Management of Patients With Relapsed Chronic Lymphocytic Leukemia

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Abstract

The management of chronic lymphocytic leukemia (CLL) has improved significantly over the last decade with multiple new and well-tolerated therapies now available for the majority of patients. Chemoimmunotherapy, with fludarabine, cyclophosphamide, and rituximab (FCR) or bendamustine and rituximab (BR), has been the mainstay for the treatment of patients with CLL, but their use is complicated by significant morbidity, especially in older and frail patients. The majority of patients relapse within five years of initial chemoimmunotherapy and outcomes are even worse in patients with short initial remission. Remission duration also decreases progressively with subsequent therapies. The advent of novel therapeutics including CD20-targeting antibodies such as obinutuzumab, ofatumumab, and BTK and PI3K inhibitors such as ibrutinib and idelalisib respectively, offers an exciting option for patients with comorbid conditions, previously untreated, relapsed, and high-risk disease. These novel agents are generally well-tolerated, have already demonstrated significant activity in all subsets of patients, and have the potential to replace conventional chemoimmunotherapy. However, resistance issues have been identified with ibrutinib and outcomes are poor for this group of patients. Moreover, specific side effects such as bleeding issues, colitis, pneumonitis, and transaminitis, limit prolonged use with kinase inhibitors in a subset of patients. Newer agents such as acalabrutinib, which targets BTK, and venetoclax, which targets the anti-apoptotic molecule bcl-2, have demonstrated extremely promising activity in early-phase trials. These developments herald an era of unprecedented progress for the management of patients with CLL and are already improving the lives of thousands of people around the world.

Key words: relapsed, chronic lymphocytic leukemia

Introduction

Therapeutic options for chronic lymphocytic leukemia (CLL) have been remarkably expanded in the last few decades. Extension of available options within particular drug classes, such as addition of fludarabine to purine analogs, the development of multiple targeted therapies, from agents such as rituximab and obinutuzumab that target B cells, and the rapid progress of specific inhibitors of the B-cell receptor-dependent signaling cascade have dramatically increased the rates of overall responses and progression-free survival (PFS).[1,2] However, sustained remissions are limited and cure remains elusive. Moreover, conventional chemotherapeutic use is associated with significant toxicity, which is particularly pronounced in patients more than 65 years of age, who constitute the majority of patients with CLL. Choosing treatment strategies for patients with relapsed CLL, therefore, presents a significant challenge. In this review, we focus on recent exploration of chemotherapeutic and targeted therapy options directed against relapsed CLL, summarize factors that may predict resistance to therapy and highlight future directions.

Chemoimmunotherapy for Initial Treatment

Rituximab in combination with fludarabine and cyclophosphamide (FCR) or bendamustine (BR) are among the most commonly used chemoimmunotherapy regimens for the initial treatment of patients with CLL. In younger patients with good performance status and limited comorbid conditions, the FCR300 phase II trial proposed FCR as an effective combination therapy and reported an overall response rate (ORR) of 95%, with 72% complete responses (CR) and a median PFS of 6 years.[3] The German CLL Study Group (CLL8) trial compared FCR with fludarabine and cyclophosphamide (FC) and further established its efficacy.[4] In a similar patient population, the CLL10 trial compared FCR to BR and demonstrated improved CR and PFS, although with a higher incidence of cytopenia and infectious complications.[5] However, tolerability and toxicity issues were substantial and survival outcomes were not significantly improved in patients more than 65 years of age, in patients with compromised renal function and multiple comorbid conditions, and in patients with high-risk del(17p) disease.

This has led to the development and recent approval of multiple targeted therapies that are very effective and well-tolerated for these patients, and include obinutuzumab,[6] ofatumumab,[7] and ibrutinib.[8] While these agents are being used more frequently, data regarding the optimal management of patients relapsing after these therapies are currently lacking.

Chemoimmunotherapy for Relapsed Disease

The REACH trial, a multicenter, randomized, phase III trial, compared 6 cycles of FCR with 6 cycles of FC) for treatment of patients with previously treated, relapsed CLL.[9] The trial enrolled 552 patients who received previous treatment with single-agent regimens containing either chlorambucil with or without a steroid, other nucleoside analogs, or an alkylator-containing combination but not an alkylator/nucleoside-analog combination. After a median follow-up of 25 months, patients who received FCR showed a significantly improved PFS by 10 months (P <.001; median 30.6 months for FCR vs 20.6 months for FC). Furthermore, ORR increased from 58% to 69% (P =.034) and CR rate increased from 13% to 24% (P <.001) in patients treated with FCR compared to those who received FC.

Combination of chemotherapy and targeted therapy was further explored in the large LUCID trial, which studied the addition of lumiliximab (L), a chimeric monoclonal antibody that targets CD23, to FCR for treatment of patients with relapsed CLL who were previously treated with 1 or 2 single-agent or combination regimens.[10] The study enrolled 615 patients who were randomized to lumiliximab in combination with FCR versus FCR alone. Even though CR, ORR, and PFS were similar between both groups, this study recognized the utility of FCR in the relapsed setting where patients had received prior combination chemoimmunotherapy and demonstrated an ORR of 72% with a CR of 15% and a PFS of 24 months.

Bendamustine in combination with rituximab was evaluated in a phase II trial of 78 patients with relapsed or refractory CLL and reported an ORR of 59%, with 9% CR and a median event-free survival of 15 months.[11] However, ORR was 45% in patients with fludarabine-refractory disease and 60% in patients with fludarabine-sensitive disease. About 50% of patients encountered severe (grade 3/4) hematologic toxicities and 13% experienced severe infections. Patients with del(17p) had only a 7% response to therapy.

Although up to 95% of patients with CLL respond to frontline FCR or BR therapy, 30% to 60% of patients fail to achieve CR and therapy results in significant toxicity.[4,7,12] Moreover, no current standard exists to treat patients with relapsed disease after frontline chemoimmunotherapy.[13] Efforts have been made to identify optimal regimens for treatment of such patients and various salvage therapeutic options have been evaluated in patients relapsing after frontline FCR, including retreatment with FCR, using lenalidomide-based or other intensive chemotherapy-based regimens.[14] Factors such as duration of initial remission were found to have a direct impact on predicted response to salvage therapy, and patients with initial remission of at least 3 years' duration showed an average post-salvage survival of 63 months versus 13 months in patients who required salvage therapy earlier than 3 years after initial course of FCR. Also affecting the response to salvage therapy were factors such as older patient age, unfavorable cytogenetics (including del[17p]), and factors dependent on the stage of disease at relapse, such as platelet count and 2-microglobulin.[14] The negative predictive value of del(17p) status is not surprising, because mechanism of disease response to fludarabine-based regimens has been previously demonstrated to rely on intact p53 function.[15] Moreover, the CLL8 trial demonstrated that FCR does not improve OS of patients with del(17p) disease (37% of patients survived at 3-year follow-up after receiving chemotherapy and 38% after chemoimmunotherapy; P =.25).[4]

Choice of salvage therapy affects response, and survival was reported to be superior in patients treated with FCR-based or lenalidomide-based regimens, compared to alemtuzumab-based or rituximab-based regimens and intensive chemotherapy (median survival of 82 months vs 29 months; P <.001).[14] Another recent retrospective study examined patient outcomes with salvage treatment after progression on FCR and showed that bendamustine-rituximab (BR) regimen was most effective when compared to retreatment with FCR, to an alemtuzumab-containing regimen, or to the combination R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone).[16] The study showed that BR produced an ORR of 86%, compared to values in the 50% to 60% range after treatment with the alternative regimens. However, patients had similar and dismal PFS of 18 months with BR or FCR and 6 months with alemtuzumab-containing regimens or R-CHOP. Predictably, patients with del(17p) disease showed lower rate of response to salvage therapy, and survival outcomes were worse in patients with disease relapse within 3 years of frontline FCR therapy.

Taken together, these studies indicate that outcomes of patients with relapsed CLL after firstline chemoimmunotherapy are poor, especially in patients who relapse less than 3 years after initial therapy, in those with del(17p), and in those with comorbid conditions. Finding effective and well-tolerated regimens for such patients that could prolong PFS and OS is vitally important and their outcomes appear to have been significantly improved with the advent of B-cell receptor (BCR) pathway inhibitors.

Specific BCR Signaling Pathway Inhibitors in Relapsed CLL

Specific inhibitors of B-cell receptor signaling, such as the BTK inhibitor ibrutinib and the phosphoinositide 3-kinase inhibitor idelalisib (in combination with rituximab), have been approved for treatment of relapsed CLL. Ibrutinib is able to inhibit BCR-signaling dependent cell division in vitro,[5,17] and has

induced substantially higher ORR and PFS in several phase II and phase III studies[18,19] in patients with relapsed and refractory CLL.[19] In a phase 1b/II study of 85 patients with previously treated CLL, 65% of whom had advanced-stage disease, 33% had de1(17p), 69% had unmutated immunoglobulin variable heavy-chain variable (IGHV) status, and 30% were >70 years of age, and had received a median of 4 previous therapies. Ibrutinib demonstrated an ORR of 91% (71% partial response [PR] and 20% PR + lymphocytosis) irrespective of the presence of high-risk features. Of note, 73% of elderly patients responded to ibrutinib, 83% of patients who were enrolled in the trial survived at 26 months, and 75% of patients were disease-free at follow-up. Ibrutinib was also shown to effectively induce an ORR in 71% and a CR in 13% of 31 elderly patients with previously untreated CLL, 6% of whom had del(17p).[20] A phase III trial compared the outcomes of ibrutinib with ofatumumab and evaluated ORR, PFS, and OS among a cohort of patients with relapsed CLL.[21] The cohort of interest included patients who were previously treated with a median of 3 prior therapies, most of whom received targeted CD20-directed therapy, and who shared the following characteristics: median age of 67 years, del(17p) in 32%, and del(11q) in 32%. At 6 months, the ibrutinib group had a PFS of 88%. The median PFS was 8 months in the ofatumumab group. Similarly, OS was significantly improved with the use of ibrutinib. These responses and improved outcomes were observed across all cohorts of patients, including patients with high-risk disease features.[21] A recent 30-month updated follow-up of the original phase I/II trial of ibrutinib demonstrated a PFS of 69% and OS of 79%. However, response frequency and durability were inferior in patients with high-risk disease features: del(17p) patients had a 30-month PFS rate of 48% and an OS rate of 65%.[22]

Idelalisib, another inhibitor that selectively targets the BCR-signaling cascade by inhibiting PI3-kinase delta, has also been tested in patients with relapsed and resistant CLL and has shown promising efficacy.[23] A phase III trial evaluated this regimen for treatment of elderly (median age 71 years) patients with comorbid conditions and high-risk relapsed disease after a median of 3 prior therapies, in comparison with placebo combined with rituximab. The trial randomized 220 patients to each arm. High-risk features included relapsed progressive disease requiring therapy within 24 months, unmutated IGHV in 83%, and del(17p) or TP53 mutations in 42% of patients. Preliminary results after 12-month follow-up showed 81% ORR, compared with 13% in the placebo-rituximab arm (P <.001), with significant improvement in response rates across all risk subgroups. While more adverse events were reported in the idelalisib plus rituximab group compared to the placebo plus rituximab group, mortality was higher in the placebo group, with 6 deaths in the idelalisib plus rituximab cohort and 13 in the placebo plus rituximab cohort.[23]

More recently, promising data have been reported with newer BTK inhibitors for the treatment of patients with relapsed disease. Prominent among these is acalabrutinib, which demonstrated an ORR of 95% with the remaining 5% of patients experiencing stable disease. Patients with del(17p) had an ORR of 100% and PFS was 100% at 12 months.[12]

Development of Resistance and Additional Limitations of Targeted Kinase Inhibitors

Review of a large, 308-patient, single-institution trial at the Ohio State University revealed that only about 10% of patients discontinued ibrutinib because of disease progression at a median follow-up of 20-months.[24] Several studies have helped to identify high-risk patients who are less likely to respond to such regimens and complex karyotype appears to be an independent predictor of resistance to ibrutinib.[24,25] Whole-exome sequencing from samples of patients with CLL at the onset of disease resistance to ibrutinib identified a C481S mutation within the ibrutinib binding site of the BTK protein that rendered the affinity interaction between BTK and ibrutinib potentially reversible.[26] The study also found R665W and L845F mutations in PLCγ2 in 2 separate samples of patients with new-onset ibrutinib resistance and identified them as potential gain-of-function mutations that could allow the BCR-dependent signaling cascade to bypass the inhibition imposed by ibrutinib.[24,26]

Additionally, other limitations of ibrutinib therapy have been identified, including an increased risk of bleeding, especially in patients on concurrent anticoagulation therapy.[27] In review of the Ohio State University experience, up to 19% of patients treated with ibrutinib stopped taking the medication because of toxicities.[24] Moreover, patients who developed resistance to ibrutinib did poorly, with most requiring alternative therapy within several weeks of stopping ibrutinib and a median survival of 17.6 months. Eighteen patients developed Richter's transformation with a median survival of only 3.5 months.[5] Similarly, idelalisib use is associated with significant pneumonitis, colitis, and transaminitis that result in significant morbidity in a subset of patients.[23]

Alternative Therapies for Relapsed Disease

Venetoclax

Targeting of Bcl-2, an anti-apoptotic protein overexpressed in CLL B cells, results in significant apoptosis in vitro and clinical activity in vivo. Venetoclax is a potent, oral Bcl-2 selective inhibitor with limited off-target effects on Bcl-xl expressed on platelets. In a large phase I study it demonstrated impressive activity in relapsed or refractory CLL with an ORR of 79% and a 20% CR. Patients with del(17p) disease had an ORR of 71% with a 16% CR.[28] Venetoclax use is complicated by serious cytopenia in almost 50% of patients and fulminant tumor lysis syndrome, especially in the presence of high tumor burden and requires

specific mitigation efforts such as stepwise dose escalation.

Lenalidomide

Lenalidomide is a potent oral immunomodulatory (IMiD) drug in the thalidomide analog class of therapeutics.[14-17] These agents, along with newer pleotropic pathway modifiers (PPM) such as CC-122, have the potential to be an option for patients with aggressive, high-risk disease. Lenalidomide has shown promising activity and reasonable tolerability in multiple clinical trials in patients with relapsed disease but its future development is questionable because the pivotal phase III trial in patients with previously untreated disease had to be halted because of increased mortality. However, it remains a reasonable option for patients with relapsed and refractory disease but patients can frequently experience tumor lysis and/or tumor flare.

Chimeric Antigen Receptor – T (CAR-T) Cells

CAR-T cells are ex vivo engineered, lentiviral-modified, autologous T cells containing an altered T-cell receptor targeting a surface antigen (eg, CD19) on CLL B cells. The chimeric T-cell receptor contains costimulatory domains that increase affinity and specificity towards the target antigen. Multiple formulations of CAR-T cells have been advanced and promising early results with sustained remissions have been reported.[29,30] Infusion of these CAR-T cells can result in severe cytokine-release syndrome that might require aggressive and intensive supportive care. Moreover, therapy results in persistent hypogammaglobulinemia from sustained normal B-cell eradication, with the resultant need for immunoglobulin supplementation and prophylaxis for infectious complications. Further design modifications may be able to overcome some of these issues.

Conclusion

While highly encouraging and durable responses are observed in patients with recurrent or resistant CLL who are treated with selective kinase inhibitors ibrutinib and idelalisib, there remains a substantial fraction of patients with relapsed CLL and high-risk disease features who fail to achieve sustained PFS with these therapies. This is despite the fact that many patients with conventional high-risk features, such as old age, unmutated IGHV status, presence of del(17p) or mutated TP53, and complex karyotype have been shown to respond to single-agent or combined therapies with kinase inhibitors. Acquisition of mutations within the mediators of BCR-dependent signaling pathway precipitates resistance to ibrutinib. Additional toxicities and individualized limitations of targeted kinase inhibitors may limit their utility in particular cases of CLL relapse. However, the advent of additional BTK inhibitors, such as acalabrutinib,[12] and other BCR pathway inhibitors, such as entospletinib,[31] along with Bcl-2 inhibitors such as venetoclax,[28] portends a bright future for the management of patients with relapsed CLL and potentially offers better-tolerated and more efficacious options for these patients. Specific considerations for the use of these agents are summarized in **Table 1**. Together, these considerations highlight the vital importance of enrolling patients with relapsed CLL, especially those with high-risk disease features, into clinical trials to ensure the development of additional potentially curative therapeutic avenues.

TABLE 1: Therapeutic Regimens for Patients With Relapsed CLL and Special Considerations

Therapeutic Regimens	Therapeutic Considerations
FCR or BR	▪ Prolonged (>3 years) first remission ▪ Younger patients (<65 years) with good performance status ▪ Patients with good-risk genetic features, including del13q and mutated IGHV
Ibrutinib	▪ Preferred agent for patients with del(17p) disease ▪ Avoid use in patients on concurrent anticoagulation
Idelalisib	▪ Promising activity in patients with del(17p) disease and/or unmutated IGHV ▪ Issues with transaminitis, pneumonitis, and colitis
Venetoclax	▪ Deeper responses even in patients with high-risk disease ▪ Issues with tumor lysis and cytopenia

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REFERENCES

1. Awan FT. Cure for CLL? *Blood*.2016;127(3):274. doi: 10.1182/blood-2015-11-678532.
2. Awan FT, Byrd JC. New strategies in chronic lymphocytic leukemia: shifting treatment paradigms. *Clin Cancer Res*. 2014;20(23):5869-5874. doi: 10.1158/1078-0432.CCR-14-1889.
3. Tam CS, O'Brien S, Wierda W, et al. Long-term results of

the fludarabine, cyclophosphamide, and rituximab regimen as initial therapy of chronic lymphocytic leukemia. *Blood*. 2008;112(4):975-980. doi: 10.1182/blood-2008-02-140582.

4. Hallek M, Fischer K, Fingerle-Rowson G, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. *Lancet*. 2010;376(9747):1164-1174. doi: 10.1016/S0140-6736(10)61381-5.

5. Eichhorst B, Fink AM, Busch R, et al. Frontline chemoimmunotherapy with fludarabine (F), cyclophosphamide (C), and rituximab (R) (FCR) shows superior efficacy in comparison to bendamustine (B) and rituximab (BR) in previously untreated and physically fit patients (pts) with advanced chronic lymphocytic leukemia (CLL): final analysis of an international, randomized study of the German CLL Study Group (GCLLSG) (CLL10 Study). American Society of Hematology website. https://ash.confex.com/ash/2014/webprogram/Paper69485.html.

6. Goede V, Fischer K, Engelke A, et al. Obinutuzumab as frontline treatment of chronic lymphocytic leukemia: updated results of the CLL11 study. *Leukemia*. 2015;29(7):1602-1604. doi: 10.1038/leu.2015.14.

7. Hillmen P, Robak T, Janssens A, et al. Chlorambucil plus ofatumumab versus chlorambucil alone in previously untreated patients with chronic lymphocytic leukaemia (COMPLEMENT 1): a randomised, multicentre, open-label phase 3 trial. *Lancet*. 2015;385(9980):1873-1883. doi: 10.1016/S0140-6736(15)60027-7.

8. Burger JA, Tedeschi A, Barr PM, et al. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. *N Engl J Med*. 2015;373(25):2425-2437. doi: 10.1056/NEJMoa1509388.

9. Robak T, Dmoszynska A, Solal-Céligny P, et al. Rituximab plus fludarabine and cyclophosphamide prolongs progression-free survival compared with fludarabine and cyclophosphamide alone in previously treated chronic lymphocytic leukemia. *J Clin Oncol*. 2010;28(10):1756-1765. doi: 10.1200/JCO.2009.26.4556.

10. Awan FT, Hillmen P, Hellmann A, et al. A randomized, open-label, multicentre, phase 2/3 study to evaluate the safety and efficacy of lumiliximab in combination with fludarabine, cyclophosphamide and rituximab versus fludarabine, cyclophosphamide and rituximab alone in subjects with relapsed chronic lymphocytic leukaemia. *Br J Haematol*. 2014;167(4):466-477. doi: 10.1111/bjh.13061.

11. Fischer K, Cramer P, Busch R, et al. Bendamustine combined with rituximab in patients with relapsed and/or refractory chronic lymphocytic leukemia: a multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. *J Clin Oncol*. 2011;29(26):3559-3566. doi: 10.1200/JCO.2010.33.8061.

12. Byrd JC, Harrington B, O'Brien S, et al. Acalabrutinib (ACP-196) in relapsed chronic lymphocytic leukemia. *N Engl J Med*. 2016;374(4):323-332. doi: 10.1056/NEJMoa1509981.

13. Buhler A, Wendtner CM, Kipps TJ, et al. Lenalidomide treatment and prognostic markers in relapsed or refractory chronic lymphocytic leukemia: data from the prospective, multicenter phase-II CLL-009 trial. *Blood Cancer J*. 2016;6:e404. doi: 10.1038/bcj.2016.9.

14. Wendtner CM, Hallek M, Fraser GA, et al. Safety and efficacy of different lenalidomide starting doses in patients with relapsed or refractory chronic lymphocytic leukemia: results of an international multicenter double-blinded randomized phase II trial. *Leuk Lymphoma*. 2016;1-9.

15. Maddocks K, Ruppert AS, Browning R, et al. A dose escalation feasibility study of lenalidomide for treatment of symptomatic, relapsed chronic lymphocytic leukemia. *Leuk Res*. 2014;38(9):1025-1029. doi: 10.1016/j.leukres.2014.05.011.

16. Wendtner CM, Hillmen P, Mahadevan D, et al. Final results of a multicenter phase 1 study of lenalidomide in patients with relapsed or refractory chronic lymphocytic leukemia. *Leuk Lymphoma*. 2012;53(3):417-423. doi: 10.3109/10428194.2011.618232.

17. Awan FT, Johnson AJ, Lapalombella R, et al. Thalidomide and lenalidomide as new therapeutics for the treatment of chronic lymphocytic leukemia. *Leuk Lymphoma*. 2010;51(1):27-38. doi: 10.3109/10428190903350405.

18. Advani RH, Buggy JJ, Sharman JP, et al. Bruton tyrosine kinase inhibitor ibrutinib (PCI-32765) has significant activity in patients with relapsed/refractory B-cell malignancies. *J Clin Oncol*. 2013;31(1):88-94. doi: 10.1200/JCO.2012.42.7906.

19. Byrd JC, Furman RR, Coutre SE, et al Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. *N Engl J Med*. 2013;369(1):32-42. doi: 10.1056/NEJMoa1215637.

20. O'Brien S, Furman RR, Coutre SE, et al. Ibrutinib as initial therapy for elderly patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma: an open-label, multicentre, phase 1b/2 trial. *Lancet Oncol*. 2014;15(1):48-58. doi: 10.1016/S1470-2045(13)70513-8.

21. Byrd JC, Brown JR, O'Brien S, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. *N Engl J Med*. 2014;371(3):213-223. doi: 10.1056/NEJMoa1400376.

22. Byrd JC, Furman RR, Coutre SE, et al. Three-year follow-up of treatment-naive and previously treated patients with CLL and SLL receiving single-agent ibrutinib. *Blood*. 2015;125(16):2497-2506. doi: 10.1182/blood-2014-10-606038.

23. Furman RR, Sharman JP, Coutre SE, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. *N Engl J Med*. 2014;370(11):997-1007. doi: 10.1056/NEJMoa1315226.

24. Maddocks KJ, Ruppert AS, Lozanski G, et al. Etiology of ibrutinib therapy discontinuation and outcomes in patients with chronic lymphocytic leukemia. *JAMA Oncol*. 2015;1():80-87.

25. Thompson PA, O'Brien SM, Wierda WG, et al. Complex karyotype is a stronger predictor than del(17p) for an inferior outcome in relapsed or refractory chronic lymphocytic leukemia patients treated with ibrutinib-based regimens. *Cancer*. 2015;121():3612-3621.

26. Woyach JA, Furman RR, Liu TM, et al. Resistance mechanisms for the Bruton's tyrosine kinase inhibitor ibrutinib. *N Engl J Med*. 2014;370():2286-2294.
27. Lipsky AH, Farooqui MZ, Tian X, et al. Incidence and risk factors of bleeding-related adverse events in patients with chronic lymphocytic leukemia treated with ibrutinib. *Haematologica*. 2015;100(12):1571-1578. doi: 10.3324/haematol.2015.126672.
28. Roberts AW, Davids MS, Pagel JM, et al. Targeting BCL2 with venetoclax in relapsed chronic lymphocytic leukemia. *N Engl J Med*. 2016;374(4):311-322. doi: 10.1056/NEJMoa1513257.
29. Porter DL, Levine BL, Kalos M, et al. Chimeric antigen receptor-modified T cells in chronic lymphoid leukemia. *N Engl J Med*. 2011;365(4):725-733. doi: 10.1056/NEJMoa1513257.
30. Gill S, June CH. Going viral: chimeric antigen receptor T-cell therapy for hematological malignancies. *Immunol Rev*. 2015;263(1):68-89. doi: 10.1111/imr.12243.
31. Sharman J, Hawkins M, Kolibaba K, et al. An open-label phase 2 trial of entospletinib (GS-9973), a selective spleen tyrosine kinase inhibitor, in chronic lymphocytic leukemia. *Blood*. 2015;125(15):2336-2343. doi: 10.1182/blood-2014-08-595934.