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POSTER ABSTRACTS

642.CHRONIC LYMPHOCYTIC LEUKEMIA: CLINICAL AND EPIDEMIOLOGICAL

Minimal Residual Disease-Guided Combination of Ibrutinib and Venetoclax Compared to FCR in Untreated Patients with CLL of Intermediate Risk : Interim Results of MRD Kinetics in the Eradic Trial from the Filo Group

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With the emergence of targeted therapies, defining the best strategy for first-line treatment in chronic lymphocytic leukemia (CLL) patients has become challenging. The aim of the ERADIC phase 2 study was to compare the efficacy of a standard FCR regimen to that of an MRD-guided combination of ibrutinib and venetoclax (IV), in fit patients with CLL of intermediate risk defined by either unmutated *IGHV* status, 11q deletion or complex karyotype in the absence of *TP53* alteration. MRD was assessed in bone marrow (BM) or peripheral blood (PB) by flow cytometry. After a lead-in phase of ibrutinib as a single agent from month (M)1 to M3, the total duration of treatment with the IV combination was based on BM M9 MRD. If it was <0.01% (uMRD) at that time, treatment was continued for 6 additional months (M15) then stopped. If M9 BM-MRD was ≥0.01%, IV treatment was continued for 18 additional months (M27). BM-MRD was reassessed at that time-point in both arms. Additionally, PB-MRD evaluation was performed every 6 months.The primary endpoint will be the percentage of patients with BM uMRD at M27. Here, intermediate safety data and MRD kinetics (M9 to M21) are presented.
Between September 2019 and February 2021, 120 patients were randomized 1:1 between the two treatment arms. The median age was 59 [34-72] and 61 [34-74] year-old in the FCR and IV arms, respectively. Patient characteristics were well balanced between the 2 arms in terms of gender (male 72% FCR, 74% IV), PS ECOG 0-1 (59% FCR, 68% IV) and Binet stage (A, B and C 15%, 64%, 21% for FCR ; 8.5%, 59% and 32% for IV). An11q deletion was found in 20% and 24% of the cases in the FCR and IV arms, respectively and all patients but one had unmutated *IGHV.*
At the time of data cut-off for this analysis, the median follow-up was 29.7 months [range: 25.3- 32.8]. Sixty-three serious adverse events (SAE) have been reported so far, 32 in the FCR arm and 31 in the IV arm. In the FCR arm, the most frequent SAE were infections (N=12 including 4 COVID-19), febrile neutropenia (N=5) biological tumour lysis syndrome (N=3), and secondary malignancies (N=2, including 1 myelodysplastic syndrome and 1 acute myeloid leukemia). In the IV arm, the most frequently reported SAE were infections (N=8 including 4 COVID-19), cardiovascular events (N=7), biological tumour lysis syndrome (N=5), acute renal failure (N=2) and secondary malignancies (N=2, including 1 colorectal cancer and 1 skin basal cell carcinoma). Four grade 5 adverse events were reported, respectively 2 in the FCR arm (1 septic shock and 1 AML) and 3 in the IV arm (2 sudden deaths and one death COVID-19-related).
In the FCR arm (intention to treat [ITT] n=57), 59.6% of the patients had BM-uMRD at M9. The kinetics of PB-uMRD was 68% at M9, 65% at M15 and 52% at M21. In the IV arm (ITT n=54), the rate of BM-uMRD at M9 was much lower at 33%. PB-MRD kinetics showed levels of uMRD of 52%,70% and 67% at M9, M15 and M21 respectively.
In terms of response, CR/CRi rates were 56% for the FCR arm and 66% for the IV arm. Three patients progressed in the FCR arm (1 at M9 and 2 at M15) and 2 in the IV arm, at respectively M13 and M39. Among the 13 patients who achieved BM-uMRD at M9 in the IV arm, 10 have indeed stopped according to the protocol and only 1 has progressed at M39.
In conclusion, monitoring MRD kinetics in this trial showed a stable level of PB-uMRD in the FCR arm yet a clear increase in the IV arm between M9 and M15. Toxicity remains an important parameter in both treatment arms that will have to be taken into account when determining whether treatment should be continued because of detectable BM-MRD at M9 (IV arm). Upcoming data of the primary enpoint analysis at M27 will be of great interest to try to determine the best strategy.

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