Choosing between family members is always a balancing act

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Received: January 23, 2023.
Accepted: February 10, 2023.
Early view: February 23, 2023.

https://doi.org/10.3324/haematol.2022.282628

In this edition of *Haematologica*, Mauro and co-authors present the results of a phase II study examining the efficacy and safety of frontline fixed-duration (12 months) combination therapy with venetoclax and rituximab in 75 fit, young patients with chronic lymphocytic leukemia (CLL).[1] This approach was well-tolerated, with high overall/complete responses rates (95%/76%), a moderate rate of undetectable minimal residual disease (MRD) in the peripheral blood (69%), and no events indicative of disease progression observed after a median follow-up of 20.8 months despite 96% of patients having unmutated IGHV status, but only a small proportion of patients (12%) with *TP53* disruption (deletion of 17p and/or *TP53* mutation).[1]

A fixed-duration venetoclax combination regimen is a preferred frontline therapy for younger patients to avoid the treatment and toxicity burden associated with continuous monotherapy with a Bruton tyrosine kinase (BTK) inhibitor. Venetoclax, a B-cell lymphoma-2 inhibitor that restores intrinsic apoptosis in CLL cells, in combination with anti-CD20 monoclonal antibodies obinutuzumab (VenO) or rituximab (VenR) are now established standards of care for treatment-naïve[2] and relapsed/refractory CLL,[3] respectively. Recently, studies (GLOW, CAPTIVATE) evaluating fixed-duration frontline venetoclax-ibrutinib treatment have displayed deep remissions with encouraging progression-free survival (PFS) with short follow-up. While the "all oral" delivery is appealing, such an approach is not clearly superior to venetoclax plus a CD20 monoclonal antibody while retaining the cardiac risks of BTK treatment and exposing the disease to both of our highly effective targeted therapies, perhaps compromising sensitivity to subsequent retreatment. Achieving a status of undetectable MRD (conventionally $<10^{-4}$ leukemic cells by flow cytometry) is strongly associated with improved PFS with fixed-duration combinations. Until the recent availability of the results of the GAIA/CLL13 studies,[4,5] there were no randomized comparisons of the efficacy or safety of VenO and VenR in treatment-naïve patients. The mechanistic and preclinical issues to be considered in the choice of the CD20 partner antibody have been published elsewhere,[6] and here we consider the relative clinical merits of VenO and VenR.

Compared to chemoimmunotherapy, VenO has demonstrated superior efficacy in treatment-naïve patients regardless of fitness. In frail patients in the CLL14 trial, rates of undetectable MRD in the peripheral blood at 15 months following VenO were 75.5% *versus* 35.2% with obinutuzumab-chlorambucil ($P<0.001$).[2] At the 5-year follow-up, the PFS of the VenO-treated patients had improved over that of the obinutuzumab-chlorambucil treated ones: 62.6% *versus* 27.0%.[7] In fit patients in GAIA/CLL13, the rates of undetectable MRD in the peripheral blood were superior with VenO than with chemoimmunotherapy (age-stratified fludarabine-cyclophosphamide-rituximab or bendamustine-rituximab) (86.5% *vs*. 52.0%; $P<0.0001$) as was the PFS (hazard ratio [HR]=0.42, 97.5% confidence interval [CI]: 0.26-0.68; $P<0.0001$) after a median follow-up of 38.8 months.[4,5]

VenR has demonstrated superior efficacy over bendamustine-rituximab in relapsed/refractory CLL; however, no benefit over chemoimmunotherapy was observed in treatment-naïve patients. In the MURANO trial, rates of peripheral blood undetectable MRD after 9 months were 62.4% (VenR) *versus* 13.3% (bendamustine-rituximab), and after 5 years of follow-up a PFS benefit was observed favoring VenR (median 53.6 months *vs*. 17.0 months; $P<0.0001$).[8] However, in GAIA/CLL13 rates of peripheral blood undetectable MRD at 15 months (57.0% *vs*. 52.0%; $P=0.317$) and PFS at a median of 38.8 months follow-up (HR=0.79, 97.5% CI: 0.53-1.18; $P=0.183$) were not significantly different between fit, treatment-naïve patients without *TP53* disruption who were given VenR or chemoimmunotherapy.[4,5] Although in different treatment settings, the apparent disparity may have been affected by extended 24-month venetoclax therapy in MURANO, or the use of an age-stratified chemoimmunotherapy comparator in GAIA/CLL13. Although not directly compared, observed 3-year PFS rates were lower with VenR (80.8%) than with VenO (87.7%) in the latter study.[5]

Compared with VenR, VenO may exhibit greater efficacy in unmutated IGHV disease. Patients with unmutated IGHV, *TP53* disruption, and/or genomic complexity treated with VenR in the MURANO trial had an inferior PFS to those

Table 1. Comparison of key safety data of venetoclax plus obinutuzumab or venetoclax plus rituximab in pivotal studies.

Study	Study treatment	Grade ≥3 adverse events	Grade ≥3 neutropenia	Grade ≥3 IRR	Grade ≥3 infections	TLS events
CLL14 Phase III: treatment-naïve, unfit patients with CLL requiring therapy (N=432) *TP53 disruption*: 13.8% *Unmutated IGHV*: 59.8%	VenO (N=216) *vs.* ChlO (N=216)	VenO: 78.8% (N=167) *vs.* ChlO: 76.6% (N=164) Fatal AE VenO: 2.4%, ChlO: 1.9%	VenO: 52.8% (N=112) *vs.* ChlO: 48.1% (N=103)	VenO: 9.0% (N=19) *vs.* ChlO: 10.3% (N=22)	VenO: 17.5% (N=37) *vs.* ChlO: 15.0% (N=32)	All - VenO: 3 pts. *vs.* ChlO: 5 pts.[&]
MURANO Phase III: R/R CLL requiring therapy (N=389) *Del(17p):* 26.9% *TP53 mutations*: 26.3% *Unmutated IGHV*: 68.3%	24 months VenR (N=194) *vs.* BR (N=195)	VenR: 82.0% (N=159) *vs.* BR 70.2% (N=132) Fatal AE VenR: 5.2%, BR: 5.9%	VenR: 57.7% (N=112) *vs.* BR: 38.8% (N=73)	VenR: 1.5% (N=3) *vs.* BR: 5.3% (N=10)	VenR: 17.5% (N=34) *vs.* BR: 21.8% (N=41)	Grade ≥3 - VenR: 3.1% (N=6) *vs.* BR: 1.1% (N=2)
GAIA/CLL13 Phase III: treatment-naïve, fit patients with CLL requiring therapy, without *TP53* disruptions (N=926) *Unmutated IGHV*: 56.0%	VenO (N=229), VenR (N=237) *vs.* CIT (FCR, N=150, or BR, N=79)	VenO: 84.6% (N=193), VenR: 71.3% (N=169) Fatal AE VenO: N=9, VenR: N=8	VenO: 55.7% (N=127), VenR: 46.0% (N=109)	VenO: 11.4% (N=26), VenR: 7.6% (N=18)	VenO: 13.2%, VenR: 10.5%	All - VenO: 11.4% (N=26), VenR: 12.2% (N=29) Grade ≥3 - VenO: 8.8% (N=20), VenR: 10.1% (N=24)
VERITAS Phase II: treatment-naïve, fit patients with CLL requiring therapy, with unmutated IGHV and/or *TP53* disruption *Unmutated IGHV*: 96% *TP53 disruption*: 9 (12%)	12-month VenR	45.3% (N=34) Fatal AE - N=3: clinical TLS (N=1), COVID-19 (N=2)	VenR: 68.0% (N=51)	VenR: 34.7% (N=26)	VenR: 12% (N=9), including 6.7% (N=5) due to COVID-19^	Grade ≥3 - VenR: 1.3% (N=1)

[&]All biochemical tumor lysis syndrome events in the venetoclax–obinutuzumab group occurred during treatment with obinutuzumab, before exposure to venetoclax. No clinical tumor lysis syndrome events. ^Near beginning of the SARS-CoV2 pandemic prior to vaccination availability. IRR: infusion-related reactions; TLS tumor lysis syndrome; CLL: chronic lymphocytic leukemia; VenO: venetoclax-obinutuzumab; ChlO: obinutuzumab-chlorambucil; pts: patients; AE: adverse events; R/R: relapsed/refractory; VenR: venetoclax-rituximab; BR: bendamustine-rituximab; CIT: chemoimmunotherapy; FCR: fludarabine-cyclophosphamide-rituximab; COVID-19: coronavirus disease 2019.

without the markers present in a 5-year follow-up, although benefit of VenR over bendamustine-rituximab was retained in each subgroup.[8] Lower rates of undetectable MRD were also observed in the subgroup with genomic complexity than in the subgroup without complex genomics.[9] The *TP53*-disrupted subgroup had the lowest 5-year PFS (70.2%). In CLL14, VenO patients with del(17p) (and/or *TP53* mutation) had an inferior median PFS (median 28 months follow-up) to those without *TP53* disruption, and with longer follow-up (median 52.4 months) PFS was also longer for patients with mutated IGHV than those with unmutated IGHV following VenO (HR=0.47, 95% CI: 0.25-0.87; *P*=0.02).[10] However, only del(17p) was associated with inferior PFS on multivariate analysis.[10] Although not directly compared in GAIA/CLL13, 3-year PFS rates for both unmutated IGHV and mutated IGHV patients appear higher with VenO than with VenR (unmutated IGHV 82.9% *vs.* 76.4%; mutated IGHV 93.6% vs. 87.0%, respectively).

Collectively these data support the superior efficacy of VenO compared with VenR for patients with treatment-naïve CLL, including those with unmutated IGHV status. The relative efficacies in *TP53*-disrupted, treatment-naïve CLL remain unclear. While 24 months of treatment with VenR is still effective in relapsed/refractory *TP53*-disrupted CLL, data supporting 12 months of VenR in *TP53*-disrupted treatment-naïve patients are limited.

Both VenO and VenR have demonstrated favorable side effect profiles without significant late adverse effects being

observed. The incidences of all grade ≥3 adverse events, including neutropenia, infections, infusion-related reactions, and tumor lysis syndrome, in the studies discussed are summarized in Table 1. Presented data from GAIA/CLL13 document a higher overall incidence of grade ≥3 adverse events with VenO than with VenR (84.6% *vs*. 71.3%, respectively), including higher rates of grade ≥3 neutropenia, infections, and infusion-related reactions. No clear difference in the small numbers of fatal adverse events was observed between the treatment arms. These observations are similar to those in a large phase III study of obinutuzumab chemotherapy *versus* rituximab chemotherapy (both with maintenance) in follicular lymphoma.[11] The incidence of severe pulmonary infection with both anti-CD20 therapies is of particular relevance in the context of the pandemic of severe acute respiratory syndrome coronavirus-2; however, detailed infection data from GAIA/CLL13 have not been reported. The risks of anti-CD20 B-cell-depleting therapy are highlighted by the two COVID-19-related deaths in the VERITAS study.[1] The more prolonged B-cell depletion observed after obinutuzumab may translate into a more sustained increased risk of severe infection.

Significant tumor lysis syndrome is now an uncommon occurrence in clinical trials and there is not a clear difference in incidence between patients treated with VenO or VenR. The three laboratory tumor lysis syndrome events (1.5%) observed in CLL14 occurred following obinutuzumab prior to exposure to venetoclax. Six grade ≥3 tumor lysis syndrome events (3.1%) were observed in MURANO following VenR, one of which was fatal during venetoclax ramp-up. In GAIA/CLL13, venetoclax ramp-up commenced on day 22 of cycle 1 for both VenO and VenR with similar grade ≥3 tumor lysis syndrome incidences observed by Cairo-Bishop criteria (VenO 8.8% *vs*. VenR 10.1%). The majority of tumor lysis syndrome events with VenO occurred prior to venetoclax ramp-up, while for VenR most occurred after initiation of venetoclax ramp-up. With this dosing schedule, one patient (1.3%) experienced tumor lysis syndrome using the more stringent Howard criteria in VERITAS.

Collectively these data suggest a trend to greater adverse events experienced with VenO compared with VenR without clearly increased treatment-related deaths or tumor lysis syndrome. Because of its more favorable safety profile, VenR may be better suited as first therapy in frail, unfit patients, and those with significant infection risk factors including risk factors for COVID-19.

Obinutuzumab is more efficacious than rituximab in combination with venetoclax as frontline therapy for CLL, independently of patients' fitness, at the cost of increased adverse events. Although both combinations (VenO and VenR) are active against *TP53*-disrupted and unmutated IGHV CLL, a frontline continuous BTK inhibitor may be preferred. While the potential benefit of frontline VenR over chemoimmunotherapy in non-*TP53*-disrupted CLL is unclear, VenR is an effective treatment and may be preferred over VenO when safety is the highest priority. It remains uncertain whether VenR with 24 months of venetoclax would improve PFS outcomes in the frontline setting.

Disclosures

RB has no conflicts of interest to disclose. JFS is a member of the board of directors or advisory committees for Abbvie, F. Hoffman-La Roche Ltd., BMS, Gilead, Janssen, and Genor Biopharma; has acted as a consultant for TG Therapeutics, Celgene and F. Hoffman-La Roche Ltd.; has received honoraria from Abbvie, BMS, Gilead, F. Hoffman-La Roche Ltd., and Janssen; and has received research funding from and participated in speaker's bureau for AbbVie, F. Hoffman-La Roche Ltd., and Celgene.

Contributions

RB and JFS co-wrote the manuscript.

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