

Review Article

Treatment algorithm for Japanese patients with chronic lymphocytic leukemia in the era of novel targeted therapies

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Treatment for patients with chronic lymphocytic leukemia (CLL) is becoming more individualized due to the recent introduction of novel molecularly targeted therapies into the therapeutic armamentarium. Genomic and molecular risk factors in CLL patients determine the individual risk for disease progression and response to therapy, and can impact survival. In this review article, we discuss current treatment strategies for CLL patients in Japan, where the novel targeted agents, the BTK inhibitor ibrutinib and BCL2 antagonist venetoclax, now are available and increasingly used in clinical practice. We also discuss the importance of CLL risk factors for making therapy decisions, focusing on immunoglobulin variable region heavy chain (*IGHV*) mutation status, 11q deletion, and 17p deletion. Treatment approaches for CLL have rapidly changed in the past few years because of these new targeted agents. They are highly effective, well tolerated, and have been demonstrated in a series of large randomized clinical trials to improve survival when compared with conventional chemotherapy-based treatment. Therefore, for most patients, especially high-risk CLL patients, BTK inhibitor and BCL2 antagonist therapies are preferred over chemo-immunotherapy. Currently ongoing studies seek to determine the best sequence for these new agents and whether a combination therapy approach is beneficial. With these developments, a new era of chemotherapy-free treatment for CLL patients is expected.

Keywords: Chronic lymphocytic leukemia (CLL), ibrutinib, venetoclax, 17p deletion, *TP53* mutation

INTRODUCTION

Treatment approaches for patients with chronic lymphocytic leukemia (CLL) are rapidly changing due to the introduction of novel molecularly targeted therapies into clinical practice.¹⁻³ In Japan, two novel agents have been approved and are available, the Bruton's tyrosine kinase (BTK) inhibitor ibrutinib, and venetoclax, a BCL2 antagonist. Both agents markedly improve the outcome of CLL patients, when compared with conventional chemotherapy-based treatment. New clinical studies and updates of seminal clinical trials with first- or second-generation BTK inhibitors (such as ibrutinib and acalabrutinib), PI3 kinase inhibitors (such as idelalisib and duvelisib), venetoclax, new anti-CD20 antibodies (such as obinutuzumab), and combinations of these agents most likely will further change the management of CLL patients within the next few years.⁴⁻⁷ However, CLL currently remains an incurable disease for most patients unless they can undergo allogeneic stem cell transplantation or have achieved long-term remission after FCR (fludarabine,

cyclophosphamide, and rituximab) chemo-immunotherapy. This emphasizes the need for physicians to develop a longer-term treatment strategy for each patient in order to achieve long-term remission and prolong survival.

In this review, we discuss the current treatment strategy for CLL patients in Japan, where ibrutinib and venetoclax are now available in routine clinical practice.

INDICATIONS FOR TREATMENT

Criteria for initiating CLL treatment include advanced stage disease with anemia and/or thrombocytopenia due to progressive marrow failure or other signs of active disease such as hepatosplenomegaly, progressive and symptomatic lymphadenopathy, rapidly progressive lymphocytosis, autoimmune complication, organ involvement, or other disease-related symptoms. The modified staging systems developed by Rai and Binet continue to be widely used for clinical staging (Table 1).^{8,9} A high absolute lymphocyte count alone is not an indicator for initiating treatment because leukostasis

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Table 1. Modified Rai and Binet staging systems for chronic lymphocytic leukemia

Risk Status	Modified Rai Stage	Binet Stage
Low risk	0: Lymphocytosis	A: < 3 involved nodal areas
Intermediate risk	I: Lymphadenopathy II: Splenomegaly and/or hepatomegaly	B: ≥ 3 involved nodal areas
High risk	III: Hemoglobin < 11 g/dL IV: Platelets < 10 × 10 ⁴ /μL	C: Hemoglobin < 10 g/dL and/or platelets < 10 × 10 ⁴ /μL

with disturbed microcirculation, also called symptomatic hyperleukocytosis, rarely occurs in patients with CLL. Patients with asymptomatic early-stage disease are monitored without anti-CLL therapy because previous studies have failed to demonstrate survival benefits from early therapeutic intervention using chemotherapeutic agents.¹⁰ An ongoing clinical trial by the German CLL study group is investigating ibrutinib in previously untreated high-risk CLL patients who are asymptomatic and have early-stage disease (CLL12). This study may define whether a subset of asymptomatic early-stage patients (i.e. high-risk patients with 17p deletion and other adverse prognostic factors) may benefit from early intervention using one of the novel agents.

The International Workshop on Chronic Lymphocytic Leukemia (IWCLL) defines active disease as the presence of one or more of the following criteria:¹¹

1. Evidence of progressive marrow failure with anemia (Hb < 10 g/dL) or thrombocytopenia (<100,000/μL);
2. Massive (>6 cm below the left costal margin), progressive, or symptomatic splenomegaly;
3. Massive nodes (>10 cm in greatest dimension), or progressive or symptomatic lymphadenopathy;
4. Progressive lymphocytosis with an increase of >50% over a 2-month period or lymphocyte doubling time <6 months;
5. Steroid-refractory autoimmune hemolytic anemia or thrombocytopenia;
6. Symptomatic extranodal involvement (e.g., skin, kidney, lung, spine);
7. Disease-related symptoms such as unintentional weight loss (>10% in 6 months), fever >38.0°C for ≥2 weeks with-

out evidence of infection, or night sweats for ≥ 1 month

TREATMENT OPTIONS

There are two major classes of treatment options, including chemoimmunotherapies and molecularly targeted therapies.

1. Chemoimmunotherapies

The two most commonly used front-line chemoimmunotherapy regimens for CLL treatment are FCR and BR (bendamustine and rituximab).^{12,13} As most chemotherapeutic agents depend on intact p53 signaling for their anti-leukemic activity, both FCR and BR are expected to have limited clinical activity in CLL patients with 17p deletion (Table 2). 17p deletion is associated with monoallelic loss of the *TP53* tumor suppressor gene, which often (≥80% of cases) coincides with *TP53* mutations in the alternate alleles. Similarly, the efficacy of chemoimmunotherapy is limited in CLL patients with 11q deletion or unmutated immunoglobulin variable region heavy chain (*IGHV*), defined as a difference of <2% from the germline nucleotide sequence. 11q deletion is associated with *ATM* mutations in the alternate alleles in 30–40% of patients. *ATM* plays a central role in a correct DNA damage response to chemotherapy. Unmutated *IGHV* status is associated with activated B-cell receptor (BCR) signaling, and often coincides with *NOTCH1*, *TP53* or *ATM* mutations compared with mutated *IGHV* cases.¹⁴ Therefore, chemoimmunotherapy is not generally recommended for patients with 17p deletion, 11q deletion, or unmutated *IGHV* status, and molecularly targeted drugs are the preferred therapeutic approach.²

An international consortium developed the International Prognostic Index for Chronic Lymphocytic Leukemia (CLL-IPI)¹⁵ based on data from 3472 treatment-naïve patients who received chemoimmunotherapy in eight phase III clinical trials. The CLL-IPI score uses five independent markers that have been identified as independent predictors of overall survival (OS) – p53 abnormalities (17p deletion and/or *TP53* mutation) (score 4), unmutated *IGHV* status (score 2), serum beta2-microglobulin concentration (> 3.5 mg/L; score 2), clinical stage (Rai I-IV/Binet B-C; score 1), and age (> 65

Table 2. Response to chemoimmunotherapy according to cytogenetic results by fluorescence in situ hybridization

Cytogenetics by FISH	FCR (Reference 12)			BR (Reference 13)		
	ORR (%)	CR (%)	3-year PFS (%)	ORR (%)	CR (%)	Median PFS (months)
13q–	96	48	76	93	13	34
11q–	93	51	64	90	40	30
+12	100	71	83	95	21	N/R
17p–	68	5	18	38	0	8
Normal*	89	35	58	97	29	N/R

FISH, fluorescence in situ hybridization; FCR, fludarabine, cyclophosphamide, and rituximab; BR, bendamustine and rituximab; ORR, overall response rate; CR, complete response; PFS, progression-free survival.

*Not including del(17p), del(11q), trisomy 12, or del(13q).

Table 3. Chronic Lymphocytic Leukemia-International Prognostic Index (CLL-IPI) Categories

Risk Group	Score*	5-year overall survival
Low	0–1	93%
Intermediate	2–3	79%
High	4–6	64%
Very High	7–10	23%

*The 5 variables included are: p53 abnormalities (17p deletion and/or TP53 mutation) (score 4), unmutated IGHV status (score 2), serum beta2-microglobulin concentration (> 3.5 mg/L; score 2), clinical stage (Rai I-IV/Binet B-C; score 1), and age (> 65 years; score 1).

years; score 1) (Table 3). Of note, p53 abnormalities received the highest score of 4 points and their presence immediately places the patient into the high-risk group. Furthermore, patients in the CLL-IPI very high-risk group should always have p53 abnormalities, further emphasizing that chemoimmunotherapy is not an appropriate choice for patients with 17p deletion and/or TP53 mutations even as the front-line treatment.

1.1. Fludarabine, cyclophosphamide, and rituximab (FCR)

FCR has been a standard of care for previously untreated patients with CLL who are younger than 65 years and have no significant comorbidities.¹⁶ FCR is the only chemoimmunotherapy that has been demonstrated to have curative potential in patients with CLL. However, this long-term benefit, with a plateau on the progression-free survival (PFS) curve and no relapse beyond 10 years, is observed only in low-risk CLL patients with IGHV mutation.¹⁷ In contrast, high-risk CLL patients harboring 17p deletion (independent of co-occurring 11q deletion or unmutated IGHV genes) had inferior outcomes (30% CR; 58% OS at 5 years; median PFS of 23 months; 11% PFS at 5 years). Intermediate-risk patients harboring unmutated IGHV genes and/or 11q deletion in the absence of 17p deletion had a survival curve between those of low- and high-risk patients, with a continuously deteriorating PFS (median PFS of 52 months). In addition to cytogenetic and molecular risk factors, achievement of minimal residual disease (MRD) status negativity, commonly assessed by flow cytometry analysis of blood or bone marrow cells, also predicted durable remissions in CLL patients treated by FCR. Although MRD detection is not currently available in clinical practice, MRD negativity may become a useful criterion to guide treatment discontinuation before the completion of six cycles of FCR¹⁸ in an individualized therapy approach in future, with the aim of reducing exposure to chemotherapy and thereby reducing the risk of secondary cancers.

FCR causes substantial myelosuppression¹⁶ and a significant number of young fit patients (approximately 25%) cannot tolerate receiving six cycles of therapy due to persistent myelosuppression and/or neutropenic fever. In addition, FCR treatment is associated with a risk of developing secondary malignancies, especially secondary myelodysplastic

syndromes and acute myeloid leukemia (approximately 5%). Therefore, FCR is currently an option only for selected young, low-risk patients, who primarily have mutated IGHV genes in the absence of 11q and 17p deletion, with the goal of achieving durable long-term remission and possible cure.¹⁹

1.2. Bendamustine and rituximab (BR)

Another widely used chemoimmunotherapy regimen is BR.¹³ When compared with FCR, BR is associated with fewer frequent infections and neutropenia, but a shorter PFS.¹⁶ As with FCR, the presence of 17p deletion, 11q deletion, and/or unmutated IGHV genes is associated with a shorter PFS in BR-treated patients.²⁰ BR may be an option for selected patients for whom novel molecular targeted therapies are not indicated and chemoimmunotherapy with less myelosuppression is considered the preferred treatment.²⁰ Bendamustine treatment also is associated with frequent and prolonged myelosuppression, which can result in opportunistic infections, including hepatitis B or cytomegalovirus reactivation, varicella zoster virus infections and *Pneumocystis jirovecii* pneumonia. The development of secondary malignancies has been reported in 5-10% of patients who received BR. As the long-term benefit in IGHV mutated patients is observed only by treatment using FCR, BR is not a substitute for FCR in young fit patients who are eligible for FCR.

1.3. Low-intensity chemoimmunotherapies

In addition to FCR and BR, there are several chemoimmunotherapy regimens for patients that are used either as single agents or in combinations. The clinical impact of such low-intensity chemotherapies on survival is modest, and they are not discussed in this review.

2. Molecular targeted therapies

Treatment using ibrutinib is increasingly replacing chemoimmunotherapies in both front-line and relapsed/refractory CLL. The concept of using chemotherapy-free front-line therapy for CLL was further supported by a series of recently published randomized phase 3 trials demonstrating improved survival rates with ibrutinib in comparison with FCR, BR, and other low-intensity chemoimmunotherapies.^{19,21,22} Venetoclax has recently emerged as an additional molecular targeted therapy option for patients with relapsed/refractory CLL, inducing higher response rates and more durable remissions in CLL patients when compared with chemoimmunotherapy.^{23,24}

2.1. Ibrutinib

Ibrutinib irreversibly inhibits Bruton's tyrosine kinase (BTK), an essential component of BCR and chemokine receptor signaling pathways, which control CLL cell survival and tissue homing, respectively. Ibrutinib monotherapy is approved in Japan for CLL therapy in the front-line and relapsed/refractory disease settings. In response to ibrutinib treatment, CLL patients exhibit a distinctive response pattern, characterized by the rapid shrinkage of enlarged lymph nodes, together with the redistribution of CLL cells into the

peripheral blood, leading to a transient increase in circulating lymphocytes, termed redistribution lymphocytosis.²⁵ Prolonged lymphocytosis remains generally asymptomatic even when persisting >1 year (it usually resolves within 8 months) and does not require treatment; redistribution lymphocytosis is an on-target effect and does not indicate a sub-optimal response to BTK inhibitor therapy. Ibrutinib is generally well-tolerated and adverse events are primarily grade 1/2, and are manageable during prolonged ibrutinib treatment by treating the side effect(s) and/or reducing the dose. Ibrutinib administration has been associated with an increased risk of bleeding, infections, atrial fibrillation, and hypertension, requiring clinical and laboratory monitoring.^{26,27} Over time, a significant proportion of patients discontinue ibrutinib therapy primarily because of side effects, but also occasionally because of the development of resistance, especially in patients with 17p deletion.

Ibrutinib resistance, if it occurs, develops after 15+ months of therapy and is mostly associated with *BTK* and/or *PLCG2* mutations.²⁸ Sequential analysis of clonal dynamics in patients with CLL treated using ibrutinib suggested that the resistant subclones were already present at the time of ibrutinib treatment initiation.²⁹ Patients with 17p deletion and multiple prior therapies have a higher risk of developing ibrutinib resistance. Updated results of front-line ibrutinib treatment after a median follow-up of 5 years from the RESONATE-2 study suggested that disease progression is relatively rare (6%) in the front-line setting.²¹ The incidence of disease progression was similarly low (7%) in the updated results of the E1912 study (median follow-up of 4 years).³⁰ In the E1912 update, the PFS after ibrutinib discontinuation unrelated to disease progression or death (median length of treatment: 15.1 months) was 22.5 months, suggesting that ibrutinib-responsive but -intolerant patients have a grace period to start the next treatment.

2.2. Venetoclax

CLL cell survival largely depends on the delicate balance between anti-apoptotic BCL-2 and pro-apoptotic BIM molecules. Venetoclax binds to the hydrophobic BH3-binding groove of BCL-2, preventing BCL-2 from sequestering BIM, which leads to the activation of the pore-formers BAX/BAK, causing permeabilization of the mitochondrial outer membrane, resulting in apoptosis.^{31,32} As p53 functions upstream of BCL-2,³³ the BCL-2 inhibitor venetoclax can kill CLL cells irrespective of p53 abnormalities. In Japan, venetoclax is approved for use for relapsed/refractory CLL in combination with rituximab. Venetoclax has a weekly dose ramp-up schedule starting at 20 mg/day up to 400 mg/day to avoid tumor lysis syndrome. Neutropenia is another adverse event associated with venetoclax therapy. The pivotal phase 3 MURANO study compared venetoclax plus rituximab with BR in patients with relapsed/refractory CLL.^{23,24} After four years, the PFS rate was 57.3% versus 4.6% with venetoclax-rituximab versus BR, respectively.²⁴ The fixed-duration venetoclax-rituximab achieved high undetectable (<10⁴) MRD rates (64% at the end of treatment), and after 22

months of no therapy (range: 1–25 months), undetectable MRD status was associated with a prolonged PFS. Patients with higher MRD levels at the end of treatment often had increasing MRD levels even prior to treatment cessation,²⁴ revealing that continuation of venetoclax will not benefit such patients. Venetoclax has not fully reversed the negative impact of p53 abnormalities, even when combined with the newer anti-CD20 antibody obinutuzumab in front-line treatment (obinutuzumab has not yet been approved for treatment of CLL patients in Japan).^{34–36} p53 abnormalities remain an adverse prognostic factor in CLL even in the era of novel molecular targeted therapies. Acquired venetoclax resistance is associated with *BCL-2* mutations, *BTG* mutations, homozygous *CDKN2A/B* deletions, and MCL-1 overexpression.^{37–39}

TREATMENT STRATEGIES

1. Front-line treatment

The front-line treatment algorithm for patients with CLL is illustrated in Figure 1. Molecular testing for 17p deletion and *IGHV* mutation status (or flow-cytometric determination of ZAP-70, CD38, and CD49d expression if determination of *IGHV* mutation status is unavailable) is highly recommended if chemo-immunotherapy is considered. Ibrutinib is recommended as front-line treatment for most patients, unless contraindicated.

2. Salvage treatment

The therapeutic algorithm for patients with relapsed/refractory CLL is illustrated in Figure 2. For patients who were initially treated using ibrutinib, venetoclax in combination with rituximab is a reasonable choice. Patients progressing on continuous ibrutinib therapy should not stop ibrutinib before an alternative therapy has been initiated to avoid a flare-up of the disease. In the case of venetoclax, ibrutinib should not be discontinued until patients are on a therapeutic dose (normally 400 mg venetoclax daily). Treatment options for patients with relapsed/refractory CLL after receiving chemoimmunotherapies include ibrutinib and venetoclax-rituximab. Both options are reasonable,⁴⁰ but longer-term follow-up data are available for ibrutinib-based treatment. Although the importance of chemoimmunotherapy for relapsed CLL is diminishing, its use may be considered in certain situations such as (1) after durable (at least >3 years) remission with front-line chemoimmunotherapy and absence of adverse biomarkers, or (2) in patients who are not compliant with daily oral drug intake. A recent study demonstrated that BR in the first relapse of CLL resulted in a 31-month period until the next treatment.⁴¹

3. Special situations

3.1. Richter transformation

Richter transformation is the development of aggressive lymphoma in CLL patients, most commonly manifesting as

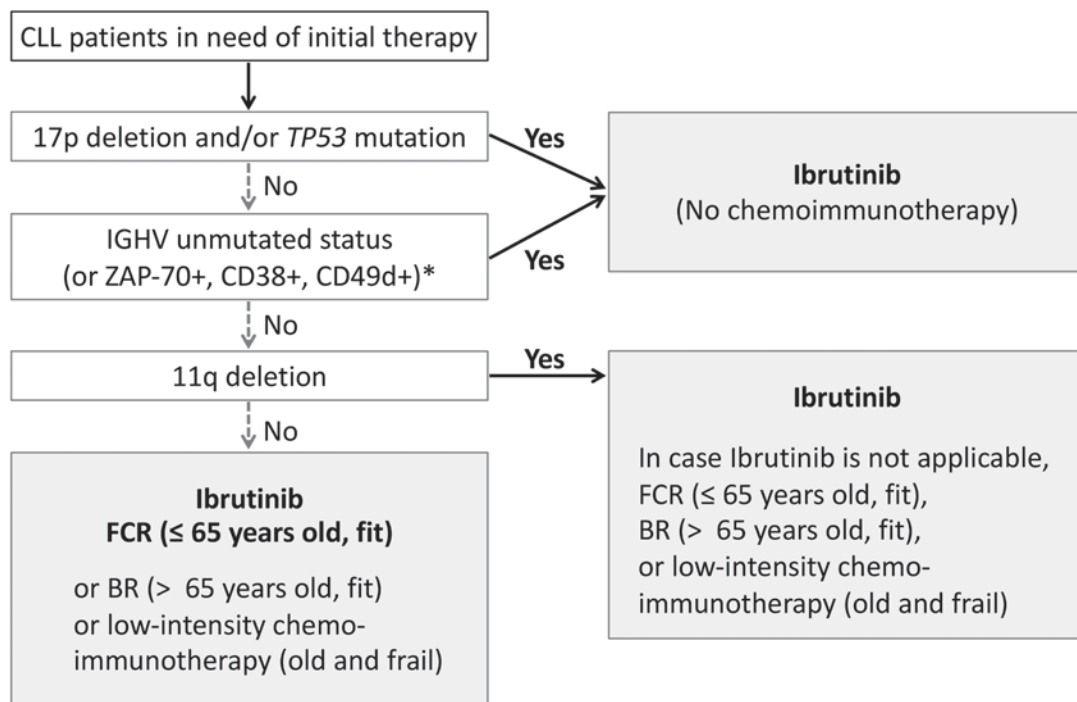


Fig. 1. Treatment algorithm for initial therapy for CLL. As of January 2020, venetoclax has not yet been approved for treatment of naïve CLL patients in Japan.

*If *IGHV* mutation status analysis is not available, flow-cytometric determination of ZAP-70, CD38, and CD49d expression may be used as a surrogate for *IGHV* mutation status. The association, however, is not absolute. *TP53* mutation analysis is offered by some commercial companies and laboratories. *IGHV* mutation status analysis is not commercially available, but it has been investigated by Japanese researchers.⁵¹

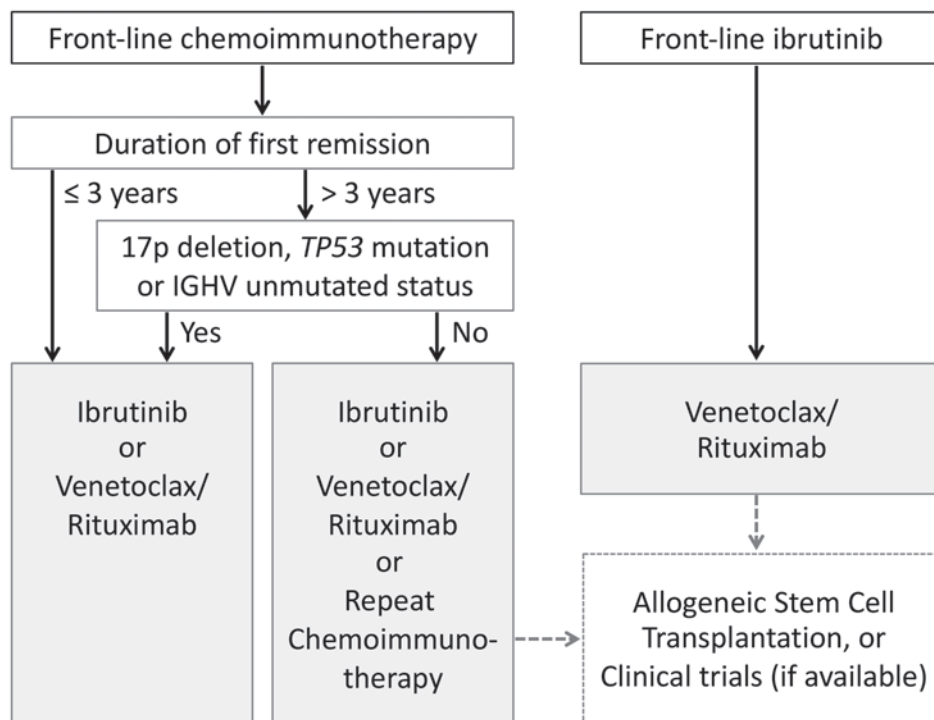


Fig. 2. Treatment algorithm for second-line therapy for CLL.

diffuse large B-cell lymphoma (DLBCL) and, less frequently, as Hodgkin lymphoma.⁴² R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) and other intensive chemoimmunotherapy regimens are used for DLBCL-type transformation. The outcome is largely determined by the clonal relationship between the DLBCL and CLL. Clonally unrelated DLBCL, which is infrequent, can be managed as de novo DLBCL and has a better outcome than the clonally related Richter transformation. Fit patients with chemo-sensitive and clonally related DLBCL should be offered allogeneic stem cell transplantation (SCT) to prolong survival.⁴³ ABVD (adriamycin, bleomycin, vinblastine, and dacarbazine) is used for patients with Hodgkin lymphoma-type transformation.⁴⁴ SCT consolidation has been infrequently used for Hodgkin lymphoma-type transformation.

3.2. Autoimmune cytopenias

Autoimmune cytopenias develop in 5–10% of CLL patients, and most commonly manifest as autoimmune hemolytic anemia or immune thrombocytopenia (ITP). In the absence of treatment indications for CLL, corticosteroids or single-agent rituximab can be used. Single-agent fludarabine may exacerbate hemolysis. Although there is limited data, ibrutinib can be administered to patients with autoimmune cytopenias.⁴⁵ Ibrutinib may cause a short flare in autoimmune cytopenias, and steroids should be added in such cases.

CONCLUSION

Following the introduction of novel molecular targeted therapies, such as ibrutinib and venetoclax, significant progress in CLL treatment has been made and the outcomes for CLL patients, especially high-risk CLL patients, are continuously improving (Table 4). These changes are reflected in the updated therapy algorithm for CLL, where novel agents are now recommended for most CLL patients, especially those with high-risk CLL, in both the front-line and relapsed

disease settings. Future studies will identify the optimal sequence of new agents, and clarify whether there are long-term benefits from combination therapy, such as ibrutinib-venetoclax, when compared with single-agent BTK inhibitor therapy or venetoclax (plus anti-CD20 antibodies). A chemo-free era for CLL patients is becoming a reality and many patients are already benefitting from these new targeted agents.

CONFLICT OF INTEREST

K.K. received honoraria and scientific grants from Janssen. J.B. received grants from Pharmacyclics and Gilead, and honoraria from Janssen and Astra Zeneca.

OFF-LABEL DRUG USE

None disclosed.

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Table 4. Phase 2 and 3 trials for relapsed CLL

Treatment	Trial Name	Patients, n	Age, y	ORR, %	CR, %	Median PFS, m	PFS	OS	Reference
Ibrutinib	–	101	64	89	10	51	44% at 5 y	60% at 5 y	46
Ibrutinib	RESONATE 1	195	67	91	9	NR	59% at 3 y	74% at 3 y	47
Ofatumumab	RESONATE 1	196	67	4	0	8.1	3% at 3 y	65% at 3 y	
Ofatumumab	DUO	159	69	45	0	9.9	–	86% at 1 y	6
Venetoclax +Rituximab	MURANO	194*	65	92	8	NR	57% at 4 y	85% at 4 y	24
BR	MURANO	195	65	72	4	17.0	5% at 4 y	67% at 4 y	24
Venetoclax	–	91†	66	65	9	24.7	75% at 1 y	91% at 1 y	48
(Relapsed/refractory CLL with 17p deletion)									
Ibrutinib	RESONATE 17	145‡	64	83	2	NR	63% at 2 y	75% at 2 y	49
Venetoclax	M13-982	153‡	67	77	20	NR	54% at 2 y	73% at 2 y	50

ORR, overall response rate; CR, complete response; PFS, progression-free survival; OS, overall survival; NR, not reached.

*including 5 (2.6%) patients with prior B-cell receptor signaling pathway inhibitor treatment

†including only patients with relapsed or refractory to B-cell receptor signaling pathway inhibitors

‡including only patients with 17p deletion

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