Contents lists available at ScienceDirect

Acta Haematologica Polonica

journal homepage: www.elsevier.com/locate/achaem

Review/Praca poglądowa

New horizons in the treatment of chronic lymphocytic leukemia

Nowe horyzonty w leczeniu przewlekłej białaczki limfocytowej

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ARTICLE INFO

Article history:
Received: 18.03.2014
Accepted: 31.03.2014
Available online: 13.04.2014

Keywords:
- ABT-199
- Ibrutinib
- Idelalisib
- Obinutuzumab
- Otlertuzumab
- CART

Słowa kluczowe:
- ABT-199
- Ibrutinib
- Idelalisib
- Obinutuzumab
- Otlertuzumab
- CART

ABSTRACT

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia in the western world, accounting for approximately 30% of all leukemias in Europe and North America. Recently, significant progress in the characterization and understanding of the biology and prognosis of CLL has provided new opportunities for the development of innovative, more effective therapies. Several new anti-CD20 monoclonal antibodies directed against lymphoid cells have been developed and are under investigation in preclinical studies and clinical trials. Currently, the most promising is obinutuzumab, a novel third generation anti-CD20 monoclonal antibody that exhibits superior caspase-independent apoptosis and antibody-dependent cellular cytotoxicity than rituximab. The antibody has shown a safety profile similar to that of rituximab and promising efficacy in patients with CLL. The CD37 antigen may be advantageous over CD20 in diseases in which the level of CD37 expression is higher than that of CD20. The results of recent preclinical and early clinical studies suggest that anti-CD37 antibodies and related agents can be useful in the treatment of CLL, and many small molecule inhibitors targeting B-cell antigen receptor (BCR) signaling pathways have recently been under investigation in patients. Promising clinical results have been observed with a Btk inhibitor, ibrutinib, and a selective inhibitor of PI3Kδ, idelalisib. Several other agents including immunomodulating agents and those targeting the antiapoptotic bcl-2 family of proteins also show promise in treating CLL. Moreover, immune-based treatment strategies intended to augment the cytotoxic potential of T cells offer exciting new treatment options for patients with CLL.

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http://dx.doi.org/10.1016/j.achaem.2014.04.008

Introduction

Chronic lymphocytic leukemia (CLL) is a B-cell malignant disease with a progressive accumulation of B cells in the blood, bone marrow and lymphatic tissue, and follows an extended disease course. It is the most prevalent leukemia in the Western World with an estimated 15, 720 new cases in 2014 and almost 4600 attributable deaths per year in the United States [1]. The median age at diagnosis is 72 years and 90% of patients are older than 50 years. The diagnosis of CLL requires the presence of at least 5000 leukemic B lymphocytes per microliter in the peripheral blood [2]. The management of CLL is determined by the stage and activity of the disease, as well as age and comorbidities. Randomized studies and a meta-analysis indicate that early initiation of chemotherapy does not show benefit in CLL and may increase mortality. There is no evidence that cytotoxic therapy based on alkylating agents has beneficial effects in patients with the indolent form of the disease [3]. The strategy of watchful waiting or observation, *i.e.* closely monitoring patient status without giving any treatment until progression, may be adopted [4]. However, patients with symptomatic and/or progressive disease should be immediately treated.

CLL is typically sensitive to a variety of cytotoxic drugs, but the disease is considered incurable. There has been an important increase in the range of available therapeutic options in recent years, and many drugs are now in the process of making the transition to the clinic [5]. The approval of rituximab-based immunochemotherapy can be viewed as a substantial therapeutic advance in CLL. A large phase III randomized trial demonstrated that rituximab combined with fludarabine and cyclophosphamide (RFC) increased the overall response (OR) and complete response (CR) rates, and prolonged progression free survival (PFS) and overall survival (OS) compared with fludarabine and cyclophosphamide (FC) in previously untreated and relapsed/refractory patients [6, 7]. For the last twenty years, significant progress in molecular and cellular biology has resulted in a better characterization and understanding of the biology and prognosis of CLL. These achievements have provided new opportunities for the development of innovative, more effective therapies in this disease.

Monoclonal antibodies and related agents

Several new anti-CD20 monoclonal antibodies directed against lymphoid cells have been developed and investigated in preclinical studies and clinical trials [8]. The results of preclinical and clinical studies suggest that therapy which uses monoclonal antibodies (mAbs) directed at a target other than CD20 can be useful in treating CLL [9]. Such treatments include lumiliximab (anti-CD23), epratuzumab (anti-CD22), apolizumab (anti-MHC-II), galiximab (anti-CD80), anti-CD40 monoclonal antibodies and TRU-016, a small modular immunopharmaceutical (SMIP) derived from the fusion of key domains of an anti-CD37 antibody with a human protein.

Novel anti-CD20 antibodies

Several new anti-CD20 monoclonal antibodies directed against lymphoid cells have been developed and investigated in preclinical studies and clinical trials [8]. Obinutuzumab (Gazyva™, GA-101, RO5072759, Roche) is a novel third generation monoclonal antibody which is distinct from rituximab [10]. The antibody is based on proprietary GlycoMAb® technology, which incorporates glycoengineered antibodies that specifically increase antibody-dependent cellular cytotoxicity (ADCC) and thereby increase immune-mediated target cell death, and is obtained by humanization of the parental B-Ly1 mouse antibody followed by a glycoengineering process developed by GlycArt Biotechnology (later Roche Glycart AG). Compared to rituximab, obinutuzumab treatment leads to 5–100 times greater induction of ADCC, as it binds with high affinity to the CD20 epitope, and also exhibits superior caspase-independent apoptosis induction [11, 12]. However, reduction in complement-dependent cytotoxicity (CDC) upon binding to CD20 was observed. Based on this data, obinutuzumab mAb is a promising therapeutic agent for CD20 positive B-cell lymphoid malignancies, including CLL.

In a phase I/IIa study, obinutuzumab was administered as a single agent to 24 patients, at doses from 50 to 2000 mg [13]. The antibody has shown a safety profile similar to that of rituximab and promising efficacy in patients with CLL and other $CD20^+$ malignant disease, for whom no therapy of higher priority was available [14]. The results of a large randomized phase III trial testing three first-line chemoimmunotherapy regimes, *i.e.* combined obinutuzumab and chlorambucil, combined rituximab and chlorambucil and chlorambucil monotherapy, in patients with comorbidities have been recently reported (CLL11) [15, 16]. In this trial 781 patients with previously untreated CLL and a score higher than 6 on the Cumulative Illness Rating Scale (CIRS) or an estimated creatinine clearance of 30–69 ml per minute were included. Treatment with obinutuzumab–chlorambucil, as compared with rituximab–chlorambucil, resulted in higher rates of complete response (20.7% *vs.* 7.0%) and molecular response. The primary end point was investigator-assessed PFS. Treatment with obinutuzumab–chlorambucil or rituximab–chlorambucil increased response rates and prolonged PFS as compared with chlorambucil monotherapy. Median PFS was 26.7 months with obinutuzumab–chlorambucil, 15.2 months for rituximab–chlorambucil, and 11.1 months for chlorambucil alone ($P < 0.001$). In addition, patients treated with obinutuzumab–chlorambucil had longer OS than those treated with chlorambucil alone ($P = 0.002$). However, infusion-related reactions and neutropenia were more common in patients treated with obinutuzumab–chlorambucil than with rituximab–chlorambucil. Obinutuzmab–chlorambucil treatment was associated with more grade 3–4 adverse events, mainly infusion-related reactions that occurred during the first infusion. Infusion-related reactions were noted in 20% of patients treated with obinutuzumab–chlorambucil and 4% of patients treated with rituximab–chlorambucil. In contrast, the risk of infection was similar in both arms. The U.S. Food and Drug Administration (FDA) approved obinutuzumab for use with chlorambucil in patients with previously untreated chronic lymphocytic leukemia [17].

Ofatumumab (HuMax-CD20; Arzerra™, GlaxoSmithKline plc/Genmab A/S) is a fully human, IgG1 mAb recognizing a different CD20 epitope to rituximab, and demonstrating a higher cytotoxic potential than rituximab [18]. Ofatumumab is more effective than rituximab at CDC induction and killing target cells [19]. The close binding proximity of ofatumumab to the cell membrane likely results in highly efficient complement deposition on B-cell membranes, without high levels of systemic release of activated complement components [20]. Ofatumumab, in comparison to rituximab, demonstrates greater CDC in B-cells and does not induce cell death by apoptosis.

The results of a phase III study demonstrate that ofatumumab monotherapy shows promising efficacy in heavily pretreated patients with fludarabine- and alemtuzumab-refractory CLL [21]. In this study, patients received eight once-weekly infusions of ofatumumab followed by four once-monthly infusions during a 24-week period. The OR rates were 58% and 47% in the fludarabine- and alemtuzumab-refractory groups and fludarabine-refractory CLL with bulky lymphadenopathy groups, respectively. The OR rates among patients refractory to RFC were 50% and 44% in the fludarabine- and alemtuzumab-refractory groups, respectively. Median PFS and OS times were 5.7 and 13.7 months in the fludarabine- and alemtuzumab-refractory groups, and 5.9 and 15.4 months, respectively, in the fludarabine-refractory patients with bulky lymphadenopathy. In 2009, the FDA granted accelerated approval to ofatumumab for the treatment of patients with fludarabine- and alemtuzumab-refractory CLL, based on a clinically meaningful and durable ORR observed in the above trial (Hx-CD20-406). In 2010, the European Medicines Agency (EMA) granted a conditional marketing authorization for ofatumumab, for the treatment of fludarabine- and alemtuzumab-refractory CLL patients.

In a recent randomized trial (Complement 1), ofatumumab + chlorambucil therapy was compared with chlorambucil alone in patients with CLL who required therapy and were considered inappropriate for fludarabine-based therapy due to advanced age and/or co-morbidities [22]. The results of this study indicate that ofatumumab + chlorambucil is superior than chlorambucil alone in this patient population. The ofatumumab + chlorambucil arm demonstrated a higher OR rate than the chlorambucil arm (82% *vs.* 69%) ($P = 0.001$), as well as a superior CR rate (12% *vs.* 1%). PFS was also significantly prolonged in the ofatumumab + chlorambucil arm (22.4 months) compared to chlorambucil alone (13.1 months, $P < 0.001$). With a median follow-up of 29 months, median OS was not reached for both the groups.

Anti-CD37 antibodies

CD37 is a heavily glycosylated 40–52 kDa tetraspanin transmembrane family protein, which consists of 4 potential membrane-spanning regions, 2 extracellular loops and 2 short intracytoplasmic tails [23]. This molecule may play a role in immune cell proliferation and influences signaling *via* the Akt pathway [24]. CD37 is selectively expressed on mature B cells, with its highest expression on peripheral blood B cells. Its significant expression was found on neoplastic cells of patients with CLL, hairy cell leukemia and non-Hodgkin's lymphoma (NHL) [25]. The relative lineage restriction of CD37 to B cells makes it a suitable target for immunotherapy. CD37 internalizes and has modest shedding in the malignant B cells which express it. It may be advantageous to target CD37 over CD20 in diseases in which the level of CD37 expression is higher than that of CD20. The predominant expression of CD37 on CLL cells makes it an ideal candidate as a therapeutic target for treatment of CLL and has aroused great interest in the investigation of anti-CD37 antibodies [26, 24].

The results of recent preclinical and early clinical studies suggest that anti-CD37 antibodies can be useful in the treatment of CLL [27]. BI 836826 (MAb 37.1) is a chimeric IgG1 type of anti-CD37 molecule which has been Fc-engineered to improve ADCC activity and enhance affinity for Fc-gRIIIa. Both mAb 37.1 and its humanised version, MAb 37.2, deplete CLL cells *in vitro* more effectively than rituximab and alemtuzumab [28]. BI 836826 is under investigation in CLL in a phase I clinical trial (ClinicalTrials.gov Identifier: NCT01296932).

Otlertuzumab (TRU-016) is produced using ADAPTIR™ Modular Protein Technology and has shown activity in preclinical studies and clinical trials [29]. ADAPTIR proteins have a differentiated structure from classical mAbs and can generate a unique signaling response. In addition, they may mediate CDC and Fc-dependent cytotoxicity in a similar way to mAbs. Otlertuzumab is an engineered protein that includes anti-CD37 variable regions linked to an immunoglobulin constant domain, produced by humanizing the precursor agent SMIP-016, a single chain monospecific protein that retains Fc-mediated effector functions [29, 30]. In preclinical studies this agent was found to employ a mechanism of apoptosis distinct from those of other agents used for CLL treatment. In addition, otlertuzumab has demonstrated a significantly greater ability to directly kill CLL cells than rituximab and greater Fc-mediated cellular cytotoxicity of CLL cells than either alemtuzumab or rituximab [31]. TRU-016 also mediates greater NK cell mediated killing of CLL cells as compared to either alemtuzumab or rituximab and mediates superior direct apoptosis of CLL and other B-cell malignancies. Moreover, otlertuzumab acts synergistically with bendamustine.

A phase I study investigated otlertuzumab in patients with relapsed/refractory CLL or SLL [32]. TRU-016 was well tolerated with minimal infusional toxicity. Response occurred in 19 of 83 treated patients (23%) according to NCI-96 criteria. All responses were partial, and occurred more commonly in patients with symptomatic, untreated CLL. Recently, the results of a randomized trial of otlertuzumab + bendamustine *vs.* bendamustine alone were reported [33]. Patients with relapsed CLL who had undergone 1–3 prior therapies received otlertuzumab (20 mg/kg) weekly by i.v. infusion for two 28-day cycles then every 14 days for four 28-day cycles, and bendamustine (70 mg/m^2) was administered i.v. on days 1 and 2 of each cycle for up to six 28-day cycles. In the control arm, bendamustine (70 mg/m^2) was given i.v. on days 1 and 2 of each cycle for up to six 28-day cycles. Among 65 patients included in the study, 32 received otlertuzumab plus bendamustine and 33 were treated with bendamustine alone. The response rate observed in patients treated with otlertuzumab + bendamustine was higher than that in those treated with bendamustine alone. According to the NCI assessment, the

OR rate in the otlertuzumab + bendamustine arm was 75%, with a CR rate of 48%, compared to an OR rate of 52% and a CR rate of 9% in the bendamustine arm. No increase in serious adverse events were noted in the otlertuzumab + bendamustine arm *versus* the bendamustine arm. A higher rate of neutropenia was observed, but no greater rate of infection was seen in the combination arm. Neutropenia was noted in 50% of patients from the otlertuzumab + bendamustine group and 39% in the control arm. Infections were noted in 50% of the patients in the otlertuzumab + bendamustine arm compared to 55% in the bendamustine arm, similarly, pneumonia was observed in 9% and 15% of patients in the combined and monotherapy groups, and grade 3/4 thrombocytopenia was observed in 19% and 12%. These results suggest that otlertuzumab can be a valuable drug in CLL, but its success will depend on it demonstrating superiority over available monoclonal antibodies and other emerging therapies in achieving and sustaining CRs and improving survival. Future phase II and III clinical trials in the development of otlertuzumab should also evaluate combinations with chemotherapy and/or other targeted therapies in comparison with what is considered standard of care, especially R-FC, in CLL patients.

The clinical development of anti-CD37 mAbs and related agents for the treatment of CLL is challenging, and future phase II and III clinical trials of otlertuzumab and BI 836826 in CLL patients should be informative. Although the development of these agents into a clinically useful therapy is probably many years away, its progress will be followed with great interest by laboratory investigators and clinicians.

B-cell receptor inhibitors

The use of B-cell antigen receptor (BCR) signal transduction inhibitors also represents a promising new strategy for targeted CLL treatment. Recently, many small molecule inhibitors targeting BCR signaling pathways have been under investigation in patients with CLL, including Bruton's tyrosine kinase (Btk) inhibitors, spleen tyrosine kinase (Syk) inhibitors and phosphatidylinositol 3-kinase-δ (PI3Kδ) inhibitors [34]. These agents induce rapid resolution of lymphadenopathy and a transient increase in lymphocytosis due to mobilization of CLL cells into the peripheral blood. BCR inhibitors are highly active and well tolerated in CLL patients, irrespective of high-risk genomic abnormalities and suggest that these drugs may be an important new targeted treatment approach for this disorder [34].

Promising clinical results have been observed with a Btk inhibitor, ibrutinib (PCI-32765, Pharmacyclics), and a selective inhibitor of PI3Kδ, idelalisib (CAL-101, GS-1101, Calistoga Pharmaceuticals/Gilead) (Fig. 1). These drugs are available in oral preparations and are given as continuous treatment. They seem to be active in traditionally poor risk disease groups, including fluarabine-refractory patients and patients with bulky lymphadenopathy. These drugs are part of a promising new strategy for targeted treatment of CLL

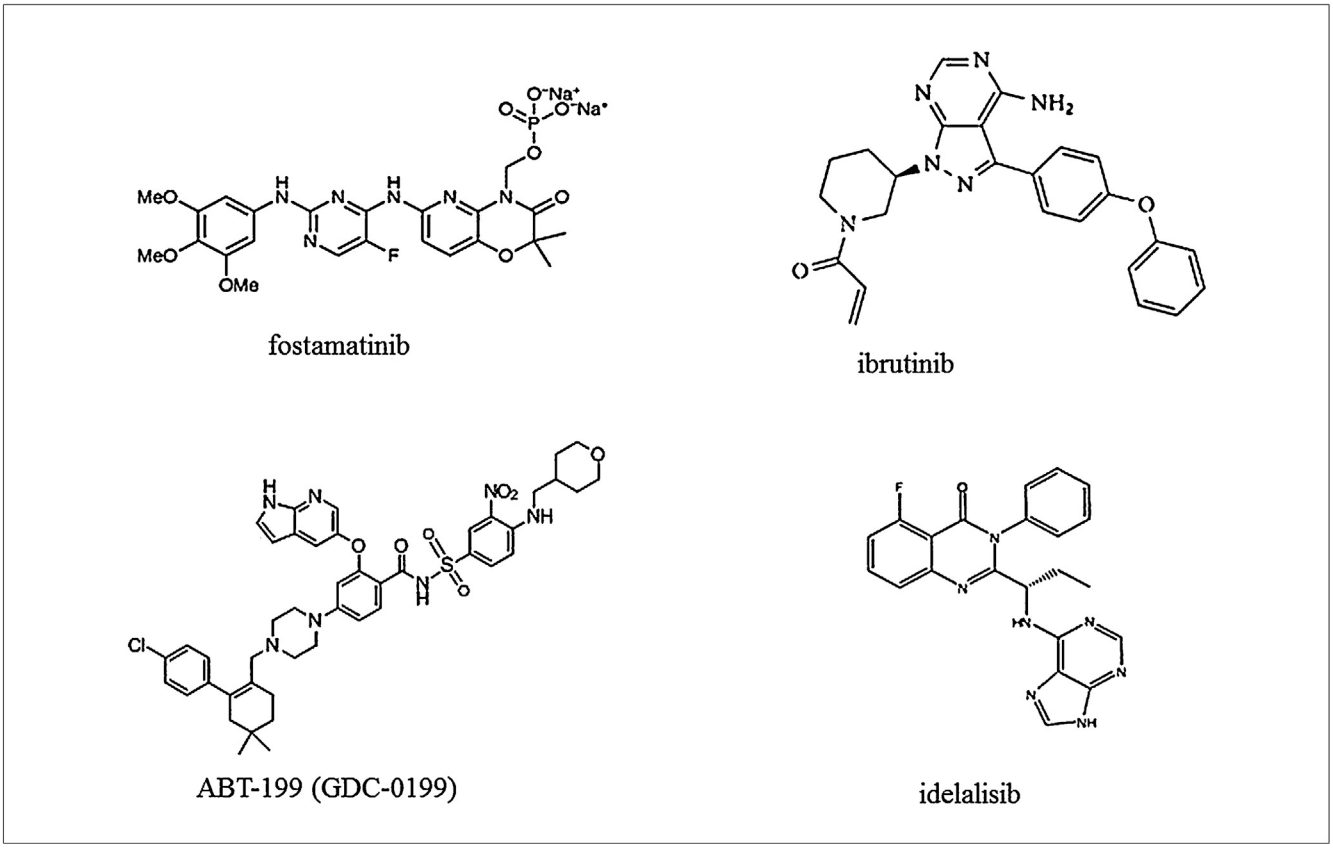

Fig. 1 – Chemical structures of new small molecules potentially useful in the treatment of CLL

and are currently undergoing clinical development. These agents induce rapid resolution of lymphadenoapathy and a transient increase of lymphocytosis due to mobilization of CLL cells into the peripheral blood. However, after several months of continuous therapy, response can be achieved in a substantial number of patients [35, 36].

Ibrutinib

Ibrutinib (PCI-32765; Imbruvica, Pharmacyclics, Inc./Johnson & Johnson) is an irreversible covalent inhibitor of the Btk, a critical enzyme in the BCR signaling pathway that is essential for B-cell proliferation, survival, migration, and tissue homing [34, 37]. It is a first-in-class, oral covalent inhibitor of Btk designed for treatment of B-cell lymphoid malignancies. Initial reports on the use of ibrutinib as a single agent found that it was well-tolerated and particularly active in patients with refractory/relapsed CLL patients. The most common adverse reactions reported in the CLL clinical trials were thrombocytopenia, diarrhea, bruising, neutropenia, anemia, fatigue, musculoskeletal pain, rash, pyrexia, constipation and arthralgia.

Byrd et al. conducted a phase Ib/II multicenter study to assess the safety, efficacy, pharmacokinetics, and pharmacodynamics of ibrutinib in relapsed CLL [38]. A total of 85 patients were treated with ibrutinib orally once daily, including 51 who received 420 mg, and 34 who received 840 mg. Ibrutinib was associated with a high frequency of durable remissions in patients with relapsed or refractory CLL. The OR rate was similar between patients who received 420 mg and those who received 840 mg (71%). In addition, CR was noted in 20% and 15% of patients, respectively. The responses were independent of clinical and genomic risk factors noted before treatment, including advanced-stage disease, the number of previous therapies, and 17p13.1 deletion. At 26 months, the estimated PFS rate was 75% and the OS rate was 83%. Toxic effects included transient diarrhea, fatigue, and upper respiratory tract infections. Hematologic toxic effects were minimal and the patients could receive extended therapy. O'Brien et al. assessed the safety and activity of ibrutinib in 29 treatment-naive patients with CLL, aged 65 years and older, in open-label phase Ib/II trial [39]. After a median follow-up of 22 months, 22 of 31 patients (71%) achieved an objective response, including 4 CR (13%), 1 (3%) nodular PR, and 17 (55%) PR. In 21 (68%) patients, diarrhea was observed including grade 2 in three patients, and grade 3 in four patients.

Ibrutinib in combination with rituximab is well tolerated and displays significant activity in high-risk CLL [40]. In updated phase II single-center clinical trial, with a median follow-up of 14 months, 40 patients were treated with ibrutinib 420 mg p.o. daily continuously throughout the study with rituximab 375 mg/m^2 administered weekly for the first four weeks in cycle 1 and then monthly until cycle 6. Twenty patients had del17p or *TP53* mutation and 13 patients had del11q. In the updated analysis, 34 (87%) patients achieved a PR, and three (8%) a CR, accounting for an OR rate of 95%. The OR rate in the 20 patients with del17p or *TP53* mutation was 90%.

A combination of ibrutinib and bendamustine (BR) is also highly active and well tolerated in patients with relapsed/refractory CLL [41]. In the study performed by Brown et al., 30 patients with refractory/relapsed CLL and a median of 2 prior therapies received up to 6 cycles of BR with a continuous fixed ibrutinib dose of 420 mg/day until disease progression or toxicity. The OR rate was 93%, including 5 CRs and 3 nodular PR (nPR), and one additional patient achieved a PR with lymphocytosis. The estimated 12 month PFS was 90%. The most frequently reported adverse events (AEs) were diarrhea (70%), nausea (66.7%), fatigue (46.7%), neutropenia (40%) and upper respiratory tract infection (36.7%). The most frequently reported grade 3 or higher AEs were neutropenia, maculopapular rash, fatigue and thrombocytopenia.

A randomized, multicenter, open-label, phase III study based on a randomized group of previously treated patients with CLL or SLL who were not considered candidates for treatment with purine analog-based treatments, was initiated in June 2012 (ClinicalTrials.gov Identifier: NCT01578707). Ofatumumab was administered over 24 weeks for 12 doses or until disease progression or unacceptable toxicity at 300 mg initial dose and then 2000 mg once weekly in week 2 through 8, and then every 4 weeks on week 12, 16, 20 and 24. Ibrutinib was given at a dose of 420 mg (3 × 140-mg capsules) orally once daily until disease progression or unacceptable toxicity. After interim analysis, the trial was stopped early because of an improvement in PFS and OS in the ibrutinib arm. In February 2014, FDA granted accelerated approval to ibrutinib for the treatment of patients with CLL who have received at least one prior therapy. The recommended dose and schedule of ibrutinib for patients with CLL is 420 mg taken orally once daily. However, ibrutinib will be an expensive drug. Some analysts estimate that it will cost $98 000 a year [37].

Idelalisib

Idelalisib (CAL-101, GS-1101, Calistoga Pharmaceuticals/Gilead) is an oral, first-in-class specific inhibitor of PI3Kδ with potent apoptotic activity against leukemic CLL cells. PI3Kδ signaling is hyperactive in many B-cell malignancies, including CLL. Idelalisib used in monotherapy has shown substantial clinical activity and a favorable safety profile in heavily pretreated, refractory and high-risk patients with CLL.

In a phase I study, patients with relapsed/refractory CLL were treated continuously with oral idelalisib as a single agent at a dose of 50 mg (QD or BID) [42]. The final results of this study were recently reported [43]. Fifty-four patients were treated continuously with single-agent idelalisib at 50–350 mg/dose (QD or BID). The overall response rate was 56% including 2 CR and 28 PR. The median time to first response was 1.9 months and median PFS was 17 months. The most common grade ≥3 AEs included fatigue, diarrhea, pyrexia, rash, upper respiratory tract infection and pneumonia. Coutre et al. report that idelalisib as a single salvage therapy offered impressive response rates in heavily pretreated patients with relapsed/refractory CLL [44]. Idelalisib showed robust activity independent of high-risk features, including del(17p)/*TP53* mutation, del(11q), *IGHV* mutation, and *NOTCH1* mutation.

Barrientos et al. presented the results of a phase I study of idelalisib in combination with rituximab and/or bendamustine in patients with relapsed or refractory CLL [45]. The overall response rate was 81%, including a CR in one patient. The median time to response was 1.9 months, and the 2-year PFS and OS were 62% and 85%, respectively. The most common grade ≥3 AEs were pyrexia, diarrhea, cough, fatigue and nausea. These results indicate that a combination of idelalisib with rituximab and/or bendamustine is tolerable and highly active in patients with relapsed or refractory CLL. O'Brien et al. recently reported the results of an up-front therapy with idelalisib and rituximab in patients over 64 years old with CLL [46]. They were treated with rituximab given at a dose of 375 mg/m^2 weekly for 8 weeks and idelalisib 150 mg BID continuously for 48 weeks. Patients completing 48 weeks of treatment without progression continued to receive idelalisib on an extension study. The overall response rate was 96% for the first 50 of the 64 enrolled patients and PFS was 91% at 24 months. Of note, all six patients with del(17p) responded, including one with a CR, and there have been no on-study relapses.

The results of a recently published multicenter, randomized, double-blind, placebo-controlled, phase III study indicate that a combination of idelalisib and rituximab significantly improved OR rate, PFS and OS in patients with relapsed CLL compared with rituximab alone [47]. The study was stopped prematurely, after the first interim analysis, due to the advantage of combination therapy over monotherapy with rituximab. Patients receiving idelalisib + rituximab had OR rate 81% and those receiving rituximab alone had OR rate 13% ($P < 0.001$). The median PFS was 5.5 months in the rituximab group and was not reached in the idelalisib + rituximab group ($P < 0.001$) and overall survival at 12 months (92% *vs.* 80% ($P = 0.02$), respectively. Serious AEs were similar in both arms and occurred in 40% of the patients receiving idelalisib + rituximab and in 35% of those receiving rituximab. Another phase III, randomized study evaluating the efficacy and safety of idelalisib in combination with bendamustine and rituximab for previously treated CLL was initiated in June 2012 [48]. In addition, a phase III, randomized, controlled study evaluating the efficacy and safety of idelalisib in combination with ofatumumab for previously treated CLL has also been initiated (NCT01659021).

Bcl-2 inhibitors

Bcl-2 proteins play a central role in enhancing cell death activity and are thought to impact tumor formation, growth and resistance. They are expressed at high levels in B-cell NHL, CLL and other B-cell neoplasms. Overexpression of the prosurvival protein Bcl-2 is a characteristic feature of many B-lymphoid malignancies and contributes to resistance to many commonly used chemotherapeutic agents. ABT-199 (GDC-0199, RG7601) is a novel, orally bioavailable, small molecule with a high-affinity Bcl-2-selective BH3 mimetic, recently developed by Abbott Laboratories [49]. This agent specifically causes Bax/Bak-mediated apoptosis triggered principally by the initiator BH3-only Bim protein. ABT-199 can trigger apoptosis *in vitro*, even in del(17p) CLL cells. Leukemic cells isolated from patients with CLL as well as normal B-cells are also highly sensitive to ABT-199 both *in vitro* and *in vivo* [50]. The results of an early clinical trial show that ABT-199 has promising potential in the treatment of CLL [51]. In contrast to the BH3 mimetic ABT-737 and the related orally available compound ABT-263 (navitoclax), ABT-199 is effective in prolonging the survival of immunocompetent tumor-bearing mice and spared human platelets *in vitro* and dog platelets *in vivo* without causing thrombocytopenia [52].

The results of a phase I, dose-escalation study of ABT-199 in high-risk relapsed/refractory CLL was recently presented [53]. Cohorts received a single dose of ABT-199 on week 1, day 3 (W1D-3) or day 7 (W1D-7), followed by continuous once-daily dosing from W1D1, until disease progression or unacceptable toxicity, at doses from 150 to 1200 mg. Fifty-six patients were enrolled, including 17 (38%) with del(17p) and 18 (32%) with fludarabine-refractory disease. The OR rate was 84%, including 20% CR/CRi. Four patients had no detectable MRD, including one patient with fludarabine-refractory disease and del(17p) and two patients with fludarabine refractory disease. The response rate was 82% in patients with del(17p), and 78% in patients with fludarabine-refractory disease. Notably, 3 of the 4 patients who had no detectable MRD and achieved a CR/CRi were high-risk disease patients. Twenty-two patients discontinued treatment: 12 due to progressive disease or other reasons, and 8 due to AEs including diarrhea (46%), neutropenia (43%), fatigue (34%) and infection (29%). Grade 3/4 AEs included neutropenia (41%), TLS (11%) and thrombocytopenia (10%).

Immunomodulating agents

Immunomodulating agents are a new class of drugs that change the expression of various cytokines and costimulate immune effector cells. Lenalidomide (Revlimid, Celgene) is a second generation thalidomide analog with possible immunomodulating and antiangiogenic properties, which may also modulate cytokine activity in the tumor microenvironment. Lenalidomide is orally available and has significant activity in multiple myeloma and myelodysplastic syndrome, and most recently it has been shown to be effective in the treatment of various lymphoproliferative disorders such as CLL and NHL [54]. A characteristic AE of treatment with lenalidomide in CLL is tumor flare reaction, as well as an immune-modulatory effect which leads to a sensation of heat and burning in the lymph nodes. Chanan-Khan et al. investigated the antileukemic effects of lenalidomide in 45 CLL patients with relapsed or refractory disease [55]. The drug was administered orally at a dose of 25 mg once a day for 21 days on a 28-day schedule. Due to the occurrence of tumor lysis syndrome (TLS) in two of the first 29 patients, the treatment protocol was revised to allow slow dose escalation in subsequent patients, in whom the initial dose was 5 mg, which was increased by 5 mg every 1–2 weeks to a maximum 25 mg. Twenty-nine patients were assessable for response and all 45 patients were evaluated for toxicity. The most common nonhematologic AEs were fatigue (83%) and flare reaction (58%). Grade 3–4 thrombocytopenia

was noted in 45% of the patients and grade 3–4 neutropenia in 70% of the patients. Major responses were observed in 21 patients (41%) with 4 CRs (9%) and 17 (38%) achieving a PR in intent-to-treat analysis. The median PFS time has not been reached.

Ferrajoli et al. report the results of a phase II study in which lenalidomide was administered at 10 mg per day by continuous daily dosing with dose escalation up to 25 mg, based on patient tolerability and response [56]. Patients who had stable disease continued treatment until disease progression. Forty-four patients with relapsed or refractory CLL were included. Three patients (7%) achieved a CR, one nodular PR and 10 patients a PR, at an OR rate of 32%. The treatment was effective in 31% of the patients with high risk cytogenetic abnormalities (del11q or del 17p), 24% of the patients with un-mutated VH and 25% of the patients refractory to fludarabine. Thirteen patients (30%) developed tumor flare reaction. Despite a median dose of 10 mg daily, significant hematologic toxicity was frequently observed. Grade 3–4 neutropenia was noted in 41% of the courses and grade 3–4 thrombocytopenia in 16% of the patients.

Subsequently, Andritsos et al. reported four consecutive patients with CLL who were treated with lenalidomide and all had serious adverse events [57]. The drug was administered at a dose of 25 mg/day for 21 days of a 28-day cycle. Tumor flare was observed in three patients and was characterized by painful lymph node enlargement, with one fatal outcome. Another patient developed sepsis and renal failure. The efficacy of lenalidomide may be increased with the addition of rituximab. Badoux et al. reported an OR rate of 66% (including 12% CR) and an estimated 36-month survival of 71% in relapsed or refractory CLL patients treated with this combination [58]. In another phase II clinical trial treatment with lenalidomide and rituximab as the first-line therapy induced OR in more than 90% of the patients, including an OR rate of 53% (CR 13%) in patients with (17p) deletion [59].

The ORIGIN trial compares the safety and efficacy of lenalidomide with those of chlorambucil in patients with CLL, 65 years and older (NCT00910910). Interim analysis showed higher rates of death in patients treated with lenalidomide compared to those treated with chlorambucil, and the recruitment for the study was stopped. Currently, lenalidomide is under evaluation for maintenance in phase III study in patients with CLL following first-line therapy (CLLM1) (NCT01556776).

Autologous CD19-targeted CAR-modified T cells

Immune-based treatment strategies to augment the cytotoxic potential of T cells offer exciting new treatment options for patients with CLL [60]. Chimeric antigen receptors (CARs) combine the antigen recognition domain of an antibody with intracellular signaling domains into a single chimeric protein. In CLL, the CD19 antigen is an ideal target for CARs since expression is restricted to normal and malignant B cells. In CLL patients, T cells may be genetically modified to express CARs targeted to CD19 antigen expressed on tumor cells [61, 62]. In a pilot clinical trial, autologous T cells genetically engineered to express an anti-CD19 CAR were used to treat 3 patients with refractory CLL. In this study a lentiviral vector expressing a chimeric antigen receptor with specificity for the B-cell antigen CD19 was coupled with CD137 and CD3-zeta signaling domains and autologous chimeric antigen receptor-modified T cells were reinfused into patients [63]. Two patients achieved a CR lasting longer than 2 years and one patient had a stable PR.

In another study, 8 patients, including 4 with B-cell NHL and 4 with CLL, were treated with cyclophosphamide daily for 2 days followed by fludarabine daily for 5 days and one day after the last dose of fludarabine, received a single i.v. infusion of anti-CD19-CAR-transduced T cells [64]. Three hours after the T-cell administration, IL-2 infusion was initiated. Six of the 7 evaluable obtained strictly defined remissions. Recently, Park et al. reported a phase I clinical trial in previously untreated CLL patients with high-risk disease features and residual disease following the first-line chemotherapy [65]. Patients received CD19-targeted CAR^+ T cells as consolidative therapy. Autologous T cells were collected by leukapheresis and transduced with a retroviral vector encoding the anti-CD19 scFv linked to CD28 co-stimulatory and CD3ζ signaling domains. CAR^+ T cells were infused two days after cyclophosphamide conditioning therapy. Among 6 patients who received the CAR^+ T cells, 2 patients who had a PR following the first-line chemotherapy achieved a CR after the T cell infusion, 2 patients maintained PR and 2 patients had progressive disease. Another group recently reported the results of a study on 14 patients with relapsed, refractory CLL treated with the CD19-targeted CAR^+ T cells [66], which indicate that CAR^+ T cells can induce potent and sustained responses for patients with advanced, relapsed and refractory CLL regardless of p53 mutation status. The overall response rate was 57%, three patients (21%) achieved a CR, five (36%) achieved a PR and six (43%) had no response, for an overall major response rate of 57%. Two of 5 patients with a PR progressed 4 months after infusion with CAR^+ T, and no patient with a CR has relapsed so far. All responding patients developed a delayed cytokine release syndrome manifested by fever, and variable degrees of nausea, anorexia, myalgia, and transient hypotension. A randomized, phase II dose optimization study of CAR^+ T cells directed against CD19 in CLL patients with relapsed, refractory disease is ongoing [67].

Authors' contributions/Wkład autorów

According to order.

Conflict of interest/Konflikt interesu

None declared.

Financial support/Finansowanie

This work was supported in part by the grant from the Medical University of Lodz (No. 503/1-093-01/503-01) and by the Foundation for the Development of Diagnostics and Therapy, Warsaw, Poland.

Ethics/Etyka

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; and Uniform Requirements for manuscripts submitted to Biomedical journals.

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