

New emerging therapies in the management of chronic lymphocytic leukemia (Review)

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Abstract. Chronic lymphocytic leukemia (CLL) is considered incurable despite advances in management strategies. New drugs targeting cell pathways are currently being developed for the efficient management of CLL. Various strategies involving different targets have been developed, or are currently in the developing stage. A search was conducted in the electronic database PubMed, for pre-clinical as well as clinically controlled trials reporting various strategies against CLL currently under investigation. Novel strategies included use of antibodies, small cell inhibitors, such as spleen tyrosine kinase, LYN, cyclin-dependent kinase, and histone deacetylase inhibitors. The present review examined these new and emerging strategies for the efficient management of CLL. The review involves a discussion of novel strategies being examined worldwide against CLL, including anti-CD20, anti-CD37, anti-CD23, anti-CD40, SYK/LYN inhibitors, BTK inhibitors, p13k inhibitors and recent developments such as the use of cyclin-dependent kinase inhibitors/histone deacetylase inhibitors.

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1. Introduction

Chronic lymphocytic leukemia (CLL) is usually characterized by the accumulation of mature B-lymphocytes in the blood, bone marrow and lymphoid tissue (1). The nature of the disease is heterogeneous in biological and clinical terms. Affected patients do not require any therapy, while other patients are required to undergo an aggressive course of therapeutic approaches, which may exhibit poor response. Despite numerous scientific endeavors the possibility of relapse may be observed in almost all patients (2). Furthermore, the etiology of CLL remains to be determined. The most obvious risk factor observed is age. Nevertheless, hereditary factors due to family history of CLL may constitute feasible risk factors (3). Additionally, environmental factors are responsible for spread of CLL, including exposure to pesticides, high magnetic fields, farming and animal breeding (4). Some viruses have also been observed to be associated with CLL occurrence (5).

The present review assessed the latest therapeutic approaches currently being developed for the better management of CLL. In recent approaches, the utilization of monoclonal antibodies has emerged for the efficient management of CLL especially in combination with chemotherapy (rituximab, ofatumumab, obinutuzumab) or as single-agent therapy in the refractory setting (6,7). The details of the important antibodies in use are to be discussed in the subsequent sections of this review. Furthermore, inhibitors targeting small molecules during CLL including spleen tyrosine kinase (SYK), LYN, BTK, and P13K inhibitors are to be discussed.

The aim of the review was to update knowledge of concerned readers including medical physicians, or scientist working in the area of CLL management in order to stimulate planning of better studies in future for the advanced and efficient management of CLL.

2. Anti-CD20

Antibodies targeting CD20 are under investigation for their therapeutic potential against CLL (7). The two types, type I and II mAbs, differ in their CD20 binding and activation of cell death pathways (7). Type I CD20 antibodies are associated with stronger complement-dependent cytotoxicity (CDC) but with fewer cell deaths. The occurrence of resistance to type I mAbs

is associated with the loss of CD20 by 'shaving' or antibody internalization. Type II CD20 antibodies have a lower CDC effect but can induce increased direct cell death. Less resistance to therapy can be expected due to less antigenic internalization which may prolong the presence of the antibody on the cell surface, thereby increasing antibody-dependent cellular cytotoxicity (ADCC) (7). Rituximab is a type I chimeric anti-CD20 antibody that exerts its function via CDC and ADCC (8). Obinutuzumab is the first humanized glycoengineered type II mAb. Preclinical studies showed a superior killing activity and a greater B-cell depletion than rituximab (7). The toxicity profile was acceptable (transient neutropenia, thrombocytopenia) with a dose-dependent incidence of adverse effects. Thus, obinutuzumab monotherapy appears active in advanced CLL but shows a higher toxicity than rituximab. The optimal dose, schedule of administration and duration of treatment remains elusive and further studies are required to gain this information. Given the encouraging results with obinutuzumab combined with chlorambucil first-line treatment, other combinations are under investigation (9). A non-randomized study in previously untreated patients that investigated obinutuzumab in combination with FC or bendamustine confirmed better and more efficient results (10).

3. Anti-CD37

CD37 is a transmembrane protein present normally on mature B cells and is usually upregulated in CLL cells. Otlertuzumab (TRU-016) is a CD37-specific protein drug that is applied in clinic (11). A phase I study evaluating safety in 223 CLL patients did not identify any maximum-tolerated dose. The most frequent adverse events (infusion-related reaction, fatigue, nausea and diarrhea) were not dose related. However, as a single agent CD37 appears to have modest clinical activity in CLL [partial response 23% and complete response (CR) 0%] and lower response rates in 17p-deleted patients (16%) (12). Responses were more common in untreated or less treated patients. Preclinical data indicated additive or synergistic activity with rituximab and bendamustine (13). The combination of otlertuzumab and bendamustine compared to bendamustine as monotherapy was investigated in 225 relapsed CLL patients and appeared tolerable with an overall response rate (ORR) of 80% (20% CR) compared to 42% (4% CR) for bendamustine alone (14). However, no patients with 17p deletion responded. In addition, whether otlertuzumab combined with bendamustine is better than bendamustine, rituximab remains unknown. Otlertuzumab combined with rituximab was investigated in previously untreated CLL and seems a feasible strategy, albeit there are currently no data on the response rates (15).

4. Anti-CD23

CD23 is expressed on B cells with significantly higher expression rates as compared to B cells with decreased expression (11). Lumiliximab is a chimeric anti-CD23 antibody that mediates cell death through ADCC and CDC. Preclinical studies have shown antitumor activity against CLL cells. However, a phase III trial comparing fludarabine, cyclophosphamide and rituximab (FCR) combined with lumiliximab to FCR was not successful due to the low benefit in relapsed CLL (16).

5. Anti-CD40

CD40 is a transmembrane protein expressed on normal and malignant B cells (17). CLL has been reported to cause activation of the PI3K and $\text{NK}\kappa\text{B}$ pathways and inhibition of apoptosis. Lucatumumab is an anti-CD40 antibody that triggers ADCC and inhibits CD40L-induced proliferation *in vitro* (11). However, phase I data in the relapsed setting showed mainly stable disease as best response (17). Anti-CD19 is a transmembrane protein expressed strictly in B cells and has been reported to enhance signaling depending on B-cell receptor (BCR) antigen stimulation.

6. Small targeted molecules

SYK and LYN inhibitors. SYK and LYN are non-receptor kinases activated following BCR ligand binding. They activate signaling pathways downstream of BCR, and modulate cell adhesion and chemotaxis of B cells and are therefore critical for survival and maintenance (18,19). Fostamatinib is an orally reversible, relatively selective SYK inhibitor. *In vitro*, its bioactive form is known as R406. It has also been observed to be well tolerated (20). Dasatinib is another reversible pan-Src kinase inhibitor that has been reported to inhibit a variety of other kinases, such as LYN and BTK. The low response rate compared to other kinase inhibitors targeting BTK or PI3K δ may be due to the function of LYN as a negative regulator of BCR signaling. Bafetinib (INNO-406) is an orally available LYN kinase inhibitor. Administration of a higher dose is currently under investigation (21).

BTK inhibitors. Ibrutinib (PCI-32765) is the first human BTK inhibitor *in vitro* and *in vivo* (22). Both *in vitro* and in patients, ibrutinib impaired microenvironment-induced survival and proliferation as well as the release of and migration towards tissue-homing chemokines (23,24). This inhibitor also impairs integrin signaling, thereby affecting CLL cell adhesion (23). Ibrutinib is generally well tolerated as a single agent and in various combination, even in a heavily pretreated and elderly population with comorbidities (25). The most common adverse effects include fibrillation, and serious bleeding, such as subdural hematoma (26). ONO-4059 is another available BTK inhibitor that binds covalently to BTK and is more specific than ibrutinib (27).

PI3K inhibitors. Idelalisib (CAL-101) is an orally available, highly specific and reversible inhibitor of PI3K δ (26). Idelalisib causes inhibition of AKT activation, which decreases myeloid cell leukemia sequence 1 (MCL-1) expression and promotes apoptosis in CLL cells *in vitro* and in patients (28,29). Conversely, it shows minimal cytotoxicity against normal T and NK cells (28). Idelalisib inhibits chemotaxis towards chemokines, pro-survival cytokines and secretion of chemokines (CCL3/4) from CLL cells *in vitro* as well as in treated patients. Idelalisib decreases CLL adhesion by interfering with CD49d/VCAM-1 binding which may explain the redistribution of CLL cells observed in treated patients (30). Idelalisib may also have immune modulating capacity as inhibition of regulatory T cells has been observed *in vitro* (31). The most common toxicities included fatigue,

rash, pyrexia and cough together with pneumonia and pneumonitis (32). Thus, idelalisib appears to be active in high-risk patients.

BCL-2 inhibitors. BH3 mimetics are small molecules. Navitoclax (ABT-263) is a BH3-mimetic targeting preferentially BCL-2 and BCL-xL proteins. Additionally, early phase I data on navitoclax in combination with bendamustine, rituximab showed promising results (ORR \leq 81% including CRs) (33). Neutropenia was the most common side effect, affecting at least one third, however, febrile neutropenia was not frequent (6%). Non-hematological side effects (diarrhea, nausea and fatigue) affected approximately one third of the patients (34).

7. New and emerging therapies

Cyclin-dependent kinase (CDK) inhibitors. Cyclins are the known rheostats of the cell cycle. Their expression fluctuates regularly and they require the presence of a CDK to accomplish their regulatory work. Several inhibitors may target cDKs to decrease anti-apoptotic proteins, and thereby induction of programmed cell death in CLL cells in a p53-independent manner (35). The broad CDK inhibitor flavopiridol (alvocidib) is the most comprehensively studied compound in this category of drugs. The pan-CDK inhibitor dinaciclib (SCH 727965) has shown potent pre-clinical activity against CLL cells independently of high-risk genomic features by down-regulating the mRNA and protein expression of MCL-1 (35). However, it appears ineffective at overcoming the protective effect between CLL and stromal cells. Dinaciclib achieved an ORR of 58% and a progression-free survival of 16 months in patients with relapsed or refractory CLL in a phase I/II trial involving 285 patients. The ORR for patients with 17p deletion was similar (57%). P1446A is a novel orally active CDK inhibitor that has shown pre-clinical activity in CLL. However, samples carrying 17p deletion showed decreased sensitivity (36). The most frequent related toxicity appears to be myelosuppression and the associated increased risk of tumor lysis syndrome (37). Thus, CDK inhibitors appear to be an effective choice as single agents and in combination with chemotherapy in relapsed and refractory CLL. However, more studies are required for their establishment as a concrete therapeutic approach.

Histone deacetylase (HDAC) inhibitors. HDACs, in several isoenzyme classes, are overexpressed in CLL (38). HDACs mediate the epigenetic silencing of certain miRNAs that are critical tumor suppressors. Inhibition of HDACs *in vitro* induces the expression of these miRNAs followed by a decreased level of MCL-1 and induction of cell death (39), i.e., HDAC inhibitors have the ability to reverse epigenetic alterations associated with CLL cell survival. Mocetinostat (MGCD0103) is an orally available HDAC inhibitor that demonstrated efficacy *in vitro* in human cancer cell lines (40). It modulated the expression of critical autophagy genes that possibly contribute to autophagy impairment in CLL cells (41). However, the clinical effectiveness in CLL appears to be limited, with no responses in CLL high-risk patients.

8. Conclusions

At present, investigations regarding the development of efficient targeted therapy for the management of CLL patients are ongoing. Subsequently, application of these new and emerging drugs remains to be confirmed.

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