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Emerging Therapies in Chronic Lymphocytic Leukemia

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1. Introduction

The introduction of new therapies has opened new therapeutic hopes in the field of treating Chronic Lymphocytic Leukemia (CLL). CLL is extremely heterogeneous in its clinical course; some patients live for decades with no need for treatment, whereas others develop aggressive clinical course with a survival of less than 2-3 years. The decision to treat CLL patients should be guided by clinical staging, the presence of symptoms and disease activity (Diehl et al. 1999).

Once the diagnosis of CLL has been made, the treating physician is faced with the decision of not only how to treat the patient, but when to initiate therapy. In general practice, newly diagnosed patients with asymptomatic early-stage disease (Rai 0, Binet A) are monitored without therapy until they have evidence of disease progression. Studies from the French Cooperative Group on CLL, (Dighiero et al. 1998) the Cancer and Leukemia Group B,(Shustik et al. 1988) the Spanish Group PETHEMA, (Montserrat et al. 1996) and the Medical Research Council (Catovsky et al. 1988) confirm that the use of alkylating agents in patients with early-stage disease does not prolong survival (Group. 1999). Patients at intermediate (I and II) or high-risk (III and IV) according to the modified Rai classification or Binet stage B or C usually require the initiation of treatment at presentation. Some of these patients (in particular Rai intermediate risk or Binet stage B) can still be monitored without therapy until they exhibit evidence of progressive or symptomatic disease.

During the past decade there have been major advances in understanding the pathogenesis of the disease and more efficient treatments have been developed. CLL treatments have seen the transition from single-agent alkyator-based therapies to nucleoside analogs, combination chemotherapy, and recently to monoclonal antibodies (MAbs) and chemoimmunotherapy.

The use of immunotherapy is emerging as an exciting modality with significant potential to advance the treatment of B-cell malignancies. In the field of lymphoproliferative diseases rituximab, followed by the anti-CD52 antibody alemtuzumab, has changed the therapeutic landscape of B-cell cancers, particularly in patients with non-Hodgkin's lymphoma (NHL) with more recent indications in the setting of CLL (Cheson 2006).

Novel therapies are being evaluated both in pre-clinical studies and in clinical trials. These treatments include new MAbs such as ofatumumab, GA101, veltuzumab, epratuzumab,

lumiliximab, TRU-016 as well as agents targeting the anti-apoptotic Bcl-2 family of proteins, antisense oligonucleotides and other agents. This review attempts to summarize the current knowledge of these treatments and point to potential opportunities in the future with other targeted therapies currently being explored.

2. Best compounds of alkylating agents and purine analogs used in CLL

Chlorambucil, an alkylating agent, has been considered the "gold standard" for several decades. Due to its low toxicity and its oral administration, this drug remains the appropriate option for non-fit, elderly patients as well as for younger fit patients. Chlorambucil achieved higher remission rates (Overall response rates (ORR) 89%, Complete responses (CR) 59%) when administered at a fixed dose of 15 mg daily up to achievement of a CR or occurrence of grade 3 toxicity, for a maximum of six months (Jaksic et al. 1997). However, chlorambucil is no longer considered an appropriate option for younger or physically fit patients because of its low to non-existent CR rate (Catovsky et al. 2007).

Besides chlorambucil, cyclophosphamide (C) is another alkylating agent with activity in CLL patients. It is generally utilized in combination regimen. (Hansen et al. 1988; Raphael et al. 1991).

Fludarabine is the best purine analog studied in CLL. When used as single agent, it achieves superior ORR and longer progression-free survival (PFS) rates compared with other treatment regimens containing alkylating agents or corticosteroids (Anaissie et al. 1998; Plunkett et al. 1993; Rai et al. 2000). In phase III studies in naive CLL patients, fludarabine induced more CRs (7–40%) as well as longer duration of remission than other chemotherapies or chlorambucil. However, overall survival (OS) was not improved by this drug when used as a single agent (Johnson et al. 1996; Leporrier et al. 2001; Rai et al. 2000; Steurer et al. 2006).

Bendamustine, a hybrid of an alkylating nitrogen mustard group and a purine-like benzimidazole, has been used for more than 30 years in Germany. Results of a recent randomized trial, comparing bendamustine to chlorambucil, showed that more patients achieved CRs with bendamustine than with chlorambucil (31% vs. 2%). Moreover, the median PFS was 21.6 months and 8.3 months for bendamustine and chlorambucil, respectively (Knauf et al. 2009).

3. Rituximab: The first anti-CD20 MAb

Rituximab has revolutionized the therapeutic approach for patients with a wide variety of B-cell malignancies, including CLL. Rituximab is a chimeric human-mouse MAb with a high affinity for the CD20 surface antigen, a transmembrane protein that is expressed on pre-B cells and normal differentiated B lymphocytes. The predominant mechanism of action of rituximab-induced cell death is proposed to be primarily the result of antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC) and direct cell death (Di Gaetano et al. 2003; Golay et al. 2000; Manches et al. 2003).

Rituximab was first approved in the United States for the treatment of relapsed or refractory, low grade or follicular, B-cell NHL (Grillo-Lopez et al. 1999) then approved in Europe, for the treatment of relapsed stage III/IV follicular NHL (Gopal & Press 1999;

McLaughlin et al. 1998). In CLL, rituximab is less active as single agent than in other lymphomas, unless very high doses or denser dosing regimen are used. The objective response rates observed in CLL patients are ranged between 25% and 35% (Huhn et al. 2001; Itala et al. 2002).

In contrast, the greatest benefit of rituximab is demonstrated when used in combination with chemotherapy. Multiple combinations are currently in use and others are in investigational phases. Here, we will present some of these combinations to highlight the synergistic effect of rituximab with other agents.

The combination of fludarabine with rituximab prolonged the PFS and OS of CLL patients compared to fludarabine alone (Byrd et al. 2005).

A phase II study performed by the German CLL Study Group (GCLLSG) of fludarabine and rituximab in both refractory and previously untreated patients resulted in an ORR of 87% with a subset achieving CR (Schulz et al. 2002).

CALGB 9712 evaluated fludarabine in combination with rituximab given either concurrently or sequentially. Patients in the concurrent arm experienced more severe hematologic and infusion-related toxicity, but the ORR was 90% with a CR of 47% compared with an ORR of 78% and CR of 28% in the sequential arm (Byrd et al. 2003).

Likewise, rituximab induced a high ORR and complete remission rates when combined either with fludarabine/cyclophosphamide in refractory/relapsed CLL patients (73% and 25%, respectively) (Wierda et al. 2005) or in those with previously untreated CLL (95% and 72%, respectively) (Tam et al. 2008). The superiority of fludarabine, cyclophosphamide plus rituximab (FCR) compared to fludarabine and cyclophosphamide, alone was also confirmed in randomized phase III trials (Hallek 2008; Robak 2008; Tam et al. 2008).

In the CLL8 protocol of the German CLL Study Group (GCLLSG), 817 treatment-naive, physically fit patients (aged 30–81 years) were randomly assigned to receive either fludarabine, cyclophosphamide, and rituximab (FCR group) or fludarabine and cyclophosphamide (FC group). At 3 years after randomization, 65% of patients in the FCR group were free of progression compared with 45% in the FC group ($P < 0.0001$); The three–year survival rates were 87% and 83% for FCR–treatment and FC–treatment ($p=0.012$), respectively. FCR treatment was more frequently associated with hematologic adverse events, particularly neutropenia; these results suggest that the choice of FCR as first-line treatment prolongs OS of CLL patients (Hallek et al., 2010).

Furthermore, when combined with pentostatin and cyclophosphamide in previously untreated CLL patients, rituximab achieved a significant clinical activity despite poor risk-based prognoses, including achievement of minimal residual disease in some patients (Kay et al. 2007; Keating et al. 2005; Tam et al. 2006).

The German CLL Study Group initiated two studies to explore the combination of bendamustine plus rituximab in patients with relapsed CLL (Fischer 2008) and in previously untreated CLL patients (Fischer 2009). Results showed an ORR of 77%, CR rate of 15% for relapsed patients and an OR of 91%, CR of 33% for untreated ones. A retrospective Italian study was conducted in 109 relapsed/refractory CLL patients. Results showed that the combination of rituxmab plus bendamustine was an effective and well-tolerated treatment

for these patients, producing a remarkable high CR rate and mild toxicity (Iannitto et al. 2011).

Investigations of the mechanism underlying the anti-tumor activity of rituximab as a single agent and in combination with chemotherapy are ongoing. By understanding these mechanisms, it might be possible to further enhance current cell killing strategies or develop novel agents and strategies.

4. Newer anti-CD20 antibodies for CLL

4.1 Ofatumumab

Ofatumumab is a fully humanized MAb targeting a small-loop CD20 epitope distinct from that of rituximab (Teeling et al. 2004). Compared to rituximab, it demonstrates an increased target-binding affinity to CD20 and slower dissociation rates. It exhibits stronger complement-mediated toxicity and shows potent lysis of rituximab-resistant cells.

In phase I/II study in relapsed/refractory CLL patients, ofatumumab achieved an ORR of 44%; however, these were almost exclusively partial responses (Coiffier et al. 2008). In a phase I/II dose-escalation trial, the efficacy and safety of single-agent ofatumumab (300-1000 mg) have been evaluated in 40 patients with relapsed or refractory Follicular Lymphoma (FL). Rapid, efficient and sustained peripheral B-cell depletion was observed in all dose groups. The ORR in evaluable patients (n=36) was 43% (Hagenbeek et al. 2008).

This antibody was recently approved by the Food and Drug Administration (FDA) for fludarabine and alemtuzumab refractory CLL patients and for fludarabine refractory patients with bulky disease. Ofatumumab was administered in these two groups with an ORR of 58% and 47%, respectively (Wierda G 2009). It is currently being combined with other agents in CLL, including bendamustine.

A recently completed phase II trial of ofatumumab in combination with fludarabine and cyclophosphamide demonstrated CRs in up to 50% of patients with previously untreated CLL, despite poor prognostic factors (Wierda G 2009). The median PFS has not been reached with the short median follow-up of 8 months.

Moreover, a randomized phase II study was conducted using two dose schedules of ofatumumab (500 mg and 1000 mg) in combination with fludarabine 25 mg/m2 and cyclophosphamide 250 mg/m2. The CR rate was 32% for the 500-mg and 50% for the 1000-mg cohort; the ORR was 77% and 73%, respectively (Wierda et al. 2010).

4.2 GA101

GA101 is the first humanized type II anti-CD20 MAb with glycolengineered Fc portion and a modified elbow hinge (Bello & Sotomayor 2007). The adapted Fc region gives GA101 a 50-fold higher binding affinity to FCγRIII (CD16) compared to a non-glycoengineered antibody, resulting in 10- to 100-fold increase in ADCC against $CD20^+$ NHL cell lines via the activation of effector cells (Umana 2006). Moreover, the modified elbow hinge area also results in strong induction of direct cell death of several NHL cell lines and primary malignant B cells *in vitro* (Alduaij W & S. 2009; Bello & Sotomayor 2007; Umana 2006). However, these modifications result in reduced CDC activity (Umana 2007). In vitro B-cell

depletion assays with whole blood from healthy and leukemic patients showed that the combined activity of ADCC, CDC, and apoptosis for GA101 was significantly superior to rituximab (Alduaij W & S. 2009; Patz M 2009; Umana 2006; Zenzl 2009).

The enhanced efficacy of GA101 has been also shown *in vivo*. In xenograft models of Diffuse large B-cell lymphoma (DLBCL) and mantle cell lymphoma, treatment with GA101 resulted in CR and long-term survival compared with tumor stasis achieved with rituximab (Umana 2006). In cynomolgus monkeys, GA101 (10 and 30 mg/kg infused on days 0 and 7) showed significantly superior depletion of B cells compared to rituximab (10 mg/kg) from day 9 to day 35 and was more efficacious at clearing B cells from lymph nodes and the spleen (Umana 2007).

Initial phase I study of patients with relapsed/refractory CD20+ disease (n=21), including CLL, DLBCL, and other NHLs, for whom no therapy of higher priority was available (95% of patients had previously received rituximab), GA101 demonstrated a favorable safety profile with no dose-limiting toxicities (Salles 2009). The depletion of B-cell was rapid and sustained in the majority of patients. Nine of the evaluable patients responded to therapy (ORR, 43%; five CR/unconfirmed CR and four partial responses), with responses observed at all dose levels and across all FcγRIIIA genotypes.

The pharmacokinetics of GA101 are generally similar to those of rituximab and dose-dependent. However, significant inter- and intra-patient variabilities have been observed, the clinical relevance of which will need further investigation [86]. Results from a phase I study in patients with previously treated B-CLL (n=13) who were given single-agent GA101 (400–2000 mg; nine infusions) showed similar safety and pharmacokinetic profiles to those observed in the previously described patients with NHL, except for an increased incidence of neutropenia (Morschhauser 2009).

GA101 is currently being explored as a single agent in phase II studies in relapsed/refractory B-CLL and indolent/aggressive NHL, and in combination with chemotherapy in a phase Ib study.

4.3 Veltuzumab (IMMU-106)

Veltuzumab is a humanized CD20 MAb (type I) constructed recombinantly on the framework regions of epratuzumab, with complementarity-determining regions (CDRs) identical to rituximab, except for a single amino acid in CDR3 of the variable heavy chain. It showed anti-proliferative, apoptotic, and ADCC effects *in vitro* similar to rituximab, but with significantly slower off-rates and increased CDC in several human lymphoma cell lines. In addition, at very low doses, given either intravenously or subcutaneously, veltuzumab showed a potent anti-B cell activity in cynomolgus monkeys and controlled tumor growth in mice bearing human lymphomas (Goldenberg et al. 2009).

In a phase I/II dose-escalating clinical trial in patients with recurrent NHL, the ORR for veltuzumab-treatement was 41% (33/81), including 17 patients (21%) with CR or unconfirmed CR (Morschhauser et al. 2009). Veltuzumab caused B-cell depletion after the first infusion even at the lowest dose of 80 mg/m^2, which persisted after the fourth infusion, and was well tolerated, with no evidence of immunogenicity.

Veltuzumab is additionally being developed for subcutaneous administration, which may provide advantages for this agent versus other MAbs (Goldenberg et al. 2010). Veltuzumab is undergoing clinical trials using a low-dose subcutaneous formulation in patients with NHL and CLL.

5. Other MAbs for CLL

5.1 Alemtuzumab

Alemtuzumab is a recombinant, fully humanized, MAb targeting the CD52 antigen. CD52 is expressed on virtually all lymphocytes at various stages of differentiation, as well as monocytes, macrophages and eosinophils, whereas hematopoeitic stem cells, erythrocytes and platelets do not express it (Hale et al. 1990). A high level of CD52 is found on T-prolymphocytic leukemia, followed by B-CLL, with the lowest levels expressed on normal B cells. The mechanisms of action of alemtuzumab include CDC, ADCC and induction of apoptosis (Mone et al. 2006).

The use of alemtuzumab monotherapy is approved in the United States in the first-line treatment of patients with CLL. In a pivotal phase II study in 93 patients with fludarabine-refractory disease, alemtuzumab yielded an ORR of 33% with a median OS of 16 months (Keating et al. 2005).

Alemtuzumab has been approved for the initial treatment of CLL based on randomized trial conducted including 297 patients who received either alemtuzumab or chlorambucil. The antibody induced an ORR rate of 83.2% with 24.2% CRs compared with 55.4% and 2%, for alemtuzumab and chlorambucil, respectively (Hillmen et al. 2007). In addition, alemtuzumab has proven efficacy even in patients with poor prognostic factors, including high-risk genetic markers such as deletions of chromosome 11 or 17 and p53 mutations (Lozanski et al. 2004; Stilgenbauer & Dohner 2002). The combination of alemtuzumab with fludarabine was investigated in a phase II trial with relapsed CLL patients. The ORR was 83% including 30% CR (Elter et al. 2005). The combination of both alemtuzumab with rituximab has been also studied in patients with lymphoid malignancies including patients with refractory/relapsed CLL, producing an ORR of 52% with 8% CR (Faderl et al. 2003).

The combination of fludarabine, cyclophosphamide plus alemtuzumab (FCA) was recently compared to fludarabine, cyclophosphamide plus rituximab (FCR) in a phase III study by "the french Cooperative Group On CLL and WM" (FCGCLL/MW) and "the Groupe Ouest-est d'Etudes des Leucemies Aigues et Autres Maladies du Sang" (GOELAMS). Response rates of the first 100 patients were reported in a preliminary analysis with safety data presented for the entire cohort of 178 patients. The ORR in the first 100 patients was 96% for FCR compared to 85% in the FCA arm (p=0.086) with a CR rate of 78% in the FCR arm versus 58% in the FCA arm (p=0.072). Increased toxicity of FCA compared with FCR was found, preventing the use of the FCA combination outside of clinical trials (Lepretre 2009).

5.2 Lumiliximab

Lumiliximab is an anti-CD23 macque-human chimeric MAb with a strong similarity to the human antibody. The CD23 antigen is a low-affinity IgE receptor that is found in high levels in CLL patients (Fournier et al. 1992). Lumiliximab inhibits the IgE secretion *in vitro,* binds complement and mediates ADCC by binding FcγRI and RII receptors.

A phase I pilot study reported a limited single-agent activity in patients with refractory/relapsed CLL (Byrd et al. 2007b). Based on preclinical evidences of synergistic improvement of survival when lumiliximab was combined with fludarabine or rituximab, a phase I/II trial evaluated the safety and efficacy of lumiliximab in combination with FCR in 31 patients of relapsed CLL patients (Byrd J 2008). This combination regimen yielded an ORR of 65%, which was comparable to the results seen with FCR in the pivotal phase II study conducted by the M.D. Anderson Cancer Center (Byrd J 2008; Wierda et al. 2005). Lumiliximab/FCR appeared to double the CR rate compared to FCR alone (52% vs. 25%) without increasing the rate of toxicities.

5.3 Epratuzumab

Epratuzumab is a humanized anti-CD22 MAb currently in clinical trials for treatment of NHL and autoimmune disorders (Leonard & Goldenberg 2007). Epratuzumab is selectively active against normal and neoplastic B-cells. This MAb acts as an immunomodulatory agent in contrast to rituximab which is an actually cytotoxic therapeutic antibody. *In vitro*, epratuzumab has demonstrated the ability to elicit ADCC and induce CD22 phosphorylation and signaling, both of which may contribute as potential mechanisms of action (Carnahan et al. 2007; Carnahan et al. 2003).

Phase I/II studies demonstrated objective responses across various dose levels in both relapsed/refractory FL (24%) (Leonard et al. 2003) and DLBCL (15%) (Leonard et al. 2004).

Epratuzumab has also been combined with rituximab in phase II studies showing at least an additive benefit while toxicities of the combination were comparable with those of single-agent rituximab (Leonard et al. 2005). In a recent international, multicenter trial evaluating rituximab plus epratuzumab in patients with post-chemotherapy relapsed/refractory, indolent NHL, an objective response was seen in 54% FL patients including 24% with CR/unconfirmed CR (CRu) whereas 57% of Small Lymphocytic Lymphoma patients had ORs including 43% with CR/Cru (Leonard et al. 2008). Rituximab-naive patients had an ORR of 50%, whereas patients who previously responded to rituximab had an ORR of 64%.

Thus, the combination of epratuzumab and rituximab induced durable responses in patients with recurrent, indolent NHL. Epratuzumab is also being evaluated in combination with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) and as a therapy in other B-cell neoplasms (Micallef et al. 2006).

5.4 TRU-016

TRU-016 is a CD37-directed small modular immunopharmaceutical protein composed of IgG1 variable regions (VL and VH) and a small, engineered constant region. CD37 is expressed at high concentrations on the surface of B cells and mature B-cell lymphomas and leukemias. *In vitro* studies demonstrated that the chimeric version of TRU-016 induced apoptosis and ADCC-dependent cytotoxicity in CLL cells (Zhao, Lapalombella et al. 2007).

Interim results of a phase I study of TRU-016 reported a favorable toxicity profile and partial responses at higher doses (Andritsos 2009).

6. Emerging drugs

6.1 Bcl-2 inhibitors

The expression of high levels of anti-apoptotic Bcl-2 protein is characteristic of CLL cells (Hanada et al. 1993). Many studies have suggested that an increased ratio of anti- to pro-apoptotic proteins such as Bcl-2/Bax is correlated with poor response to chemotherapy, disease progression and shorter survival (Pepper et al. 1997; Robertson et al. 1996).

Modulation of anti-apoptotic proteins is a promising strategy to sensitize cells to antileukemic agents. Preclinical data have shown that inhibition of Bcl-2, inhibition of the interaction between Bcl-2 or Bcl-xL and partner proteins with compounds such as ABT-737 (Mason et al. 2009) or inhibition of Mcl-1 were associated with increased sensitivity to antileukemic agents (Hallaert et al. 2007).

Numerous novel agents have shown *in vitro* promise in overcoming the pro-apoptotic defects in CLL cells. These do not, however, always translate into a therapeutic *in vivo* effect.

6.2 Oblimersen sodium (G3139)

Oblimersen sodium is a phosphorothioate antisense oligodeoxynucleotide composed of 18 nucleotides targeting the first six codons of the open reading frame of the bcl-2 mRNA. Preclinical evaluation has demonstrated good antineoplastic effect in B-cell cancers; several clinical trials have confirmed its safety and efficacy both alone and in combination with other therapeutics.

A phase I/II clinical trial was conducted in patients with relapsed or refractory CLL to determine the maximum tolerated dose (MTD), efficacy, safety, and pharmacokinetics of oblimersen sodium. A total of 40 patients (who had received at least one prior chemotherapy regimen containing a purine analogue) were treated (14 in Phase I and 26 in Phase II) with single-agent oblimersen sodium in doses ranging from 3 to 7 mg/kg/day in the phase I portion of the study. The MTD for the phase II part of the study was determined to be 3 mg/kg/day with higher doses of oblimersen sodium being associated with a cytokine release reaction characterized by fever, rigors and hypotension. This was attributed to the release of large amounts of cytokines. Thus, oblimersen sodium has shown a modest single-agent activity in heavily pretreated patients with advanced CLL (O'Brien et al. 2005).

A phase II trial was conducted to evaluate the safety and efficacy of the combination of fludarabine, rituximab and oblimersen in previously untreated or relapsed/previously treated CLL patients. Preliminary results have been encouraging especially in the setting of CLL with poor prognostic markers (Marvromatis 2006; Mavromatis 2005).

A randomized phase III trial of fludarabine and cyclophosphamide (FC) with or without oblimersen sodium in 241 patients with relapsed or refractory CLL who had received at least one prior fludarabine-containing regimen has been conducted. The rate of CR/nodular PR was significantly higher for patients treated with FC plus oblimersen, 17% versus 7%, respectively. The oblimersen treated group was associated with a significant survival benefit (O'Brien et al. 2007).

Overall, oblimersen has shown new hope and potential in the management of CLL, enhancing the efficacy of other commonly used agents. Further studies with oblimersen should have a special focus on correlating response and survival outcomes with Bcl-2 overexpression and subsequent decrease in Bcl-2 protein.

6.3 Navitoclax (ABT-263)

Navitoclax (ABT-263), a novel, orally bioavailable, small molecule, binds with high affinity to anti-apoptotic proteins Bcl-2, Bcl-xL, and Bcl-w, promoting apoptosis. *In vitro*, navitoclax shows potent targeted cytotoxicity against T and B lymphoid malignancies that over-express Bcl-2. A phase I trial demonstrated oral navitoclax monotherapy to be well-tolerated and to have anti-tumor activity in CLL patients.

Phase II study was conducted in patients with heavily pretreated CLL, the drug attained an objective response rate of 33% (currently confirmed in 19% of patients); 58% of patients with baseline nodal enlargement showed shrinkage of greater than 50%.

The combination of navitoclax with bendamustine/rituximab was effective for patients with relapsed or refractory CLL and presented encouraging results in a phase II trial. Moreover, phase III studies showed that the combination of navitoclax with fludarabine/cyclophosphamide/rituximab combination improved outcomes in CLL patients (Kipps 2010).

6.4 Obatoclax (GX15-070)

Obatoclax is a hydrophobic molecule, developed as a Bcl-2 family antagonist. This agent inhibits several anti-apoptotic Bcl-2 family proteins including Bcl-x_L, Bcl-2, Bcl-w, BCL-B, A-1 and Mcl-1. It induces the release of Bak from Mcl-1, the liberation of Bim from both Bcl-2 and Mcl-1 as well as the formation of an active Bak/Bax complex. Moreover, it can promote the release of cytochrome c from mitochondria leading to apoptosis (Konopleva et al. 2008).

A phase I trial of obatoclax was conducted in heavily pretreated patients with advanced CLL. Obatoclax was administered at doses ranging from 3.5 to 14 mg/m^2 as a 1-hour infusion and from 20 to 40 mg/m^2 as a 3-hour infusion every 3 weeks. Obatoclax demonstrated biologic as well as modest clinical activity in these patients with one (4%) of 26 patients achieving a partial response (O'Brien et al. 2009).

7. Newer treatment options

7.1 Lenalidomide

The immunomodulatory agent lenalidomide has shown activity in CLL in the relapsed/refractory as well as in the untreated setting.

Activity in CLL was first demonstrated by Chanan-Khan *et al.* in a phase II study. 25 mg of lenalidomide was administered in this trial daily on days 1 through 21 of a 28-day cycle in 45 pretreated CLL patients (Chanan-Khan et al. 2006). This regimen was associated with a 47% ORR and a 9% CR rate.

Ferrajoli *et al.* adopted this dose escalation scheme in 45 patients with relapsed CLL. The dosing started at 10 mg daily for 28 days, with dose escalation to a maximum of 25 mg/day as tolerated. The ORR was 32% with 7% of patients achieving a CR (Ferrajoli et al. 2008). Moreover, lenalidomide therapy was well tolerated and induced durable remissions in elderly patients with CLL (Badoux et al. 2011).

The combination of lenalidomide plus rituximab is currently being investigated in 60 patients with relapsed CLL patients. 37 patients are to date evaluable for response. The ORR was 68%, no CR was achieved. The results obtained suggest that the combination of rituximab and lenalidomide is superior to the single agent lenalidomide.

Currently, a study is recruiting participants to evaluate the combination of fludarabine plus rituximab with or without lenalidomide or cyclophosphamide in treating patients with symptomatic CLL.

7.2 Flavopiridol (Alvocidib)

Flavopiridol, a synthetic flavon, induces apoptosis in CLL cell lines by targeting cyclin-dependent kinases.

It shows high activity in CLL patients with relapsed high-risk CLL (Byrd et al. 2007a; Phelps et al. 2009). A phase II trial on relapsed CLL patients with genetically high risk features achieved an ORR of 53%, including one CR (Lin et al. 2009). Currently, a registration trial for flavopiridol in relapsed CLL is conducted in the United States and Europe.

8. Conclusion

A refreshing change is taking place in CLL research. There is an increasing interest to fully understand all subsets of CLL patients in order to develop novel and specific agents which cater to individualized needs of each subset. Currently available therapies are only partially efficient in CLL; thus, obvious clinical and scientific needs to develop new therapeutic options are under investigation to circumvent the limitations of currently used therapies in CLL.

Further studies should elucidate the role of these new agents and their combinations in the management of CLL.

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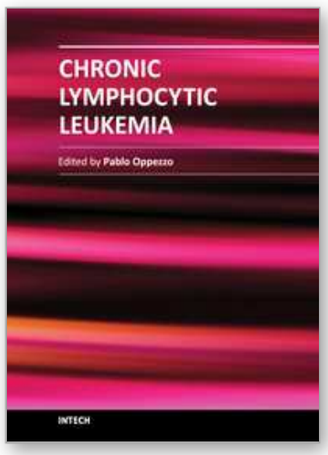

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B-cell chronic lymphocytic leukemia (CLL) is considered a single disease with extremely variable course, and survival rates ranging from months to decades. It is clear that clinical heterogeneity reflects biologic diversity with at least two major subtypes in terms of cellular proliferation, clinical aggressiveness and prognosis. As CLL progresses, abnormal hematopoiesis results in pancitopenia and decreased immunoglobulin production, followed by nonspecific symptoms such as fatigue or malaise. A cure is usually not possible, and delayed treatment (until symptoms develop) is aimed at lengthening life and decreasing symptoms. Researchers are playing a lead role in investigating CLL's cause and the role of genetics in the pathogenesis of this disorder. Research programs are dedicated towards understanding the basic mechanisms underlying CLL with the hope of improving treatment options.

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