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Therapeutic advancement of chronic lymphocytic leukemia

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Abstract

Despite the combinations of chemotherapy with monoclonal antibodies have further improved response rates, chronic lymphocytic leukemia (CLL) remains an incurable disease with an extremely variable course. This article reviews the ongoing clinical advances in the treatment of CLL in both previously untreated and relapsed disease and focuses on the benefit of different therapeutic strategies, the most effective therapy combinations and the potential activity of novel agents. Novel agents and combination therapies have been investigated by several studies in both the upfront and relapsed setting, particularly for patients with 17p deletion, TP53 mutation and fludarabine-refractory CLL. While these agents and combination therapies have improved initial response rates, ongoing studies are continued to determine and improve the efficacy and safety. Despite advancements in the treatment of CLL have led to high response rates, allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains the only curative option and reduced-intensity conditioning (RIC) allo-HSCT must be strongly considered whenever feasible. As such, ongoing studies of these agents and other novel approaches in clinical development are needed to expand and improve treatment options for CLL patients.

Keywords: Chronic lymphocytic leukemia, Treatment, Monoclonal antibodies

Introduction

Chronic lymphocytic leukemia (CLL) remains an incurable disease with an extremely variable course; survival after diagnosis can range from months to decades [1]. Genomic features such as mutational status of immunoglobulin heavy chain variable region genes (IGHV), ataxia telangiectasia mutated (ATM) and TP53 tumor suppressor genes, β2-microglobulin, zeta-chain-associated protein kinase 70 (ZAP70) expression, interphase cytogenetics, and complex karyotype on metaphase cytogenetics, provide further differentiation of disease prognosis [2]. As a result, therapy must be flexible and tailored for different patient groups [3]. With the improvement of its associated prognostic and therapy response factors, the treatment of CLL has dramatically changed. Focusing on the benefit of different therapeutic strategies, this article reviews recent advancements, the most effective therapy combinations and potential activity of novel agent in the treatment of CLL.

Chemotherapy

Although chlorambucil gave lower overall response rates (ORRs) and a shorter progression-free survival (PFS) compared with the purine analogue fludarabine [4], chlorambucil administered as front-line therapy to elderly CLL patients $\geq$65 years proved as effective in sustaining remissions as fludarabine (Table 1) [5]. Bendamustine, a cytotoxic hybrid of an alkylating agent and a purine analog, was introduced for the treatment of CLL in 2008 [6]. Based on the results of an open-label phase 3 trial in 319 previously untreated CLL patients, single-agent bendamustine has shown improved ORR and complete response (CR) rate (68% and 31%) when compared with chlorambucil (31% and 2%) [7]. The median PFS was 21.6 months with bendamustine and 8.3 months with chlorambucil (P < 0.0001) (Table 1). A retrospective chart review showed that bendamustine, either alone or with rituximab, provided meaningful response rates and was generally well tolerated in patients $\geq$70 years old with CLL [8].

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Table 1 Phase 3 trials of chemotherapy in previously untreated CLL patients

Reference (year)	Regimen	Number of patients	Median age (years)	CR,%	ORR,%	Median PFS (months)	OS
Rai, 2000 [4]	Chlorambucil	181	62	4	37	14	Median 56 m
	Fludarabine	170	64	20	63	20	Median 66 m
Eichhorst, 2009 [5]	Chlorambucil	100	70	0	51	18	Median 64 m
	Fludarabine	93	71	7	72	19	Median 46 m
Knauf, 2009 [7]	Chlorambucil	157	66	2	31	8.3	NR
	Bendamustine	162	63	31	68	21.6	NR
Eichhorst, 2006 [9]	Fludarabine	164	59	7	83	20	81% at 3 y
	FC	164	58	24	94	48	80% at 3 y
Catovsky, 2007 [10]	Fludarabine	194	64	15	80	23	52% at 5 y
	FC	196	65	38	94	43	54% at 5 y
	Chlorambucil	387	65	7	72	20	59% at 5 y
Flinn, 2007 [11]	Fludarabine	137	61	5	60	19	80% at 2 y
	FC	141	61	23	74	32	79% at 2 y
Robak, 2010 [13]	CC	192	58	47	88	28	62.4% at 4 y
	FC	203	59	46	82	27	60.6% at 4 y
Robak, 2011 [15]	Cladribine	174	61	21	78	27.2	Median 45 m
	CC	171	62	29	83	22.4	Median 48 m
	CMC	163	59	36	80	25.6	Median 46 m

Abbreviations: CC, cladribine, cyclophosphamide; CMC, cladribine, cyclophosphamide, mitoxantrone; CR, complete response; FC, fludarabine, cyclophosphamide; NR, not researched; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

Three randomized trials in untreated CLL patients comparing fludarabine and cyclophosphamide (FC) with fludarabine monotherapy showed superior CRs, ORRs and PFS for the FC arm [3,9-11], while a analysis of the subgroup of patients without high-risk genetic deletions showed superior overall survival (OS), in these patients comparing FC with fludarabine monotherapy [12]. A randomized phase 3 trial showed that cladribine and fludarabine in combination with cyclophosphamide are equally effective and safe first-line regimens for progressive CLL. However, both combinations have unsatisfactory activity in patients with 17p13 (TP53 gene) deletion (Table 1) [13]. One trial of cladribine (C) versus cladribine and cyclophosphamide (CC) versus cladribine, cyclphosphamide plus mitoxantrone (CMC) showed superior CRs for the CMC arm over C but not the CC arm [14]. However, long term results for these patients confirmed that cladribine alone, CC and CMC regimens produced comparable PFS and OS in previously untreated progressive CLL (Table 1) [15].

Monoclonal antibodies
Rituximab
As the first approved therapeutic antibody for the treatment of cancer, rituximab used in CLL has been extensively explored. Numerous studies combining rituximab with other therapies have been pursued, as summarized in Table 2. In a randomized phase 2 study, a total of 104 patients were enrolled. Fludarabine with concurrent rituximab (n = 51) was compared to fludarabine with sequential rituximab (n = 53) in untreated patients with CLL [16]. After a median follow-up of 117 months (range, 66 to 131 months), the median PFS and OS times for the treatment groups were similar, with an overall estimated median PFS of 42 months (95% CI, 31 to 46 months) and median OS of 85 months (95% CI, 71 to 95 months) [17]. These long-term data support fludarabine plus rituximab as one acceptable first-line treatment for symptomatic patients with CLL.

The combination of pentostatin, cyclophosphamide, and rituximab (PCR) achieved an ORR >90%, with >40% CR in patients with untreated CLL [18]. Moreover, the findings of a phase 2 trial suggested that increasing the dose of the purine nucleoside analogue did not eliminate the need for cyclophosphamide in chemoimmunotherapy for the treatment of CLL [19]. A phase 3 trial compared the combination of fludarabine, cyclophosphamide, and rituximab (FCR) and PCR in previously untreated or minimally treated B-cell CLL [20]. The infection rate (FCR/PCR) was 31%/36%, 12 (14%)/6 (7%) patients achieved CR; the ORR including CR, partial response (PR), and nodular PR (nPR) was 59%/49%.

A phase 1/2 trial of fludarabine, bendamustine, and rituximab (FBR) chemoimmunotherapy for previously

Table 2 Selected trials of chemoimmunotherapy with rituximab in CLL patients

Reference (year)	Regimen	Phase	Number of patients	Treatment status	CR,%	ORR,%	Median PFS (months)	Median OS (months)
Woyach, 2011 [17]	FR (C)	2	51	Untreated	47	90	42	85
	FR (S)		53	Untreated	28	77		
Kay, 2007 [18]	PCR	2	64	Untreated	41	91	32.6	Not Rep
Kay, 2010 [19]	PR	2	33	Untreated	27	76	12	Not Rep
Reynolds, 2011 [20]	PCR	3	92	20% Pretreated	7	49	NR	NR
	FCR		92	20% Pretreated	14	59	NR	NR
Wierda, 2011 [21]	FBR	1/2	14	Untreated	36	93	Not Rep	Not Rep
Bosch, 2011 [23]	R-FCM	2	72	Untreated	82	93	Not Rep	Not Rep
Jenke, 2011 [24]	CHOP-R	2	26	Pretreated, F-ref	0	54	11	27
			15	Pretreated, RT	7	67	15	27
			15	Pretreated, AIC	0	82	14	50

Abbreviations: AIC, autoimmune cytopenia; CHOP-R, cyclophosphamide, adriamycine, vincristine and prednisone plus rituximab; CR, complete response; FBR, fludarabine, bendamustine, and rituximab; FR (C), fludarabine, rituximab, concurrent; FR (S), fludarabine, rituximab, sequential; FCR, fludarabine, cyclophosphamide, rituximab; F-ref, fludarabine-refractory; NR, not researched; Not Rep, not reported; ORR, overall response rate; OS, overall survival; PCR, penostatin cyclophosphamide, rituximab; PFS, progression-free survival; R-FCM, rituximab, fludarabine, cyclophosphamide, mitoxantrone; RT: Richter's transformation.

treated patients with CLL indicated that the FBR regimen was tolerated up to the highest bendamustine dose evaluated with significant efficacy [21]. In another study, retherapy with bendamustine, mitoxantrone and rituximab in patients with relapsed/refractory CLL and indolent lymphomas also achieved high response rates [22]. Another chemoimmunotherapies with rituximab in CLL patients were also studied in recent trials [23,24].

Alemtuzumab

As a recombinant monoclonal antibody that targets the CD52 cell-surface antigen, alemtuzumab significantly improved PFS, time to alternative treatment, ORR and CR, and minimal residual disease-negative remissions in previously untreated CLL patients, compared with chlorambucil (Table 3) [25]. Furthermore, alemtuzumab demonstrated significant activity in patients with bulky nodes, as evidenced by an ORR in patients with lymph nodes ≥5 cm of 76% in alemtuzumab-treated patients versus 44% in chlorambucil-treated patients (P = 0.0125). Alemtuzumab also showed a promising safety profile coupled with satisfactory effectiveness in poor prognosis CLL [26,27]. The combination of alemtuzumab and oral dexamethasone showed high response rates in elder patients with ultra high-risk CLL, with promising preliminary findings for PFS and OS. However, the improved initial response by adding dexamethasone did not seem to translate into improved long-term results, when compared to the preceding CLL2H study with single agent alemtuzumab (Table 3) [28].

Alemtuzumab based chemoimmunotherapy has also shown good responses in relapsed/refractory disease

Table 3 Selected trials of alemtuzumab monotherapy and chemoimmunotherapy in CLL patients

Reference (year)	Regimen	Phase	Number of patients	Treatment status	CR,%	ORR,%	Median PFS (months)	Median OS (months)
Hillmen, 2007 [25]	Alemtuzumab	3	149	Untreated	24	83	14.6	NR
	Chlorambucil		148	Untreated	2	55	11.7	NR
Gritti, 2012 [27]	Alemtuzumab	2	18	F-ref	8	44	10.3	29.1
Stilgenbauer, 2011 [28]	AD	2	30	Untreated, del(17p)	20	97	16.9	>24 , NR
			17	Relapse, del(17p)	0	76	10.4	15
			40	F-ref	5	70	8.4	12
Geisler, 2011 [29]	AFC	3	129	Untreated, high-risk	57	88	37	NR
	FC		133	Untreated, high-risk	45	80	31	NR
Badoux, 2011 [30]	CFAR	2	80	Refractory /relapse	29	65	10.6	N/A
Zent, 2011 [31]	PAR	2	19	Refractory /relapse	32	74	7	23

Abbreviations: A, alemtuzumab; AD, alemtuzumab and dexamethasone; AFC, alemtuzumab plus fludarabine and cyclophosphamide; CFAR, fludarabine, cyclophosphamide, alemtuzumab and rituximab; CR, complete response; FC, fludarabine and cyclophosphamide; F-ref, fludarabine-refractory; N/A, not applicable; NR, not researched; Not Rep, not reported; ORR, overall response rate; OS, overall survival; PAR, pentostatin, alemtuzumab, and rituximab.

(Table 3). An early analysis of the randomized phase 3 CLL trial recently indicated that chemoimmunotherapy with low-dose subcutaneous alemtuzumab plus oral fludarabine and cyclophosphamide was safe and induced more and deeper CRs in untreated patients with high-risk CLL than chemotherapy with FC alone [29]. Good response rates in highly pretreated high-risk group of patients were indicated in a phase 2 study of alemtuzumab plus FCR (CFAR), although there was no benefit in survival outcomes [30]. Another study also indicated that pentostatin, alemtuzumab, and low dose rituximab was effective therapy for relapsed/refractory CLL/small lymphocytic lymphoma (SLL) [31].

Final results of a phase 2 study in previously untreated elderly CLL patients indicated that three courses of FC only yielded a rather high response rate and a short (8 weeks) alemtuzumab consolidation course could thereafter be administered safely, leading to a 52% rate of PR to CR switches, a high proportion of patients with undetectable blood MRD after the end of treatment and durable responses. Overall, 26 patients were in CR after the whole treatment strategy accounting for 51% of the entire cohort [32]. In another study, Alemtuzumab consolidation for residual disease after treatment with high-dose methylprednisolone plus rituximab (HDMP-R) was well tolerated and effective in patients with CLL [33]. However, alemtuzumab consolidation did not improve outcome for CLL patients with high risk genomic features on successive Cancer and Leukemia Group B (CALGB) trials [34].

Ofatumumab

Ofatumumab is a fully humanized CD20 monoclonal antibody that targets an epitope different from the epitope targeted by rituximab. Based on the interim analysis of the pivotal international clinical trial, which included data from 138 CLL patients refractory to fludarabine and alemtuzumab (FA-ref) and refractory to fludarabine but did not receive treatment with alemtuzumab due to bulky disease (BF-ref), ofatumumab had been approved by the FDA for patients with CLL refractory to fludarabine and alemtuzumab in October 2009 [35]. At this interim analysis, the ORR (primary endpoint) with single-agent ofatumumab was 58% (99% CI: 40, 74) in the FA-ref group and 47% (99% CI: 32, 62) in the BF-ref group. The final results for the primary endpoint of this study in 206 enrolled patients indicated that the ORR was 51% for the FA-ref group and 44% for the BF-ref group (Table 4) [36]. In another phase 2 trial of ofatumumab for older patients and patients who refused fludarabine-based regimens with previously untreated CLL or SLL, 13 patients (44%) achieved an objective response (CR, 0; PR, 13); 16 (53%) patients had

stable disease (SD); 1 patient (3%) had progressive disease (PD) (Table 4) [37].

Front-line ofatumumab-based chemoimmunotherapy appeared to be well-tolerated in patients with CLL. An international phase 2 trial investigated the efficacy and safety of 2 dose levels of ofatumumab combined with fludarabine and cyclophosphamide (O-FC) in previously untreated patients with CLL. In this trial, 61 patients were randomized to the ofatumumab 500 mg (n = 31) or 1000 mg (n = 30) dose cohorts. The CR rate was 32% for the 500 mg and 50% for the 1000 mg cohort, and the ORR was 77% and 73%, respectively. The most frequent Common Terminology Criteria grade 3–4 investigator-reported adverse events were neutropenia (48%), thrombocytopenia (15%), anemia (13%), and infection (8%) (Table 4) [38]. Another clinical trial has been initiated to study the effect of ofatumumab in combination with pentostatin and cyclophosphamide (PCO) for patients with previously untreated CLL (Table 4) [39]. Compared to the historic experience with rituximab-based chemoimmunotherapy, ofatumumab-based chemoimmunotherapy appeared to have less hematologic toxicity and improved efficacy.

Lumiliximab

Lumiliximab is a macaque-human primatized monoclonal antibody that targets the CD23 antigen. In a phase 1 trial, investigators found that lumiliximab was well tolerated but showed minimal activity [40]. In a phase 1/2 trial, FCR plus lumiliximab resulted in an OR rate of 65% and a CR rate of 52%, and the toxicity of the combination appeared no different from that which was previously reported with FCR in treatment of relapsed CLL [41]. However, a phase 3 study comparing FCR to FCR plus lumiliximab in relapsed CLL showed no benefit in terms of improved response rate of PFS with the addition of lumiliximab to FCR [42].

Obinutuzumab

Obinutuzumab (GA101) is a humanized, third generation, type II CD20 IgG1 antibody with a glycoengineered Fc region [43]. It exhibits enhanced antibody-dependent cellular cytotoxicity and superior caspase-independent apotosis induction in comparison with classic type I CD20 antibodies, such as rituximab. Modification of elbow hinge sequences within the antibody variable framework regions resulted in a strong apoptosis-inducing activity of obinutuzumab. Complement and antibody-dependent cellular cytotoxicity are believed to be the major effector mechanisms of obinutuzumab in whole blood assays [44]. 13 patients with relapsed or refractory disease were enrolled in a phase 1 study of obinutuzumab. The results showed that the ORR was 62%

Table 4 Phase 2 trials of ofatumumab monotherapy and chemoimmunotherapy in CLL patients

Reference (year)	Regimen	Number of patients	Treatment status	CR,%	ORR,%	Median PFS (months)	Median OS (months)
Wierda, 2010 [36]	Ofatumumab	95	FA-ref	0	51	5.5	14.2
		111	BF-ref	2	44	5.5	17.4
Flinn, 2011 [37]	Ofatumumab	42	Untreated	0	44	NR	NR
Wierda, 2011 [38]	O-FC (500 mg)	31	Untreated	32	77	NR	NR
	O-FC (1000 mg)	30	Untreated	50	73	NR	NR
Shanafelt, 2011 [39]	PCO	33	Untreated	45	94	NR	NR

Abbreviations: BF-ref, fludarabine-refractory CLL with bulky (>5 cm) lymphadenopathy; CR, complete response; FA-ref, fludarabine- and alemtuzumab-refractory; NR, not researched; O-FC (500 mg), 500 mg ofatumumab combined with fludarabine and cyclophosphamide; O-FC (1000 mg), 1000 mg ofatumumab combined with fludarabine and cyclophosphamide; ORR, overall response rate; OS, overall survival; PCO, pentostatin, cyclophosphamide and ofatumumab.

(1 CRi, 7 PRs, and 5 SDs) with no clear dose relationship established [45].

Immunomodulatory drugs

The encouraging antitumour activity of thalidomide in various malignant disorders led to development of subsequent analogues. The immunomodulatory agents lenalidomide and pomalidomide have shown promising antineoplastic activity in various tumor types [46,47]. Lenalidomide has demonstrated clinical efficacy in CLL through various mechanisms [48]. The results of a recent study showed that lenalidomide therapy was well tolerated and induced durable remissions in the population of elderly, symptomatic patients with CLL [49]. In this study, sixty patients with CLL, which were 65 years of age and older, received treatment with lenalidomide. At a median follow-up of 29 months, 53 patients (88%) are alive and 32 patients (53%) remain on therapy. Estimated 2-year PFS was 60%. The ORR to lenalidomide therapy was 65%, including 10% CR, 5% CR with residual cytopenia, 7% nPR, and 43% PR. Neutropenia was the most common grade 3 or 4 treatment-related toxicity observed in 34% of treatment cycles. Major infections or neutropenic fever occurred in 13% of patients.

A phase 2, 2-stage study was designed to evaluate the combination of lenalidomide and rituximab for the initial treatment of patients with CLL [50]. 40 patients enrolled into arm A (age under 65), and 29 into arm B (age 65 or older). The median age on arm A was 57 years (range 45–64) and arm B 70 years (range 65–80). The ORR to therapy for arm A was 94%, with 20% achieving a CR and 17% a nPR. The ORR for arm B was 77% with 9% achieving a CR. Arm A patients had median follow-up of 17 months with an estimated median PFS of 19 months. Arm B had a median follow-up of 7 months, with an estimated 85% remaining progression free at 7 months. Another phase 2 study of lenalidomide and rituximab in patients with relapsed or refractory CLL indicated that the combination of lenalidomide and rituximab led to durable responses in patients with relapsed and refractory CLL and was active also in patients with 17p deletion [51]. The combination therapy with ofatumumab and lenalidomide in patients with relapsed CLL was also conducted in a phase 2 trial. 5 patients (15%) achieved CR (including 1 CRi) and 17 patients (50%) PR, for an ORR of 65% [52].

Lenalidomide-based consolidation for CLL patients receiving first-line chemoimmunotherapy induction appeared to improve the quality of response and prolonged time to retreatment [53]. Based on early experience, lenalidomide consolidation after chemotherapy could further improve responses in 27% of patients with CLL. Elimination of MRD was seen in 12% of patients treated [54].

High-Dose Methylprednisolone

High-dose methylprednisolone (HDMP) has proved to be an active treatment in patients with relapsed/refractory CLL, including those with unfavorable cytogenetic features by numerous studies [55-57]. A phase 2 study combining rituximab with HDMP as a salvage regimen for the treatment of patients with fludarabine-refractory CLL showed an ORR of 93%, with a CR rate of 36% [58]. Another report from the same group showed a similar efficacy in the front-line setting: an ORR of 96%, with a CR rate of 32% using a reduced number of days of methylprednisolone [59]. Although a lower ORR of 78% (22% CR) was reported by a larger single-institution review of 37 patients who were treated with the same HDMP plus rituximab combination, a high response rate was showed for those with high-risk cytogenetic abnormalities, including ORRs of 55.6% and 66.7% for those with 17p deletion and 11q deletion, respectively [60].

Another study evaluated the efficacy and safety of dose-dense HDMP plus rituximab in patients with high-risk CLL. 29 patients with relapsed or progressive CLL with adverse cytogenetics (17p deletion, TP53 mutation, 11q deletion, and/or trisomy 12) and/or progression within 12 months of fludarabine treatment were included. The ORR was 62%, and 28% of patients had

SD. In 13 patients with 17p deletion/TP53 mutation, ORR was 69%. After 22 months, the median PFS and OS were 12 and 31 months, respectively. The most frequent toxicity was hyperglycemia, and three deaths occurred in the study [61]. Combination of HDMP and ofatumumab was also demonstrated as an effective salvage treatment for heavily pretreated, unfit or refractory patients with CLL [62].

Cyclin-dependent kinase (CDK) inhibitors

As a broad CDK inhibitor, flavopiridol (alvocidib) could induce apoptosis in human CLL cells and is independent on p53 ways. Flavopiridol has demonstrated activity in patients with relapsed CLL, including those with high-risk genomic features and bulky lymphadenopathy [63-65]. Outcomes of refractory CLL patients in two age categories (≥70, <70 years) treated with single-agent flavopiridol indicated that flavopiridol treatment of patients aged 70 or older with refractory or relapsed CLL was a feasible therapeutic approach, and may have similar efficacy relative to younger patients. No significant difference between older and younger patients was observed in response rates (43% versus 47%) or median PFS (8.7 versus 9.9 months, $P > 0.80$). Although median OS was worse in older patients (2.1 versus 2.4 years, $P = 0.02$), when adjusted for other factors, this difference was no longer significant ($P > 0.10$). With exception to infections (older = 29% versus younger = 62%), no significant association with toxicity was observed [66].

Activity of combined flavopiridol and lenalidomide in patients with cytogenetically high risk CLL was observed in a phase 1 trial. The results showed that the combination of flavopiridol and lenalidomide was well tolerated without increased risks of tumor lysis syndrome or tumor flare, with significant activity in patients with bulky, cytogenetically high-risk CLL. In 23 evaluable patients who completed 1 or more cycles of combined lenalidomide and flavopiridol, PRs were observed in 13 patients (57%). 6 patients were able to proceed to allogeneic transplant after 1–3 cycles, and 4 of these patients remain in remission. Median PFS and OS are 7 months (range 0–24 months; 95% CI 5, 11) and 23 months (range 0–27 months; 95% CI 13, 27), respectively [67].

Other related CDK inhibitors, such as dinaciclib (SCH 727965), BMS-387032 (SNS-032), sunitinib and sorafenib are being investigated in patients with relapsed or refractory CLL. In a phase 1 trial, dinaciclib appeared to have a similar response rate but less toxicity than flavopiridol in patients with relapsed or refractory CLL [68].

Bcl-2 inhibitors

Navitoclax (ABT-263) is a small-molecule BH3 mimetic that potently inhibits BCL-2, BCL-xL, and BCL-w and is able to induce apoptosis in primary CLL cells. In a phase 1/2a trial in patients with relapsed or refractory CLL, 90% patients showed at least a 50% decrease in absolute lymphocyte count, and the ORR was 35%, all PRs. The median treatment duration was 7 months, with median PFS and time to progression of 25 months. Furthermore, the PFS was similar in fludarabine-refractory and fludarabine-sensitive patients. However, significant toxicity of thrombocytopenia may limit the use of navitoclax in heavily pretreated fludarabine-refractory CLL patients [69,70]. Combination study has been conducted to examine whether navitoclax could be used safely in combination with FCR or bendamustine plus rituximab (BR) for treatment of patients with CLL. Of the 16 patients assessed in Arm B (BR), 6 achieved CR, 7 PR, 2 SD and 1 with PD. The ORR was 81% (13/16). In this arm, 3/5 patients with 17p deletion achieved PR. Of the 4 patients assessed in Arm A (FCR), 2 achieved PR, 1 SD and 1 with PD. The combination of navitoclax with BR appeared well-tolerated and to have anti-tumor activity [71]. Other Bcl-2 inhibitors included oblimersen, gossypol (AT-101), obatoclax, SPC2996 are also in investigational phases and further studies with these agents are warranted [72-75].

Kinase inhibitors of B-cell receptor (BCR) signaling pathways

Phosphatidylinositol-3-kinase (PI3K) inhibitors

In lymphocytes, the PI3K isoform p110δ (PI3Kδ) transmits signals from surface receptors, including the B-cell receptor (BCR). GS-1101 (CAL-101), an isoform-selective inhibitor of PI3Kδ that inhibits PI3K signaling, which induces apoptosis of CLL cells and reduces interactions that retain CLL cells in protective tissue microenvironments in vitro, displays clinical activity in CLL, causing rapid lymph node shrinkage and a transient lymphocytosis [76]. A phase 1 study of GS-1101 in 37 patients with relapsed or refractory CLL was reported [77]. GS-1101 reduced lymphadenopathy in all of the patients, and 91% achieved a lymph node response (≥50% reduction in target nodal lesions). The ORR was 33% (all PRs) and the median duration of response had not been reached. 75% of patients with CLL-related thrombocytopenia had either an improvement to >100,000/μL or a >50% increase from baseline. Another phase 1 trial studied GS-1101 in combination with rituximab and/or bendamustine in 27 patients with previously treated CLL [78]. The results indicated that GS-1101 offered major and rapid reductions in lymphadenopathy. Recently, the preliminary data from a phase 1 trial suggested that SAR245408, an oral pan-PI3K inhibitor, was generally well tolerated in heavily pretreated relapsed/refractory CLL [79].

Bruton tyrosine kinase (Btk) inhibitors

Ibrutinib (PCI-32765), a specific inhibitor of Btk, can disrupt several signaling pathways involved in tumor microenvironment interactions, induce apoptosis and inhibit cellular migration and adhesion in malignant B-cells [80]. An early analysis of the phase 1b/2 study PCYC-1102 showed ibrutinib to be highly active and tolerable in patients with CLL [81]. Nodal response was seen in 89% of patients with lymphadenopathy, with an increase in absolute lymphocyte count in 75%. At a median follow-up of 4 months, the ORR was 44% (39% PRs, 5% CRs) and 4 of 12 patients with deletion 17p had responded, suggesting activity in this subgroup. Longer-term follow-up of this multicenter phase 1b/2 trial has been recently reported [82]. Results of this analysis indicated that ibrutinib was well tolerated and was associated with high rates of 6-month PFS in relapsed or refractory CLL/ SLL. Grade 1 or 2 diarrhea, fatigue, nausea, and ecchymosis have been the most frequently reported adverse events. Serious adverse events have occurred in 38% of patients. ORR in the 420 mg cohort was 48% with 6.2 months median follow-up and 70% with 10.2 months median follow-up. ORR in the 840 mg cohort was 44% at 6.5 months median follow-up. An additional 19%, and 35% of patients in these cohorts, respectively, had a nPR with residual lymphocytosis.

Spleen tyrosine kinase (Syk) inhibitors

Syk is a protein tyrosine kinase that couples BCR activation with downstream signaling pathways, promoting cell activation and migration. In CLL, Syk could be activated by external signals from the tissue microenvironment. Fostamatinib disodium (R788) is the first clinically available oral Syk inhibitor. A multicenter phase 1/2 clinical trial of fostamatinib disodium in patients with recurrent B-cell NHL was reported [83]. The 11 patients with CLL/SLL enrolled in this study achieved an ORR of 55% (all PRs) and a PFS of 6.4 months. Common toxicities included diarrhea, fatigue, cytopenias, hypertension, and nausea. Preclinical studies of other Syk inhibitors such as R406 and two highly selective Syk inhibitors (PRT318 and P505-15) demonstrated responses in CLL cells supporting the development of a novel and active therapeutic approach for CLL and other selected B-cell malignancies [84,85].

Lyn tyrosine kinase inhibitors

Dasatinib, a tyrosine kinase inhibitor originally developed as a pan-Src kinase inhibitor, can inhibit Lyn kinase (a Src-family kinase) and lead to apoptosis of the CLL cells in vitro. A phase 2 clinical trial of dasatinib monotherapy in patients with relapsed CLL showed a 20% ORR and reported myelosuppression as the major toxicity [86]. However, another phase 2 study of single-agent dasatinib showed a lack of efficacy in heavily pretreated CLL patients, with an only ORR of 6% and a high incidence of neutropenia [87]. Bafetinib, another Lyn kinase inhibitor, also showed efficacy in patients with relapsed/refractory B-CLL in a phase 2 trial [88].

Hematopoietic stem cell transplantation (HSCT)

Both autologous HSCT (auto-HSCT) and allogeneic HSCT (allo-HSCT) have been increasingly used to treat relapsed or refractory CLL. Auto-HSCT, which solely relies on dose intensity, does not yield better results than modern chemoimmunotherapy. Results of a phase 3 randomized trial of autografting in CLL versus observation for 223 responding patients after first- or second-line treatment indicated that consolidating autografting reduced the risk of progression by more than 50% but had no effect on OS in CLL [89]. Although early treatment intensification including auto-HSCT could provide effective disease control in poor-risk CLL, its clinical benefit compared to FCR regimens remained uncertain [90].

Allo-HSCT has been proven to be the only potentially curative treatment for relapsed CLL patients with fludarabine-refractory disease or a 17p deletion, leading to long-term survival [91,92]. However, myeloablative allo-HSCT showed unacceptable toxicity and mortality in CLL patients [93,94]. Reduced-intensity conditioning (RIC) regimens decrease high transplant-related mortality resulted from severe graft-versus-host disease and infections. The improvement of RIC regimens allows allo-HSCT administrated in older patients and younger patients with co-morbidity [95]. In general, depending on the conditioning regimen and follow-up, RIC allo-HCT was associated with a 11% to 34% nonrelapse mortality, a 34% to 67% PFS, and a 48% to 72% OS [96]. Published literature supports the use of RIC allo-HCT for patients who fulfill acceptable consensus criteria for hematopoietic stem cell allografting, once a suitable donor is identified [97]. In a feasibility analysis of patients with CLL and 17p deletion, Yvonne Hsu et al. reviewed nonmyeloabltive allo-HSCT outcomes for 17p deletion CLL patients transplanted between 2005 and 2010. With a median follow-up of 18 months (range, 3–60), the 2-year OS and PFS rates were 62% and 38%, respectively. Chemosensitivity was associated with significantly higher PFS (73% versus 12%, *P* = 0.02) and a trend for higher OS (91% versus 45%, *P* = 0.09). Nonmyeloabltive allo-HSCT is more effective in 17p deletion CLL patients when recipients have chemosensitive disease [98].

Conclusion and future directions

Numerous treatment strategies for CLL have emerged over the years, from the use of chlorambucil to RIC

allo-HSCT, which revolutionized the treatment and prognosis of CLL. Treatment must be flexible and tailored for different patient groups [3]. The combination of chemotherapy with monoclonal antibodies has further improved response rates and is now the preferred regimen for younger patients requiring treatment. Nonetheless, allo-HSCT remains the only curative option. RIC allo-HSCT must be strongly considered whenever feasible. Newer antibodies such as anti-CD20 antibodies veltuzumab, AME-133v, LFB-R603 and small modular immunopharmaceutical (SMIP) TRU-015, anti-CD37 SMIP TRU-016, anti-CD40 antibodies dacetuzumab (SGN-40), lucatumumab (HCD122), and novel targeted therapeutic agents such as heat shock protein 90 inhibitors SNX-7081, 17-AAG and 17-DMAG, histone deacetylase inhibitors depsipeptide, MS-275, valproic acid, belinostat, MGCD0103, p53 inhibitor cenersen, murine double minute 2 inhibitor RO5045337, and mammalian target of rapamycin (mTOR) inhibitor RAD001, are being investigated in early-phase clinical trials in patients with CLL or NHL [99-111]. Such agents with novel mechanisms of action and targeting different pathways will open a new way to the future treatment for CLL.

Abbreviations
ATM: Ataxia telangiectasia mutated; BCR: B-cell receptor; BF-ref: Fludarabine-refractory chronic lymphocytic leukemia with bulky (>5 cm) lymphadenopathy; CC: Cladribine and cyclophosphamide; CCR: Clinical complete responses; CDK: Cyclin-dependent kinase; CFAR: Cyclophosphamide, fludarabine, alemtuzumab, and rituximab; CHOP-R: Cyclophosphamide, adriamycin, vincristine and prednisone plus rituximab; CLL: Chronic lymphocytic leukemia; CMC: Cladribine, cyclphosphamide plus mitoxantroneshowed; CR: Complete responses; CRi: Complete responses with incomplete blood recovery; FA-ref: Refractory to fludarabine and alemtuzumab; FBR: Fludarabine, bendamustine, and rituximab; FC: Fludarabine and cyclophosphamide; FCR: Fludarabine, cyclophosphamide, and rituximab; FDA: Food and drug administration; HDMP: High-dose methylprednisolone; HSCT: Hematopoietic stem cell transplantation; IGHV: Immunoglobulin heavy chain variable region genes; MRD: Minimal residual disease; mTOR: Mammalian target of rapamycin; nPR: Nodular partial response; ORR: Overall response rate; OS: Overall survival; PCR: Pentostatin, cyclophosphamide, and rituximab; PD: Progressive disease; PFS: Progression-free survival; PI3K: Phosphatidylinositol-3-kinase; PR: Partial response; RIC: Reduced-intensity conditioning; SD: Stable disease; SLL: Small lymphocytic lymphoma; SMIP: Small modular immunopharmaceutical; ZAP70: Zeta-chain-associated protein kinase 70.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
Both authors participated in drafting and editing the manuscript. Both authors read and approved the final manuscript.

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