Evolving Strategies in First-Line Chronic Lymphocytic Leukemia: Is There a Role for Chemoimmunotherapy?

Presented by Jennifer R. Brown, MD, PhD, and William G. Wierda, MD, PhD

ABSTRACT

With the enormous progress made in treatment and management, many oncologists have called this the golden age of chronic lymphocytic leukemia (CLL). The past few years alone have seen the approval of multiple agents, including small molecule inhibitors that have led to longer, more durable periods of disease control. However, the introduction of these new drugs into the armamentarium has raised an important question regarding standard of care: is there still a role for chemoimmunotherapy in the first-line setting? At the NCCN 2019 Annual Congress: Hematologic Malignancies, Drs. William G. Wierda and Jennifer R. Brown presented opposing sides of the debate.

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The advent of more effective agents for chronic lymphocytic leukemia (CLL) has ushered in a new era of treatment, shifting previous lines of therapy and evolving strategies of disease control. Although chemoimmunotherapy has long been the mainstay of treatment, its role in induction therapy and beyond has been limited by small molecule inhibitors that promise durable remissions. At the NCCN 2019 Annual Congress: Hematologic Malignancies, William G. Wierda, MD, PhD, Professor of Medicine, The University of Texas MD Anderson Cancer Center, and Jennifer R. Brown, MD, PhD, Professor of Medicine, Harvard Medical School, and Director of the CLL Center, Dana-Farber Cancer Institute, debated the merits of using chemoimmunotherapy in the first-line setting. Moderated by Andrew D. Zelenetz, MD, PhD, Memorial Sloan Kettering Cancer Center, the debate was followed by a panel discussion that included Jeremy S. Abramson, MD, MMSc, Massachusetts General Hospital Cancer Center; Nitin Jain, MD, The University of Texas MD Anderson Cancer Center; and Jae Park, MD, Memorial Sloan Kettering Cancer Center.

No Role for Chemoimmunotherapy

According to Dr. Wierda, there are currently 2 approaches with non-chemoimmunotherapy-based treatment. The first approach using small molecule inhibitors, particularly Bruton tyrosine kinase (BTK) inhibitors, is to have a sustained and durable period of disease control with continuous therapy. The other strategy, said Dr. Wierda, is to have deep remissions with fixed-duration

treatment using a selective inhibitor of B-cell lymphoma 2 (Bcl-2). “I would argue that small molecule inhibitors offer a better approach than being exposed to genotoxic chemotherapy,” he said.

However, Dr. Wierda also highlighted essential tests that must be conducted before starting patients on treatment. Routine fluorescence in situ hybridization analysis detects deletion of the region of chromosome 17 (17p13–) that includes the gene coding for p53 (*TP53*). It is important to know the percentage of cells with the deletion, he said, and noted that del(17p) status and *TP53* mutation status can change. *IGHV* mutation status is also important to test for because it factors into treatment selection, he added.

Recent results of several phase III randomized clinical trials have shown the effectiveness of BTK inhibitor–based therapy in frontline CLL. These trials include RESONATE-2,¹ which compared ibrutinib with chlorambucil; iLLUMINATE,² which analyzed ibrutinib + obinutuzumab versus chlorambucil + obinutuzumab; the 3-arm Alliance trial,³ which randomized patients to ibrutinib monotherapy versus ibrutinib + rituximab versus bendamustine/rituximab; and the ECOG E1912 trial,⁴ which compared ibrutinib + rituximab versus a fludarabine/cyclophosphamide/rituximab (FCR) regimen.

“All of these trials were positive in showing longer progression-free survival [PFS] for the ibrutinib-based arm compared with chemoimmunotherapy,” said Dr. Wierda. “Although no differences in overall survival [OS] were found, I would argue that is partly due to study design. With longer follow-up, we may see

differences in OS emerging, and the ECOG study did, in fact, demonstrate a difference.”

A separate trial called CLL14,⁵ conducted by the German CLL Study Group, also showed positive outcomes in PFS for patients randomized to venetoclax/obinutuzumab versus chlorambucil/obinutuzumab, although no differences in OS were seen. More importantly, although treatment with ibrutinib is continuous therapy, venetoclax-based therapy is fixed duration. As shown in the CLL14 trial, PFS at 2 years was comparable to the outcomes seen with ibrutinib (80% to 90%).

“The other key point to remember,” Dr. Wierda added, is that in patients for whom chemoimmunotherapy initially fails, they “can still go on to a small molecule inhibitor, which is associated with a very long survival.”

Furthermore, the advantage of using small molecule inhibitor-based therapy is not limited to PFS. As Dr. Wierda explained, chemotherapy is genotoxic and carries risk for long-term complications. Patients treated with the FCR regimen have 3% to 5% incidence of developing myelodysplastic syndromes. Nevertheless, for a subset of patients with *IGHV* mutation, chemoimmunotherapy may still be the preferred option, he acknowledged. As evidenced by the MD Anderson phase II data⁶ and the CLL8 trial,⁷ approximately 50% of patients with mutated *IGHV* experienced long-term PFS suggestive of a cure, and 60% were negative for minimal residual disease. However, this plateau was not achieved in patients randomized to bendamustine-based treatment in CLL10.⁸

“If you’re thinking about chemoimmunotherapy, FCR is the best treatment to give patients because of this plateau,” said Dr. Wierda. “It’s potentially curative in half of patients with *IGHV* mutation.”

A Role for Chemoimmunotherapy

Despite the positive outcomes achieved with these new agents, Dr. Brown argued that there remains a role for chemoimmunotherapy in CLL. “We know that ibrutinib, with or without obinutuzumab, substantially improves PFS compared with chlorambucil and also compared with chemoimmunotherapy, although not quite as dramatically as when compared to chlorambucil-based therapy,” she said. “We also know that venetoclax/obinutuzumab improved PFS compared with chlorambucil/obinutuzumab in the CLL14 study, as recently reported.”

Nevertheless, improvements in PFS have not necessarily translated to an OS benefit. “If the patients were actually living longer, short-term PFS would matter, but they’re not,” said Dr. Brown. “I contend that ibrutinib did not improve OS compared with chemoimmunotherapy in these studies.”

Although the RESONATE-2 trial reported an OS benefit,¹ this was due to a poor comparator of chlorambucil and very limited crossover, she said. When obinutuzumab was added to chlorambucil in the iLLUMINATE study,² OS curves completely overlapped.

“ECOG E1912 reported an OS benefit based on extremely few events, many of which were not clearly related to the disease or its treatment,”³ said Dr. Brown. “These need to be further evaluated with more follow-up.” Furthermore, said Dr. Brown, not all patients are experiencing improved PFS with small molecule inhibitors versus chemoimmunotherapy. Data from the ECOG and Alliance trials^{3,4} showed that patients with low-risk mutated *IGHV* disease did equally well with chemoimmunotherapy as targeted agents, and in the CLL14 study,⁵ this subgroup experienced similar results with chlorambucil/obinutuzumab as with venetoclax/obinutuzumab.

“The half of patients who have mutated *IGHV* are not even getting an improved PFS,” said Dr. Brown. “In fact, this mutated subgroup has the potential for prolonged treatment-free remission or even cure with chemoimmunotherapy.” According to data from the MD Anderson phase II study,⁶ more than half of patients with *IGHV*-mutated disease treated with FCR with more than 12-year follow-up have shown the potential for cure.

“In what diseases do we give up potentially curative therapy for the requirement of continuous therapy with ongoing residual disease, accumulative side effects, and clearly no cure, which is what we’re talking about with ibrutinib?” said Dr. Brown. “Even if ibrutinib did eventually have similar PFS, it would still have the requirement of continuous therapy, toxicity, and cost.”

Nonhematologic and Financial Toxicity

Although the ECOG E1912 trial³ showed worse hematologic toxicity with the FCR regimen, nonhematologic toxicity with ibrutinib and rituximab is “quite significant,” said Dr. Brown. Grade ≥ 3 treatment-related adverse events throughout observation included cardiac toxicity (6.5%), ventricular arrhythmia or cardiac arrest (0.9%), atrial fibrillation (3.2%), hemorrhage (1.1%), hypertension (18.8%), and diarrhea (4.3%).⁹ Moreover, said Dr. Brown, nonhematologic toxicity was even worse on the Alliance trial,⁴ which had an older patient population.

“In both of the ibrutinib arms, patients had increased infections, increased atrial fibrillation, increased hypertension, and increased rates of unwitnessed death,” she said. “In fact, the chance of dying of an adverse event on the ibrutinib arms with the median follow-up of 2.5 years was 7%.”

As Dr. Brown reported, older patients on ibrutinib have a higher rate of discontinuation, and patients

with comorbidities have reduced event-free survival and OS. In the real-world setting, discontinuation rates on ibrutinib are twice what is seen on trial, she added. The toxicity is not limited to ibrutinib, either. Data from CLL14 showed an 8% rate of death related to adverse events in the venetoclax arm, with more infections and cardiac disorders, primarily after therapy was completed.

Financial toxicity must also be considered. One estimate of the impact of oral BTK targeted therapy moving from the relapsed setting to the first-line setting (for ibrutinib) found a 6-fold increase in cost.¹⁰ “Novel agents are not saving money, and the financial impact extends beyond the healthcare system,” said Dr. Brown. “Out-of-pocket costs for Medicare patients receiving ibrutinib in the frontline setting have been estimated at \$60,000. Most patients cannot afford this.”

According to Dr. Brown, young fit patients with *IGHV*-mutated CLL should clearly receive 6 months of FCR therapy for possible cure, but young fit patients with CLL with unmutated *IGHV* or older patients can receive chemoimmunotherapy, as well. “Even though you don’t see the same plateau, bendamustine/rituximab can also be effective in the older patients and have prolonged remissions without a survival disadvantage,” she said. “They have a predictable side-effect profile for 6 months, and certainly in the older patients, bendamustine/rituximab is often less toxic than ibrutinib is with its cardiac side effects.”

Finally, given the success of novel agents in the second line of treatment, patients may be losing a line of therapy if novel agents are used early on.

“We don’t know that chemoimmunotherapy will work after ibrutinib, but we know that ibrutinib works well in the second-line setting,” said Dr. Brown. “That’s something to consider as we manage this

chronic disease over a patient’s lifetime. We need to continue to have chemoimmunotherapy in our armamentarium.”

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