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Editorial

Novel Drugs for Chronic Lymphocytic Leukemia in 2014

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Chronic lymphocytic leukemia (CLL) is a mature B-cell lymphoid neoplasm characterized by the proliferation and accumulation of small CD5/CD19/CD23-positive lymphocytes in the blood, lymph nodes, spleen, liver and bone marrow [1]. 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 [2]. The management of CLL is determined by the stage and activity of the disease, as well as age and comorbidities [3]. CLL is typically sensitive to a variety of cytotoxic drugs, but the disease is considered incurable. Over the past few years, more effective therapies have emerged in the treatment of CLL, especially combinations of anti-CD20 monoclonal antibodies (mAbs) with purine analogs and bendamustine. These more intensive treatments induce higher response rates and longer response duration and longer survival in younger, fit patients. Currently FCR immune chemotherapy (Fludarabine + Cyclophosphamide + Rituximab) is the first-line choice for younger, physically-fit patients with CLL [4]. Chemo immunotherapy with bendamustine and rituximab (BR) is also effective and safe in patients with previously treated and untreated CLL [5]. Therefore, BR can be considered as a therapeutic option for previously untreated CLL patients, particularly those who are less suitable for FCR. However, older patients with several comorbidities experience increased toxicity with these newer therapies. In addition, there is still a subset of patients who are refractory to standard treatments based on purine analogs, and who demonstrate very poor survival. Recently, significant progress in the knowledge of the biology of CLL has promoted the development of new drugs directed to new biological targets that have shown promise in treating this disease [6]. Several new mAbs directed against lymphoid cells have been developed and investigated in preclinical studies and clinical trials [7], some of which are highly active in chronic lymphoid malignancies and are potentially useful in the treatment of CLL.

Anti-CD20 Monoclonal Antibodies

New mAbs directed against CD20, ofatumumab and obinutuzumab (GA-101) have been recently approved for the treatment of CLL.

Ofatumumab (HuMax-CD20; Arzerra™, GlaxoSmithKline plc/Genmab A/S) is a fully human, IgG1 mAb which recognizes a different CD20 epitome than rituximab and demonstrates a higher cytotoxic potential [8]. Ofatumumab is more effective than rituximab at CDC induction and killing target cells. The results of a phase III study demonstrate that ofatumumab monotherapy shows promising efficacy in heavily pretreated patients with fludarabine- and alemtuzumab-refractory CLL [9]: the overall response (OR) rates were 58% and 47% in the fludarabine- and alemtuzumab-refractory groups and fludarabine-refractory CLL with bulky lymphadenopathy groups, respectively. Median progression free survival (PFS) and overall survival (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 group of 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.

In a recent randomized trial (Complement1), 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 [10]. The results of this study indicate that ofatumumab + chlorambucil is superior to 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 groups.

Obinutuzumab (Gazyva™, GA-101, RO5072759, Roche) is a novel third generation monoclonal antibody which is distinct from Rituximab [11]. The antibody is based on proprietary GlycoMAb(®) technology, which incorporates glycol engineered antibodies that specifically increase antibody-dependent cellular cytotoxicity (ADCC) and thereby increase immune-mediated target cell death. The results of a large randomized phase III trial testing two first-line chemo-immunotherapy regimes, i.e. obinutuzumab and rituximab combined with chlorambucil, and chlorambucil monotherapy as a comparator, in CLL patients with comorbidities have been recently reported (CLL11) [12]. The trial included 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 to 69 ml per minute. Treatment with obinutuzumab + chlorambucil resulted in higher rates of complete response than rituximab–chlorambucil (20.7% vs. 7.0%). Treatment with combined obinutuzumab + chlorambucil or Rituximab +chlorambucil therapy increased OR 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 demonstrated longer OS then chlorambucil alone (P=0.002). However, infusion-related reactions and neutropaenia were more common in patients treated with obinutuzumab + chlorambucil than with rituximab +

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Table 1: Novel and emerging drugs for chronic lymphocytic leukemia.

MoAb	Target	Drug characteristics	Clinical status
Ofatumumab(HuMax-CD20; Arzerra™,GlaxoSmithKline plc/Genmab A/S)	CD20	Type I, 2nd generation, human IgG1, binding to different CD20 epitope than rituximab, more effective at CDC and less at ADCC than rituximab	In 2009, the FDA granted accelerated approval for the treatment of patients with fludarabine- and alemtuzumab-refractory CLL. In 2010, similar approval by the EMA
Obinutuzumab,(GA-101, RO5072759, Hoffmann–La Roche)	CD20	Type II, 3rd generation, glycoengineered, humanized IgG1, antibody with superior ADCC than rituximab and superior direct cell-killing properties	In 2013 FDA approved obinutuzumab for use with chlorambucil in patients with previously untreated CLL; in July 2014, EMA recommended the granting of a marketing authorisation treatment of relapsed or refractory CLL.
Ibrutinib (PCI-32765; Imbruvica, Janssen – Cilag International NV / Pharmacyclics))	BTK	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	In 2013FDA granted accelerated approval for the treatment of pretreated patients with CLL, In July 2014, EMA recommended the granting of a marketing authorisation treatment of relapsed or refractory CLL
Idelalisib (Zydelig, Gilead Sciences International Ltd. /Calistoga Pharmaceuticals),	PI3Kδ	**Inhibitor of** PI3Kδ signalling with potent apoptotic activity against leukemic CLL cells	In July 2014, the FDA and EMA granted traditional approval for idelalisib (Zydelig) to treat patient with relapsed CLL.
BI 836826 (MAb 37.1; Boehringer Ingelheim)	CD37	Chimeric IgG1-type of anti–CD37 molecule which has been Fc-engineered to improve ADCC activity and enhance affinity for Fc-gRIIIa	Phase I clinical trial in pretreated CLL ongoing (NCT01296932).
Otlertuzumab (TRU-016; Emergent Product Development Seattle LLC)	CD37	Antibody-based single-chain homodimeric therapeutic protein produced on the platform of ADAPTIR™ consisting of antibody-derived, single-chain variable fragments linked to	Phase I study in relapsed/refractory CLL or SLL completed [94]; phase II study of otlertuzumab / bendamustine vs. bendamustine alone ongoing (NCT01188681).
MOR208 (XmAb5574, MorphoSys AG)	CD19	Humanized IgG1 mAb with a engineered constant fragment (Fc)–domain designed to enhance binding of FcgammaRIIIa	Phase I study in relapsed/refractory CLL; phase II study in patients with CLL and NHL ongoing (NCT02005289).
ABT-199 (GDC-0199, Genentech /BioOncology/ Roche)	Bcl-2	Induction of Bax/Bak-mediated apoptosis triggered principally by the initiator BH3-only Bim protein	Phase I, dose-escalation study in high-risk relapsed/ refractory CLL completed, studies of ABT-199 in combination with obinutuzumab (NCT01685892), rituximab(NCT02005471), bendamustine (NCT016719040 ongoing

Abbreviations: ADCC: Antibody-Dependent Cell Mediated Cytotoxicity; mAb: Monoclonal Antibody; BCR: B-Cell Antigen Receptor; BTK: Bruton's Tyrosine Kinase; PI3Kδ**:** phosphatidylinositol 3-kinase δ 110d

chlorambucil. The U.S. Food and Drug Administration (FDA) and European Medicinal Agency (EMA) have approved obinutuzumab for use with chlorambucil in patients with previously untreated CL [13].

BCR Signal Transduction Inhibitors

The use of B-cell antigen receptor (BCR) signal transduction inhibitors also represents a promising new strategy for targeted CLL treatment. Recently, two small molecule inhibitors targeting BCR signaling pathways, Ibrutinib and idelalisib, have been investigated and approved in CLL patients [14].

Ibrutinib (PCI-32765; Imbruvica, Janssen – Cilag International NV / Pharmacyclics) is an irreversible covalent inhibitor of the Burton's tyrosine kinase (BTK) a critical enzyme in the BCR signalling pathway that is essential for B-cell proliferation, survival, migration, and tissue homing. In a Phase Ib/II study, ibrutinib demonstrated rapid absorption and elimination at doses of 420 and 840 mg/day. Ibrutinib can be dosed once daily despite relatively rapid clearance. 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, including patients with high-risk genetic lesions [15,16]. Byrd et al conducted a phase Ib/II multicenter study to assess the safety, efficacy, pharmacokinetics, and pharmacodynamic of Ibrutinib in 85 patients with relapsed or refractory CLL or small lymphocytic lymphoma (SLL) [17]. The patients received ibrutinib orally once daily; 51 received 420 mg, and 34 received 840 mg. The OR rate was 71% in both groups, and an additional 20% and 15% of patients in the respective groups had a PR with lymphocytosis. The response was independent of clinical and genomic risk factors present before treatment, including advanced-stage disease, the number of previous therapies, and the 17p13.1 deletion. At 26 months, the estimated PFS rate was 75% and the rate of OS was 83%.

Subsequently, ibrutinib was compared with ofatumumab in a randomized, multicenter, open-label, and phase III study in previously-treated patients with relapsed or refractory CLL or SLL [18]. After interim analysis, at a median follow-up of 9.4 months, the trial was stopped early because of an improvement in PFS and OS in the Ibrutinib arm. The OR rate was significantly higher in the ibrutinib group than in the ofatumumab group (42.6% vs. 4.1%, P<0.001). At 12 months, the OS rate was 90% in the ibrutinib group and 81% in the ofatumumab group. An additional 20% of ibrutinib-treated patients had a partial response with lymphocytosis. The improvements were noted regardless of whether patients had a chromosome 17p13.1 deletion or resistance to purine analogues.

The recommended dose and schedule of Ibrutinib for patients with CLL is 420 mg taken orally once daily. The most common side effects are neutropaenia, infections, thrombocytopenia, anemia, dizziness, headache, diarrhea, vomiting, nausea, constipation, rash, arthralgia, musculoskeletal pain, pyrexia and peripheral edema. Interestingly, treatment with ibrutinib is associated with increased levels of immunoglobulin IgA and IgM , and a stable level of IgG level [19]. Ibrutinib is indicated for the treatment of patients CLL who

have received at least one prior therapy, or in first line in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy. However, Ibrutinib will be an expensive drug: some analysts estimate that it will cost $98,000 a year [20]. In February 2014, FDA granted accelerated approval to ibrutinib (Imbruvica) for the treatment of patients with CLL who have received at least one prior therapy. In July 2014, the European Medicines Agency (EMA) recommended the granting of a marketing authorization for ibrutinib (Imbruvica) for the treatment of relapsed or refractory CLL.

Idelalisib (GS-1101, CAL-101, Zydelig, Gilead Sciences International Ltd. /Calistoga Pharmaceuticals), is a first-in-class, selective, oral inhibitor of phosphatidylinositol 3-kinase P110d (PI3Kδ) that reduces proliferation, enhances apoptosis, and inhibits homing and retention of malignant B cells in lymphoid tissues [21]. Idelalisib has shown substantial clinical activity when used in monotherapy and a favorable safety profile in heavily pretreated, refractory and high-risk patients with CLL. The most common side effects are infections, neutropaenia, increased transaminase, increased triglycerides, diarrhoea/colitis, rash and pyrexia. In a phase I study, heavily pre-treated relapsed/refractory CLL patients with bulky lymphadenopathy, unmutated IGHV, and/or del17p/TP53 mutations patients with relapsed/refractory CLL were treated continuously with oral idelalisib as a single agent at a dose of 50 mg 350 mg once or twice daily. The OR rate was 72%, with 39% of patients meeting the criteria for partial response (PR) per IWCLL 2008 and 33% meeting the recently updated criteria of PR with treatment-induced lymphocytosis. The PFS for all patients was 15.8 months. Serious adverse events (AEs) were noted for 36 patients (67%). Most common grade ≥ 3 AEs included were pneumonia (20%), neutropaenia fever (11%), and diarrhoea (6%). Idelalisib showed robust activity independent of high-risk features, including Del (17p)/*TP53* mutation, Del (11q), IGHV mutation, and *NOTCH1* mutation.

The combination of idelalisib with rituximab in patients with relapsed/refractory CLL also demonstrates impressive efficacy and good tolerability. The combination of idelalisib and rituximab significantly improved PFS, OR rate and OS among patients with relapsed CLL as compared with rituximab alone. In a multicenter, randomized, placebo-controlled, phase III study comparing rituximab with either idelalisib or placebo, the OR rate was 81% vs 13% and OS at 12 months was 92% vs. 80%, 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 alone. O'Brien et al recently reported the results of up-front therapy with idelalisib and rituximab in patients over 64 years old with CLL [22]. They were treated with rituximab given at a dose of 375 mg/m2 weekly for 8 weeks and 150 mg BID idelalisib continuously for 48 weeks. Patients completing 48 weeks of treatment without progression continued to receive idelalisib on an extension study. The OR 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. At present, idelalisib is indicated in patients with CLL who have received at least one prior therapy, or as first line treatment in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy. In July 2014, the FDA and EMA granted traditional approval for idelalisib (Zydelig) to treat patient with relapsed CLL.

Emerging Drugs

Several other agents, including anti-CD37 and anti-CD19 monoclonal antibodies, and agents 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.

The results of recent preclinical and early clinical studies suggest that anti-CD37 antibodies can be useful in the treatment of CLL [23]. 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. Otlertuzumab (TRU-016, Emergent, Seattle LLC) is a novel humanized anti-CD37 protein therapeutic produced using ADAPTIR™ Modular Protein Technology with anti leukemic activity in preclinical studies and clinical trials [24,25]. BI 836826 (MAb 37.1, Boehringer Ingelheim) 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 [26]. BI 836826 is under investigation in CLL in a phase I clinical trial (NCT01296932).

MOR208 (XmAb5574, MorphoSys AG), an anti- CD19 mAb is also being explored for clinical applications in CLL. CD19 is an excellent tumor target for antibody therapy of CLL patients as it is not expressed on hematopoietic stem cells or other normal tissue. In preclinical studies, MOR208 has shown antitumor activity including direct Cytotoxicity, ADCC and antibody-dependent cellular phagocytosis against leukemic CLL cells [27]. MOR208 was found to have a tolerable toxicity profile and preliminary evidence of antitumor activity was observed in high-risk patients with relapsed/refractory CLL [28]. A phase II study of this agent in patients with CLL and other B- cell malignancies is ongoing (NCT02005289).

ABT-199 (GDC-0199, RG7601, Genentech Bio Oncolog /Roche) is a novel, orally bio available, small molecule with a high-affinity Bcl-2–selective BH3 mimetic, recently developed by Abbott Laboratories [29]. ABT-199 can trigger apoptosis *in vitro*, even in Del (17p) CLL cells. The results of a phase I, dose-escalation study of ABT-199 in high-risk relapsed/ refractory CLL were recently presented [30]. The response rate was 82% in patients with del (17p), and 78% in patients with fludarabine-refractory disease. Grade 3/4 AEs included neutropaenia, tumour lyses syndrome and thrombocytopenia.

In conclusion, significant progress in the characterization and understanding of the biology and prognosis of CLL has provided new opportunities for the development and clinical applications of innovative, more effective therapies.

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