HemaSphere
Powered by EHA

EHA EUROPEAN HEMATOLOGY ASSOCIATION

Chronic lymphocytic leukemia - Section 5

Combining novel agents in chronic lymphocytic leukemia: Greater than the sum of its parts?

Iris de Weerdt[1,2], **Arnon P. Kater**[1,2]

[1] *Department of Hematology, Cancer Center Amsterdam, Amsterdam Infection and Immunity Institute, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands;* [2] *Lymphoma and Myeloma Center Amsterdam, LYMMCARE, Amsterdam, The Netherlands*

Take home messages

- Although the novel agents ibrutinib and venetoclax are effective in chronic lymphocytic leukemia, their use as monotherapeutic agents requires continuous treatment.
- Combination strategies with novel agents can induce deep remissions and durable disease control following treatment cessation.
- Future studies will evaluate possibilities to tailor treatment duration to individual responses.

Two novel agents acting alone

The therapeutic possibilities for chronic lymphocytic leukemia (CLL) have greatly increased over the last few years. Novel agents such as ibrutinib and venetoclax induce high response rates and are generally well-tolerated, but their use as monotherapeutic agents is not curative. As a consequence, continuous therapy is required, leading to high costs, toxicity, lower compliance and an increased risk of resistance. Indeed, for both drugs, mechanisms of resistance have now been described that are directly attributable to long-term drug exposure.[1,2] Using these novel agents in combination regimens may increase the depth of responses, allowing treatment cessation and thereby mitigating the risks associated with constant treatment. While such combination strategies could be designed as fixed duration regimens, another approach would be to tailor treatment cessation to individual responses. Such decisions could be based on (repeatedly) undetectable minimal residual disease (MRD). MRD has recently been shown to predict progression-free survival (PFS) not only following immunochemotherapy but also following a venetoclax-containing regimen,[*3] although future studies have yet to establish the best marker to guide treatment cessation. Novel agent combination strategies include the addition of monoclonal anti-CD20 antibodies, combining multiple novel agents, and combining novel agents with chemotherapy.

Current state of the art

Combining a novel agent with an anti-CD20 antibody

Preclinical studies have demonstrated synergy between venetoclax and monoclonal anti-CD20 antibodies, which have since been evaluated in clinical trials. Venetoclax-rituximab results in prolonged PFS in comparison to immunochemotherapy in R/R patients[*4] and high rates of MRD-undetectable responses, that predict prolonged PFS after treatment cessation.[*3] Interim results suggest a similar depth of response obtained with venetoclax in combination with obinutuzumab as first-line treatment.[5,6] Although the combination with monoclonal anti-CD20 antibodies has not been directly compared to venetoclax monotherapy, monoclonal anti-CD20 antibodies do not appear to increase safety concerns associated with venetoclax. Venetoclax is more often than obi occompanied by tumor lysis syndrome (TLS), the risk of which can be lowered when obinutuzumab preinduction precedes combined venetoclax-obinutuzumab.[6]

Ibrutinib deprives CLL cells of their microenvironmental stimuli by abrogating homing and migration; however, it does not induce direct cell death and complete responses (CR) are rare with monotherapy. Monoclonal anti-CD20 antibodies therefore seem a sensible partner for ibrutinib, although in vitro studies suggested that ibrutinib might hamper antibody-dependent cellular cytotoxicity.[7] Recently, ibrutinib in combination with a monoclonal anti-CD20 antibody has been shown to extend PFS in comparison with immunochemotherapy as first-line therapy.[8,*9,*10] However, the first trial to compare ibrutinib alone or in combination with an anti-CD20 antibody did not find

Funding/support: None.
Disclosure: The authors have indicated they have no potential conflicts of interest to disclose.

HemaSphere (2019) 3:S2
Received: 3 February 2019 / Accepted: 26 February 2019
Citation: de Weerdt I, Kater AP. Combining Novel Agents in Chronic Lymphocytic Leukemia: Greater than the sum of its parts? *HemaSphere*, 2019;3:S2. http://dx.doi.org/10.1097/HS9.0000000000000197.

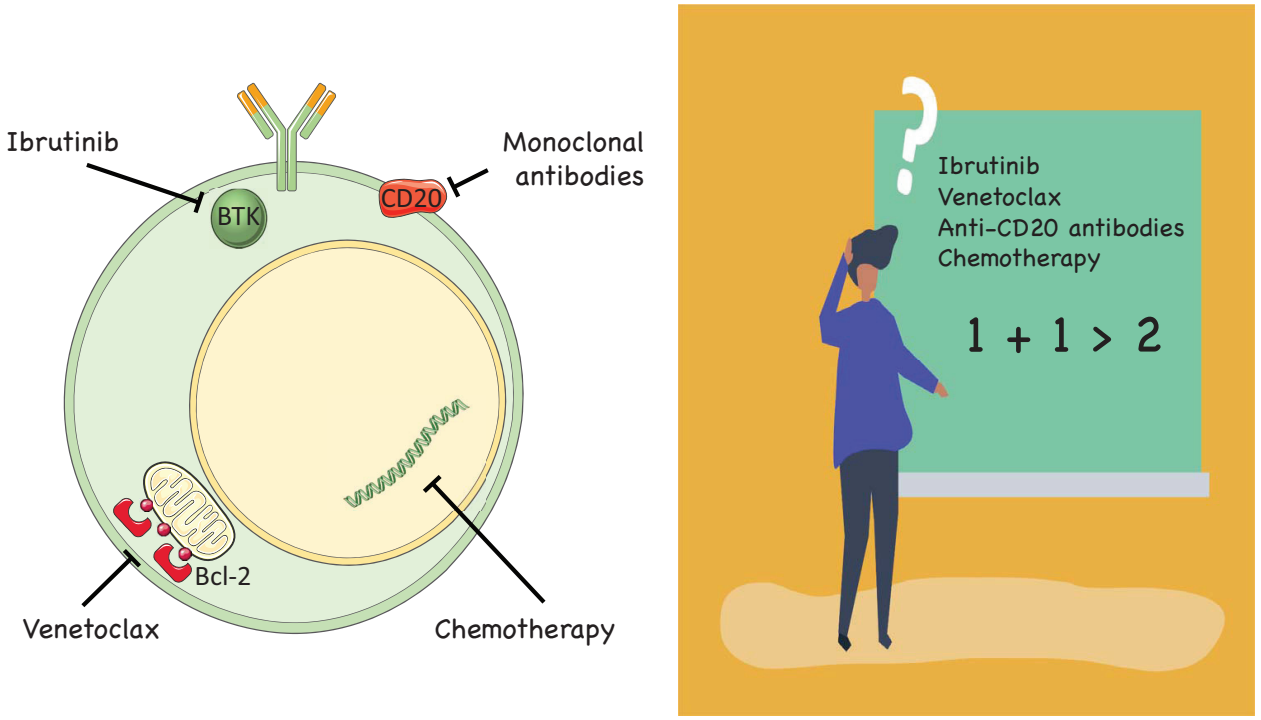

Figure 1. Combination strategies for the treatment of chronic lymphocytic leukemia will combine agents with distinct mechanisms of action, such as the BTK inhibitor ibrutinib, BCL-2 antagonist venetoclax, monoclonal anti-CD20 antibodies, and chemotherapeutic agents. This figure was created with images adapted from Servier Medical Art. Original images are licensed under a Creative Commons Attribution 3.0 Unported License.

an improvement in CR rate or PFS with the addition of rituximab.[*10] By contrast, a smaller nonrandomized trial enrolling relapsed or refractory (R/R) patients found higher levels of MRD-undetectable responses when ibrutinib was combined with obinutuzumab, especially when obinutuzumab was given after at least 1 year of ibrutinib monotherapy.[11] The improved responses with delayed obinutuzumab may be explained by the fact that CD20 expression is transiently downregulated during the first months of ibrutinib treatment.[12] Infusion-related reactions associated with rituximab and more frequently with obinutuzumab appear to be less frequent when ibrutinib is given simultaneously.[8,13] Given the fact that MRD-undetectable responses are not yet observed in the majority of patients treated with ibrutinib and monoclonal anti-CD20 antibodies, treatment cessation is not feasible and the value of monoclonal anti-CD20 antibodies remains unclear.

Combining both novel agents

Whereas ibrutinib treatment leads to replacement of CLL cells out of the lymph node and increased BCL-2 dependency, venetoclax is particularly active in the peripheral blood compartment. Alongside evidence of preclinical synergy and nonoverlapping toxicity profiles, this has raised a particular interest in strategies combining ibrutinib and venetoclax. Indeed, preliminary results demonstrated a high overall response rate (ORR 100%) and MRD-undetectable response rate (68%) after 1 year of a first-line ibrutinib-venetoclax regimen in high-risk patients.[14] A similar regimen is currently evaluated in R/R patients, of which an interim analysis also reported objective responses in all patients after 12 months of treatment, with 58% of the patients achieving an MRD-undetectable response.[15] In the future, both trials will evaluate the durability of these responses upon MRD-based treatment cessation. The adverse events during ibrutinib-venetoclax were in line with single-agent treatment. Clinical TLS did not occur in either trial after minimizing the risk by initiation treatment with ibrutinib monotherapy and subsequent venetoclax ramp-up.

A phase 1 trial demonstrated that triple combination of ibrutinib, venetoclax, and obinutuzumab can achieve high rates of MRD-undetectable responses without TLS[16] and triple combinations are currently evaluated in phase 2 and 3 trials.

Novel agents in combination with chemotherapy

Despite the advancement of novel agents, immunochemotherapy remains a valuable option for patients with mutated IGHV status (M-CLL). The addition of novel agents may limit toxicity by shortening chemotherapy exposure, while retaining efficacy. The CLL2-BXX trials evaluate this strategy, by initiating treatment with 2 cycles of debulking with bendamustine, followed by a combination of ibrutinib and ofatumumab, ibrutinib and obinutuzumab, or venetoclax and obinutuzumab. The venetoclax-obinutuzumab (CLL2-BAG) strategy results in an ORR of 95% and an MRD-undetectable response rate of 87% in a population of both previously untreated and R/R patients.[*17] The ORR with ibrutinib-obinutuzumab induction following bendamustine (CLL2-BIO) was 100%, with MRD still detectable in 52%.[18] A considerable proportion of patients encountered serious adverse events including infections and neutropenia (23% and 11% in CLL2-BAG, respectively), emphasizing the need to reconsider the role of bendamustine.

Another trial investigated ibrutinib and obinutuzumab in combination with short-term fludarabine-cyclophosphamide in previously untreated M-CLL patients, after which patients received continued ibrutinib and obinutuzumab based upon MRD analysis.[19] The percentage of patients reaching an MRD-undetectable CR increased was 86% after 1 year,

which was maintained in all patients after ibrutinib discontinuation.

Simultaneous treatment with bendamustine, venetoclax, and an anti-CD20 antibody followed by venetoclax monotherapy was associated with high toxicity, necessitating discontinuation in 29%.[20]

Future perspectives

Promising results are obtained with novel agents in combination strategies. The depth of response seen with combination therapy may allow long-lasting responses in an extended group of patients. An important challenge for the near future will be to find an optimal balance between achieving deeper remissions, while minimizing toxicity. Beyond the choice of agents, this requires strategic dosing and sequencing with still many uncertainties. Another consideration is whether the application of multiple agents in an early stage to magnify efficacy, limits therapeutic possibilities for relapsed disease. Although the basic assumption is that the same novel agent, such as venetoclax, can be reinitiated following relapse of a fixed-dose regimen, this has never been tested. Furthermore, the translation of results obtained in trials to routine practice represents an important future challenge. Finally, the best parameter to guide treatment continuation needs to be established now that durable responses after cessation have come into sight.

References

1. Woyach JA, Furman RR, Liu TM, et al. Resistance mechanisms for the Bruton's tyrosine kinase inhibitor ibrutinib. *N Engl J Med*. 2014;370:2286–2294.
2. Blombery P, Anderson MA, Gong JN, et al. Acquisition of the recurrent Gly101Val mutation in BCL2 confers resistance to venetoclax in patients with progressive chronic lymphocytic leukemia. *Cancer Discov*. 2019;9:342–353.

*3. Kater AP, Seymour JF, Hillmen P, et al. Fixed duration of venetoclax-rituximab in relapsed/refractory chronic lymphocytic leukemia eradicates minimal residual disease and prolongs survival: post-treatment follow-up of the MURANO phase III study. *J Clin Oncol*. 2019;37:269–277.

This paper demonstrates that MRD also predicts disease control following venetoclax-containing regimens.

*4. Seymour JF, Kipps TJ, Eichhorst B, et al. Venetoclax-rituximab in relapsed or refractory chronic lymphocytic leukemia. *N Engl J Med*. 2018;378:1107–1120.

This paper shows that fixed-duration venetoclax-rituximab is highly active in relapsed or refractory CLL.

5. Fischer K, Al-Sawaf O, Fink AM, et al. Venetoclax and obinutuzumab in chronic lymphocytic leukemia. *Blood*. 2017;129: 2702–2705.
6. Kater AP, Kersting S, van Norden Y, et al. Obinutuzumab pretreatment abrogates tumor lysis risk while maintaining undetectable MRD for venetoclax + obinutuzumab in CLL. *Blood Adv*. 2018;2:3566–3571.
7. Da Roit F, Engelberts PJ, Taylor RP, et al. Ibrutinib interferes with the cell-mediated anti-tumor activities of therapeutic CD20 antibodies: implications for combination therapy. *Haematologica*. 2015;100:77–86.
8. Moreno C, Greil R, Demirkan F, et al. Ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic lymphocytic leukaemia (iLLUMINATE): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2019;20: 43–56.

*9. Shanafelt TD, Wang V, Kay NE, et al. A randomized phase III study of ibrutinib (PCI-32765)-based therapy vs. standard fludarabine, cyclophosphamide, and rituximab (FCR) chemoimmunotherapy in untreated younger patients with chronic lymphocytic leukemia (CLL): a trial of the ECOG-ACRIN Cancer Research Group (E1912). *Blood*. 2018;132:LBA-4.

This study is the first to demonstrate a survival benefit of ibrutinib over FCR as a first-line treatment in fit patients.

*10. Woyach JA, Ruppert AS, Heerema NA, et al. Ibrutinib regimens versus chemoimmunotherapy in older patients with untreated CLL. *N Engl J Med*. 2018;379:2517–2528.

This paper shows improved progression-free survival with first-line ibrutinib over chlorambucil in elderly patients, with no additional benefit of rituximab.

11. Rawstron A, Munir T, Brock K, et al. Ibrutinib and obinutuzumab in CLL: improved MRD response rates with substantially enhanced MRD depletion for patients with >1 year prior ibrutinib exposure. *Blood*. 2018;132:181.
12. Spina V, Forestieri G, Zucchetto A, et al. Mechanisms of adaptation to ibrutinib in high risk chronic lymphocytic leukemia. *Blood*. 2018;132:585.
13. Dimopoulos MA, Tedeschi A, Trotman J, et al. Phase 3 trial of ibrutinib plus rituximab in Waldenstrom's macroglobulinemia. *N Engl J Med*. 2018;378:2399–2410.
14. Jain N, Keating MJ, Thompson PA, et al. Combined ibrutinib and venetoclax in patients with treatment-naïve high-risk chronic lymphocytic leukemia (CLL). *Blood*. 2018;132:696.
15. Hillmen P, Rawstron A, Brock K, et al. Ibrutinib plus venetoclax in relapsed/refractory CLL: results of the bloodwise TAP clarity study. *Blood*. 2018;132:182.
16. Rogers KA, Huang Y, Ruppert AS, et al. Phase 1b study of obinutuzumab, ibrutinib, and venetoclax in relapsed and refractory chronic lymphocytic leukemia. *Blood*. 2018;132:1568–1572.

*17. Cramer P, von Tresckow J, Bahlo J, et al. Bendamustine followed by obinutuzumab and venetoclax in chronic lymphocytic leukaemia (CLL2-BAG): primary endpoint analysis of a multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2018;19:1215–1228.

This paper demonstrates that short-term chemotherapy followed by novel agents is feasible and highly active.

18. von Tresckow J, Cramer P, Bahlo J, et al. CLL2-BIG: sequential treatment with bendamustine, ibrutinib and obinutuzumab (GA101) in chronic lymphocytic leukemia. *Leukemia*. 2019;33:1161–1172.
19. Jain N, Thompson PA, Burger JA, et al. Ibrutinib, fludarabine, cyclophosphamide, and obinutuzumab (iFCG) for firstline treatment of patients with CLL with mutated *IGHV* and without *TP53* aberrations. *Blood*. 2018;132:695.
20. Stilgenbauer S, Morschhauser F, Wendtner C-M, et al. Safety and efficacy of venetoclax (VEN) in combination with bendamustine (B) plus rituximab (R) or obinutuzumab (G) in patients (pts) with previously untreated chronic lymphocytic leukemia (CLL): results from a phase Ib study (GO28440). *Blood*. 2018;132:1859.