Chronic lymphocytic leukemia paradigm continues to be refined: news from the American Society of Hematology 2018 annual meeting

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There were a number of important updates and advances presented at the 2018 Annual American Society of Hematology meeting. With respect to the treatment of chronic lymphocytic leukemia, the American Society of Hematology 2018 was notable for an improved understanding of ibrutinib-based therapies. In fact, three prospective Phase III trials presented at the meeting indicate, in turn, that ibrutinib alone, ibrutinib plus rituximab, or ibrutinib plus obinutuzumab, should be the new standard of care for chronic lymphocytic leukemia. However, additional clinical trials comparing chemo-immunotherapy with ibrutinib alone or in association with an anti-CD20 monoclonal antibody remain a reasonable avenue to complete results of these large studies.

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A variety of encouraging data across various hematologic disease settings have been presented this year at the American Society of Hematology (ASH) 2018 annual meeting. In the realm of chronic lymphocytic leukemia (CLL), three landmark trials presented at the meeting have suggested, in turn, that ibrutinib alone, ibrutinib plus rituximab or ibrutinib plus obinutuzumab should be the new standard of care for chronic lymphocytic leukemia. However, additional clinical trials comparing chemo-immunotherapy with ibrutinib alone or in association with an anti-CD20 monoclonal antibody remain a reasonable avenue to complete results of these large studies.

The merit of Alliance A041202 is that of establishing ibrutinib as the new standard of care for older patients with CLL because of its superiority over the best available chemo-immunotherapy regimen, the association of bendamustine and rituximab (BR) [1].

In detail, patients with treatment-naïve, symptomatic CLL were randomized to receive ibrutinib alone (n = 182), ibrutinib plus rituximab (n = 182) or BR (n = 183). At the time of progression, patients receiving the combination of BR were allowed to cross over and receive ibrutinib. Patients had a median age of 71 years and two thirds were men. According to modified Rai staging, slightly more than half (54%) had high-risk disease, 53% had ZAP70-unmethylated disease (a surrogate for IGVH-unmutated status) and 27% had del(17p13.1) or del(11q22.3) disease. After a median follow-up time of 38 months, median progression-free survival (PFS) was not reached for patients in either ibrutinib group and was 43 months for patients in the BR group. The 2-year PFS was 87% with ibrutinib, 88% with the ibrutinib–rituximab combination and 74% for the BR combination (p < 0.001). With hazard ratios (HR) of 0.39 for ibrutinib and 0.38 for ibrutinib–rituximab combination compared with BR, patients in either ibrutinib group was at a greater than 60% reduced risk for progression or death. Of note, in the low-risk subgroup of patients who are IGVH-mutated, there does not appear to be a difference in PFS at this time between the three regimens; however, it will require a longer follow-up time to really be able to answer this question [1,4]. Many of the side effects related to ibrutinib occurred early with some persisting throughout treatment; 14% of patients on each ibrutinib arm discontinued therapy due to toxicity.
In young, fit, CLL patients, the combination of ibrutinib and rituximab was shown to beat the current gold standard represented by fludarabine, cyclophosphamide and rituximab (FCR), according to the results of E1912 study a large trial sponsored by the National Cancer Institute [2]. In this prospective Phase III study, patients were randomized to receive ibrutinib plus rituximab (n = 354) until progression or unacceptable toxicity for standard six cycles FCR (n = 175). Patients enrolled were ≤70 years of age and those with 17p deletion were excluded due to poor disease response to FCR. The median age of patients was 58 years and 41% were ≥60 years; 75% of patients had IGVH-unmutated disease.

After a median follow-up of 33.4 months the combination of ibrutinib and rituximab was associated with a 65% reduced risk for progression or death (HR), 0.35; 95% CI: 0.22–0.5; p < 0.00001). Three-year PFS was 89% for the ibrutinib–rituximab combination and 73% for FCR. Overall survival was also found to be superior for the combination of ibrutinib and rituximab (HR, 0.17; 95% CI: 0.05–0.54; p < 0.0003). The superiority of the combination of ibrutinib and rituximab was seen regardless of age, performance status, disease stage or presence or absence of del11q23. The superiority was also established for IGVH unmutated but not IGVH-mutated disease. Compared with ibrutinib plus rituximab, FCR was associated with a significantly higher incidence of grade 3/4 neutropenia (22.7 vs 43.7%), anemia (2.6 vs 12.0%), thrombocytopenia (2.9 vs 13.9%) and infectious complications (7.1 vs 19.0%) [2].

The third landmark trial presented at the 2018 annual ASH meeting was the industry sponsored ILLUMINATE study [3]. In this Phase III trial, patients older than 65 years or, if younger than 65, with Cumulative Illness Rating Score >6, creatinine clearance <70 ml/min and/or del(17p)/TP53 mutation were randomized to receive a combination of ibrutinib plus obinutuzumab or chlorambucil plus obinutuzumab. At a median follow-up of 31.3 months, ibrutinib plus obinutuzumab significantly prolonged PFS compared with chlorambucil plus obinutuzumab, with a 77% reduction in risk of progression or death (median NR vs 19 months). Also, the objective response rate was higher in the ibrutinib plus obinutuzumab arm versus the chlorambucil plus obinutuzumab arm (88 vs 73%) with complete response and complete response with incomplete blood recovery rates of 19 versus 8%, respectively. Depth of remission, as reflected by undetectable minimal residual disease (MRD) in blood and/or bone marrow, was greater in patients with ibrutinib plus obinutuzumab with 35% of patients showing undetectable MRD compared with 25% of patients with chlorambucil plus obinutuzumab [3].

The results from the ALLIANCE, E1912 and ILLUMINATE trials suggest that, based on the patient age, ibrutinib as a single agent or in association with rituximab should be a preferable option in the treatment of CLL [1–5]. The practical implications of these results are relevant. For instance, data of E1912 trial imply that FCR should be used less in young CLL patients [2]; however, FCR is still the most appropriate choice for patients with mutated IGVH disease (low risk). Long-term data from the FCR studies have shown that a proportion of low-risk patients have the potential for very long-term remission and even cure [6–8]. Whether data of noninferiority between the ibrutinib–rituximab arm versus ibrutinib as a single agent arm in older patients (Alliance A041202) are generalizable to the entire CLL population is not clear [1,4]. The FLAIR trial, a prospective, large Phase III study, is addressing the issue comparing four treatment regimens: FCR, ibrutinib–rituximab, ibrutinib–venetoclax and ibrutinib alone (Trial ID: ISRCTN01844152). Results of this ongoing study, when available, will provide a more definitive answer.

It should be noted that an important issue with ibrutinib is the undefined time of administration. In all Phase III studies presented at annual ASH meeting, ibrutinib was administered until disease progression or unacceptable toxicity [1–5]. If the aim is to limit the therapy of CLL to a fixed duration period, the achievement of deeper response, possibly characterized by undetectable MRD, becomes crucial [9]. From this perspective, the use of ibrutinib in association with drug able to increase the depth of response such as obinutuzumab (as in the ILLUMINATE trial) becomes a desirable option. This is a challenging issue for future studies.

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