 patients who had karyotyping performed, CK was not an independent prognostic risk factor for patients treated with idelalisib [39].

Two large phase 3 randomized clinical trials were published in 2017. The first compared idelalisib with BR to placebo with BR in patients with R/R CLL [22]. Patients treated with idelalisib had an improvement in median PFS along all pre-specified subgroups, including those with U-*IGHV*, del(17p), and *TP53* mutations. Among patients with *TP53* abnormalities, median PFS was 11.3 months versus 24.5 months among those without this prognostic feature. In contrast to BTK inhibition, U-*IGHV* was associated with

shortened median PFS of 19.5 months, compared with 26.4 months for patients with M-I*GHV*. Thus, *TP53* gene aberrations and U-*IGHV* predict an inferior prognosis when idelalisib is added to CIT [22]. The second phase 3 clinical trial randomized patients with R/R CLL to idelalisib in combination with ofatumumab versus ofatumumab alone [19]. Similarly, in this trial, *TP53* aberrations predicted inferior median PFS (15.5 versus 19.1 months for patients with intact *TP53*) but this was not found to be statistically significant (HR of 1.36 (0.91–2.03), $p = 0.13$) [19].

Duvelisib is a dual PI3K$\gamma\delta$ inhibitor approved for patients with CLL who had two prior treatments based on the results of DUO trial [12]. In this trial, duvelisib was compared to ofatumumab monotherapy. Median PFS was 13.3 months versus 9.9 months, correspondingly, among all patients. Patients with del(17p) or *TP53* mutation had a median PFS of 12.7 months when treated with duvelisib, whereas median PFS for patients without such lesions was not reported [12].

All 4 of these clinical trials were performed in the R/R setting, of which at least one trial rendered a signal suggesting that patients with high-risk features fare worse when treated with a PI3K inhibitor. These results are confounded since this clinical trial included chemotherapy (BR). Thus, so far, the only statement that can be made in confidence is that targeted therapy, including PI3K inhibitors, is a superior approach in treatment of patients with high-risk features. In our opinion, these trials lend to the idea that high-risk features continue to be less prognostic in the setting of targeted therapy, especially in the R/R setting. However, more follow-up data and further analysis is needed to concretely determine if high-risk features continue to confer poor risk for patients treated with PI3K inhibitors.

Venetoclax

Venetoclax, a BCL-2 inhibitor, was first studied in multiple phase 1 and 2 trials prior to the phase 3 MURANO trial, which led to its FDA approval. There have been multiple analyses of these phase 1 and 2 trials to determine the role of prognostic markers for patients treated with venetoclax. In a pooled analysis, investigators analyzed 387 patients who had received single-agent venetoclax in 4 different phase 1 or 2 clinical trials in the R/R setting [40]. PFS at 24 months was lower for patients who had either a del(17p) or *TP53* mutation versus those without (50.9% versus 66.7%, respectively). However, an overlap between the associated confidence intervals and lack of a statistical analysis of significance in the publication renders those numbers difficult to interpret [40]. Meanwhile, in a retrospective analysis of 204 patients who received venetoclax across 20 academic and community centers in a real-world setting, prior kinase inhibitor exposure, prior cellular therapy (chimeric antigen receptor T cell therapy, or transplantation), *TP53* mutation, and CK were all found to be risk factors predicting inferior PFS in a univariate analysis (HR 3.7, 4.6, 2.8, 1.9 respectively) [41]. Also, in 2017, a series of 67 patients who were treated with single-agent venetoclax for R/R CLL was published. In a univariate analysis, CK and fludarabine refractoriness were independent risk factors for treatment failure, and earlier disease progression (HR of 6.61 and 7.01 respectively). Del(11q), del(17p), and del(17p) and/or *TP53* mutation were not identified as significant risk factors [42].

These studies led to the phase 3 MURANO trial [14]. Patients with R/R CLL were randomized to 2 years of treatment with venetoclax plus rituximab versus BR. In a subset analysis, treatment with venetoclax was favored for all subgroups including U-*IGHV*, del(17p), and mutated *TP53* [14]. Updated results were presented at the 2018 ASH Annual Meeting [43]. The investigators showed that the presence of a *TP53* mutation, and del(17p) and/or *TP53*, was a significant independent risk factor of a shorter 2-year PFS in a univariate analysis. At 2 years, 23.3% of patients with del(17p) and/or a *TP53* mutation developed progressive disease compared with only 6.4% of patients without either abnormality when treated with venetoclax, suggesting that any type of *TP53* abnormality is unfavorable. Presence of del(11q) and U-*IGHV* was also evaluated, and not found to be statistically significant variables. Patients with *TP53* aberrations seem to be as likely to achieve undetectable MRD as patients without them. Regardless, it is encouraging that at a median follow-up of 9.9 months after cessation of therapy, PFS at 1 year was 87.4% for all-comers [43]. We eagerly await more data evaluating prognostic factors for these patients followed after 2 years.

Unlike the BTK and PI3K inhibitors, it appears that there is a signal that high-risk features continue to predict a worse prognosis when venetoclax is used. Presence of del(17p) and/or *TP53* mutation continues to predict worse outcomes for patients treated with venetoclax. However, the data is conflicting at this time as to what other high-risk features continue to matter, and we will need further analysis to better determine the role of high-risk features for patients treated with venetoclax.

Next-Generation Sequencing

Using NGS techniques to determine genetic mutations that may affect prognosis continues to be explored in CLL. In the RESONATE trial, *SF3B1* mutation conferred inferior prognosis in patients treated with ibrutinib [25]. A recent study examined 72 patients treated with single-agent ibrutinib demonstrating a statistically significant decrease in 24-month PFS for patients with *NOTCH1* mutations versus those without (42% versus 75% respectively, $p = 0.002$) [44]. Finally, in an analysis of only 9 patients with a *NOTCH1* mutation

having received single-agent idelalisib in a phase 1 trial, of the 6 patients that responded, duration of response was shorter (by 13 months) for patients with a *NOTCH1* mutation compared to those without [45].

We do have more data of NGS use for CIT, which we can make some inferences from. Landau et al. conducted a large whole-exome sequencing analysis of 538 samples from patients with CLL [9]. Genetics aberrations found with frequency > 10% were deletion 3q, *SF3B1*, *ATM*, del(11q), and trisomy 12. *TP53*, *NOTCH1*, *POT1*, amplification 2q, and del(17p) rounded out the top 10 mutations [9]. In the CLL8 phase 3 clinical trial, which randomized patients to FCR or fludarabine plus cyclophosphamide, presence of *TP53* or *SF3B1* mutations was found to be independent prognostic risk factors for PFS in a multivariate cox proportional hazards regression analysis [8•]. Interestingly, patients with a *NOTCH1* mutation saw a decrease in benefit with the addition of rituximab to fludarabine and cyclophosphamide. In the paper by Landau et al., they also included 238 samples from CLL8 and reported a shorter PFS for patients with *TP53*, *SP3B1*, and *RPS15* mutations [9]. Furthermore, authors also noted that there is clear clonal evolution when patient samples were compared pre and post treatment for a group of 58 patients that had this data available [9]. This and other data suggest that CD20 antibodies fail to overcome the negative biological impact of *NOTCH1* mutations [8•, 46, 47]. This suggests that patients with *NOTCH1* mutations should be considered for targeted therapy earlier in their disease course, and reinforces the role of NGS in the era of targeted therapies. In 2017, the Stilgenbauer group looked at recurrent gene mutations and clinical outcomes for patients with R/R treated with lenalidomide [10]. Of the 162 gene mutations, only *NOTCH1* demonstrated a trend towards shortened OS (HR = 1.66, p = 0.08). Interestingly, all other mutations tested, including *TP53* and *SF3B1* mutations, showed no significant association to a change in PFS or OS. This finding was supported by a multivariate cox regression analysis, which identified *NOTCH1* as the only independent predictor of OS (HR 2.74, $p < 0.01$) [10]. Although these findings are hypothesis generating, more prospective validation is needed to determine NGS utility. There appears to be a signal that *NOTCH1* mutations may confer a poor prognosis for patients with CLL.

Future Directions

Given the advent of novel pathway inhibitors, there has been movement to redefine what we classify as high-risk CLL into 2 new categories, high-risk-1 and high-risk-2 [48•]. High-risk-1 is comprised of patients who have a *TP53* mutation who have failed CIT but are responding to first-line targeted therapy. High-risk-2 has failed both CIT and the first-line targeted therapy regardless of *TP53* mutation. The goal is to stratify patients into those who would benefit from oral therapies versus those who require alternative approaches, such as cellular therapy [48•]. Determining which biomarkers may predict response to pathway inhibition becomes even more pertinent when thinking about these two new classifications.

The following is needed to better understand the role of and employ traditional prognostic biomarkers in the era of targeted therapies:

1. Elucidate long-term outcomes to further delineate the predictive value of traditional biomarkers in a prospective setting.
2. Use traditional biomarkers to identify patients who are able to safely stop therapy with BTK inhibitors, currently prescribed until disease progression or emergence of adverse events.
3. Determine the role of biomarkers to identify patients who will most benefit from combination approaches. Here, patients with *TP53* abnormalities are the most obvious candidates, given their inferior outcomes with single-agent novel therapy and CIT-novel therapy combinations. Early therapy, prior to emergence of indications to treat CLL, should also be studied in high-risk patients, and such patients should be monitored for clonal evolution.
4. Identify groups of patients who will benefit from alternative treatment approaches, such as cellular therapy.

Conclusions

Testing for high-risk features should continue to be utilized in the clinic, as well as in clinical trials, so that further characterization of their effects on prognosis can be validated. However, it is clear that not all biomarkers will retain their place in everyday practice. For example, we believe that the value of testing for CD38 and Zap-70 expression has diminished, and such testing should be supplanted by testing for *IGHV* mutational status. The latter has the most value in patients for whom CIT is being considered, and may not be necessary if only targeted therapy is contemplated. By contrast, testing for FISH abnormalities, including del(17p) and del(11q), as well as *TP53* mutations (by NGS) and for CK, where possible, remains important to guide therapy. We routinely test all patients by NGS prior to starting new therapy, to garner information on the status of *TP53*, *NOTCH1*, and *SF3B1* given their prognostic value.

High-risk CLL will need to be redefined in the era of targeted therapy, as previously validated high-risk features no longer have the same magnitude of effect on prognosis when targeted therapy is used as compared to CIT. NGS is a promising tool that may help guide clinicians in prognosis, and may help predict responses to targeted therapy.

However, more prospective data is needed to validate this testing. CIT should no longer be offered as a treatment option for patients with del(17p), and/or presence of *TP53* mutation, with possible exception of bridging to cellular therapy in patients whose disease is refractory to novel agents. These patients consistently have improvements in clinical outcomes when novel pathway inhibitors are employed. The jury is still out on whether patients with del(11q) or U-*IGHV* should receive small molecule inhibitors upfront as opposed to CIT, but the emerging data suggests that novel therapy should be strongly considered as a standard approach.

Compliance with Ethical Standards

Conflict of Interest Matthew Lunning reports grants from Celgene, TG Therapeutics, Janssen, other from AbbVie, Celgene, Genentech, Gilead, Janssen, TG Therapeutics, Verastem, and Novartis outside the submitted work. Alexey Danilov reports grants from Takeda Oncology, Bristol-Meyers Squibb, Aptose, MEI, grants and personal fees from Gilead Sciences, Bayer Oncology, Genetech, Verastem Oncology, Astra Zeneca, personal fees from Pharmacyclics, Teva Oncology, Abbvie, Celegene, and Juno Therapeutics, outside the submitted work. Adam S. Kittai declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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