Update on the role of venetoclax and rituximab in the treatment of relapsed or refractory CLL

Ther Adv Hematol

2019, Vol. 10: 1–12

DOI: 10.1177/2040620719844697

James D'Rozario and Samuel K. Bennett

Abstract: For the treatment of mature B cell malignancies including chronic lymphocytic leukemia (CLL), the last 5 years has brought major advances in the application of targeted therapies. Whilst monoclonal anti-CD20 agents such as rituximab have a central role in combination with traditional cytotoxic therapy, their combination with novel agents that target the B cell receptor signaling pathway and other intracellular mechanisms of B cell proliferation is a new approach to treatment. Venetoclax is a highly specific novel agent inhibiting the bcl-2 anti-apoptotic pathway and has potent activity in CLL. Its combination with rituximab results in deeper and more durable responses and this regimen is a valuable option in the treatment of relapsed or refractory CLL including adverse prognostic variants such as cases that are fludarabine refractory or harbor the 17p chromosomal deletion. This review centers on the use of venetoclax and rituximab in relapsed or refractory CLL.

Keywords: chronic lymphocytic leukemia, rituximab, venetoclax

Received: 8 September 2018; revised manuscript accepted: 24 March 2019.

Correspondence to:
James D'Rozario
Canberra Hospital and Health Service, Garran, Canberra, Australian Capital Territory 2605, Australia
james.d'rozario@act.gov.au

Samuel K Bennett
Canberra Hospital, Canberra, Australian Capital Territory, Australia

Introduction

Chronic lymphocytic leukemia (CLL) is the most common form of leukemia worldwide with an estimated 21,000 new cases in the USA in 2018. CLL is principally a disorder of older persons with a median age of diagnosis of 70 although it can occur in patients decades younger.[1] It is an incurable, indolent disease characterized by a neoplastic expansion of mature B lymphocytes resulting in bone marrow infiltration and peripheral blood lymphocytosis. The disorder is associated with autoimmune cytopenias and often lymph node enlargement and hepatosplenomegaly where it is biologically indistinguishable from small lymphocytic lymphoma.[2]

The diagnosis is based on the demonstration of a clonal (light chain restricted) B lymphocytosis in the peripheral blood expressing a characteristic immunophenotypic profile (CD5+/ CD19+/ CD20+/ CD23+/ CD10–).[2] Most persons with CLL are diagnosed in the early stage of the disorder when asymptomatic and have a lymphocytosis as the only manifestation. Persons progressing to the later stages of the disorder have concurrent cytopenia, extensive lymphadenopathy, and/or hepatosplenomegaly and are eligible for specific treatment.[3]

Frontline therapy consists of combination of cytotoxics and immunotherapy with the anti-CD20 monoclonal agent rituximab. For younger, relatively fit patients lacking comorbidities, the combination of fludarabine, cyclophosphamide, and rituximab has become standard.[4,5] In older patients or those with significant comorbidities, bendamustine and rituximab[6] or chlorambucil with either obinutuzumab or ofatumumab represent feasible and effective first-line approaches to therapy.[7] Until recently, treatment for relapsed disease had consisted of retreatment with the original first line protocol especially where the initial remission was durable,[8] or where feasible, the use of alemtuzumab, the anti-CD 52 antibody[9,10] or a combinations of cytotoxics and antibodies.[11] The results of second-line treatment with such approaches have generally been disappointing with the outcome of treatment highly dependent

on clonal acquired genetic changes. Deletion of the short arm of chromosome 17 (17p-) and the long arm of chromosome 11 (11q-) are particularly adverse anomalies as are mutations of the *TP53* tumor suppressor gene located on 17p.[12] Similarly unmutated immunoglobulin heavy chain (*IgHV*) loci appear to portend poorer outcomes with standard therapies.[13]

In the last 5 years, the treatment of CLL has advanced rapidly with the advent of new classes of agents targeting the aberrant signaling and intracellular regulatory pathways seen in the disorder, entering clinical practice. These new classes of drug have significantly more sophisticated, targeted mechanisms of action and bring the promise of less toxicity and easier deliverability in both younger and older patients.[14] Indeed one agent ibrutinib, a member of the new class of Bruton tyrosine kinase (BTK) inhibitors, has undergone rapid preclinical and clinical development with demonstrably superior efficacy and improved deliverability in one major phase III trial in older patients requiring first-line treatment.[15] Furthermore, ibrutinib, particularly when administered as monotherapy, in patients with relapsed or refractory CLL is now established as the standard of care for patients requiring second-line or subsequent treatment options. Having entered the treatment landscape before other agents belonging to novel classes, there remains no direct comparison in a clinical trial context, amongst agents of these newer classes.[14]

Venetoclax (ABT-199), another of these new agents, is a highly selective oral inhibitor of the bcl-2 anti-apoptotic pathway, which is constitutively overexpressed in CLL clones.[16] It has highly significant activity as a single agent in CLL as demonstrated in preclinical and early phase I studies.[17]

Rituximab is a humanized murine monoclonal antibody targeting CD20 on mature B lymphocytes. It has well-established therapeutic efficacy in a variety of B cell lymphoproliferative disorders including CLL.[18] The therapeutic combination of rituximab and venetoclax is both feasible and synergistic in its effect and the combination was designated a 'break-through therapy' by the US FDA in 2016. Here we review the current use of this combination in the treatment of relapsed or refractory (r/r) CLL.

Mechanisms of action and pharmacology of venetoclax and rituximab

The bcl-2 signaling protein is a key component of the apoptotic pathway of human B lymphocytes. In CLL cells it is constitutively overexpressed resulting in inappropriate cell survival and proliferation.[19] The normal physiological role of bcl-2 in expiring cells involves an interaction with pro-apoptotic proteins known as BH3 peptides and include BIM, BBC3, and BAD. The interaction involves antagonistic binding of the bcl-2 protein group by these BH3 peptides and thus initiation of the apoptotic pathway.[20] The binding of bcl-2 proteins result in increased intracellular activity of BAK and BAX proteins, subsequent mitochondrial injury and cell death (Figure 1).

The elucidation of this pathway has led to the development of small molecule inhibitors with BH3 mimetic activity.[21] The most active of these is venetoclax (ABT-199 or GDC–0199). Venetoclax, or its chemical name 4-(4-{[2-(4-chloro-phenyl)-4,-4-dimethylcyclohex-1-en-1y]methyl}piperazin-1-y1)-N-({3-nitor-4-{(tetrahydro-2Hpyrrolo[2,3-b]pyridine-5-yloxy)benzamide, is a second-generation BH3 mimetic with much greater selectivity for bcl-2 and less binding of BCLxL.[21,22] Because CLL cells harbor particularly high levels of bcl-2, inhibition of pro-survival signaling molecules by venetoclax is amplified by the intracellular accumulation of activated BAK and BAX and bound naturally occurring BH3 proteins (e.g. BIM). Their extracellular release and subsequent facilitation of further pro-survival inhibition is through inactivation of peptides such as MCL1.[23]

Venetoclax is administered orally in a highly bioavailable form with a mean half-life of about 18 h. With once-daily dosing, steady state is achieved at about 6 days.[24] Ingestion on an empty stomach appears to enhance rate of gastrointestinal (GI) tract absorption, with peak serum concentration seen at 4–5 h after ingestion but when taken with a fatty meal, area under the receiver operating characteristic curve (AUC) and C_{max} are increased.[25] As such, for clinical dosing schedules, it is recommended venetoclax be taken once daily with food, preferably of low fat content.[26]

Venetoclax is a substrate of the CYP3A4/5 enzymatic system and the p-glycoprotein trans -membrane pump. Consequently, concomitant therapy with strong CYP3A inhibitors is best avoided. Where necessary dose reduction should

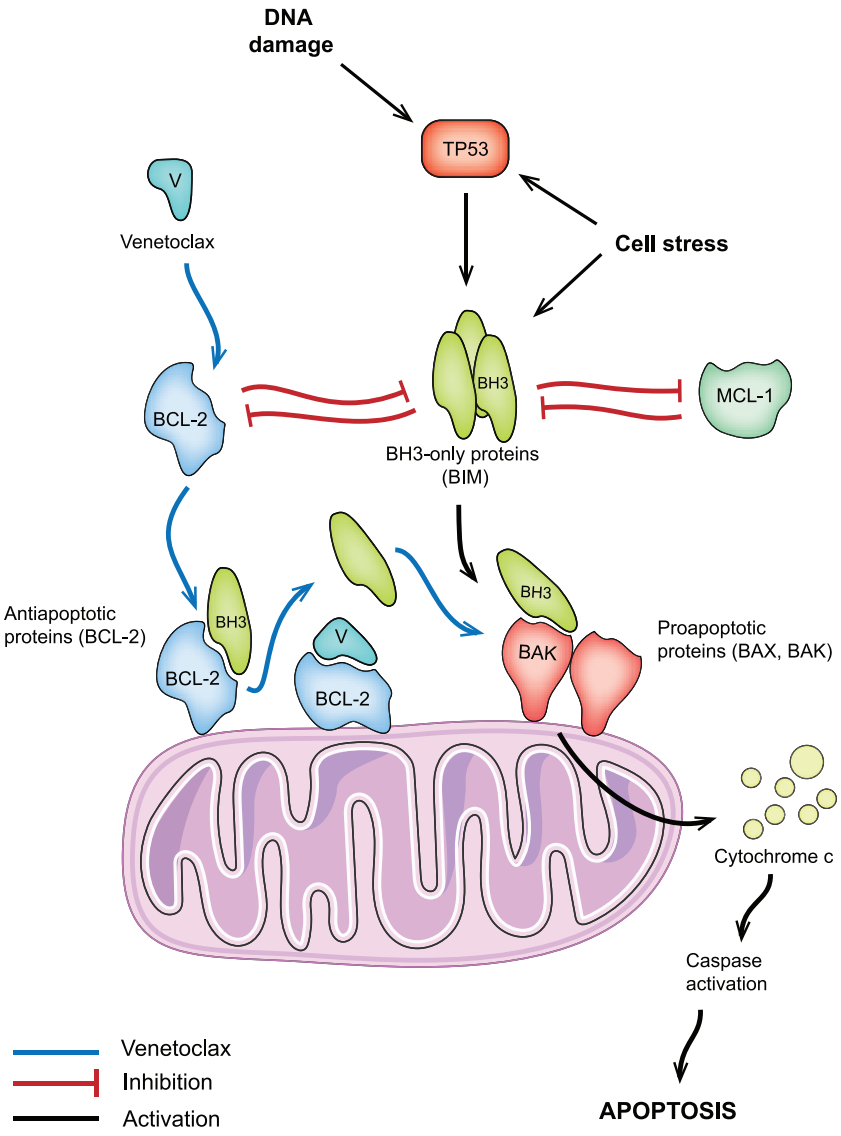

Figure 1. The mechanism of action of venetoclax and its anti-apoptotic effect.
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be considered if there is concurrent administration of agents such as imidazole antifungals, calcineurin inhibitors, and macrolide antibiotics, all of which may saturate binding of the CYP3A or p-glycoprotein systems.[26] Inactivation of venetoclax appears to be by hepatic degradation with renal excretion of inactive metabolites. Mild hepatic or renal impairment has no discernible pharmacological effect although the pharmacokinetics have not been studied in advanced hepatic or renal injury.[27]

There are currently no laboratory assays of serum concentration of venetoclax that reliably predict optimum intracellular accumulation and BH3 mimetic activity. Based on initial dose-finding studies, there is no established maximal tolerable dose and for CLL, the recommended dose is 400 mg/day.[26]

Rituximab is a humanized murine chimeric monoclonal antibody with CD20 specificity. CD20 binding causes cell death by a variety of mechanisms including complement activation and rituximab coated tumor cells adhering to the Fc receptor of cells of the monocyte–macrophage system with subsequent cell-mediated cytotoxicity.[18] The specific moiety of the CD20 molecule targeted by rituximab is a relatively small amino acid sequence which when bound, induces redistribution of the

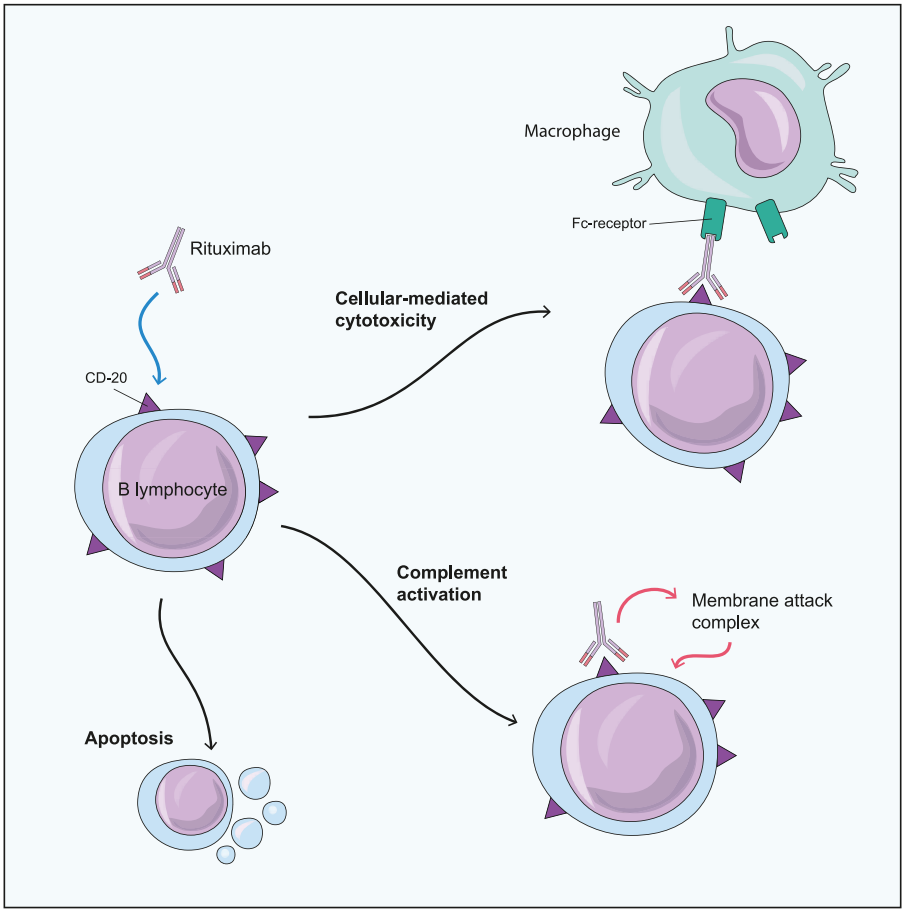

Figure 2. The three major mechanisms of action of rituximab resulting in B cell cytotoxicity.
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CD20 molecule within the bi-lipid cell membrane and induction of the antibody-dependent, cell-mediated cytotoxicity and complement activation (Figure 2).

Following intravenous infusion, rituximab appears to exhibit a two-compartment model of distribution and elimination. Volume of distribution is large and elimination half-life long at 21 days. Concentrations of rituximab can be found in serum at up to 6 months after last administration.[28] Distribution results in widespread organ infiltration including lung, liver, kidney, and heart although where the blood–brain barrier is intact, central nervous system (CNS) penetration is less.[29]

Rituximab metabolism is by nonspecific proteolytic degradation in liver macrophages and FcγR-independent endocytosis with subsequent renal elimination of metabolites.[30] Rituximab appears to be safe in patients with either severe renal or hepatic injury with no observed heightened toxicity and therefore no necessity to modify dose in these situations. For CLL, dosing of rituximab is slightly different to that used in other B cell lymphoproliferative disease. An initial infusional dose of 375 mg/m^2 is usually followed by five other doses at 500 mg/m^2. This dosing schedule arose out of dose escalation and response studies performed early on during the era of its clinical use in the context of single-agent therapy in a relatively small cohort of CLL patients.[31] Further studies appear to indicate that circulating CD20+ B cells are greater in CLL compared with other forms of B cell lymphoma and result in a rapid decline of C_{max} particularly with the first dose, which in part explains the relative 'rituximab resistance' seen in CLL.[32]

More recently the pharmacokinetics and clinical efficacy of subcutaneously administered rituximab in combination with fludarabine and cyclophosphamide have been evaluated in a phase Ib

open-label, randomized, noninferiority trial. Here a flat dose of 1600 mg administered subcutaneously resulted in comparable serum levels and noninferior toxicity and efficacy when compared with intravenous dosing in the conventional schedule.[33] Rituximab was the first anti-CD20 monoclonal antibody approved for the treatment of B cell lymphomas including CLL and there is now over 20 years of experience in its clinical use. All studies so far that have evaluated its use in combination with venetoclax have utilized intravenous administration.

Use in relapsed or refractory CLL and current evidence base

Initial phase I trials of venetoclax monotherapy confirmed its potent antitumor activity *in vivo* in patients with relapsed/refractory CLL. Single doses resulted in the appearance of apoptotic cells and chemical features of tumor lysis. In 56 patients with relapsed or refractory CLL or small lymphocytic lymphoma receiving between 150 and 1200 mg daily of venetoclax, tumor lysis was observed in 5 during the dose escalation phase, which resulted in two deaths and one case of renal failure. This lead to a protocol revision with a new dose ramp-up schedule up to 400 mg/day in the dose expansion cohort of 60 patients. Of the 116 patients who received venetoclax, the investigators observed an overall response rate of 79%. In patients with adverse prognostic factors including 17p-, unmutated *IGHV* and fludarabine resistance, response rates were, in fact, similar ranging between 71% and 79% depending on prognostic subgroup. A complete remission (CR) was observed in 20% of study participants. No maximal tolerable dose was identified during the dose escalation phase with doses up to 1200 mg daily.[34] Owing to the prior occurrence of tumor lysis, the expansion phase utilized a dose ramp-up protocol with the aim of escalating to a single daily dose of 400 mg. With this dosing schedule, the same overall and complete response rates were seen in the patients on the modified dose expansion protocol.[17] Of note, was the unheralded efficacy of venetoclax monotherapy in cases with mutated *TP53* confirming its *TP53* independent mechanism of action and its ability to override this otherwise adverse prognostic factor[34] (Figure 1).

These results were subsequently confirmed with the results of a phase II trial enrolling only patients with 17p deletion. Final long-term results of 152 patients with relapsed or refractory CLL with a median of two prior therapies and including six previously untreated patients, have been published. All were given 400 mg/day of venetoclax after an initial dose ramp up, a dosing protocol established in the previous studies. Overall response rate was 77% with a CR rate of 20%. minimal residual disease (MRD) negativity was seen in 30%. Sixteen patients had received prior therapy with a BTK inhibitor and of these, the objective response rate was still 63%. For the entire cohort, progression-free survival (PFS) at 24 months was 54% indicative of the durability of response in an otherwise prognostically adverse group.[35]

The CLL-8 trial and other studies had established the efficacy of rituximab in combination with fludarabine and cyclophosphamide in the first-line setting. The addition of rituximab to the cytotoxic combination of fludarabine and cyclophosphamide was clearly associated with superior results.[4,5] Moreover, retreatment with the fludrabine, cyclophosphamide and rituximab (FCR) regimen has demonstrable efficacy in relapsed patients especially where the duration of the first remission is of the order of several years.[8]

Subsequently, the combination of bendamustine and rituximab was shown to be effective also in the relapsed and refractory setting with notable activity in patients having previously been exposed to fludarabine. In one pivotal phase II study, overall response rate was 59% with a CR rate of 9%. At 24 months, the median PFS was 14 months. Significantly shorter PFS was associated with 17p deletion and unmutated immunoglobulin heavy chain.[36] As such, at the end of the last decade, there was no standard regimen for relapsed or refractory CLL with patients requiring retreatment receiving FCR, bendamustine and rituximab or alemtuzumab depending on the physician's familiarity with a specific treatment, patient preference and toxicity profile of each regimen.[37]

The combination of rituximab and venetoclax as a cytotoxic-free regimen was shown to be feasible and effective. In 49 patients with relapsed/refractory CLL enrolled in an open-label phase Ib study an overall risk ratio (ORR) of 86% was seen with a corresponding CR rate of 51%. Of the 20 patients achieving a CR or complete remission with incomplete marrow recovery (CRi), 50% were shown to be MRD negative. A detailed safety analysis found the regimen to be well tolerated with transient,

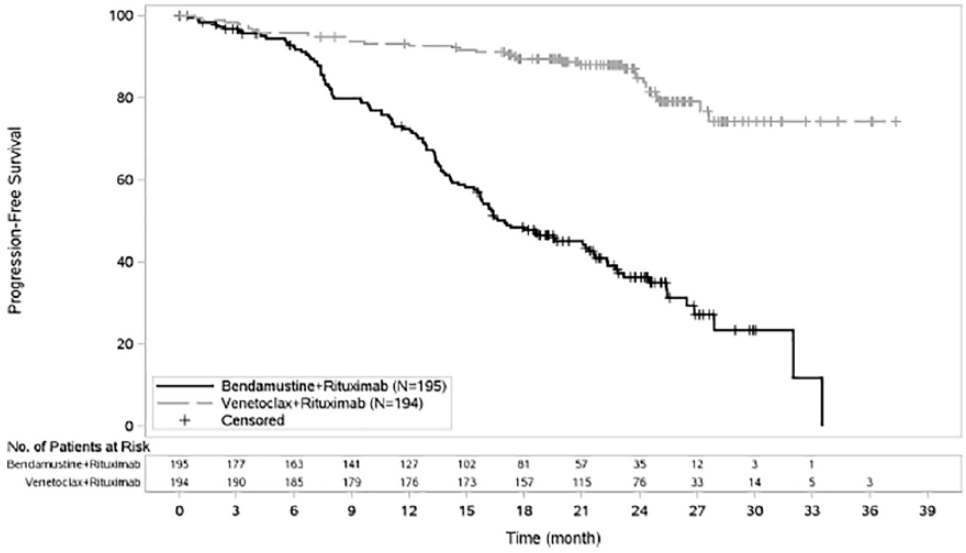

Figure 3. Progression-free survival in the investigational (venetoclax–rituximab) *versus* control (bendamustine–rituximab) arms of the MURANO phase III trial.
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manageable neutropenia being the most frequent adverse effect and seen in 55%. Mild diarrhea and nausea were seen in half of patients. Thrombocytopenia was seen in 22% but was not generally associated with clinically significant bleeding.[38]

The pivotal MURANO phase III trial is the largest to compare venetoclax and rituximab with bendamustine and rituximab (BR). Of note is the fact that the trial was designed and began recruiting sometime before the wide availability of ibrutinib. As such, the efficacy of ibrutinib in relapsed/refractory CLL had not been clearly established in the clinical trial setting and BR was considered the appropriate control arm.

The primary analysis of its results have recently been published.[39] With a multicenter, international open-label design, 389 patients were randomized to receive either venetoclax for 2 years with concurrent rituximab for the first 6 months (VR), or BR for 6 months. Patients enrolled to the VR arm were administered a slowly increasing dose of venetoclax (ramp up phase) during which there was close monitoring for tumor lysis. Once the optimal 400 mg/day dose was reached, rituximab was introduced. Initially at 375 mg/m^2 for cycle one, the dose was increased to 500 mg/m^2 for the subsequent five cycles. Patients were not permitted to cross over to the VR arm in the event of disease progression whilst being treated with BR.

In MURANO, 2 year PFS was 85% for the VR arm and 36% for the BR arm (Figure 3). The superiority of VR was maintained across all prognostic and biologic subgroups including patients harboring the 17p deletion in whom 2 year PFS was 81% in those treated with VR. Clinically meaningful benefit in overall survival (OS) was also demonstrated in the VR group compared with the BR group with 2 year rates of 92% and 87%, respectively. This corresponds with a hazard ratio of 0.48 for the VR combination although the difference was not statistically significant and neither arm reached a median after 24 months.

Overall response rates as assessed by investigators were 93% in the VR group compared with 68% in the BR group. CR/CRi rate was 27% in the VR group and 8% in the BR group. MRD assessment of peripheral blood was undertaken in 366 patients and of bone marrow in 115 patients. Here, the superiority of the VR combination was confirmed with a MRD negativity rate at 9 months of 62% *versus* 13% in the BR group. This was maintained over time with assays undertaken at 12, 15, and 18 month time points (Figure 4). Of note is that this rate of clearance of MRD observed with the VR combination appears higher than

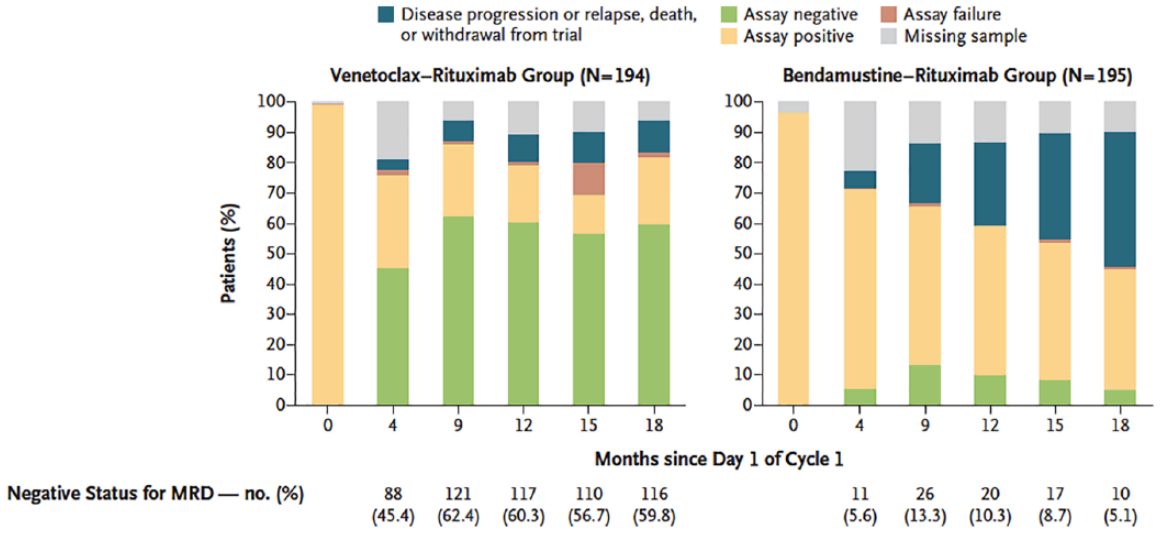

Figure 4. Rates of minimal residual disease (MRD) negativity over time in the investigational (VR) and control (BR) arms of the MURANO phase III study. Assays were performed up to 1 year after completion of the combination phase of treatment in each arm (in the VR arm, venetoclax monotherapy was continued for a further 18 months following combination therapy).
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rates observed with other agents and combinations in relapsed/refractory CLL. The longer-term durability of this observation remains to be confirmed, especially as to whether it can be maintained with treatment discontinuation after 2 years. Encouragingly, previous studies suggest MRD clearances with VR are long lasting.[38]

An updated analysis presented at the ASH meeting in San Diego in December 2018 in which all patients still enrolled on study had under gone at least 3 years of follow up and all those in the VR arm had completed at least 2 years of venetoclax treatment revealed similarly impressive results for PFS and OS: 71.4% (VR) *versus* 15.2% (BR) and 87.9% (VR) and 79.5% (BR) respectively.[40] Again, the updated analysis of patients in MURANO who had progressed after venetoclax therapy showed 14 of the 16 patients had been MRD + at 24 months. Its value as a very powerful prognosis predictive tool was further confirmed with the first prospective analysis of the MURANO dataset in patients undergoing time limited treatment.[41]

Safety of the venetoclax-rituximab combination

With increasing experience and data accruing from patients enrolled in clinical trials, the VR combination appears to be safe with acceptable toxicity. Neutropenia is the most commonly observed adverse effect with severe (grade 3 or 4) neutropenia occurring in up to 58%.[16,34,39] The onset of neutropenia is much more likely during the combination period of treatment than with venetoclax monotherapy with new onset neutropenia occurring during combination therapy at a rate of 54% compared with 11% during the 18 month period of venetoclax monotherapy.[38] Despite the regular occurrence of neutropenia, the incidence of infection and febrile neutropenia is lower however at 17% and 4%, respectively. Thrombocytopenia is seen in 6–36% but has not been associated with clinically significant bleeding.[39,42] Infusion-related reactions with rituximab are low when specific premedication is employed.

When venetoclax dosing employs a ramp-up phase with appropriately close clinical and laboratory monitoring as in clinical trial subjects, the incidence of tumor lysis syndrome is low at 2.1%.[39] In a recently published retrospective analysis of 141 real-world patients treated with either venetoclax monotherapy or a variety of different combinations, across different settings in the USA, the incidence of tumor lysis syndrome (TLS) was seen to be substantially higher overall at 13%. Of these, about a third developed

demonstrable clinical TLS with the remaining two-thirds having laboratory abnormalities only.[42]

Updated safety analysis of the MURANO trial patients after a longer follow-up period revealed no new safety signals and confirmed the greater probability of serious adverse events occurring in the combination therapy phase specifically neutropenia, infection, and fever. The incidence of tumor lysis remained similar to the primary analysis at 3.1%. The incidence of Richter's transformation was comparable in both the VR and BR arms at 3% each. Second primary malignancies were seen in 12% of patients treated with VR and 8% treated with BR; however, when nonmelanomatous skin cancers are excluded the rate of second primary malignancy in the VR-treated group is only 5%. With the longer follow-up period, fatal adverse events remain a relatively uncommon event occurring in 7% of patients treated with VR.[43] The longer-term MURANO safety data presented in oral abstract form revealed a similar pattern although fatal AEs in both arms were pleasingly low at 4% each.[40]

Future directions

Having established the unprecedented clinical benefit of the VR combination in relapsed/refractory CLL with the results of the trials outlined above, there remains a small proportion of patients in the range of 15–25%, who develop venetoclax failure with either venetoclax monotherapy or the VR combination.[39] Furthermore, whether time limited therapy is successful in all or most patients, as against indefinite maintenance as employed with BTK inhibitor treatment, remains an unanswered question. In addition, the use of MRD negativity as a predictor of successful long-term remission with time-limited treatment with venetoclax awaits confirmation but early prospective data looks promising.[41]

Whilst some reports suggest patients can be salvaged following venetoclax failure,[44] studies are ongoing with novel agents combined with venetoclax seeking to improve upon the success of the VR combination. 'BH3 profiling' is an area of active preclinical research and have thus far identified mediators of resistance amongst the bcl-2 anti-apoptotic protein family including MCL-1 and BCLX.[45] Inhibition of MCL-1 transcription *via* CDK9 blockade is one approach and may be synergistic with venetoclax.[45] Increased synthesis of BCL-XL in cultures systems mimicking nodal CLL, mediates resistance to the related bcl-2 antagonist, ABT-737. Evidence from mantle cell lymphoma cell lines suggests that obinutuzumab may overcome BCL-XL induction through nuclear factor (NF)-κB inhibition and it is thus possible that venetoclax-resistant CLL may be similarly sensitive although this has not yet been proven *in vitro*.[45]

As suggested, alternative combination therapies with venetoclax as a 'backbone' may be able to circumvent these resistance mechanisms. Ongoing areas of active clinical research include the use of venetoclax with other monoclonal antibodies that may have a more potent B cell depleting effect than rituximab, and the combination of venetoclax with BTK inhibitors ± anti-CD20 monoclonals.

Preliminary phase Ib data (GP28331, ClinicalTrials.gov identifier: NCT01685892) published in abstract form by Flinn *et al.*, suggest that the combination of venetoclax with another anti-CD20 monoclonal antibody (glycoengineered to have greater FCyRIII binding and direct program cell death induction capacity) obinutuzumab, is also safe and efficacious in setting of relapsed/refractory CLL.

Over a median time on study of 5 months, with the highest venetoclax dose level administered 400 mg daily, 100% of the 17 assessable patients demonstrated a complete response (CR/CRi) rate of 23.5%. However of the 76.5% achieving only a partial response after three cycles, further therapy resulted in a CR/CRi in up to a quarter of these study participants. Laboratory tumor lysis occurred in 12.5% of patients but all continued treatment and only one disease progression and one death occurred on study. The most common grade 3 adverse event was neutropenia (34.4%), but the consequent rate of febrile neutropenia was reassuringly low at 6.4%.[46]

Following on from this promising study preliminary data from the German CLL study group CLL14 trial (ClinicalTrials.gov identifier: NCT02242942) show favorable results with the same obinutuzumab/venetoclax combination.[45] This open-label randomized control trial in patients with a Cumulative Illness Rating Score (CIRS) >6 will assess PFS with obinutuzumab/chlorambucil (an 'old standard' protocol for frailer/older CLL patients albeit in the

'upfront' setting) compared with obinutuzumab/venetoclax.

Data from the safety run-in phase of this study were presented in abstract form at the 2015 and 2016 ASH meeting.[45] Thirteen participants with a median age of 75 and CIRS score of 8 were randomized to receive the obinutuzumab/venetoclax combination. Half of these patients had high-risk karyotypic changes (del17p or del11q). Only two failed to complete the 12 months of study.

Mirroring the findings of Flinn *et al.*, laboratory tumor lysis occurred in 16.7% and grade 3/4 neutropenia was frequent (58.4%) but a higher rate of febrile neutropenia was noted (25%). The adverse event rate in the comparator arm is as yet unpublished but expected to be lower noting the grade 3/4 neutropenia rate in the CLL11 study was 35% (infections 11%).[7] Duration of therapy was shorter, compared with CLL14, where treatment continued in both study arms for a further 6 months of chlorambucil and venetoclax respectively after the obinutuzumab ceased. Obinutuzumab/chlorambucil as a comparator is of less clinical relevance in the relapse/refractory setting, and the more pertinent comparison is the rate of serious neutropenia in the MURANO trial (57.7% with 3.6% febrile neutropenia), which is roughly equivalent. In spite of these adverse events, impressive responses were seen with 100% of patients achieving a response 3 months after completion of therapy (of which 58% were CR, with one Cri). In those seven patients with available marrow MRD at the conclusion of treatment, five were MRD negative.[47]

Without question these two studies confirm that combination therapy with venetoclax and obinutuzumab can achieve not only meaningful *clinical* responses but also deep *molecular* responses. However, until the long-term results of CLL14 are published the durability of these responses remains unknown. Presuming these impressive MRD results are replicated in the CLL14 cohort at large, projected PFS will also be of the order of years if the MURANO data are any guide (where MRD responses predicted longer-term PFS in both arms).[38,41]

Whether the notion that preclinical data anticipating a more potent anti-CLL effect of obinutuzumab when combined with venetoclax will lead to better clinical outcomes remains to be seen, noting that studies in other low-grade lymphoma, for example GALLIUM,[48] have only shown marginal (albeit statistically significant) differences in PFS when obinutuzumab is substituted for rituximab, and only when prolonged 'maintenance' administration of the obinutuzumab occurs. Furthermore it is unclear whether the apparent risk of increased incidence of some adverse events, in particular the rate of infusion related reactions of 8.3% with obinutuzumab, is sufficiently low relative to any advantage in PFS to warrant obinutuzumab supplanting rituximab as the monoclonal antibody of choice to use with venetoclax for relapsed/refractory CLL.

Perhaps even more promising than the combination of venetoclax with other anti-CD20 antibodies is the prospect of pairing it with a BTK inhibitor. BTK inhibitors appear to downregulate MCL-1[49] making the rationale for their addition to a venetoclax-based regimen a compelling one. This combination is currently being investigated in two actively recruiting clinical trials (ClinicalTrials.gov identifiers: NCT03422393 and NCT02756897).

NCT02756897 is a phase II trial exploring the effect on complete response of sequential addition of venetoclax to relapsed/refractory patients after three initial monthly cycles of ibrutinib over 27 months, whereas the phase I NCT03422393 study is exploring the safety and optimal dosing of ibrutinib (in particular, high-dose ibrutinib) when venetoclax is added for patients experiencing disease progression on single-agent ibrutinib. The study is predicated on the conceptual notion that progression represents growth of a subclone (which may be sensitive to a new agent such as venetoclax) but that continued therapy with the current agent may remain worthwhile in order to maintain suppression of the previously dominant clone.

Notably a phase IB/ II study of the sequential combination of obinutuzumab with ibrutinib and venetoclax, in the upfront setting showed acceptable tolerability with the phase II component of the study is ongoing.[50] Following on from this initial experience it is highly likely that the combination of venetoclax + anti-CD20 antibody + BTK inhibitor for relapsed/refractory patients will in turn form the basis of multiple future trials in relapsed/refractory CLL.

Conclusion

With the therapeutic armamentarium for relapsed/refractory CLL expanding rapidly, venetoclax–rituximab is now clearly established as a key treatment option that is both safe and efficacious across all prognostic subgroups. It is clear that in the coming years, venetoclax is likely to form the basis of other highly active combinations, which represent a true paradigm shift in the treatment of a disease that is both highly prevalent and had previously been difficult to treat when relapsed/refractory.

These combination studies of novel agents are at the vanguard of experimental clinical medicine in CLL and represent an unparalleled opportunity to establish the safest and most efficacious means of achieving optimal patient outcomes. In contrast to prior single-agent studies in the relapsed/refractory space, the expectation is that they may offer the very real possibility of not only meaningful disease control but MRD negative responses in some, and thus even the tantalizing possibility that a minority of relapsed/refractory CLL patients may be effectively 'cured' of their disease.

Authorship and contribution

SB and JD'R contributed equally to the content of this article.

Funding

This work received no specific grant nor funding from any agency in the public, commercial or not-for-profit sector.

Conflict of interest statement

JD'R has received consultancy fees from Roche pharmaceuticals for participation on advisory boards.

ORCID iD

James D'Rozario https://orcid.org/0000-0002-5983-753X

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