(S804) HIGH RATE OF COMPLETE RESPONSE BUT MINIMAL RESIDUAL DISEASE STILL DETECTABLE AFTER FIRST-LINE TREATMENT COMBINING OBINUTUZUMAB AND IBRUTINIB IN CHRONIC LYMPHOCYTIC LEUKEMIA (CLL): ICLL07 FILO TRIAL

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Abstract: S804

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Background

Achievement of CR with undetectable residual disease (uMRD) may be associated with a longer survival in CLL. New therapeutic agents have recently emerged, including new anti-CD20 antibodies and agents targeting BCR signaling.

Aims

We conducted a multicenter phase II trial aimed to explore the efficacy of an induction treatment associating obinutuzumab and ibrutinib, followed by immunochemotherapy only in case of PR or detectable MRD. The primary objective of this study was to obtain 30% of CR (according to IWCLL 2008 guidelines) with uMRD in BM at month 16.

Methods

FIT treatment-naïve patients with active Binet stage A to C CLL and no *TP53* mutation/deletion were eligible if CIRS score was < 7 and ECOG 0 or 1. Induction treatment consisted of 6 courses of obinutuzumab (1000 mg D1, D8, D15 for cycle 1 and D1 for cycles 2 to 6) along with ibrutinib 420 mg daily for 9 months. A first assessment of response was performed at month 9, including CT-scan, bone marrow (BM) biopsy and peripheral blood (PB) and BM MRD testing. Patients in CR with uMRD ($<10^{-4}$, by 8-color cytometry) received ibrutinib alone for 6 additional months whereas the others received 4 courses of fludarabine + cyclophosphamide and obinutuzumab while continuing ibrutinib. Patients with stable or progressive disease were taken off study. Final evaluation of response was performed at Day 1 Month 16.

Results

Between November 2015 and May 2017, 135 planned patients were enrolled including 89 males and 46 females; 7% were Binet stage A, 67% stage B and 26% stage C. The median age was 62 years (range, 35-80 years) and 57% have an unmutated mutational status. Patients with del11q, del13q and trisomy 12 were 20%, 51% and 22% respectively; and 13% had a complex karyotype (>3 abnormalities).

A total of 37 serious AEs were observed with 24 related to the treatment. Two patients died during the study at the cut-off date, one sudden death and one of brain hemorrhage due to accidental fall not reliable to therapy.

Among the other AE, 57% of the patients have presented, at least one G3-4 toxicity along the 6 cycles. Hematological toxicity was neutropenia (24% G3-4) and mainly during cycle 1 anemia and thrombocytopenia for respectively 6% and 31% of the patients. Infusion Related Reaction (IRR) only occurred during cycle 1 at day 1 for 69.5% of the patients (8% G3). Other significant toxicity was digestive (nausea, vomiting and diarrhea) occurring in 35% of the patients (grade 1 and 2) but only during cycle 1.

At Month 9, 92% of the patients had received the 8 planned infusions of obinutuzumab; Ibrutinib dosage was reduced for 4 patients and definitively stopped in 3 out of them due to AE (atrial fibrillation, atrial flutter and neutropenia).

One hundred twenty three are evaluable so far for the response at M9. The ORR was 100% with 41% in CR (IWCLL criteria) and 59% in PR. Only 16 patients (12.5%) had uMRD in PB and BM including 9 patients in CR and 7 in PR (2 bone marrow not evaluable but normal CT scan; 5 patients with lymph nodes > 15 mm respectively: 15, 17, 19, 20 and 21).

Conclusion

These preliminary results indicated that this 9 month « chemo-free » induction is associated with a high CR rate (41%) without excess of toxicity. However, the majority of the patients required subsequent immuno-chemotherapy because of detectable BM MRD.

Session topic: 6. Chronic lymphocytic leukemia and related disorders - Clinical

Keyword(s): Chronic Lymphocytic Leukemia, Complete Remission, MRD