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A Prospective Multicenter Study of FCR Alternating with Ibrutinib in Treatment-naive Patients with Chronic Lymphocytic Leukemia (CLL)

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OBJECTIVES

- This regimen aims to achieve deep remissions in CLL patients while enhancing tolerability and establishing a fixed treatment duration.

CONCLUSIONS

- The HAMBURGER regimen showed remarkable efficacy, inducing durable remissions with manageable toxicity. The high CR rate of 66% and CR-uMRD rate of 38% are particularly impressive, especially considering the fixed treatment duration. This innovative approach presents a cost-effective and patient-centric alternative to continuous BTKi therapy, especially in healthcare settings with limited access to newer treatment agents. These findings support the potential of the HAMBURGER regimen as a front-line treatment option for appropriately selected CLL patients, including those with high-risk features.

INTRODUCTION

BTK inhibitors, such as ibrutinib, have propelled chronic lymphocytic leukemia (CLL) into the era of targeted therapy[1]. Nevertheless, continuous treatment with these agents not only leads to a progressive increase in resistance but also escalates treatment costs. On the other hand, the FCR regimen, consisting of fludarabine, cyclophosphamide, and rituximab, holds curative potential for CLL[2-3]. However, its clinical application is significantly hampered by severe toxicity and long-term risks[4-5]. To address these challenges, we developed the HAMBURGER regimen, a novel time-limited, alternating treatment approach combining ibrutinib with three cycles of FCR.

METHODS

- This multicenter, single-arm, phase II clinical trial (NCT03980002) enrolled 50 previously untreated CLL patients aged between 18 and 65 years.
- Primary endpoint : CR after induction therapy.
- Secondary endpoints: overall response rate (ORR), uMRD rate, progression-free survival (PFS), overall survival (OS), and safety assessment.

RESULTS

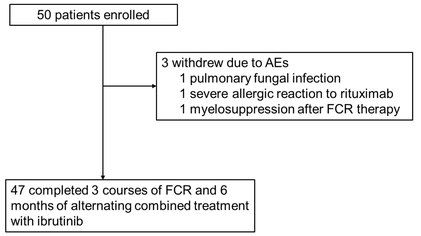
Tabel 1. Baseline characteristics

	Number (%) or median [range]
Age, years	57 (37-65)
Gender, male	36/50 (72)
IGHV unmutated	18/47 (38.2%)
TP53 del/mutated	4/50(8%)
Complex karyotype	8/43 (18.6%)
11q(ATM) deletion	3/49 (6.1%)
13q(RB1) deletion	13/49 (26.5%)
trisomy 12	13/49 (26.5%)
MYD88 mutation	14.9% (7/47)
SF3B1 mutation	12.8% (6/47)
CLL-IPI	
Low	11/50 (22)
Intermediate	23/50 (46)
High/very high-risk	16/50 (32)

Figure 1. Study design

FCR:
F (Fludarabine): 25mg/m2·d, d1-3;
C (Cyclophosphamide): CTX 250mg /m2·d, d1-3;
R (Rituximab): 375mg/m2 d0 (first course), 500mg/m2 d0 (subsequent courses)
Ibrutinib: 420mg/d

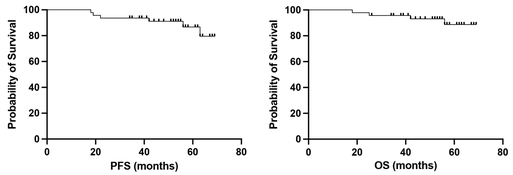
Figure 2 Study Flow



Survival

- With a median follow-up of 55 months, the 5-year PFS and OS rates were 86.7% and 88.7%, respectively.

Figure 3. Survival outcomes



Tabel 2. PFS and OS for all and subgroup patients

Subgroup		5-Year PFS (%)	P-value	5-Year OS (%)	P-value
IGHV Mutation Status (n=44)	Mutated (n=26)	80.8		84.1	0.561
	Unmutated (n=18)	94.4		94.4	
TP53 Abnormality Status (n=47)	TP53 Abnormal (n=4)	75.0	0.527	75.0	0.211
	TP53 Normal (n=43)	87.3		89.5	
IGHV Mutation Status in Non-TP53 Abnormal Patients (n=40)	Mutated (n=25)	79.7	0.342	83.1	0.190

Response Rate

Among the 4 patients with TP53 abnormalities, 3 achieved partial remission (PR) and 1 achieved CR with uMRD after induction therapy, and 2 patients achieved CR during the maintenance therapy phase.

Table 3. Response assessment over time

Number of patients (%)	Post induction (n=47)			
	All pts (n=47)	IGHV Mutated (n=26)	IGHV Unmutated (n=18)	P value
ORR	46（97.9）			
CR	31（66.0）	19(73)	10 (55.6)	0.228
PR	15（31.9）	6(23.1)	8(44.4)	0.135
BM-uMRD4	20（42.6）	14 (53.8)	4 (22.2)	**0.036**
CR-BM uMRD4	18（38.3）	12 (46.2)	4(22.2)	0.105
CR-PB uMRD4	21（44.7）	12 (46.2)	7(38.9)	0.632

Safety

No therapy-related myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) cases were reported, and ibrutinib dosage reduction was required in only two patients due to tolerable toxicities.

Table 3. Safety profile

Toxicity Type (n=50)	Grade 1-2	Grade 3	Grade 4
Hematologic Toxicity			
Thrombocytopenia	16 (30.8%)	4 (7.7%)	0
Lymphocytopenia	15 (30%)	6 (12%)	6 (3%)
Neutropenia	6 (11.5%)	13 (25.0%)	0
Leukopenia	16 (32%)	9 (18%)	2 (5%)
Non-Hematologic Toxicity			
Nausea	28 (56%)	0	0
Infusion-related reaction	18 (36%)	0	0
Fatigue	6 (12%)	1 (2%)	0
Rash	6 (12%)	–	0
Hemorrhage	5 (10%)	–	0

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DISCLOSURES

The authors declare no competing financial interests.