Poster #: 1429

XXI IWCLL International Workshop on CLL

Orelabrutinib, fludarabine, cyclophosphamide and obinutuzumab (OFCG) for first-line treatment of chronic lymphocytic leukemia: a multicenter, investigator-initiated phase II trial (cwcll-001 trial)

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OBJECTIVES

- This study evaluated the efficacy and safety of the orelabrutinib, fludarabine, cyclophosphamide, and obinutuzumab regimen as the first-line treatment for patients with CLL/SLL without restriction by TP53 aberrations[del(17p) and/or TP53 mutation] and IGHV status.

CONCLUSIONS

- The OFCG regimen showed promising efficacy and a favorable safety profile as a first-line treatment for previously untreated patients with CLL/SLL, which indicated that this time-limited treatment regimen would provide a new choice for patients, especially those with mutated IGHV.

INTRODUCTION

- Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) are incurable B-cell malignancy with a heterogeneous clinical course despite advancements in therapies including targeted agents. Ibrutinib combined with fludarabine, cyclophosphamide, and rituximab or obinutuzumab (iFCR or iFCG) in patients with CLL/SLL as first-line therapy demonstrated remarkable efficacy[1][2]. Orelabrutinib is a novel and highly selective second generation irreversible BTK inhibitor with remarkably less off-target inhibition. This study evaluated the efficacy and safety of the orelabrutinib, fludarabine, cyclophosphamide, and obinutuzumab regimen as the first-line treatment for patients with CLL/SLL without restriction by TP53 aberrations[del(17p) and/or TP53 mutation] and IGHV status.

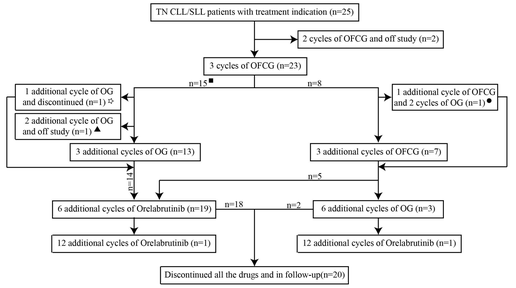
METHODS

- This is a multicenter, open-label, non-randomized phase II study for previously untreated patients with CLL/SLL. Eligible patients were 18-65 years old with ECOG performance status 0-1. Patients received single-agent oral orelabrutinib during a 7-day lead-in period, followed by OFCG regimen for three 28-day cycles. Patients who achieved BM-uMRD4 (undetectable MRD<10^{-4}) by FCM after 3 cycles of OFCG therapy would receive 3 cycles of OG therapy, and other patients would receive additional 3 cycles of OFCG therapy. After six cycles of therapy, patients who achieved BM-uMRD4 would receive 6 cycles of orelabrutinib monotherapy, and other patients would receive 6 cycles of OG therapy. After 12 cycles of therapy, patients who achieved BM-uMRD4 would discontinue all therapy, and others would receive 12 cycles of orelabrutinib monotherapy. The primary endpoint was the rate of BM-uMRD4 after 6 cycles by FCM. Exploratory endpoints included the rates of PB-uMRD6 (undetectable MRD<10^{-6}) and BM-uMRD6 by NGS.(Figure 1)

RESULTS

- Twenty-five patients with CLL were enrolled from May 30, 2022, to Jun 30, 2023. At the data cut-off (December 31, 2024), 2 patients voluntarily discontinued the study after receiving 2 cycles of OFCG. 23 patients completed 3 cycles of OFCG therapy and 13 of them achieved BM-uMRD4. After 6 cycles of treatment, 95.2% (20/21) of patients achieved PB-uMRD4 and 86.4% (19/22) achieved BM-uMRD4 by FCM. 22.7% (5/22) of patients achieved CR/CRi with BM-uMRD4 after 3 cycles of treatment, 59.1% (13/22) after 6 cycles of treatment and 72.7% (16/22) after 12 cycles of treatment. 61.9% (13/21) of patients achieved PB-uMRD6 and 57.1% (12/21) of patients achieved BM-uMRD6 after 6 cycles of treatment and changed to 79.0% (15/19) and 55.0% (11/20) after 12 cycles of treatment. (Figure 2)(Figure 3)

Figure 1. Trial profile



✩One patient only recieved 1 cycle of OG due to recurrent Thrombocytopenia(AE4). ▲One patient was off study and died due to COVID-19 infection. ●One patient discontinued FC due to persistent COVID-19 infection. ■Including 2 patients who did not achieve BM-uMRD4 discontinued FC due to recurrent Thrombocytopenia(AE4), Neutropenia(AE3) and ALT/AST increased(AE3).

- The median PFS and OS were not reached with a 2-year PFS rate of 96% (95% CI: 89%-100%) and a 2-year OS rate of 96% (95% CI: 89%-100%). (Figure 4) Compared with patients with unmutated IGHV, patients with mutated IGHV are more likely to achieve PB-uMRD4 (OR=0, 95%CI: 0-0.4671; *P*=0.0167) and BM-uMRD4 (OR=0, 95%CI: 0-0.2268; *P*=0.0016) at C4D0. Significant differences in BM-uMRD6 at C7D0 (OR=0, 95% CI: 0-0.22; *P*=0.0011) and C13D0 (OR=0.06, 95% CI: 0.01-0.61; *P*=0.02) were also observed between IGHV mutated and unmutated patients.

Figure 2. Swimmer plot of treatment duration and response

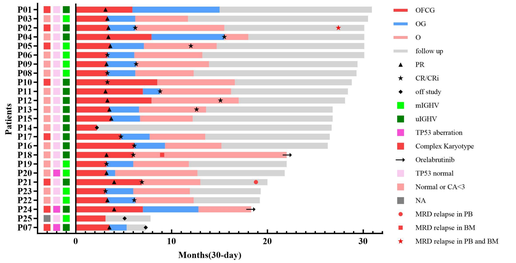


Figure 2. *P01, P04, P10, P12, P18, P21, P24 received 6 cycles of OFCG. P11 received 4 cycles of OFCG and discontinued FC due to persistent COVID-19 infection. P16 and P17 only received 3 cycles of OFCG. The scheduled time for therapy was put off due to COVID-19 infection and increased ALT/AST (AE3). P20 discontinued G after 3 cycles of OFCG and 1 cycle of OG due to recurrent thrombocytopenia (AE4).

- Most AEs were mild and manageable with dose interruptions or supportive care during the 12 treatment cycles. The most common grade 1-2 AEs were anemia (25/25, 100.0%) and nausea/vomiting (18/25, 72.0%). Neutropenia (20/25, 80.0%) and thrombocytopenia (15/25, 60.0%) were the most common grade 3-4 AEs.(Table 1)

Figure 3. Response assessment

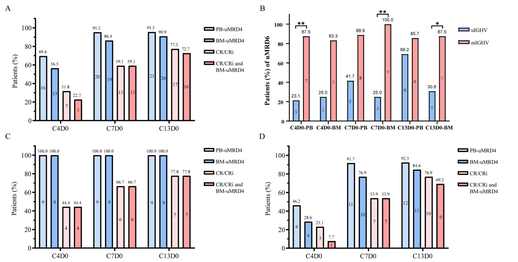
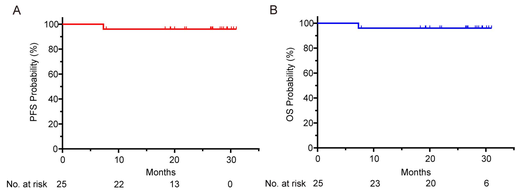


Figure 3. A) Response assessment and MRD in 24 patients*; B) MRD by NGS (sensitivity of 10 $^{-6}$) in 23 patients with IGHV mutated and with IGHV unmutated, including TP53 aberration; C) Response assessment and MRD in 9 patients with IGHV mutated regardless of TP53 aberration; D) Response assessment and MRD in 14 patients with IGHV unmutated regardless of TP53 aberration. * One patient withdrew from the study after 2 cycles, and the other patient withdrew after 2 cycles but had PB-MRD data at C4D0.

Figure 4. Kaplan-Meier outcome estimates



\Figure 4. A) progression-free survival for 25 patients; B) overall survival for 25 patients.

Table 1. Adverse events within the 12 cycles in the safety analysis set

	Grade 1-2	Grade 3-4
Hematological adverse events, n (%)		
Anemia	25 (100)	0 (0)
Neutropenia	5 (20·0)	20 (80·0)
Thrombocytopenia	9 (36·0)	16 (64·0)
Febrile neutropenia	-	4 (16·0)
Non-hematological adverse events, n (%)		
Nausea/Vomiting	18 (72·0)	0 (0)
Infusion related reaction	12 (48·0)	5 (20·0)
ALT/AST increased	13 (52·0)	3 (12·0)
Malaise	9 (36·0)	2 (8·0)
Infection*	1 (4·0)	7 (28·0)
Arthralgia	6 (24·0)	1 (4·0)
Skin rashes	5 (20·0)	1 (4·0)
Diarrhea	5 (20·0)	1 (4·0)
Purpura	5 (20·0)	0 (0)
Pruritus	4 (16·0)	1 (4·0)
Tumor lysis syndrome	-	4 (16·0)
Pain	2 (8·0)	2 (8·0)
Hypertension	0 (0)	1 (4·0)
Shingles	1 (4·0)	0 (0)

Table 1. n=25. A total of 22 (88.0%) patients were infected with COVID-19. Abbreviations: ALT/AST, alanine aminotransferase/aspartate aminotransferase.

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ACKNOWLEDGMENTS

THIS STUDY WAS SUPPORTED BY FUNDING INCLUDING 82170166, 82370193, 82170186, KY202305, YNRCQN035, BE2023775, ZDXK202209, DL202406.