Bendamustine plus rituximab in chronic lymphocytic leukemia: is there life in the old dog yet?

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The results of the multicenter international MABLE trial published in this issue of *Haematologica* represent the first randomized phase III data comparing two frequently used chemoimmunotherapies, chlorambucil plus rituximab (Clb-R) *versus* bendamustine plus rituximab (BR), in patients with chronic lymphocytic leukemia (CLL) and concomitant comorbidities.[1] Michallet and colleagues report a significant benefit for BR with respect to complete response (CR) rate, progression-free survival (PFS) and minimal residual disease (MRD) negativity rate, while the safety profiles of both chemoimmunotherapies were quite similar. A dominant inclusion criterion was that patients had to be ineligible for treatment with fludarabine due to comorbidities. Altogether, 357 patients were randomized while 241 of them were treatment-naive. In this frontline population the primary endpoint of the trial was met, i.e., higher CR rates after 6 cycles of treatment in favor of BR (24% *vs.* 9%, respectively). As secondary endpoints, PFS (30 months *vs*. 20 months, respectively) and the MRD negativity rate (66% *vs*. 36%, respectively) were also significantly superior in the BR arm, whereas overall response rate (ORR) and overall survival (OS) did not differ between arms.

While the differences in efficacy endpoints between both treatment arms are quite impressive, some critical points need further reflection. The entire MABLE trial contains a quite heterogeneous and not well-defined group of CLL patients, i.e., first-line and second-line patients, while the aforementioned analysis carried out by Michallet *et al.* focuses only on the subgroup of treatment-naive CLL patients. The recruitment of second-line patients had been stopped by an amendment of the trial, caused by slow accrual. Furthermore, comorbidity is not well-characterized as an inclusion criterion for this trial, and seems rather subjective when given the discriminator "fludarabine-ineligibility". It would have been desirable if a comorbidity scoring, based, for example, on the cumulative illness rating scale (CIRS), as has been used in similar trials (e.g., COMPLEMENT-1, CLL11, etc.), had also been applied for the MABLE trial population.[2,3] In addition, the dose of bendamustine that was chosen for first-line use (90mg/m^2) attests to a reasonably fit patient population (70 mg/m^2 is the typical standard for unfit patients) and makes a comparison with the COMPLEMENT-1 trial (Clb *vs*. Clb plus ofatumumab) or the CLL11 trial (Clb *vs*. Clb-R *vs*. Clb plus obinutuzumab [Obi]) difficult. In the initially reported first-line data for BR at a dose of 90 mg/m^2 based on a phase II trial (CLL2M trial) of the German CLL Study Group (GCLLSG), only a minority of patients was comorbid and/or over 70 years of age.[4] In a phase III trial comparing BR against fludarabine, cyclophosphamide, and rituximab (FCR) in fitter patients, it was shown that the 90 mg/m^2 bendamustine dose was quite toxic in patients over the age of 65, inducing severe infections of grade III and IV in more than 20% of patients.[5] Therefore, an international consensus panel recommended a lower dose of bendamustine (70 mg/m^2) in elderly patients.[6] Excepting the question of the adequately-dosed chemotherapy backbone, there is a need to discuss whether the anti-CD20 monoclonal antibody (mAb) rituximab should still be the standard-of-care for unfit CLL patients nowadays. Within the CLL11 trial of the GCLLSG a combination of chlorambucil plus the type II mAb obinutuzumab has been shown to be superior to the doublet of Clb-R, at least with respect to PFS.

Besides the problematic comparison of MABLE data to other chemoimmunotherapy trials focusing on a less fit CLL population, there must be a critical discussion as to whether the question regarding which chemoimmunotherapy is superior as a frontline approach in CLL patients is still relevant nowadays, given the fact that many other therapeutic options have become available over the last few years. We have learned from the RESONATE-II trial that the Bruton's tyrosine kinase (BTK) inhibitor, ibrutinib, is very effective as a first-line therapy in CLL patients, regardless of the risk factors, e.g., an unmutated IGHV status.[7] Although a direct comparison of ibrutinib monotherapy to a chemoimmunotherapy standard, such as Clb-R or BR, is lacking thus far, it is difficult to imagine that one of the main players of the MABLE trial could beat ibrutinib, which induces durable responses in the frontline setting (median PFS not reached after a median observation time of 18.4 months). However, data from the ILLUMINATE trial performed by the UK CLL Study Group, which is comparing chlorambucil plus obinutuzumab *versus* ibrutinib plus obinutuzumab, are pending. In addition, the U.S. based trial A041202 (Alliance) will answer the question of whether BR still has a role compared to ibrutinib or ibrutinib plus

Table 1. Efficacy of different first-line treatment options in less fit/elderly CLL patients.

	Median age (yrs)	ORR (%)	CR (%)	MRD negativity (%)	PFS (months)
Clb-R (MABLE)[1]	72	75	9	13	30
BR (MABLE)[1]	72	74	24	41	40
Clb-Obi (CLL11)[3]	74	77	22	38	27
Ibrutinib (RESONATE-II)[7]	73	86	4	0	NR
Venetoclax-Obi (CLL14)[8]	75	100	58	92	NR

ORR: overall response rate; CR: complete response; MRD: minimal residual disease; PFS: progression-free survival; Clb: chlorambucil; R: rituximab; BR: bendamustine plus rituximab; Obi: obinutuzumab; NR: not reached.

rituximab. In addition to the potential role of ibrutinib as a broad future first-line standard in CLL, we have to be aware that the BCL2 inhibitor, venetoclax, will further challenge any chemoimmunotherapy standard, both alone and in combination with antibodies, or even as a doublet including ibrutinib. The initial data regarding venetoclax in combination with the type II anti-CD20 mAb, obinutuzumab, seem to be very promising, with a MRD negativity rate of 100% in peripheral blood, based on a small run-in cohort as part of a large randomized phase III trial of the GCLLSG (CLL14 trial), which is correlating this combination with that of chlorambucil plus obinutuzumab (Table 1).[8]

Taken together, and in spite of some limitations in the trial design and trial performance, the data from MABLE are important as they represent the only available phase III data of the BR combination regimen compared to a chlorambucil/anti-CD20 comparator arm. The data from MABLE provide important cognizance with regard to the frontline treatment portfolio, keeping in mind that in many countries worldwide, upcoming treatment options based on B-cell receptor inhibitors, like ibrutinib, or BCL2 inhibitors such as venetoclax, will not be an available or affordable option in the near future.9 On account of the MABLE data, treating physicians will now have a rationale to use BR as an alternative treatment option compared to chlorambucil-based regimens in patients who are not eligible for more aggressive, fludarabine-based therapies. In other words, with respect to BR, and for the time being, there seems to be life in the old dog yet.

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