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COMMENTARY

A final note about ibrutinib in relapsed or refractory CLL: Conclusive results from RESONATE sound definitely good!

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In this issue of the *American Journal of Hematology* Munir et al[1] reported the final results of up to 6 years follow-up of the randomized RESONATE study, comparing the first-in-class Bruton Tirosin's kinase inhibitor (BTKi) ibrutinib, vs ofatumumab in patients with relapsed or refractory (r/r) chronic lymphocytic leukemia (CLL). Two previous reports described earlier results of this pivotal registration trial: the primary analysis and the latter one with median follow-up of 9.4[2] and 44 months,[3] respectively. This final analysis, here reported, is highly relevant, as it adds two additional years of observation (median 65.3 months), for the 195 patients originally assigned to ibrutinib (median treatment duration 41 months). Data result in the longest follow-up for a cohort of CLL patients treated continuously with ibrutinib (exceeding also the recently published long-term update of the seminal PCYC 1102-1103 study).[4] This observation time in the context of a well conducted randomized trial makes this report a treasure trove for defining efficacy and safety of ibrutinib in various CLL subgroups in the long term.

Ibrutinib, together with PI3K inhibitor idelalisib, changed the treatment paradigm of B-cell neoplasms, switching from numbers of chemo-cycles to a continuous dosing of oral medication until progression or unacceptable toxicity. From the time of its full approval, ibrutinib largely replaced other options in r/r CLL, due to its efficacy especially in molecularly-defined high risk patients over chemo-immunotherapy regimens like BR[5] or FCR,[6] and a substantial superior tolerability profile over idelalisib-rituximab.[7]

Looking in details to RESONATE updated results, cumulative overall response rate (ORR) reached 91%, with a further slight increase of complete response (CR) rate up to 11%. At this mature time-point, median PFS remained impressively higher for ibrutinib compared to ofatumumab (44.1 vs 8.1 months). This happened even (44.1 vs 8.0 months) for patients with well-known genomic high-risk characteristics (del17p, TP53 mutation, del11q and/or unmutated IGHV status), which were enriched (82%) in this heavily pre-treated r/r CLL population. Dissecting PFS results according to different highrisk subgroups, a significantly lower PFS was observed in del17p and/or TP53 mutated patients (40.7 vs 56.9 months). Complex karyotype (CK) did not result associated with worse outcome. Notably, even in the PCYC-1102/1103 study, CK was not identified as an independent prognostic factor for PFS or OS, as survival in patients with CK was largely influenced by the coexistence of del17p.[4] Unmutated IGHV prognostic value was completely overcome by ibrutinib as clearly illustrated by superimposable PFS curves, in line with other studies.[4] Finally, patients with del11q experienced a noteworthy benefit with median PFS (60.7 months) exceeding the one of the whole ibrutinib cohort, consistent with a pooled analysis in about 600 patients.[8] This fact qualifies ibrutinib as a precision medicine for this specific genomic subset of patients.

The crude OS rate benefit is now reduced to only borderline significance, mainly as a result of the crossover effect to ibrutinib (68%) of patients originally randomized to ofatumumab. In fact, after adjusting for the crossover, ibrutinib arm retained significant OS benefit. Lastly, the rate of patients still on ibrutinib decreased to 22% (from 46% at 4 years),[3] with disease progression (37%, including 10% of patients with evidence of Richter's transformation) and adverse events (AEs, 16%) being the major reasons of discontinuation.

Richter's syndrome (RS) occurring during ibrutinib treatment warrants some special considerations. RESONATE population was heavily pre-treated (median three prior treatment lines) and more than half of patients carried *TP53* mutation, which is one the most recurrent genetic risk factor for RS. Moreover, RS occurred early in the course of ibrutinib treatment: 8/20 occurring in the first and 10/20 during the second and third. This pattern parallels that of studies with novel agents in this setting, suggesting the presence of unrecognized transformation foci before treatment initiation. Richter's transformation events were reported also in idelalisib-rituximab (with apparent lower rate)[7] and venetoclax-rituximab treated patients,[9] as well. Type of treatments per se does not appear to affect the risk of RS, while the burden of previous treatment does.[10]

Beside efficacy, long-term follow-up of studies with novel agents provide information on late toxicities. In this respect, the safety profile of ibrutinib in the present final analysis remained largely consistent with earlier reports, with overall and grade ≥ 3 AEs rate decreasing over time, except hypertension. Note, no new sign of unexpected toxicity emerged with infections (grade ≥ 3 45%, including 21% pneumonia events), atrial fibrillation (12%, any grade) and major hemorrhage (10% being the most relevant AEs. Cytopenias and infections seem to be largely associated to the burden of previous treatments.[11] This pointed out the need of a careful monitoring and appropriate institution of anti-infective prophylaxis in this setting.

For more than 80% of patients progressing under ibrutinib without Richter's transformation, specific resistance mechanisms related to development of recurrent single base mutation of direct (BTK C481S) and downstream targets of ibrutinib (PLCG2 R665W and L845F) have been detected.,[12,13] This highlights that the clonal evolution is not abrogated by ibrutinib, being qualitative different but quantitatively similar to clonal evolution under chemo-immunotherapy.[13,14] Future studies will address if adding or early switching to potential pre-emptive targeted treatment (after acquisition of ibrutinib-resistance mutations) would be able to prevent overt clinical progression.

Many alternative second generation BTKi (acalabrutinib and zanubrutinib), specifically designed to offer enhanced BTK selectivity, are currently in advanced stages of clinical evaluation. Although preclinical and clinical data suggest a lower off-target toxicity, it is unlikely that these agents would overcome ibrutinib resistance. Acalabrutinib demonstrated good tolerability and high response rate (81%) in r/r CLL patients who were intolerant to ibrutinib, and may represent an option in this specific setting.[15] Randomized trials of acalabrutinib and zanubrutinib against ibrutinib in r/r CLL patients are currently underway.

The most effective alternative treatment option in r/r CLL is represented by the first-in-class BCL2 inhibitor venetoclax, which demonstrated high response rate in high-risk patients (del17p), even in patients pre-treated with ibrutinib or idelalisib.[16] Differently from ibrutinib, a portion of patients treated with venetoclax were able to achieve bone marrow MRD negativity, and to discontinue treatment without losing the response. The most impressive results came from the large phase III MURANO trial, which evaluated venetoclax (administered for a fixed time of maximum 2 years) in combination with rituximab vs BR in r/r CLL patients. With 36 months of median follow-up, 71.4% of patients on venetoclax plus rituximab remained free from progression, with only 14% receiving subsequent therapy. In addition, more than 60% of patients achieved undetectable MRD, which resulted highly predictive for PFS at 10 months after stopping therapy (97.6% vs 64%). However, preliminary genetic mechanisms of resistance to venetoclax involving BCL2 specific mutations[17] and other molecular aberrations[18] have been already reported.

Considering the different mechanisms of actions and non-overlapping toxicities, it is not surprising that ibrutinib and venetoclax have been tested early in combination with the aim to reduce the acquisition of resistance and to exploit the possibility of institute timely-defined treatment strategies, eventually guided by MRD response. Preliminary results applying this approach, both in r/r[19] and untreated setting,[20] are highly encouraging, showing impressive PFS and MRD results as well as favorable tolerability profile, fostering a further improvement in standard of treatment.

In conclusion, final results of RESONATE study consolidate a large body of knowledge about long-term continuous administration of ibrutinib in r/r CLL patients, confirming substantial durable benefit even in heavily pre-treated high-risk population. It must be remembered, however, that ibrutinib in the relapsed setting is obviously no longer an option in patients who are receiving the drug as first line treatment that are anticipated to rapidly increase soon. In fact, a growing fraction of standard risk patients will be likely treated soon with first line ibrutinib based on results of randomized trials, demonstrating unequivocally better outcome over chemo- (chlorambucil)[21] or chemo-immunotherapy (BR)[22] in elderly and even in young population. The only exception is the group of young fit patient with IGHV mutated disease, who may be cured by aggressive chemo-immunotherapy (FCR).[23] Taking also this point into account, many important questions, however, remain to be addressed in the future clinical research in CLL: (a) which is the optimal sequence of treatments between ibrutinib and venetoclax (plus rituximab)? (b) will the combined administration (eventually with the adjunction of the novel more potent anti-CD20 antibody obinutuzumab) demonstrate to prevent acquisition of resistance mutation of both drugs? (c) Although mature follow-up of RESONATE sounds good, confirming that ibrutinib represented a real cornerstone in changing the treatment landscape of CLL, we have still a long way to go before establishing the best comprehensive strategy for the management of this so far incurable disease.

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