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REVIEW

Targeting chronic lymphocytic leukemia cells in the tumor microenviroment: A review of the *in vitro* and clinical trials to date

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Abstract

Chronic lymphocytic leukemia (CLL) is the most common leukemia in the western world. Despite significant advances in therapy over the last decade CLL remains incurable. Current front-line therapy often consists of chemoimmunotherapy-based regimens, most commonly the fludarabine, cyclophosphamide plus rituximab combination, but rates of relapse and refractory disease are high among these patients. Several key signaling pathways are now known to mediate the survival and proliferation of CLL cells *in vivo*, the most notable of which are the pathways mediated by the B-cell receptor (BCR) and cytokine receptors. A better understanding of the pathogenesis of the disease, the underlying biology of the CLL-cell and the roles of the tumour microenvironment has provided the rationale for trials of a range of novel, more targeted therapeutic agents. In particular, clinical trials of ibrutinib and idelalisib, which target the Brutons tyrosine kinase and the delta isoform of phosphoinositol-3 kinase components of the BCR signaling pathway respectively, have shown extremely promising results. Here we review the current literature on the key signaling pathways and interactions of CLL cells that mediate the survival and proliferation of the leukemic cells. For each we describe the results of the recent clinical trials and *in vitro* studies of novel therapeutic agents.

Key words: Chronic lymphocytic leukemia; Therapy; Microenvironment; Leukemia; Novel

Core tip: The treatment of chronic lymphocytic leukemia (CLL) is in a period of unprecedented revolution. A better understanding of the mechanisms that drive the survival and proliferation of CLL cells has led to the development of novel therapeutic strategies. This review article is a timely summary of the results of many of the recent key clinical and pre-clinical studies of novel therapeutic agents for CLL.

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INTRODUCTION

Chronic lymphocytic leukemia (CLL) is characterized by the proliferation and accumulation of CD5/CD19 positive monoclonal B-lymphocytes in the peripheral blood, bone marrow and lymphoid organs. The introduction of the fludarabine (F), cyclophosphamide (C), rituximab (R) regimen[1,2] represented a major advance in the clinical management of the disease with durable remissions beyond 10 years being achievable in a proportion of patients[3]. However, novel treatment strategies are still required for the significant proportion of patients that do not respond to or relapse following FCR treatment.

In recent years it has become increasingly apparent that successful treatment of CLL must target the proliferative compartment of the disease that resides in proliferation centres within the lymph nodes and marrow. Interaction of CLL cells with the tumour microenvironment is believed to be a major contributing factor to resistance and relapse following treatment with the more conventional regimens, including FCR[4]. A better understanding of the role of the microenvironment in CLL-cell survival, proliferation and in drug-resistance has provided the rationale for the clinical trials discussed in this review.

B-CELL RECEPTOR PATHWAY

Given the importance of B-cell receptor (BCR)-mediated signaling in the survival and proliferation of CLL cells[5] much of the recent work on novel therapeutic agents in CLL has focused on inhibitors which target specific components downstream of the receptor. Most notably, clinical trials of ibrutinib and idelalisib, which target the Brutons tyrosine kinase (Btk) and delta isoform of phosphoinositol-3 kinase (PI3-kinase δ respectively, have shown extremely promising results in recent clinical trials.

Ibrutinib

Ibrutinib has been shown to induce apoptosis of CLL cells *in vitro* against both cells in media alone and cells cultured with micro-environmental mimics such as stromal contact or culture with soluble factors such as CD40L, interleukin 4 (IL-4) and BAFF[6]. Ibrutinib interferes with CLL-cell adhesion and migration, which is believed to be important in its mechanism of action[7,8].

RESONATE, a randomized trial comparing ibrutinib to the CD20 monoclonal antibody ofatumumab as single agents in previously treated patients demonstrated significantly better overall response (OR) and survival (OS) rates in the ibrutinib arm of 42.6% *vs* 4.1% and 90% *vs* 81% respectively[9]. The findings of the RESONATE trial have recently been updated showing that these effects are seen regardless of genetic mutation and previous treatment, furthermore an improved haematologic function has also been shown[9,10]. In patients treated with ibrutinib, the phenomenon of treatment-induced lymphocytosis occurs, which is thought to be due to the redistribution of leukemic cells from the tissue microenvironments into the circulation[11], highlights the mechanisms that CLL cells rely on to populate the lymph node and marrow environments. In a phase Ⅱ trial combining ibrutinib with rituximab in 40 high-risk patients (defined as patients with deletion of 17p, mutation of *TP53* or deletions of 11q with disease relapse) the OR rate was 95% of which 8% of patients achieved a complete remission (CR)[12]. It is worth noting that the treatment-induced lymphocytosis in this trial resolved faster than in patients treated with single agent ibrutinib, supporting the rationale for combining inhibitors of Btk with agents that target CLL cells liberated from the lymph nodes and marrow. Investigations into ibrutinib-containing regimens are continuing with a recent dose escalation trial that investigated ibrutinib in combination with lenalidomide. With only 11 patients enrolled and evaluable data on 9 the results of this trial are currently limited, but have shown an OR rate of 100% and do suggest that the combination is well tolerated[13].

Idelalisib

Idelalisib specifically targets the - isoform of PI3-kinase, which in turn decreases phosphorylation of Akt and induces caspase-dependent apoptosis. Idelalisib induces apoptosis of primary CLL cells *in vitro* cultured either in media alone or in combination with factors such as CD40L and tumor necrosis factors (TNF)-α. As well as its cytotoxic effects, idelalisib inhibits the interaction of the leukemic cells with the tumour microenvironment[14,15].

Several phase Ⅰ, Ⅱ and Ⅲ studies of idelalisib as a single agent or in combination with the CD20 antibodies ofatumumab or rituximab and bendamustine have been conducted or are on-going for relapsed/refractory or previously untreated elderly patients. In a phase I trial of idelalisib as a single agent in 54 patients with poor risk characteristics the OR rate was 72%, with 81% of patients demonstrating a nodal response[16].

A phase Ⅰ trial of idelalisib in combination with ofatumumab or rituximab demonstrated that these combinations are well tolerated. Among 40 patients the OR rate was 83% with 3% of patients achieving a CR. Notably, among the 11 patients with deletion or mutation of *TP53* the OR rate was 73%[17]. More recently, the results of a phase Ⅲ trial comparing idelalisib plus rituximab with placebo plus rituximab in 220 relapsed, co-morbid patients demonstrated a significant improvement in OR rate and survival in those patients treated with idelalisib in combination with rituximab; OR

rates were 81% *vs* 13% in the idelalisib and placebo arms respectively with OS rates of 92% *vs* 80%[18]. A phase Ⅱ trial of idelalisib in combination with rituximab in 50 previously untreated elderly (> 65 years) CLL or small lymphocytic leukemia (SLL) patients demonstrated an OR rate of 96% with a progression-free survival at 24 mo of 91%[19], supporting the use of the PI3-kinase inhibitor as potential first-line therapy. An extension to this trial is now underway investigating the use of idelalisib as a mono-therapy in elderly CLL/SLL patients; to date 37 patients have been enrolled and 27 evaluated with an OR rate of 81%[20].

A phase Ⅰ trial of idelalisib in combination with bendamustine and/or rituximab, fludarabine or chlorambucil and/or rituximab in relapsed refractory disease has proven these combinations are also highly active with an OR rate of 82% and a CR rate of 10%[21,22]. Phase Ⅲ trials of idelalisib in combination with rituximab are on-going with promising results[23].

Fostamatanib

The tyrosine kinases SYK and Lyn are also key components of the BCR signaling cascade and as such have been proposed as therapeutic targets. Suljagic *et al*[24] established a rationale for clinical trials of the SYK inhibitor fostamatanib by showing that the drug inhibits signaling downstream of the BCR and increases the survival of Eμ-TCL1 transgenic mice, which represent an *in vivo* model of CLL disease.

A phase Ⅱ trial of fostamatanib (R788) demonstrated activity against relapsed/refractory CLL/SLL disease, with 6 of 11 patients achieving an objective response[25]. Interestingly, 9 of the 11 patients had evidence of treatment-induced lymphocytosis, similar to the effects observed with both ibrutinib and idelalisib. Although there appear to be no plans to pursue clinical trials of fostamatanib for CLL, studies of the next generation of SYK inhibitors, PRT318 and P505-15, have shown that both compounds induce apoptosis under *in vitro* conditions that mimic the microenvironment, inhibit CLL cell migration and chemokine secretion and prevent BCR-induced activity of mitogen activated protein kinase (MAPK)-extracellular regulated kinase (ERK)1/2[26].

Dasatinib

Dasatinib is a broad-spectrum inhibitor of Src-kinases and Abl and in CLL patients appears to function mainly through inhibition of Lyn. Dasatinib has been shown to inhibit the phosphorylation of Akt, ERK1/2 and p38 and induce apoptosis of CLL cells *in vitro*[27].

In a phase Ⅱ trial of dasatinib, among 15 relapsed/refractory CLL patients, 3 (20%) achieved a partial response (PR), 5 a nodal response and 1 had a reduction in node size and lymphocyte count[28]. A similar PR rate (16.7%) was observed in a more recent phase Ⅱ trial of dasatinib in combination with fludarabine[29], suggesting that either as mono-therapy or in combination with fludarabine, dasatinib has, at best, modest effects against relapsed/refractory, fludarabine-resistant CLL disease.

Novel BCR-pathway inhibitors in pre-clinical development

The clinical trial data of idelalisib discussed above highlight the potential of PI3-kinase targeted therapies for CLL and provide the rationale for investigations of novel agents that target multiple isoforms of PI3-kinase. SAR245409 and duvelisib (IPI-145) are inhibitors of the α/δ and δ/γ isoforms of PI3-kinase respectively. Thijssen *et al*[30] have shown that unlike SAR245409 neither BYL719, a specific α isoform inhibitor, nor idelalisib, completely block the phosphorylation of mTOR and that SAR245409 is more cytotoxic *in vitro* than idelalisib. Similarly, Dong *et al*[31] have shown that duvelisib is cytotoxic against CLL-B cells *in vitro* with little effect on normal B cells and that duvelisib prevents the spontaneous development of leukemia and delays leukemic cell engraftment in the Eμ-TCL1 mouse model. Early results of a phase Ⅰ clinical trial of duvelisib for relapsed/refractory CLL disease suggests that the drug is well tolerated with an OR rate of 55% among 54 patients. Pharmacodynamic studies within this trial suggest that duvelisib modulates chemokine and cytokine levels, cell proliferation and the activity of Akt[32]. Direct inhibition of Akt has also been proposed as a therapeutic option for CLL. In a recent study, Ding *et al*[33] demonstrated that the Akt inhibitor MK2006 induces apoptosis of CLL irrespective of poor prognostic characteristics.

MEK1/2 is a key component of the MAPK, ERK pathway, which promotes the survival and proliferation of multiple forms of cancer cell. In B-CLL cells MAPK-ERK signaling is activated in response to BCR ligation and as such is believed to play a role in promoting CLL-cell survival. However, we recently demonstrated that MEK1/2 inhibition by Binimetinib (MEK162, Novartis) has little effect against CLL cells in the absence of factors that mimic the tumor microenvironment[34]. The efficacy of Binimetinib only under *in vitro* conditions that mimic tonic BCR stimulation highlights the importance of considering the interaction of leukemic cells with the tumour microenvironment as part of similar *in vitro* studies[34]. Similar studies have also recently been described for the MEK1/2 inhibitor trametinib. Apollonio *et al*[35] described the efficacy of this MEK1/2 inhibitor against primary CLL cells and in a mouse xenograft model of CLL. In this study trametinib had a marked effect on the viability of primary CLL cells in which ERK1/2 was constitutively phosphorylated, an indication of CLL cell anergy, and inhibited tumour growth and delayed leukemic cell dissemination in the mouse model.

In normal B-cells the Raf-1/MEK/MAPK-ERK1/2 pathway is negatively regulated by the Raf kinase inhibitory protein (RKIP). However, in CLL-cells dysfunction of RKIP may lead to over activity of the Raf-1 and Akt-mediated pathways. Our recent studies suggest that the RKIP inhibitor locostatin induces apoptosis in CLL cells cultured in media and on a CD40L fibroblast layer *via* a

mechanism that involves the down-regulation of both ERK1/2 and Akt, highlighting the potential of RKIP as a therapeutic target in CLL[36].

CC-115 is a novel dual inhibitor of both the mammalian target of rapamycin (mTOR) and DNA protein kinase (DNA-PK). Signals downstream of PI3-kinase and Akt are mediated by a complex consisting of mTOR1 and 2, while DNA repair and genomic stability rely on the function of DNA-PK. DNA repair pathways are of interest in CLL as mutations in the DNA repair machinery, particularly in the *ATM* and *TP53* genes, are associated with poor prognosis. Thijssen *et al*[37] demonstrate that CC-115 is cytotoxic against primary CLL cells irrespective of *ATM* mutational status.

The clinical efficacy of fostamatanib discussed above and several recent *in vitro* studies suggest that CLL cells are sensitive to SYK inhibition. A study by Purroy *et al*[38] suggests CLL cells may be more sensitive to SYK inhibition by TAK-659 than to fostamatanib in a co-culture model of the CLL tumour microenvironment and that this agent may be effective in synergy with fludarabine, ibrutinib and idelalisib. Based on promising results in acute myeloid leukemia, Dielschneider *et al*[39] investigated the efficacy of gefitinib against CLL cells. The drug was effective particularly against CLL cells expressing ZAP-70, which represents a poor prognostic sub-group. Similar studies of the SYK inhibitor GS-9973, also demonstrate cytotoxicity against primary CLL cells *in vitro* and synergy with idelalisib[40].

Finally, the constitutive activity of protein kinase C (PKC) in CLL cells and its role in nuclear factor-kappa B (NF-κB)-mediated cell survival[41] suggest that it may also represent a therapeutic target in CLL[42]. Enzastaurin and sotrastaurin (AEB071) are PKC inhibitors in pre-clinical and early clinical trials for a range of malignancies including CLL. El-Gamal *et al*[43] have shown that sotrastaurin is cytotoxic against CLL cells in both *in vitro* and *in vivo* pre-clinical trials. While the results of trials of enzastaurin (reviewed in[44]) suggest that targeting PKC may well have well have some efficacy in B-cell malignancies, including CLL, as the authors suggest understanding the mechanisms that account for the limited therapeutic actions of enzastaurin may lead to the development of novel PKC-targeted agents or novel combinations.

CELL TO CELL INTERACTIONS WITHIN THE CLL TUMOUR MICROENVIRONMENT

Successful treatment of CLL relies on targeting the proliferative pool of CLL cells that populate the lymph node and bone marrow microenvironments. Pre-clinical models of the tumour microenvironment involving co-culture of primary CLL cells with nurse-like, mesenchymal, stromal or T-cells significantly reduce the spontaneous apoptosis rate of the leukemic cells through mechanisms that likely depend on direct cell to cell contact and the production of cytokines and growth factors. The association between CLL and stromal cells is also likely to facilitate the interaction of CLL cells with T-cells.

It is now widely acknowledged that the proportions and function of each of the T-cell subsets is abnormal in CLL; a high proportion of T-regulatory cells and the limited cytotoxic capacity of $CD8^+$ T-cells may suppress the anti-tumour functions of $CD4^+$ T-cells and allow CLL cell proliferation to proceed unchecked[45]. Recent studies suggest that the formation of the immunological synapse between T-cells and antigen presenting cells is defective in CLL due to dysfunction of the actin cytoskeleton in the T-cells[46]. Data from the same study, involving culture of CLL cells with allogeneic T-cells from healthy individuals, suggested that the CLL cells induce these defects in the cytoskeleton of the T-cells enabling the tumour cells to escape normal immune surveillance.

Lenalidomide

On the strength of trials in other B-cell malignancies lenalidomide was initially trialed in a cohort of CLL patients with relapsed or refractory CLL, with OR and CR rates of 47% and 9% respectively[47]. While the exact mechanisms of action of lenalidomide are not clear a recent study employing lenalidomide to consolidate first line therapy with pentostatin, cyclophosphamide, rituximab (PCR), identified a long-term improvement in anti-tumour T-cell synapse formation and overall response to chemo-immunotherapy[48], suggesting that as well as direct tumor activity through altered activity of an E3 ubiquitin-ligase[49] lenalidomide has immuno-modulatory properties and may at least partially correct the T-cell defect and improve immune surveillance in CLL. Lenalidomide also has marked anti-inflammatory effects that will be discussed in more detail later.

Clinical trials of lenalidomide as a single agent have demonstrated its efficacy against relapsed/refractory disease[50] and in the treatment of elderly patients[51] and more recently as a frontline therapy in combination with rituximab[52,53]. Lenalidomide has also proven effective in combination with rituximab as a salvage therapy for relapsed/refractory disease[54]. Several trials using lenalidomide as maintenance therapy following first and second-line FCR therapy are in progress (CONTINUUM study, clinicaltrials.gov NCT00774345, ALLG Residuum and DCLLSG)[55,56].

CAR-T cells

Studies suggest that the *ex vivo* manipulation of T-cells from CLL patients to produce T-cells with chimeric antigen receptors (CAR T-cells) also represents a method of overcoming the defect in T-cell surveillance of the leukemic clone[57]. In CLL, trials of CAR T-cells expressing a receptor to the CD19 antigen (CTL019) have proven successful in the treatment of relapsed/refractory disease or as consolidation following first-line treatment of high-risk patients (defined as those patients with un-mutated *IgVH* genes, or deletion

of 17p- or 11q-) with PCR. In a trial of 14 relapsed/refractory patients, 4 (29%) achieved a CR and 4 (29%) a PR with an OR rate of 57%[58]. Of the 6 patients enrolled on the phase Ⅰ consolidation trial 2 patients who were in PR after therapy with PCR achieved a CR following the infusion of the CAR-T cells, suggesting that CAR-T cells may be useful in increasing CR rates[59].

The study by Porter *et al*[58] suggests that the advantages of this form of cellular therapy include the provision of ongoing tumor surveillance through the *in vivo* expansion of the CAR T-cells and the specificity of the therapy for B-cells, although the effects on normal B-cells may result in B-cell aplasia. The long-term activity of CAR T-cells is illustrated by the delayed onset of tumour lysis syndrome[60]. Porter *et al*[61] have now commenced a phase Ⅱ trial of CTL019 cells in patients with relapsed or refractory CLL, to 23 patients have been evaluated with a CR rate of 22% and a PR rate of 17%.

Lucatumumab

Targeted blockade of CD40-mediated signaling in CLL cells represents a rational approach to interfering with the interaction between CLL and T cells, since CD40-mediated signaling promotes CLL-cell survival and proliferation[62]. Lucatumumab, a humanized anti-CD40 agonist antibody was shown to inhibit B-cell growth and induce antibody-dependent cellular cytotoxicity *in vitro*[63]. However, the results of a phase Ⅰ trial of lucatumumab (HCD122) were disappointing; of the 26 patients on trial, 17 had stable disease for a mean duration of 76 d but only 1 patient achieved a PR. The authors concluded that further trials of lucatumumab should focus on incorporating the antibody in combination therapies[64].

Bevacizumab

Despite data highlighting the important angiogenic role of vascular endothelial growth factor (VEGF) in CLL proliferation centres within the secondary lymphoid structures[65] and promising pre-clinical data[66,67] the results of a phase Ⅱ trial of the VEGF inhibitor bevacizumab in CLL proved disappointing. No clinical efficacy of bevacizumab was demonstrated among 13 patients with relapsed/refractory disease resulting in early closure of this trial[68].

Novel inhibitors of cell-to-cell interactions in pre-clinical development

CC-122 is a next generation immunomodulatory drug that is believed to have mechanisms of action similar to lenalidomide. Blocksidge *et al*[69] demonstrate that the anti-proliferative effects of CC-122 against primary CLL cells cultured in a CD154/IL-21 tumour model were superior to those of lenalidomide.

C6-ceramide is a nanoliposomal molecule and a member of the ceramide family of lipids. Ceramides are "tumor suppressor" lipids that induce anti-proliferative and anti-apoptotic responses in a variety of malignant cells[70]. Doshi *et al*[71] have shown that C6-ceramide induces tumour regression in an *in vivo* mouse model of CLL and that these effects are likely mediated by its effects on STAT3 phosphorylation and signaling.

BI 836826 is an anti-CD37 monoclonal antibody that mediates its effects on CLL cells through both antigen dependent cell-mediated cytotoxicity and by directly inducing apoptosis[72]. Stephens *et al*[73] investigated the effects of BI 836826 in combination with established BCR pathway inhibitors and suggest that BI 836826 may be effective in combination with idelalisib for CLL, particularly for those patients with *TP53* mutations.

The immunomodulatory drug dimethyl fumarate (DMF) is believed to exert its effects *via* down-regulation of NF-κB activity and TNF signaling. DMF is currently in clinical use for the treatment of psoriasis[74]. In keeping with the role of NF-κB in the survival of CLL cells[75], Wu *et al*[76] demonstrated that DMF is cytotoxic against CLL cells *in vitro* and is synergistic with ibrutinib, *via* a mechanism of action that involves down-regulation of Wnt signaling.

INFLAMMATORY PATHWAYS

Cytokines and chemokines play a significant role in the survival, proliferation and homing of CLL cells to the tumour microenvironment. Studies suggest many of these soluble factors are elevated in the sera of CLL patients compared to normal individuals[77], while *in vitro* studies involving the addition of cytokines to primary CLL cells in culture highlight their role in promoting cell survival, proliferation and migration[78]. Levels of cytokine expression have been linked with the disease course of CLL[77]. However, it remains to be elucidated whether many of these factors are derived from the leukemic cells or accessory cells within the tumour microenvironment.

Targeting the mechanisms that enable CLL cells to home to lymph nodes and to the marrow or interfering with the soluble factors that promote CLL cell survival have been proposed as being effective methods of limiting their longevity and proliferation.

Lenalidomide

In addition to the anti-leukemic effects discussed earlier there is also evidence suggesting lenalidomide, as with its analogue thalidomide, may have potent anti-inflammatory activity through suppression of cytokine and TNF-α production[79].

Plerixafor (AMD3100)

Data from a preclinical study of the CXCR4 inhibitor plerixafor suggests that the agent effectively blocks the capacity of CLL cells to home to the tumour microenvironment, overcomes the protective effect of *in vitro* models of the microenvironment and may represent a means of mobilizing tumor cells to increase the efficacy

of chemotherapies[80]. In a phase Ⅰ dose-escalation trial of 14 patients with previously treated disease plerixafor in combination with rituximab was well tolerated and was associated with a marked increase in lymphocyte count, suggesting successful mobilization of CLL cells from the lymph nodes and marrow[81].

PRO-APOPTOTIC/CELL-CYCLE INHIBITION

CLL-cell survival and proliferation relies on the over-expression of the anti-apoptotic protein B-cell lymphoma 2 (Bcl-2)[82] and the activity of cyclin-dependent kinases (CDKs)[83]. Redressing the balance of expression of the Bcl-2 family proteins towards a pro-apoptotic profile and inhibition of CDKs has been a focus of several recent clinical trials in CLL.

ABT-199

ABT-199 is the most clinically advanced compound among several developed known as BH3 mimetics, so-called after the binding domain that is common to the BH3-family of proteins, which includes Bcl-2. Tumour lysis syndrome appears to be a complication associated with treatment with ABT-199, particularly in the earlier trial cohorts; Souers *et al*[84] reported tumour lysis in three of their relapsed/refractory CLL patients on trial. In a recent phase Ⅰ clinical trial, ABT-199 was highly active against relapsed/refractory, FCR-refractory or 17p-deleted disease; in 56 relapsed/refractory CLL or SLL patients the OR rate was 84%, of which 20% achieved a CR[85]. Within this same trial those patients with deletion of 17p or fludarabine-refractory disease displayed similar OR rates of 82% and 78% respectively. Phase Ⅱ trials of ABT-199 as a single agent or in combination with rituximab (ClinicalTrials.gov NCT01682616) or obinutuzumab (ClinicalTrials.gov NCT01685892) for 17p-deleted or relapsed/refractory CLL patients are ongoing. To date, 49 patients have been enrolled in a trial combining ABT-199 and rituximab, which has had an OR rate of 86% and CR rate of 31%[86]. A trial of ABT-199 and obinutuzumab has recruited 9 participants to date but has yet to report any response or remission rates. Findings of these latter trials suggest the adjusted regimens and novel combinations of ABT-199 are well tolerated with tumour lysis syndrome having only been observed in 1 study participant[87].

Dinaciclib

Pre-clinical studies of flavopiridol provide a strong rationale for CDK inhibition as a therapeutic option in CLL, with a mechanism of action that includes both cytostatic and pro-apoptotic effects. While flavopiridol is undoubtedly the most thoroughly studied CDK inhibitor in CLL, its narrow therapeutic window and toxicity has prompted development of newer, more specific inhibitors, including dinaciclib. While *in vitro* studies suggest that dinaciclib induces apoptosis in CLL cells irrespective of poor-risk indications, including 17p deletion, it fails to overcome the protective effects of CLL-cell co-culture with a stromal layer[88]. These data suggest that the clinical efficacy of dinaciclib may require its incorporation into combination therapies. The results of a phase Ⅲ trial of dinaciclib are yet to be presented but recent data from an update on a phase Ⅰ dose escalation trial of 52 relapsed/refractory patients suggests that dinaciclib is clinically active and well tolerated in this setting. Of the 48 patients assessed, the overall response rate was 58%. Importantly, 57% of the patients with deletion of 17p13 and 63% with deletion of 11q23 achieved at least a PR[89]. A phase 1b/2 study of dinaciclib and ofatumumab has also recently commenced and to date 36 patients have been enrolled with a PR rate of 33% and stable disease in 56% of patients[90].

Novel pro-apoptotic/cell cycle inhibitors in pre-clinical development

MLN4924 is an inhibitor of the NEDD8-activating enzyme. It is believed that MLN4924 induces DNA damage and cell cycle arrest through its effects on Cdt1[91]. MLN4924 has been shown to induce apoptosis in primary CLL cells stimulated with CD40L and IL-21 and, although the exact mechanisms of action remain unclear, Cdt1 accumulation was also demonstrated in two further studies[92,93].

It is well established that mutations of *TP53* and *ATM* are associated with unchecked DNA repair in cancer and poor risk disease in CLL[94]. Inhibition of DNA repair which triggers accumulation of DNA damage has been proposed as a method for overcoming resistance to genotoxic agents. AZD6738 is one such drug which targets the Ataxia Telangiectasia and Rad3 related (ATR) protein and inhibits ATR-mediated DNA repair. Stankovic *et al*[95] and Kwok *et al*[96] have shown that AZD6738 is cytotoxic against CLL cells *via* a mechanism of action that involves the accumulation of DNA damage. Furthermore, studies suggest AZD6738 is synergistic with the DNA-damaging agents chlorambucil, fludarabine, bendamustine and cyclophosphamide and the PARP inhibitor, olaparib.

TARGETED THERAPY RESISTANCE MECHANISMS AND COMBINATION THERAPIES

There is emerging evidence that a subset of patients develop resistance to BCR-pathway targeted therapy. In data presented at the recent European Haematology Association meeting late disease progression while on ibrutinib was found to be associated with the acquisition of mutations in *BTK* and *PLCγ2*[97].

In a recent report that utilised an *in vitro* model of the CLL tumour microenvironment, prolonged CD40

stimulation resulted in resistance to ABT-199, due to induction of Bcl-XL, Mcl-1 and Bfl-1. Interestingly, these CD40-mediated effects could be blocked by the broad-spectrum kinase inhibitor dasatinib[98]. Using interaction proteomics, Abl and Btk were identified as dominant targets of dasatinib in primary CLL cells. Like dasatinib, the Abl inhibitor imatinib, but not ibrutinib, can overcome resistance to the BH3-mimetics. Conversely, BCR and chemokine-mediated adhesion can be abolished by dasatinib and ibrutinib, but not by imatinib[98]. These reports highlight the complexity of potential resistance mechanisms and the potential of drug combinations for overcoming resistance to these agents. They also highlight the need for ongoing research into signal pathways, their interactions and the relationship between CLL cells and the microenvironment.

CONCLUSION

The treatment of CLL is in a period of extraordinary revolution with the advent of multiple novel, targeted therapies. Unprecedented response rates among relapsed/refractory, high-risk and elderly patients suggest that there may very soon be more effective treatment options available for these patients. While the trials of treatment naïve patients support the use of the novel agents in the frontline setting, this would currently be difficult to justify in patients other than the 17p-deleted subgroup, given the high response rates to FCR. Extended follow-up data from on-going and future trials will provide the key to determining the response duration or curative potential of the novel agents reviewed here.

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