

# Updates to the Management of Chronic Lymphocytic Leukemia

Presented by William G. Wierda, MD, PhD

## Abstract

The decision of when to start treatment for patients with chronic lymphocytic leukemia (CLL) has not markedly changed; it is triggered by parameters of active disease, such as progressive symptoms or progressive cytopenias related to bone marrow compromise from disease. How to treat patients with CLL has become less complicated, given the growing list of options for CLL, and generally depends on the patient's age, presence of comorbidities, and risk factors (such as chromosome 17 or 11 deletion). During his presentation at the NCCN 20th Annual Conference, Dr. William Wierda focused attention on many of the new kids on the therapeutic block for CLL—the CD20 monoclonal antibodies obinutuzumab and ofatumumab, the BTK inhibitor ibrutinib, the PI3K inhibitor idelalisib, and the BCL-2 inhibitor venetoclax—and reviewed some of the clinical data supporting the use of these agents in different patient populations with CLL. (*J Natl Compr Canc Netw* 2015;13:662–665)

“There is a lot happening with second- and subsequent-line therapies for chronic lymphocytic leukemia [CLL], and combinations with the new small molecule inhibitors and sequencing of them are the new direction that we are taking,” pronounced William G. Wierda, MD, PhD, Professor and Center Medical Director in the Department of Leukemia, Division of Cancer Medicine, at the University of Texas MD Anderson Cancer

Center, and a panel member of the NCCN Guidelines Panel for Non-Hodgkin's Lymphomas. Chemoimmunotherapy with FCR (fludarabine, cyclophosphamide, and rituximab) remains the first-line standard of care for young fit patients with CLL, and chlorambucil with obinutuzumab for the elderly or those with comorbidities. However, the second-line small molecule inhibitor ibrutinib may be promoted in the near future to the first-line setting, he predicted, based on data from the RESONATE-2 study.

## To Treat or Not to Treat

The standard approach for patients with early-stage untreated CLL is to watch and wait. “The period of observation and monitoring could be for several years,” explained Dr. Wierda. The rationale behind this strategy is that early treatment has not been shown to significantly change overall outcome, particularly survival, he said. Indications for treatment include progressive symptoms such as night sweats, fatigue, weight loss, and anemia, which have not changed over the years. “The 1996 NCI guidelines are consistent with the 2008 IW-CLL guidelines in regard to when to start treatment,” revealed Dr. Wierda.

Furthermore, this initial recommendation to watch and wait holds true for patients with high-risk features, such as the presence of the 17p deletion. “These patients are watched more closely than those who do not have these features,” stated Dr. Wierda.

## Frontline Standards of Care

Considerations that guide selection among first-line treatments include patient age, presence of comorbidities, and cytogenetics. For instance, FCR remains the

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standard of care for young and fit patients with CLL. The study data supporting this recommendation predominantly come from the CLL8 and CLL10 trials.<sup>1,2</sup> In the extended follow-up of CLL8, FCR chemoimmunotherapy produced superior outcomes over the combination of fludarabine and cyclophosphamide, with improvements shown in both progression-free survival (PFS) and overall survival.<sup>1</sup> “In our MD Anderson experience with FCR, approximately 60% of patients with a mutated immunoglobulin heavy chain variable gene (*IGHV*) had a PFS that extended beyond 10 years,” added Dr. Wierda. “This subgroup of patients has done exceptionally well, and there is now discussion about the possibility of a portion of these patients being cured with FCR.”

In CLL10, although PFS favored FCR over BR (bendamustine and rituximab) by nearly 14 months (55.2 vs 41.7 months), there appeared to be no difference in overall survival.<sup>2</sup> However, the clear benefit with FCR over BR was noted in patients younger than age 65; there was more myelosuppression with FCR and less clear improvement in PFS over BR for patients older than 65. As a result of the high toxicity (myelosuppression) and infection rates in elderly fit patients who received FCR, Dr. Wierda indicated that BR represents an effective alternative regimen for this elderly patient population.

As for elderly or frail patients with CLL who have comorbidities, less-intense chemotherapy regi-

mens than FCR, such as chlorambucil combined with a CD20 monoclonal antibody, such as obinutuzumab or ofatumumab, have received much recent attention.<sup>3-5</sup> One clinical trial showed that the combination of obinutuzumab and chlorambucil yielded longer PFS than rituximab and chlorambucil but showed no significant difference in overall survival in older patients with higher comorbidity scores.<sup>3</sup> However, Dr. Wierda said there did appear to be a statistically significant difference in overall survival favoring obinutuzumab plus chlorambucil over chlorambucil alone.

In the phase III COMPLEMENT 1 study, ofatumumab plus chlorambucil produced a PFS benefit of approximately 9 months compared with chlorambucil alone in patients with untreated CLL who were not considered to be appropriate candidates for fludarabine-based treatments.<sup>4</sup> However, there is currently no difference in overall survival. Data are also emerging that support maintenance treatment with CD20 mAb, such as in the PROLONG study, with ofatumumab maintenance therapy showed more benefit than observation after chemoimmunotherapy.<sup>5</sup>

For all patients with CLL who have del(17p), ibrutinib received approval as first-line therapy approximately a year ago. Dr. Wierda discussed this agent with much potential further in the following section.

### Newer Salvage Therapies

Second-line treatments for active disease center on 2 newly approved agents: the first-in-class BTK inhibitor ibrutinib and the reversible inhibitor of PI3K idelalisib.

According to the long-term follow-up study of ibrutinib in both treatment-naïve and previously treated patients with CLL and small lymphocytic leukemia,<sup>6,7</sup> ibrutinib monotherapy produced durable responses, even in those with del(17p), lasting more than 3 years out from treatment initiation. “Most patients responded, upward of 90%,” revealed Dr. Wierda, with most partial responses. “The results for the treatment-naïve group were impressive, with only one patient among 31 with disease progression with current follow up,” he added. Furthermore, the investigators learned that the best response to ibrutinib seems to improve over time, and so Dr. Wierda emphasized the importance of patients remaining on the drug.

Agent	Development Phase
<b>CD20 mAb</b> Obinutuzumab Ofatumumab	Approved Approved
<b>BCL-2 inhibitor</b> Venetoclax (ABT/GDC-199)	Registration phase III
<b>BTK inhibitors</b> Ibrutinib CC-292 ONO-4059 ACP-196	Approved Phase Ib Phase I Phase II
<b>PI3K <math>\gamma/\delta</math> inhibitors</b> Idelalisib GS-9820 IPI-145 AMG/ACP 319 TGR-1202 SAR245408 (XL147)	Approved Phase I Pending phase III Phase II Phase I Phase I
<b>Syk inhibitors</b> GS-9973 Fostamatinib PRT-2070	Phase II Phase I/II Phase I

**Figure 1** Newer treatments for patients with chronic lymphocytic leukemia.

Wierda

- Untreated, high-risk early intervention
- First-line therapy
  - ◆ Fit CIT-eligible – *IGHV*-Mutated
    - ◆ FCR with maintenance or Tx for MRD
  - ◆ Fit-*IGHV*-Unmutated & Elderly
    - ◆ BCR- / Bcl-2-inhibitor
- Second-line Therapy for active disease
- Treatment (consolidation) for persistent disease on BTK-inhibitor (1<sup>st</sup> and later)
- Richter's transformation work-up and "novel treatments" program

**Figure 2** Chronic lymphocytic leukemia treatment directions.

Perhaps the most encouraging data have emerged from the extended follow up from the phase II and III studies, according to Dr. Wierda.<sup>8,9</sup> In the phase II trial,<sup>8</sup> the effectiveness of ibrutinib was demonstrated in various patient populations, including elderly patients and those with relapsed or refractory del(17p), in terms of overall response rate, duration of response, and PFS. In the phase III trial,<sup>9</sup> where ibrutinib was compared with ofatumumab in relapsed or refractory disease, overall survival benefits with ibrutinib were shown as well.

"Results of the phase III first-line trial [RESONATE-2] comparing ibrutinib versus chlorambucil in elderly patients with CLL should be out in the next year, and we expect it to be a positive trial, showing superior results with this agent in the front-line setting," declared Dr. Wierda. Furthermore, he believes that when the data are available, its first-line indication may be expanded. "When we have the label indication and the supportive data, most patients will receive ibrutinib in the frontline setting," Dr. Wierda predicted.

Results of the second interim analysis of the phase III study data supporting the use of the combination of idelalisib and rituximab in the salvage setting were presented at the 2014 American Society of Hematology meeting.<sup>10</sup> According to Dr. Wierda, these updated results clearly showed a statistically significant benefit with combination treatment in terms of PFS, overall response rate, and overall survival in frail patients with relapsed CLL, even in those with high-risk features. "Outcomes were similar regardless of *IGHV* mutation status or whether or not a patient had del(17p)," he added.

Finally, Dr. Wierda briefly reviewed results with the BCL-2 inhibitor venetoclax, which he antici-

pates will be approved in the next few years. This potent monotherapy appears to be active in very high-risk relapsed patient categories (such as del[17p] and fludarabine-refractory disease). The tumor lysis events that occurred in the initial studies with this agent necessitated subsequent trial redesigns, starting with a carefully monitored step-wise escalated dose schedule. This was a better strategy for avoiding the earlier risk of rapid tumor lysis events, commented Dr. Wierda.

Early studies with venetoclax have confirmed its activity and the durability of responses in patients with high-risk CLL, including those with unmutated *IGHV*, del(17p), and fludarabine-refractory disease.<sup>11,12</sup> Seymour et al<sup>11</sup> reported response data for 78 patients, with overall survival rates of between 75% and 79%. "Responses were seen similarly across the risk categories," stated Dr. Wierda. And almost one-fourth of treated patients achieved complete remission.

A smaller study of venetoclax combined with rituximab in less heavily pretreated patients with relapsed or refractory CLL was reported by Roberts et al.<sup>12</sup> In 44 patients evaluated thus far, nearly 90% showed a response, with 34% experiencing complete remission. "For me, this study does not speak to whether or not venetoclax is better with rituximab, it speaks more to the safety and the fact that you can safely combine the agents," Dr. Wierda concluded.

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