ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

Section Editor: Susan O'Brien, MD

Lessons Learned From the GAIA/CLL13 Trial in Chronic Lymphocytic Leukemia

Moritz Fürstenau, MD
Faculty of Medicine and University Hospital Cologne
University of Cologne
Cologne, Germany

H&O What was the rationale for designing the GAIA/CLL13 trial?

MF We planned this study nearly 10 years ago, when continuous Bruton tyrosine kinase inhibitor therapy was the one targeted treatment that was available for patients with chronic lymphocytic leukemia (CLL). This approach had several disadvantages, including the acquisition of resistance mutations, the lack of any time off treatment, and the development of cumulative toxicities such as atrial fibrillation, bleeding, and hypertension. That is why we ideally wanted a time-limited treatment.

We knew from previous trials, including phase 2 trials and early safety run-ins from other trials, that the combination of venetoclax (Venclexta, AbbVie/Genentech) and obinutuzumab (Gazyva, Genentech) was good at achieving deep remissions, which made it highly suitable for a time-limited combination. We designed the CLL13 trial to compare time-limited treatment with venetoclax plus 1 or 2 additional agents vs the standard chemoimmunotherapy at that time, which was bendamustine/rituximab or fludarabine/cyclophosphamide/rituximab. The 3 experimental arms were venetoclax plus rituximab (RV), venetoclax plus obinutuzumab (Gazyva, Genentech; GV), and venetoclax plus obinutuzumab and ibrutinib (Imbruvica, Pharmacyclics/Janssen; GIV).

H&O Could you describe the design of the trial?

MF It is a bit unusual to have 3 experimental arms, but apart from that, the design was relatively straightforward. This was a phase 3 trial in which we randomly assigned 926 fit patients with CLL who were treatment-naive and did not have *TP53* aberrations to one of 4 groups: chemoimmunotherapy (n=229), RV (n=237), GV (n=229), or GIV (n=231). We did not include patients with *TP53* aberrations because we already knew at that time that these patients would not do well in the chemoimmunotherapy control arm. Treatment was limited to 6 months for patients in the chemoimmunotherapy arm, 1 year for those in the RV and GV arms, and approximately 1 year for those in the triplet combination arm, although patients in the GIV arm who did not have undetectable measurable residual disease (MRD) at the end of treatment could continue ibrutinib monotherapy for another 2 years.

The study had 2 coprimary efficacy endpoints: undetectable MRD at month 15, which was 2 months after the end of treatment, and progression-free survival (PFS) in the experimental arms vs the chemoimmunotherapy arm.

H&O How did the results of this trial differ between year 3 and year 5?

MF The primary endpoint analysis we did at 3 years showed that both GV and GIV were significantly superior to both chemoimmunotherapy and RV in terms of PFS.[1] The percentage of patients with undetectable MRD at month 15 was significantly higher in the GV group (86.5%) and the GIV group (92.2%) than in the chemoimmunotherapy group (52.0%), but it was not

significantly higher in the RV group (57.0%) than in the chemoimmunotherapy group.

The most important change with longer follow-up is that we also saw a significant difference between PFS in the GV arm and PFS in the GIV arm; we presented these data at the European Hematology Association (EHA) Congress.[2] The addition of ibrutinib to GV resulted in a significantly longer PFS, with a hazard ratio of 0.61. The estimated 5-year PFS rates were 50.7% for chemoimmunotherapy, 57.4% for RV, 69.8% for GV, and 81.3% for GIV.

> Now we know that obinutuzumab is a more efficacious antibody drug than rituximab and that triplet therapy offers advantages over doublet therapy in certain situations.

No differences in overall survival (OS) were noted among the treatment arms. The 5-year OS rates were 90.7% for chemoimmunotherapy, 94.7% for RV, 93.6% for GV, and 94.3% for GIV.

H&O What were the differences in side effects among the groups?

MF Longer follow-up has given us a little more information about the differences in side effects among the groups. We saw a higher rate of infectious adverse events in the chemoimmunotherapy arm than in the experimental arms. Among the 3 experimental arms, the triplet combination of GIV was associated with the most severe infections. We also saw a significant increase in cardiac adverse events with the triplet combination, which was what we expected to see when ibrutinib was added to the doublet combination.

Fatal adverse events occurred in 59 patients: 18 in the chemotherapy group, 14 in the RV group, 14 in the GV group, and 13 in the GIV group. The most common fatal adverse events were Richter transformation, which occurred in 10 people; COVID-19, which occurred in 6 people; and pneumonia, which occurred in 5 people.

An interesting piece of information, which we described at last year's American Society of Hematology Annual Meeting, is the significant difference in patient-reported quality of life with these 3 treatment options; patients who received RV or GV experienced the fastest improvements in quality-of-life measures and key functioning scales.[3] The triplet combination was associated with a greater symptom burden and a poorer quality of life in comparison with RV and GV. Therefore, if a patient does not have high-risk disease, we may have good reason to choose doublet therapy rather than triplet therapy.

H&O Were you surprised to learn that improved PFS with the addition of ibrutinib did not translate into improved OS?

MF We were not surprised that the addition of ibrutinib did not improve OS. In a well-designed contemporary CLL trial in which patients receive good post-protocol care, including salvage treatment as needed, we should not see OS differences among the treatment arms. The only exception would be if one of the interventions caused a lot more toxicity.

H&O How do these results change your approach to the first-line treatment of patients with CLL?

MF This is the first study to confirm that GV is feasible and very efficacious in young, fit patients, although in Europe we were already using GV often in both fit and unfit patients with CLL. What this study really changed for me is that formerly I had been very hesitant to use the GIV triplet combination in the first-line setting for patients with CLL. I used to have doubts about tolerability and whether triplet therapy was more efficacious than doublet therapy. Now that we know that the triplet is more efficacious when it comes to PFS, I will consider using it in young and fit patients with higher-risk disease. Now that the European Medicines Agency has approved acalabrutinib (Calquence, AstraZeneca) in combination with venetoclax and obinutuzumab, we also have the option to use that triplet.

H&O What key lessons should clinicians take away from GAIA/CLL13 for future trial design?

MF What stood out in the design of GAIA/CLL13 was the clean comparison of 4 treatment arms: 1 control arm and 3 experimental arms. We all benefited from this study design; now we know that obinutuzumab is a more efficacious antibody than rituximab and that triplet therapy offers advantages over doublet therapy in certain

situations. This information is much more useful than learning that a single treatment is better than an old, outdated chemotherapy regimen.

Some additional data from the trial that we did not present at the EHA Congress are that the MRD status at month 9 was already highly predictive of PFS. This information is useful for designing MRD adaptive trials, which are common now. MRD at 9 months has the potential to be used to guide whether treatment should be escalated or even de-escalated.

H&O What should be the next step in research?

MF We are already seeing good results in patients with mutated immunoglobulin heavy chain variable (*IGHV*) region gene status and in other patients with relatively indolent disease, who might have a median PFS of approximately 10 years with just 1 year of doublet therapy. The logical next step is to look at improving the quality of first-line treatment in patients who have a higher risk of early disease progression. For example, the phase 3 CLL16 trial is comparing triplet therapy with acalabrutinib, venetoclax, and obinutuzumab vs therapy with venetoclax and obinutuzumab in previously untreated patients with high-risk CLL (NCT05197192). High risk in this study is defined as the presence of at least one of the following: 17p deletion, *TP53* mutation, complex karyotype, or unmutated *IGHV* status.

Disclosures

Dr Fürstenau has no disclosures.

References

1. Eichhorst B, Niemann CU, Kater AP, et al; GCLLSG, the HOGVN and Nordic CLL Study Groups, the SAKK, the Israeli CLL Association, and Cancer Trials Ireland. First-line venetoclax combinations in chronic lymphocytic leukemia. *N Engl J Med*. 2023;388(19):1739-1754.

2. Fürstenau M, Robrecht S, von Tresckow J, et al. The triple combination of venetoclax-ibrutinib-obinutuzumab prolongs progression-free survival compared to venetoclax-CD20-antibody combinations and chemoimmunotherapy in treatment-naïve chronic lymphocytic leukemia: final analysis from the phase 3 GAIA/CLL13 trial. Presented at: European Hematology Association Congress; June 12-15, 2025; Milan, Italy. Abstract S191.

3. Fürstenau M, Rotbain EC, Eurelings L, et al. Patient-reported quality of life outcomes with venetoclax-based first-line combinations in CLL: an analysis from the phase 3 GAIA/CLL13 trial [ASH abstract 3238]. *Blood*. 2024;144(1)(suppl).