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Still a role for second-line chemoimmunotherapy in chronic lymphocytic leukemia?

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In this issue of the Journal, Cuneo *et al*. report a retrospective observational study of the efficacy of bendamustine rituximab (BR) given as first salvage therapy for chronic lymphocytic leukemia (CLL) patients within the GIMEMA and ERIC networks.[1] Among 237 patients, the median progression-free survival (PFS) was an excellent 25 months and the median time to next treatment 31.3 months. Predictors of shorter PFS in multivariable analysis included del(17p), unmutated *IGHV* and advanced stage. Cuneo *et al.* further performed a matched adjusted comparison of overall survival (OS) between the subset of BR-treated patients without del(17p) who had received front-line chemoimmunotherapy (CIT), and similar patients who had received ibrutinib second-line in named patient programs in the UK and Italy. Interestingly, there was no difference in OS, with 63% alive in the ibrutinib group at 36 months, as compared to 74.4% in the BR group.[1]

At first glance these data may seem surprising, as ibrutinib has had OS benefit in both the RESONATE trial,[2] comparing ibrutinib with ofatumumab in relapsed refractory CLL, and in the RESONATE-2 trial,[3] comparing ibrutinib with chlorambucil in previously untreated CLL. It is important to note that the control arms of both of these trials did not unfortunately represent particularly effective therapy, especially in comparison to the BR presented here; they were also both relatively small studies. A US Intergroup trial comparing ibrutinib to ibrutinib rituximab to BR for front-line therapy of CLL in older patients has completed accrual and results are awaited.

While these data from randomized trials are invaluable, they often do not capture the full picture of a new therapy, hence the value of observational studies like that of Cuneo *et al*.[1] Eligibility, particularly for phase III trials, is typically strict, resulting in a selected healthy patient population. This may be particularly true of the ibrutinib randomized studies. For example, although the median age of patients receiving ibrutinib in RESONATE-2 was 73 years, only 31% had a cumulative illness rating score (CIRS) over 6, indicating a very low level of comorbidity for their age.[3] Why does this matter? Although ibrutinib is often said to be well-tolerated among older patients with comorbidities, the data supporting this claim are actually quite limited, and a recent multicenter retrospective study has found that a CIRS score of over 6 was in fact associated with inferior event-free survival and OS, as well as increased risk of dose reduction or discontinuation, among ibrutinib-treated patients.[4]

Other real-world analyses with ibrutinib, as well as longer follow up of the prospective trials, have also made

it clear that many patients do not tolerate extended therapy. A multicenter retrospective analysis of 616 ibrutinib-treated patients reported a 41% discontinuation rate with a median time to ibrutinib discontinuation of seven months.[5] The predominant cause of discontinuation was toxicity, including atrial fibrillation, arthralgia, rash, infection and pneumonitis. The median PFS for the entire cohort of predominantly relapsed patients was 36 months, as compared to the recently reported 51-month median PFS in the phase Ib/II ibrutinib clinical trial.[6] Additionally, with more mature follow up of the ibrutinib clinical trials, discontinuation rates are rising and are beginning to look more similar to the earlier real-world data. In the admittedly small previously untreated cohort of the phase Ib/II study,[6] the discontinuation rate has reached 45% at five years, although PFS is 92%, indicating that these discontinuations are not predominantly due to progressive disease. More frequent discontinuation, dose holds and dose reductions seem likely to explain some of the differences in outcome between ibrutinib clinical trials and real-world reports.

The real-world analysis presented by Cuneo *et al.*[1] focuses on an interesting CLL patient niche that has perhaps been neglected, namely those receiving first salvage therapy. These patients are often pooled with more heavily pre-treated patients, making it difficult to assess their outcomes. The BR population in this study has a median age of 70 years and is reasonably healthy based on Eastern Cooperative Oncology Group (ECOG) performance status, comorbidities and creatinine clearance.[1] Their disease, however, is advanced, with 78.6% in advanced stage, 91% with bulky lymphadenopathy, and 73% with unmutated *IGHV*. High-risk FISH is relatively limited at 20.8% with del(11q) and 12.6% with del(17p), although approximately half had progressed within 36 months of their prior therapy. In comparison to the ibrutinib arm of RESONATE, for example, these patients are much less heavily pre-treated and at much lower risk according to FISH, yet have more advanced disease according to stage and bulk. Despite the latter, and likely related to the former, they did well with BR, with a median PFS of 25 months that compares favorably to the previously reported 15-18-month PFS for BR in the first or second salvage settings.[7,8] As expected, PFS was worse for genetically higher risk patients, but reached 40.4 months in those without del(17p), with mutated *IGHV*, and Rai stage 0-2 disease.

The overall analysis, and particularly the comparison to ibrutinib, is certainly limited by its retrospective nature and potential differences in the patient populations under comparison. For the comparative analysis, Cuneo *et al.*[1] wisely chose to focus on patients without del(17p) who had had front-line CIT, and in doing so the cohorts were statistically comparable for age, ECOG, response to first-line therapy, and *IGHV*, although the ibrutinib cohort still had more patients with less than 36 months from first-line therapy (76.1% *vs*. 59.1%). Furthermore, the ibrutinib cohort also showed a trend to more ECOG-2 patients: 17.4%, compared to 8.1% in the BR cohort. The former had an estimated 2-year OS of 35%, much less than the 73% OS of ibrutinib-treated ECOG 0-1 patients. In this context, a detailed listing of the causes of death among the ibrutinib-treated patients would be helpful. In addition, the ibrutinib cohort in particular is quite small, and several early deaths due to infection or Richter's syndrome, of unclear relationship to ibrutinib, may also have affected the OS curve. While these differences certainly confound the results, nonetheless the findings are provocative in demonstrating comparable OS between second-line ibrutinib and BR in two approximately matched real-world patient populations.

Despite its limitations, the Cuneo *et al.*[1] study demonstrates that six months of CIT can be very effective second-line therapy in appropriate patients, and challenges the increasingly widespread belief that if ibrutinib is not used first line, it should certainly be used second line. Ibrutinib's initial overwhelming efficacy was evident particularly among very heavily pre-treated patients with 17p and 11q deletions[9] whose response to traditional CIT is dismal. The Authors of this paper note that the real-world data with ibrutinib show similar duration of therapy and benefit in first *versus* later relapses, suggesting that relative ibrutinib benefit in the real world is greater in more heavily pre-treated patients. I would agree that the still limited data currently available generally support this claim, although the relative proportion of discontinuations for disease progression is higher in later line patients, and it is hard to ignore the clinical trial results demonstrating longer PFS in less heavily pre-treated patients, at least in the relapsed setting.[10] In a cross-trial comparison performed with 24-month follow up and excluding del(17p) patients, the PFS was similar for first-line patients in RESONATE-2 to that of second-line patients in RESONATE,[11] but better than that of later line RESONATE patients. A further issue raised by the clinical trial data is whether ibrutinib or idelalisib should be added if later-line BR were given, since the addition of either drug improved PFS and possibly OS among a more heavily pre-treated higher risk patient population.[12,13] Further complicating this landscape are the recently reported MURANO data in which venetoclax-rituximab greatly improved PFS compared to BR in relapsed CLL patients, most of whom had one prior therapy, albeit with a higher risk profile including del(17p) and *TP53* mutation.[14]

How then to reconcile the clinical trial and real-world data, while also taking into account patient preference for time-limited therapy and cost considerations? Notably absent from this discussion has been a deeper focus on risk stratification as well as individualized patient management, including comorbidities and performance status, in selecting therapy. The relative benefit of ibrutinib and other novel agents is certainly greatest in higher risk disease, and, at least with ibrutinib, among patients able to remain on drug for extended times. Yet to date, only del(17p) has been widely accepted as altering therapy choice and trial design, with the result that most of our CLL trials enroll a broad patient population which may not be well stratified for disease risk or directly comparable to the population enrolled on other studies or seen in our clinics. The most important example here is *IGHV* mutation status, which clearly predicts long-term benefit from FCR CIT,[15-17] yet has not been widely incorporated into our thinking about relapsed or older patients, despite evidence, as in this paper,[1] that the mutated subgroup can often respond well to a diversity of therapies.

Additionally, the negative impact of genomic complexity as measured by complex karyotype[18] or multiple driver mutations[19,20] has become increasingly clear, and these features would likely add further nuance to a patient-specific risk stratification. Increasingly, I take into account all of these disease features, as well as the patient's age, general health, preferences and reason for needing therapy, when considering their therapeutic options. The time has come for clinical trials and long-term population-based studies informed by this deeper risk stratification in order to understand the natural history of sequential therapy choices in these increasingly differentiated unique patient subgroups. Only in this way can we best serve and advise our patients among the myriad of choices.

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