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Real-World Evidence on Therapeutic Strategies and Treatment-Sequencing in Patients with Chronic Lymphocytic Leukemia

51st General Assembly of ERIC Members at ELN Symposium 2022
Tuesday 15th March 2022, Mannheim, Germany

Aim of the study

We designed a study focusing on treatment sequencing in patients with CLL aiming to:

- Compare the outcome of patients treated with **chemoimmunotherapy (CIT)** combinations in 1st line vs those receiving **Bruton's tyrosine kinase inhibitors** (BTKi)
- Characterize the **efficacy** and **tolerability** of **venetoclax-based regimens**
- Assess the impact of **treatment sequencing** of chemo-free options (venetoclax after BTKi and vice versa)

Patient Characteristics

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Patient characteristics (n=9173)			
Median age (years, range)		67 (27-92)	
Median follow up (months, IQR)		78 (48-120)	
Gender		Male/Female	6008/3165
Status at last follow up	**Alive**	5870 (64.0%)	
	Dead	3229 (35.2%)	
	Lost follow-up	74 (0.8%)	
Total lines of treatment		1	58,3%
		2	19,4%
		3	12%
		≥4	10,3%
Novel agents (at any line)		BTKis	1860 (20.2%)
		Venetoclax	631 (6.9%)
		Idelalisib	447 (4.9%)

1st line treatment

First line treatment		
	ORR	**CR/CRi**
CIT (n=5465)	87%	49,9%
BTKi (n=517)	87.7%	27,3%
Venetoclax +/- antiCD20 (n=100)	90.3%	68.1%

Venetoclax:

9	Venetoclax monotherapy
73	Venetoclax+ Obinutuzumab
15	Venetoclax + Rituximab
2	Venetoclax+ Obinutuzumab+ Ibrutinib
1	Venetoclax+ Obinutuzumab + Acalabrutinib

1st line treatment

BTKi

- *Baseline characteristics:*
  - *TP53* aberrations: 32.7% [del(17p) 27.6%, *TP53* mutation 26.3%]
  - unmutated IGHV: 69%
- *Discontinuation*: 136 (26.3%)/ median of 1.2 years (0.07-5.98). Main reasons were
  - toxicity (40.5%)
  - failure (26.2%)

Venetoclax

- *Baseline characteristics:*
  - *TP53* aberrations: 15% [del(17p) 10%, *TP53* mutation 11%]
  - unmutated IGHV: 52%
- *Discontinuation*: 14 (16.4%) median of 1 year (0.9-1.2). Main reasons were
  - toxicity (28.6%)
  - failure (14.3%)

2nd line treatment

Second line treatment patterns		
Before 2014 (n=1086)	**CIT**	**865 (79.7%)**
	Alemtuzumab	55 (5%)
	Other	166 (15,3%)
After 2014 (n=984)	**BTKi**	**415 (42.1%)**
	Venetoclax +/- antiCD20	93 (9.5%)
	Idelalisib	70 (7.2%)
	CIT	315 (32%)
	Alemtuzumab	50 (5%)
	Other	41 (4,2%)

2nd line treatment

Venetoclax after 1st line treatment				
	ORR	CR/CRi	Discontinuation	
			Progression	Toxicity
2nd line treatment (n=170)	94%	58%	20.6%	17.6%
≥ 3rd line treatment (n=361)	71.5%	30.5%	33.6%	21.8%

2nd line treatment: 76 Venetoclax monotherapy, 94 Venetoclax + Rituximab

≥ 3rd line treatment: 253 Venetoclax monotherapy, 108 Venetoclax + Rituximab

Treated with both BTKi and venetoclax

Sequential BTKi → venetoclax and vice versa (n=199)			
	ORR	**CR/CRi**	**PR**
BTKi → venetoclax (n=175)	73.7%	30.8%	42.9%
Venetoclax → BTKi (n=24)	66%	20.8%	45.2%

Patients with *TP53* aberrations

Patients with *TP53* aberrations (n=1075)			
	ORR	**CR/CRi**	**PR**
CIT (n=694)	68.7%	28.3%	40.4%
BTKi (n=171)	86.5%	22.2%	64.3%
Venetoclax +/- antiCD20 (n=15)	91%	45.5%	45.5%

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Conclusions

- Major shift in treatment patterns before and after the introduction of novel targeted agents
- Evident safety and efficacy of novel agents, even in high-risk CLL
- Patients who failed on venetoclax can be rescued with a BTKi and vice versa

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Other malignancies in the history of CLL– a retrospective, multicenter study by ERIC, in HARMONY

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Background

- Other malignancies occurring in patients with CLL are a well-known, but insufficiently investigated area

- The purpose of the present project is to determine the incidence and prevalence of other malignancies both preceding or following CLL diagnosis and their impact on the disease course and overall survival (OS).

Study design

- Multicentric retrospective analysis on real-world evidence (RWE) patient data

- Analysis of other malignancy incidence in a population of patients with CLL in relation to the disease itself and CLL therapy

Endpoints of the study

Primary

Descriptive statistics of other malignancies in patients with CLL

Secondary

- Patient characteristics (gender, age, CLL prognostic factors)
- CLL therapy duration and sequence of therapies in patients with CLL with other malignancies
- Overall survival of patients with CLL and other malignancies

Inclusion criteria

- Data from consecutive set of patients with CLL
- Clinical and laboratory data available
- Patients diagnosed with CLL between years **2000 and 2016**

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Data collection

Variables:

- Diagnosis CLL/SLL/MBL
- Demographics (age, gender)
- CLL data (date of diagnosis, staging, FISH, IGHV, treatment, treatment response, death, reason of death)
- Other malignancy (type, date of diagnosis)

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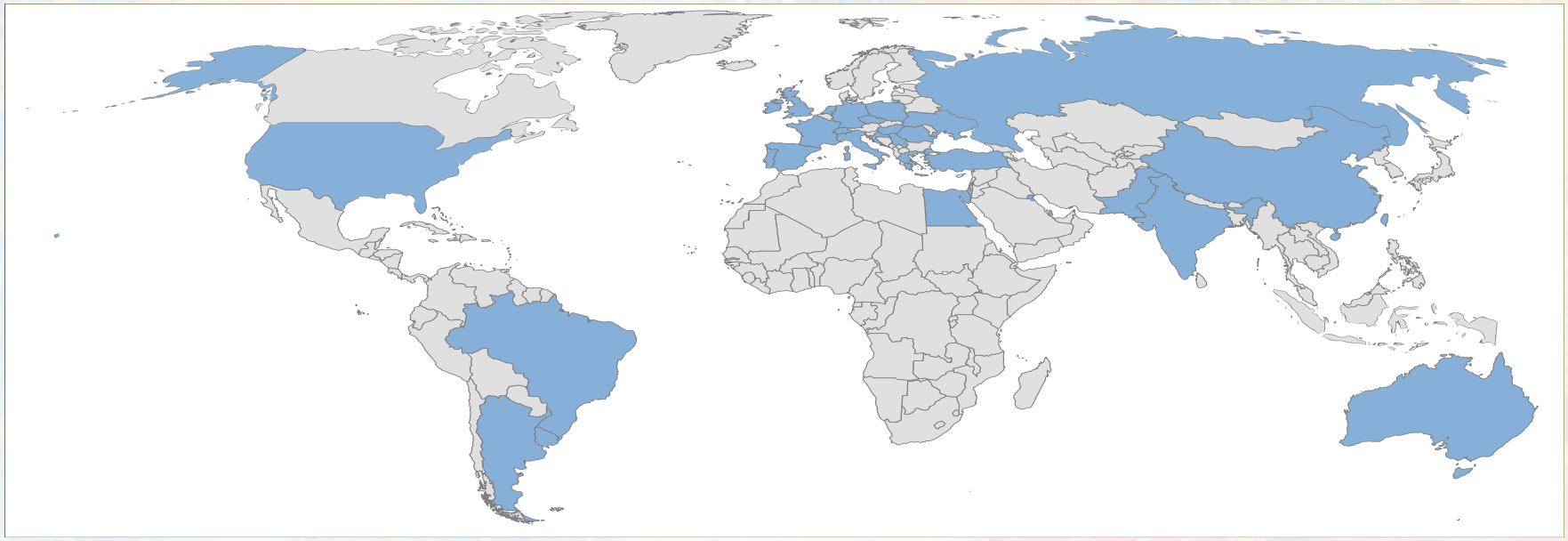
Participating sites

Number of sites	86
Number of countries	33
Total number of patients diagnosed 2000-2016	>18.000
Median age at diagnosis (range)	66 years (27-92)
Median follow-up (range)	77 months (49-199)



Patient Characteristics

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Patient characteristics (n=13,808)		
Sex	Male/ Female	61.7%/38.3%
Binet stage at diagnosis	A	74%
	B	16%
	C	10%
del(11q)	Positive/ Negative	14.1%/85.9%
del(17p) and/or TP53 mutation	Positive/ Negative	10.8%/89.2%
IGHV gene status	Mutated/ Unmutated	52%/48%
Treatment status	Treated/ Untreated	53.6%/46.4%
Total lines of treatment	1	59.3%
	2	19.3%
	3	11%
	≥4	10.3%
Therapies received (at any line)	CIT	71.5%
	CIT +novel agents	21.3%
	Only novel agents	7.2%

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Results

Other malignant neoplasms in the history of CLL		
All other malignancies besides CLL (excluding Richter's transformation)	2919	21,1%
Richter's transformation	390	3,8%
Timing of other malignancy in relation to CLL diagnosis		
Before CLL diagnosis	980	7,1%
After CLL diagnosis	1939	14%

Other malignant neoplasms –after CLL diagnosis

Other hematological neoplasms diagnosed after CLL (2,3%)		
MDS/AML	98	31%
Other lymphoid malignancies	155	49%
Other	64	20%
Non- hematological neoplasms diagnosed after CLL (11,7%)		
Non-melanoma skin cancer	502	31%
Prostate cancer	211	13%
Colon cancer	176	10,9%
Breast cancer	96	5,9%
Bronchus/lung cancer	139	8,6%
Melanoma	94	5,8%

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Non-hematological neoplasms diagnosed after CLL-CLL-directed treatment

- Breast, prostate, colon were significantly more prevalent in untreated patients ($p<0.01$)
- The follow-up of treated vs untreated patients did not differ significantly
- Only NMSC was significantly more prevalent ($p=0.007$) in treated patients

MDS/AML in patients with CLL

Subgroups with increased incidence of MDS/AML	p value
Unmutated IGHV	0.05
del(11q)	0.009
Treated patients	<0.001
≥3 treatment lines	<0.01
Treated with FCR	<0.001

*On multivariate analysis, treatment with FCR was the only significant predisposing factor

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Conclusions

- The development of other hematological malignancies, especially MDS/AML, was associated certain biological features as well as treatment for CLL.
- A highly relevant risk was identified for patients treated with CIT, particularly the FCR regimen.
- Solid tumors appeared unaffected by treatment administration, indicating that solid tumor occurrence in patients with CLL is mainly an age-related phenomenon.

THANK YOU

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THANK YOU VERY MUCH FOR YOUR ATTENTION

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