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In this month's Leukemia Insights newsletter, written by William Wierda, Ph.D., M.D., and sponsored in part by the Charif Souki Cancer Research Fund, we discuss current treatment options available at MD Anderson Cancer Center for patients with chronic lymphocytic leukemia (CLL).

Current Treatment Options for Patients with Chronic Lymphocytic Leukemia

Outcomes for patients with chronic lymphocytic leukemia (CLL) have remarkably improved with the development of oral small molecule inhibitor-based treatments. Several inhibitors of the B-cell receptor signaling pathway (those that target BTK and PI3K) and venetoclax, which blocks BCL2 have paved with the way to durable disease control and deep remissions for many patients, including those with high-risk features, such as del(17p), del(11q), and an unmutated-IGHV gene (UM-IGHV). Monotherapy with the BTK inhibitor (BTKi) ibrutinib, provides effective disease control and is now one of the standard treatments for patients with CLL. Newer combinations of these agents have been studied (± anti-CD20 monoclonal antibody [mAb] and/or chemotherapy) in clinical trials and have been shown to induce complete remission (CR) and undetectable minimal residual disease (U-MRD) in the majority of patients, which is anticipated to be associated with longer progression- and treatment-free survival.

Newly Diagnosed Patients with High-Risk CLL

Despite great therapeutic advances, the indications to initiate treatment for both first-line and relapsed disease have not changed. No trial has shown clinical benefit or improved survival with early treatment. This is in part because many untreated patients have indolent disease and never need treatment. At MD Anderson Cancer Center, we developed a model to identify patients who may need early treatment and are testing new strategies for untreated high-risk patients likely to need treatment soon. For the latter patients, who have no other indication for treatment, we are evaluating ibrutinib as an early first treatment (NCT03207555). This trial includes up to 24 cycles of ibrutinib and will evaluate for response and clonal evolution. Ibrutinib is provided free. Telomerase functions in maintaining proliferative capacity of malignant cells and is overexpressed in CLL. A vaccine against human telomerase (hTERT) is being evaluated for early treatment in high-risk patients with CLL and in patients on ibrutinib with persistent measurable residual disease (NCT03265717). The hTERT vaccine (INVAC-1) is provided at no charge.

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The Evolution of Frontline Therapy for CLL

Standard first-line treatment for CLL is rapidly evolving. In 2019, results from three randomized Phase III clinical trials were reported, all of which evaluated standard chemoimmunotherapy (CIT) regimens against ibrutinib-based treatment. The CIT regimens ranged in intensity from minimally myelosuppressive chlorambucil plus obinutuzumab (appropriate for older, less fit patients); to bendamustine plus rituximab (BR); to fludarabine, cyclophosphamide, rituximab (FCR - appropriate for younger, fit patients). All three showed improved outcomes with ibrutinib-based treatment. A notable caveat, however, is that ibrutinib-based treatment is continuous, until progression, in contrast to fixed-duration treatment with CIT. Continuous ibrutinib treatment does have potential toxicity and substantial associated cost. The Alliance trial was a three-arm randomized trial evaluating ibrutinib monotherapy versus ibrutinib plus rituximab versus BR. Ibrutinib-based treatment resulted in improved progressive-free survival over CIT. Outcomes were similar for ibrutinib +/- rituximab. This is likely because the ibrutinibIbrutinib was continuous, which is what "drives" progression-free survival more than what treatment was provided in the early phase of the regimen.

Another important finding from the ECOG E1912 trial was improved outcomes with ibrutinibIbrutinib-based treatment, particularly for patients with UM-IGHV. However, there did not appear to be improved outcome among patients with mutated-IGHV (M-IGHV) when compared with CIT. Together with a long-term finding of approximately 50% progression-free survival of greater than 10 years with FCR-based treatment among patients with M-IGHV, this has stimulated continued interest in FCR-based treatment for younger, fit patients with M-IGHV. Therefore, in these patient, we continue to use fixed-duration, CIT-based treatment, with the objective of increasing the BM U-MRD rate and reducing the length of chemotherapy exposure. At MD Anderson, we developed the iFCG regimen (ibrutinib, fludarabine, cyclophosphamide, obinutuzumab). CIT is given for 3 cycles, and ibrutinib plus obinutuzumab is given for up to one year. The duration of obinutuzumab treatment depends on response and MRD status after cycle 3. We have reported favorable preliminary results with this regimen (NCT02629809); all agents are provided free on this trial.

For all other groups, including young fit with UM-IGHV; older, less fit patients regardless of IGHV mutation status; and any patient with del(17p) or mutated TP53, we recommend small molecule inhibitor-based treatment. Venetoclax recently received broad Food and Drug Administration approval (first-line and relapsed CLL) combined with a CD20 mAb. Venetoclax offers a potential for fixed-duration treatment, deep remission, including BM U-MRD for a high proportion of treated patients, and a reasonable expectation for long, treatment-free remission. The CLL14 trial recently reported improved outcomes with venetoclax-based treatment over CIT. We developed a clinical trial with venetoclax, obinutuzumab and the PDL-1 mAb atezolizumab for first-line treatment in older (>65 years) and younger fit patients with at least one high-risk feature [del(17p), mutated-*TP53,* del(11q), orUM-IGHV] **(NCT02846623).** The rationale for this trial is to achieve deep BM U-MRD remission, with and inclusion of atezolizumab as a strategy for immune reconstitution. All drugs are provided free on this trial.

IbrutinibIbrutinib-based treatment has been highly successful for long-term disease control with continuous treatment, however, achieving a deeper remission with BM U-MRD status may allow for a treatment-free interval. At MD Anderson, we developed a clinical trial adding venetoclax for patients who have been on ibrutinib for 12 months or longer and who also have a high-risk feature and measurable CLL.The goal of this consolidation strategy is to eliminate residual measurable disease **(NCT03128879).** Patients who achieve a confirmed BM U-MRD CR status may stop venetoclax. It is provided free on this trial.

The Treatment of Richter's Transformation

Despite the development of targeted therapies for CLL, some patients develop RT. Rare among untreated patients, RT is more common among relapsed patients, including those with high-risk features such as del(17p) and complex karyotype. CIT has been associated with poor outcomes; response rates are low and not durable. Allo-SCT could achieve durable disease control but has limited application for this patient population. Recently, promising outcomes were associated with checkpoint inhibitor-based treatment with PD-1 mAbs (nivolumab and pembrolizumab). Responses occurred in 40%-50% of treated patients and were relatively durable. We plan to evaluate nivolumab combined with CTLA-4 mAb and ibrutinib for patients with RT. We also are looking for markers that might predict response to this immune-based treatment.

Owing to the apparent susceptibility to immune-based treatment, we are also evaluating blinatumomab, the CD19xCD3 by specific T-cell engager, for patients with RT **(NCT03121534).** This trial is being modified also to include nivolumab. In addition, we are evaluating venetoclax, obinutuzumab, and atezolizumab (PD-L1 mAb) **(NCT02846623).** Our goals with these new trials for patients with RT are to identify predictive markers for response and to optimize activity. These agents have been well-tolerated in patients with CLL and RT with minimal toxicity and notable activity.

Conclusion

Much progress has been made in treatments for patients with CLL. We continue to work on curative strategies and are optimistic that this soon will be achieved in larger numbers of patients. Despite these advances, however, there is continued need for new drug development and treatment strategies. To this end, we urge you to consider referring patients for trials for relapsed and refractory CLL.

Faculty Contacts

Completing these studies in a timely manner will allow us to move quickly on positive leads. We appreciate referrals and will make every effort, once a patient is enrolled on a study, to continue as much of the care as possible through the referring oncologist. We also will keep you apprised of the patient's progress.

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