Fine-tuning front-line therapy in chronic lymphocytic leukemia

News from ASH 2019

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Received: 1 April 2020 / Accepted: 28 April 2020 / Published online: 19 May 2020
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Summary A deeper understanding of disease biology and the advent of targeted drugs have implemented chemotherapy-free treatment options in chronic lymphocytic leukemia (CLL). With consistently superior outcome data and good tolerability, the Bruton's kinase inhibitor ibrutinib as well as the B-cell lymphoma 2 inhibitor venetoclax +/- CD20 antibody have recently been licensed for first-line treatment independently of TP53 status and are currently recommended as therapy of choice in most patient subgroups according to international management guidelines. Survival curves, however, have not reached a plateau and relapse due to acquired resistance or drug intolerance remain major hurdles in CLL treatment. Clinical trials currently focus on the most promising combinations and sequences of highly effective targeted drugs aimed at avoiding drug resistance by further enhancing eradication of minimal residual disease and optimizing drug tolerability. This brief review provides an update on the recently presented clinical trial data in first-line CLL at ASH 2019 and discusses clinically relevant obstacles to overcome.

Keywords First-line · Ibrutinib · Acalabrutinib · Venetoclax · Obinutuzumab

Introduction

Novel scientific insights into disease biology have facilitated introduction of targeted therapies to the treatment landscape of chronic lymphocytic leukemia

(CLL). In particular, the Bruton's kinase (BTK) inhibitor ibrutinib and the B-cell lymphoma 2 (BCL2) inhibitor venetoclax +/- CD20 antibody have become front-line treatment of choice in vast parts of the CLL patient spectrum based on consistently superior outcome and tolerability data when compared to chemoimmunotherapy (CIT) [1–4]. Nonetheless, relapse due to acquired resistance and drug intolerance remain major hurdles in patient management [5].

Current clinical trials focus on the most promising sequences and combinations of targeted drugs to prevent resistance formation by enhancing eradication of minimal residual disease (MRD) and optimize drug tolerability. This short review provides an update on currently ongoing first-line clinical trials in CLL presented at ASH (American Society of Hematology) 2019 and discusses clinically relevant obstacles to overcome.

Targeting Bruton's tyrosine kinase

Aberrant B-cell receptor (BCR) signaling plays a key pathogenetic role in CLL by regulating several pathways essential for B-cell proliferation and apoptosis [6]. BTK functioning downstream of BCR can be selectively targeted and has provided the framework for the striking efficacy seen with the BTK inhibitor ibrutinib in CLL treatment [7].

At ASH 2019 follow-up the ECOG-ACRIN E1219 phase 3 study investigating ibrutinib *plus* the CD20 antibody rituximab versus CIT with fludarabine, cyclophosphamide and rituximab (FCR) in treatment-naïve fit CLL patients without deletion 17p was presented and confirmed prolonged progression-free survival (PFS) at 3 years with ibrutinib plus rituximab, including at least equal efficacy even in the subgroup of patients with unmutated immunoglobulin heavy-chain genes (IGHV). The 3-year overall survival (OS)

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Table 1 Efficacy of targeted drugs in treatment-naïve CLL patients in selected randomized controlled clinical trials presented at ASH 2019

Trial	Regimen	<i>n</i>	Age ^a	ORR	CR	PR	uMRD	PFS	OS
ECOG-ACRIN E1912 [3, 8]	Ibrutinib 420 mg/d, d1–28, until PD	354	58	96%	17%	NA	8%	3 years	3 years
	Rituximab 50/325 mg/m ² , d1/2, cycle 2							89%	
	Rituximab 500 mg/m ² , d1, cycles 3–7							IGHV	
								UM M	
ELEVATE TN [11]	Fludarabine 25 mg/m ² , d1–3	175	57	81%	30%	NA	59%	71%	93%
	Cyclophosphamide 250 mg/m ² , d1–3							65% (n = 71)	
	Rituximab 50/325 mg/m ² , d1/2, cycle 1							82% (n = 44)	
	Rituximab 500 mg/m ² , d1, cycles 2–6								
CLL14 [4, 26]	Acalabrutinib 100 mg bid until PD	179	70	86%	1%	85%	NA	87%	94%
	Obinutuzumab 1000 mg d1, 2, 8, 15 cycle 2							87% (n = 119)	
	Obinutuzumab 1000 mg d1 cycles 3–6							83% (n = 58)	
CLL14 [4, 26]	Chlorambucil 0.5 mg/kg d1, 15 for 6 cycles	177	71	79%	5%	74%	NA	47%	90%
	Obinutuzumab 1000 mg d1, 2, 8, 15 cycle 2							33% (n = 116)	
	Obinutuzumab 1000 mg d1 cycles 3–6							76% (n = 59)	
CLL14 [4, 26]	Venetoclax Ramp-up starting d22 of cycle 1	216	72	85%	50%	35%	76% 57% (BM)	3-years	3-years
	Venetoclax 400 mg/d cycles 3–12							82%	
	Obinutuzumab 1000 mg d1, 8, 15 cycle 1							IGHV	
	Obinutuzumab 1000 mg d1 cycles 2–6							UM M	
CLL14 [4, 26]	Chlorambucil 0.5 mg/kg d1, 15 for 12 cycles	216	71	71%	23%	48%	35% 17% (BM)	50%	87%
	Obinutuzumab 1000 mg d1, 8, 15 cycle 1							≈80% (n = 133)	
	Obinutuzumab 1000 mg d1 cycles 2–6							≈90% (n = 83)	
								≈30% (n = 127)	

ORR overall response rate, CR complete response rate, PR partial response rate, uMRD rate of patients with undetectable minimal residual disease ($<10^{-4}$) in peripheral blood, BM bone-marrow, PFS progression-free survival, OS overall survival, NA not available, IGHV immunoglobulin heavy-chain genes, UM unmutated, M mutated, d day, bid twice a day, PD progressive disease, CLL chronic lymphocytic leukemia

^aMedian, years

benefit for the experimental study cohort persisted based on very few events (Table 1). Nevertheless, after a median time on treatment of 15.1 months, 21% of patients ($n=352$) discontinued ibrutinib for reasons other than disease progression or death, including adverse events (AE) such as arterial hypertension, cardiac events, and arthralgia in 51% of cases (Table 2). In these patients, median PFS after drug discontinuation was confined to 22.5 months [8].

Facing the relatively high rate of drug discontinuations due to AE, efforts have been made to develop next-generation BTK inhibitors with a more favorable toxicity profile. As many AE with ibrutinib are considered a result of kinase inhibition beyond the BTK, more selective second-generation BTK inhibitors such as acalabrutinib have been developed [9, 10].

At ASH 2019 early results of ELEVATE TN, a phase 3 study investigating acalabrutinib alone or in combination with the CD20-antibody obinutuzumab versus chlorambucil and obinutuzumab (GCLb) in previously untreated CLL patients were presented. The 2-year

PFS was significantly prolonged with acalabrutinib, a benefit that was consistent across all subgroups, including patients with TP53 dysfunction, deletion 11q and/or complex karyotype. Of interest, there was a trend towards an additional benefit in overall response rate (ORR) and PFS when acalabrutinib was combined with obinutuzumab (Table 1). The drug discontinuation rate of approximately 20% due to reasons other than disease progression or death was similar among study arms and mostly due to AE (9–14%). The most common AE with acalabrutinib were headache, diarrhea, fatigue, and arthralgia (Table 2). A higher incidence of neutropenia (32% vs. 12%) as well as high-grade infections, foremost pneumonia (6.7% vs. 2.8%), was reported with the addition of obinutuzumab. Notably, low-grade bleeding events were more frequent with acalabrutinib with/without obinutuzumab compared to GCLb (40% vs. 11%) [11].

A comparative controlled randomized trial in relapsed high-risk CLL patients is ongoing to help define

Table 2 Most common adverse events of novel agents in presented phase III studies

Clinical trial	E1912 [8]	ELEVATE TN [11]	CLL14 [4]
Regimen	IR	Acala ± G	VenG
<i>Baseline characteristics</i>			
<i>n</i>	354	358	216
Age ^a	57	70	72
ECOG	0–2	0–2	0–3
Follow-up ^b	48	28	28
<i>Adverse events grade 1–4</i>			
Diarrhea %	NA	35–39	28
Nausea %	NA	20–22	19
Fatigue %	NA	18–28	15
Headache %	NA	37–40	11
Bleeding %	NA	39–43	NA
Cough %	NA	18–22	16
URTI %	NA	18–21	NA
Arthralgia %	NA	16–22	NA
Neutropenia %	NA	11–32	58
Hypertension %	NA	5–7	NA
Atrial fibrillation %	NA	3–4	NA
<i>Adverse events grade 3–4</i>			
Pneumonia %	7	32–39	4
Febrile neutropenia	2	1–2	5
Neutropenia %	26	10–30	53
Anemia %	4	2	8
Thrombocytopenia %	3	NA	14
Hypertension %	9	2–3	NA
Atrial fibrillation %	3	0–1	0.5
<i>Drug discontinuations due to adverse events %</i>			
	14	9–11	16
<i>n</i> number, <i>URTI</i> upper respiratory tract infection, <i>IR</i> ibrutinib/Rituximab, <i>Acala</i> Acalabrutinib, <i>G</i> Obinutuzumab, <i>VenG</i> Venetoclax/Obinutuzumab, <i>NA</i> not available, <i>CLL</i> chronic lymphocytic leukemia			
^a Median, years			
^b Median, months			

whether acalabrutinib is indeed superior to ibrutinib (NCT02477696).

Despite high ORR and long-term remissions accomplished with BTK inhibition even in genetic high-risk patients, MRD frequently persists and indefinite therapy appears obligatory [12]. The consequence of continuous selection pressure, however, may provoke resistance formation [13]. Indeed, CLL cells of patients progressing under ibrutinib commonly harbor cysteine to serine mutations in BTK at the cysteine 481 residue (C481S) keeping ibrutinib off its binding site or gain-of-function mutations of PLCG2 that reactivate hyperactive BCR signaling. Of interest, these resistance mutations seem to develop early after a median of only 9.4 months on treatment [14].

Although second-generation inhibitors such as acalabrutinib offer more selectivity for BTK than ibrutinib, all of these agents share the same covalent

binding site at C481 and, thus, remain susceptible to resistance formation via C481S mutations [15].

Reversible BTK inhibitors such as LOXO-305 represent a novel class of compounds, which do not require covalent binding to BTK and may be effective regardless of C481S mutations [16]. At ASH 2019 very early results of a phase 1 study investigating LOXO-305 in patients with relapsed B-cell malignancies demonstrated a PR in all 5 CLL patients evaluable for response, including one patient harboring a C481S mutation [17]. At this early stage, however, the role of non-covalent BTK inhibitors in CLL treatment is unclear and remains to be better defined in comparative randomized clinical trials.

Targeting B cell lymphoma 2

The B cell lymphoma 2 (BCL2) family encompasses pro- and anti-apoptotic proteins, which operate in concert to keep the balance between cell survival and cell death [18]. CLL cells typically evade apoptosis by overexpression of prosurvival protein BCL2 via several mechanisms, including BCL2 repressor deletion as a result of deletion 13q [19, 20]. Venetoclax, a BCL2 inhibitor, causes prompt apoptosis of CLL cells and has proven high ORR and durable remissions in relapsed refractory CLL patients, including those failing BTK inhibition [21, 22]. Although undetectable MRD (uMRD, <10⁻⁴) is frequently observed with venetoclax [23], long-term monotherapy commonly leads to acquired resistance [24]. Similar to ibrutinib, continuous selection pressure is considered to drive clonal evolution towards resistance formation [25].

Recently, venetoclax plus obinutuzumab (VenG) was approved as first chemotherapy-free fixed-duration regimen in first-line treatment by the European Medicines Agency. At ASH 2019, the underlying CLL14 trial, which randomized treatment-naïve CLL patients with comorbidities to VenG or GClb, was updated [4]. With a 40 month follow-up, the PFS advantage for the experimental study arm persisted with survival curves further separating after end of fixed-duration treatment at month six. As seen with other novel compounds in CLL, the PFS benefit is mainly derived from the subgroup of patients with unmutated IGHV-status with PFS curves splitting in the first 6 months.

Three months after completion of treatment, a remarkably higher rate of uMRD was confirmed for VenG (Table 1). Notably, next-generation sequencing analysis demonstrated uMRD of <10⁻⁶ in 42% of patients. Although uMRD appears to remain stable on treatment, MRD kinetics off treatment reveal reoccurrence over time. Nevertheless, uMRD correlates with PFS, as demonstrated by durable remissions in 90% of uMRD patients with 24 months of follow-up [26].

VenG was generally well tolerated. Table 2 provides an overview of most frequently observed AE.

Table 3 Efficacy of targeted drugs in treatment-naïve CLL patients in selected phase 2 trials presented at ASH 2019

Trial	Regimen	<i>n</i>	Age ^a	ORR	CR/CRi	PR	uMRD	PFS	OS
CAPTIVATE MRD Cohort [28]	Ibrutinib 420 mg/d, d1–28, cycles 1–15 Venetoclax Ramp-up starting cycle 4 Venetoclax 400 mg/d cycles 4–15	164	58	100%	NA	NA	74% 68% (BM)	NA	NA
								IGHV UM M NA (n = 97) NA (n = 67)	
NCT02756897 [29]	Ibrutinib 420 mg/d, d1–28, cycles 1–27 Venetoclax Ramp-up starting cycle 4 Venetoclax 400 mg/d cycles 5–27	80	65	100%	96%	4%	75% (BM)	2 years ≈96%	2 years ≈98%
								IGHV UM M NA (n = 63) NA (n = 13)	
NCT02629809 [31]	Ibrutinib 420 mg/d, d1–28, cycles 1–12 Obinutuzumab 1000 mg d1/2, 8, 15, cycle 1 Obinutuzumab 1000 mg d1, cycles 2–6 Fludarabine 25 mg/m ² , d1–3, cycles 1–3 Cyclophosphamide 250 mg/m ² , d1–3, cycles 1–3 + Obinutuzumab 1000 mg d1, cycles 7–9 if PR or BM-MRD ^{POS} after cycle 6 + Ibrutinib 420 mg/d, d1–28, until PD if BM-MRD ^{POS} after cycle 12	45	60	100%	73%	35%	100% (BM)	3 years ≈97%	3 years ≈97%

ORR overall response rate, CR complete response rate, PR partial response rate, uMRD rate of patients with undetectable minimal residual disease ($<10^{-4}$) in peripheral blood, BM bone marrow, PFS progression-free survival, OS overall survival, NA not available, IGHV immunoglobulin heavy-chain genes, UM unmutated, M mutated, d day, bid twice a day, PD progressive disease

^aMedian, years

Combined inhibition of BTK and BCL2

A critical mechanism of action of ibrutinib relies on separating CLL cells from their protective microenvironment and, thus, depriving them from essential survival signals [6]. As a result, preclinical data demonstrated increased BCL2 dependence and expression of the anti-apoptotic protein BIM in the remaining CLL cells resulting in increased sensitivity to venetoclax [27].

At ASH 2019 two phase 2 studies investigating fixed-duration ibrutinib *plus* venetoclax followed by MRD-guided maintenance in a total of 244 treatment-naïve CLL patients were updated. Treatment schedule encompassed a 3-month induction phase of ibrutinib followed by 12 months of combination therapy in the CAPTIVATE MRD cohort [28] and 24 months in the investigator initiated trial by Jain and coworkers [29], respectively. In all, 90% of the CAPTIVATE MRD cohort ($n = 164$) completed combination treatment with uMRD in 74% of patients (Table 3). Common grade 3–4 AE included neutropenia (35%), infections (8%) and hypertension (7%) and decreased over time with 39% of AE being reported within the first three cycles of combination treatment (Table 4; [28]). In all, 86% of the patients ($n = 80$) reported by Jain and colleagues completed 24 months of combination therapy and 75% of them achieved uMRD in the bone marrow (Table 3). Most common grade 3–4 hematologic toxicity was neutropenia seen in 51% of patients. Besides infections (19%, foremost pneumonia), atrial flutter/fibrillation and arterial hypertension were the most

frequent non-hematologic grade 3–4 toxicities seen in 10% of cases each (Table 4). One patient died of sudden cardiac death [29]. With a median follow-up of nearly 2 years in both trials, only one patient of the CAPTIVATE MRD cohort has experienced disease progression [28].

The role of chemoimmunotherapy

CIT has widely faded into the background with novel agents demonstrating superior efficacy and good tolerability in most patient subgroups. FCR has long been treatment of choice for young and fit CLL patients without high-risk genetics achieving MRD negativity and long-term PFS ≥ 10 years in most cases [30]. Recently, however, the E1912 trial suggested at least comparable outcomes with ibrutinib *plus* rituximab even in patients with mutated IGHV status.

At ASH 2019, the 30 month follow-up of the phase 2 iFCG trial investigating CIT with fludarabine, cyclophosphamide, and obinutuzumab in combination with ibrutinib (iFCG) in 45 treatment-naïve IGHV-mutated CLL patients was presented. Treatment schedule incorporated three cycles of iFCG followed by 9 months of ibrutinib paralleled by MRD-guided courses of obinutuzumab (Table 3). All 41 patients completing 12 months of treatment achieved uMRD in the bone marrow. The most common grade 3–4 AE are summarized in Table 4. Three patients discontinued therapy due to AE including one 26-year-old patient who died of new onset congestive heart failure [31].

Table 4 Most common adverse events of novel agents in presented phase II studies

Clinical trial	CAPTIVATE MRD Cohort [28]	NCT02756897 [29]	NCT02629809 [31]
Regimen	Ibr-Ven	Ibr-Ven	iFCG
<i>Baseline characteristics</i>			
<i>n</i>	164	80	45
Age ^a	58	65	60
Follow-up ^b	15	27	34
<i>Adverse events grade 1–4</i>			
Diarrhea %	60	50	NA
Nausea %	35	40	NA
Fatigue %	21	16	NA
Headache %	17	8	NA
Bleeding %	NA	77	NA
Cough %	NA	NA	NA
URTI %	25	NA	NA
Arthralgia %	20	50	NA
Neutropenia %	40	NA	NA
Hypertension %	12	16	NA
Atrial fibrillation %	NA	15	11
<i>Adverse events grade 3–4</i>			
Pneumonia %	NA	19 ^c	6
Neutropenia %	35	51	58
Febrile neutropenia	1	NA	13
Thrombocytopenia %	5	2	40
Hypertension %	7	10	NA
Atrial fibrillation %	1	10	NA
<i>Drug discontinuations due to adverse events %</i>			
	5	8	7
<i>n</i> number, <i>URTI</i> upper respiratory tract infection, <i>Ibr-Ven</i> ibrutinib/venetoclax, <i>iFCG</i> ibrutinib, fludarabine, cyclophosphamide, obinutuzumab, <i>NA</i> not available			
^a Median, years			
^b Median, months			
^c All infections			

Longer follow-up will help determine whether CIT ± novel compounds remains an appropriate first-line option for fit patients with low-risk disease.

Conclusion

The advent of novel compounds has facilitated a paradigm shift in CLL treatment from unspecific DNA damaging agents to targeted therapy. Foremost, BTK- and BCL2- inhibitors allow remarkably high ORR and long-term PFS even in genetic high-risk patients.

Indefinite treatment, however, is commonly associated with acquired resistance formation within months unleashing the need to pursue more effective fixed-duration regimens. VenG has recently been approved for front-line therapy as the first chemotherapy-free fixed-duration regimen and has found integration in widely accepted international treatment guidelines.

Clinical trials currently focus on the most promising combinations and sequences of highly effective targeted drugs with unprecedentedly high uMRD rates

at convenient drug tolerability possibly inhibiting secondary resistance formation. Longer follow-up will help elucidate whether these combined fixed-duration treatment approaches embrace the ability to ultimately cure CLL in individual patients.

Take home message

- Targeted therapies have become first-line treatment of choice in most patients with chronic lymphocytic leukemia.
- Indefinite treatment may drive clonal evolution towards resistance formation and hamper drug tolerability.
- Clinical trials currently focus on fixed-duration combinations of highly effective targeted drugs in order to prevent acquired resistance and reduce treatment-related toxicity.

Funding Open access funding provided by University of Innsbruck and Medical University of Innsbruck.

Conflict of interest J.-P. Bohn reports personal fees from AbbVie and Astra-Zeneca for advisory board participation. D. Wolf declares that he has no competing interests.

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