

Advances in treating chronic lymphocytic leukemia

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Abstract

Chronic lymphocytic leukemia (CLL) is the most prevalent type of leukemia, affects mostly elderly patients, and is incurable without allogeneic transplantation. Although classic chemo(immuno)therapy is still the standard of care for patients in need of treatment, this paradigm might change in the near future with the advent of new therapeutic agents targeting major pathogenic pathways in CLL.

Introduction

With more than 15,000 newly diagnosed cases in the US in 2012, CLL is the most common leukemia in the Western world and affects mainly elderly patients [1]. Different manifestation patterns and a wide range of genetic variations like hypermutation of the immunoglobulin heavy-chain genes (IGHV), genomic aberrations, and recurrent gene mutations in oncogenes and tumor suppressor genes reflect the clinical and biological heterogeneity of the disease [2,3]. CLL is still incurable without allogeneic stem cell transplantation, although treatment outcome has considerably improved by using risk stratification and novel therapeutic agents [4,5]. This article gives an overview of classic treatments and new compounds in clinical use. First, we cover traditional treatment with chemoimmunotherapy, and then we highlight key features of novel agents (see also Figure 1).

Chemo(immuno)therapy as initial approach

The gold standard for first-line treatment of fit patients is the combination of the monoclonal antibody rituximab with the cytostatic drugs fludarabine and cyclophosphamide (known as FCR) or with bendamustine (BR) [6-11]. Although FCR as compared with BR appears to be more efficacious, it is also more toxic and the choice between the two regimens is sometimes difficult, depending mostly on age and comorbidity. In patients not eligible for intensive treatment because of comorbidities, chlorambucil (Clb) in combination with CD20

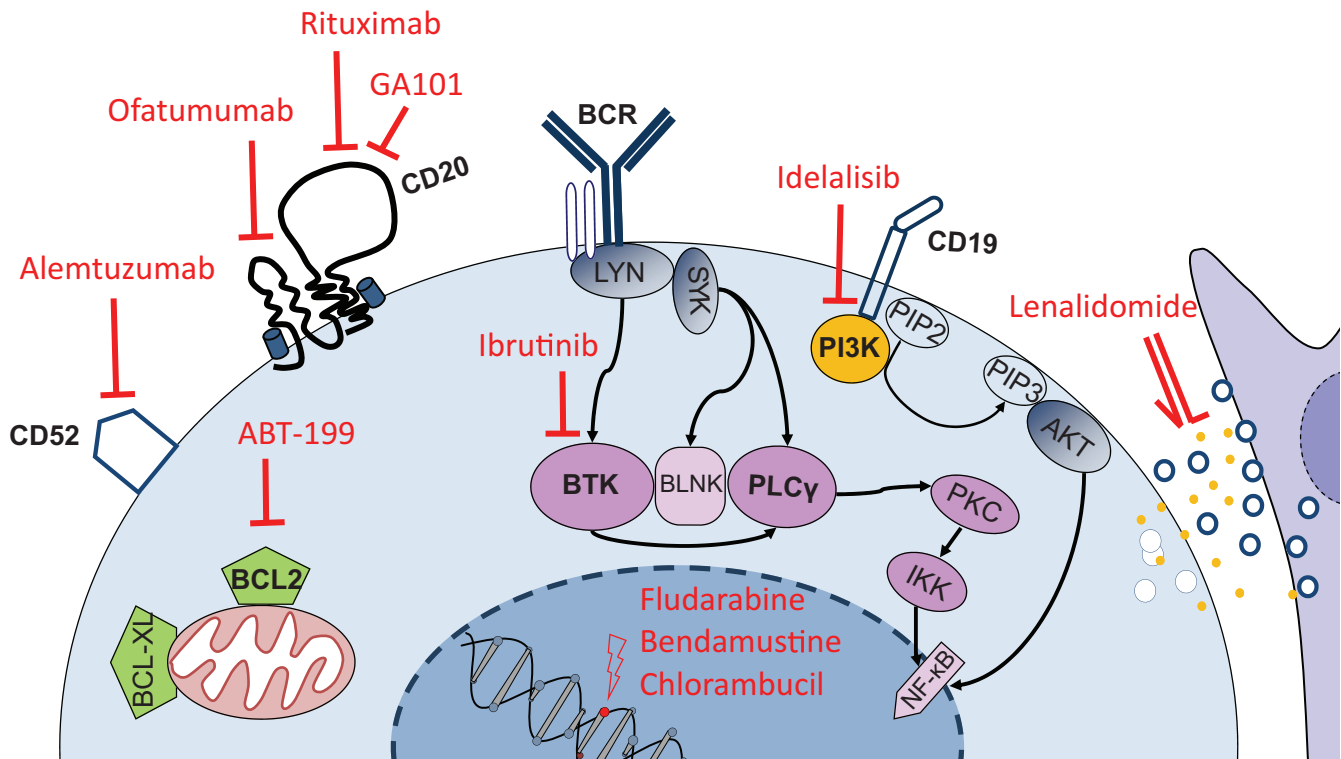
antibodies is a less effective alternative [12,13]. Although the addition of rituximab to chemotherapeutics in lymphoid malignancies started at the end of the last century, a general recommendation for utilization up front evolved from results of phase II and phase III studies and above all the CLL8 study in 2010 [14]. In this two-arm prospective trial (FC [fludarabine and cyclophosphamide] versus FCR), progression-free survival (PFS) and overall survival (OS) were improved by the addition of rituximab.

First-, Second-, and third-generation antibodies against CD20 and CD52

Rituximab is a chimeric type 1 antibody against the B-cell antigen CD20, which is expressed on the surface of B-cell non-Hodgkin lymphomas, including CLL. Mechanisms like complement activation (complement-dependent cytotoxicity), opsonization to macrophages causing antibody-dependent cell-mediated cytotoxicity (ADCC), and induction of apoptosis were observed [15,16]. Nevertheless, the exact mode of action remains unclear, especially with respect to the intracellular pathways influenced by CD20 binding [17].

Although rituximab has limited efficacy as a single agent in CLL, the CD20 antibody ofatumumab is efficacious as a monotherapy as well as in combination with chemotherapeutics. This fully humanized type 1 monoclonal antibody that targets a different epitope of CD20

Figure 1. New therapeutic agents and their targets in a chronic lymphocytic leukemia cell



BCL2, B-cell lymphoma 2; BCR, B-cell receptor; BTK, Bruton's tyrosine kinase; NF-κB, nuclear factor kappa B; PI3K, phosphoinositide 3-kinase; PKC, protein kinase C; PLC, phospholipase C.

with a higher binding affinity in comparison with rituximab results in a stronger complement-dependent cytotoxicity but similar ADCC and apoptosis induction [18]. Ofatumumab is approved as a single agent in CLL refractory to fludarabine and alemtuzumab in Europe and the US. Interestingly, response rates of patients pretreated with rituximab were quite similar to those of patients not previously exposed (54% vs. 63%, respectively) [19,20]. Another phase III trial in untreated CLL patients with comorbidities showed that the addition of ofatumumab to Clb treatment is more efficacious without an increase of severe side effects (PFS 13.1 vs. 22.4 months without and with ofatumumab, respectively) [13]. In April 2014, the US Food and Drug Administration (FDA) approved ofatumumab in combination with Clb for the treatment of previously untreated CLL patients, for whom fludarabine-based therapy is considered inappropriate. Of note, mutation of *NOTCH1* appears to be a predictive factor for reduced benefit from ofatumumab addition [21].

In contrast to rituximab and ofatumumab, obinutuzumab (GA101) is a glycoengineered type 2 antibody targeting CD20 with increased antibody-dependent cellular cytotoxicity and direct, non-apoptotic cell death induction

mediated through lysosomes [22]. Phase I trials in patients with refractory disease showed promising results, with 62% of patients responding overall (overall response rate, or ORR) [23]. In a recently published phase III study, the addition of obinutuzumab to Clb was compared with a rituximab-Clb combination and Clb monotherapy. Patients receiving GA101-Clb had a significantly better response and were more frequently negative for minimal residual disease (MRD) and prolonged PFS (median PFS) (27.6 vs. 16.3 months) in comparison with rituximab-Clb. Benefits with regard to OS were seen as well but did not reach significance. Side effects were similar with both treatments, particularly with regard to infections, although more infusion-related reactions were observed in the obinutuzumab treatment arm (20% vs. 4%) [12]. Based on this data, obinutuzumab appears to be more potent and equally well tolerated as compared with rituximab in CLL, which has recently led to FDA approval in combination with Clb for untreated patients not eligible for more intensive therapy.

The CD52 antibody alemtuzumab has been approved for the treatment of fludarabine-refractory CLL in the USA and EU in 2001. Several studies confirmed its efficacy

[24,25]. Infusion-related symptoms were overcome by a switch to subcutaneous administration without a loss of efficacy, as shown in the CLL2H trial of the German Chronic Lymphocytic Leukemia Study Group (GCLLSG) [26]. Since 2008, alemtuzumab can also be considered up front for patients with a compromised TP53 DNA damage response pathway, caused by either deletion of 17p or mutations in TP53. This genetic risk group is associated with a reduced therapy response and shorter OS when treated with chemotherapy that takes effect by induction of DNA damage and subsequent apoptosis [3,27]. Interestingly, these risk factors had no impact on ORR, PFS, and OS for the treatment with alemtuzumab, suggesting an efficacy of the CD52 antibody independent of the *p53* signaling pathway [26,28,29]. According to the number of pretreatments, ORR was 34% to 98%. Alemtuzumab showed superiority in complete remission rate compared with Clb but more frequent severe cytotoxic side effects like neutropenia and thrombocytopenia grade III and IV. Opportunistic infections with cytomegalovirus (CMV) and non-CMV infections were extensive in both untreated and pretreated patients [30]. However, alemtuzumab for treatment of CLL was withdrawn from the market in Europe and the US and is available only through a named patient program.

Immune modulatory drugs

Lenalidomide is an immune-modulating drug that likely exerts its action in CLL via inhibiting cytokines such as tumor necrosis factor alpha, interleukin-7, and vascular endothelial growth factor and stimulating T and natural killer cells. Additionally, it resolves immunosuppressive mechanisms against healthy T cells induced by lymphoma cells and thus reconstitutes the so-called *immune synapse* [31,32]. Lenalidomide is a successor of thalidomide with improved potency in CLL and fewer side effects, but also of potential teratogenicity [33,34]. In two phase II trials, lenalidomide was administered daily for 21 days of a 4-week cycle or continuously. Response rates in pretreated patients ranged from 32% to 47% [35,36]. Combination with rituximab increased the ORR to 66% and time-to-treatment failure to 17.4 months, results comparable to other phase II studies in similar populations (ORR 59%, time-to-treatment failure 14.7 months) [37,38]. Treatment with lenalidomide caused grade 3 and 4 neutropenia (up to 78%) independent of usage as mono- or combination therapy [35,37]. Anemia, thrombocytopenia, or fatigue was a rare side effect. Frequency of tumor flare reaction, a lenalidomide-associated side effect, could be reduced by slowly escalating the administered dose [35,36,39]. This combination of leukocytosis, rash, fever, and abdominal pain occurs typically in the first treatment cycle and can be serious, especially in patients with renal

dysfunction. Additionally, cases of tumor lysis syndrome were described. Currently, lenalidomide is further developed in combination regimens. Most prominently, the maintenance setting after remission induction with conventional chemo(immune)therapy is studied in ongoing trials (NCT00774345 and NCT01556776).

Drugs targeting B-cell receptor signaling

The B-cell receptor (BCR) signaling pathway is essential for CLL cell survival [40]. Several new drugs in clinical development are effective in CLL through inhibition of this pathway. The small-molecule ibrutinib is one of these agents. It binds covalently to the cysteine 481 of the enzyme Bruton's tyrosine kinase (BTK) and subsequently interrupts BCR pathway activation. This results in a reduced migration and proliferation of the malignant cells and induces apoptosis. Initial phase Ib/II trials including 85 relapsed/refractory patients showed impressive survival rates of 75% for PFS and 83% for OS at 26 months [41]. Although patients with adverse genomic aberrations (11q-, 17p-) or unmutated IGHV status had response rates similar to those of patients without risk factors, 10 of 11 patients with progressive disease had 17p- or 11q-abnormalities and the PFS of these groups was significantly inferior. Earlier results of another cohort of 24 high-risk patients showed a partial response in 50% of cases but no complete remissions [42]. Interestingly, specific resistance mechanisms to ibrutinib have been found: mutations in BTK at position 481, abrogating covalent binding of ibrutinib, and activating mutations in a downstream enzyme, PLC γ 2, were found in patients who displayed acquired resistance to ibrutinib [43]. It is unclear whether mutation of BTK or PLC γ 2 (or both) is restricted to specific patient subgroups with impaired DNA repair.

However, most importantly, ibrutinib is a very well-tolerated drug, and most of the side effects are grade I or II, including transient diarrhea, fatigue, and upper airway infections. Of 85 patients, only 6 discontinued treatment because of adverse events [41]. A remarkable side effect is a transient increase of lymphocytes in peripheral blood up to six-fold of baseline counts in the first weeks after treatment start. This sometimes worrisome but usually harmless phenomenon is concurrent with a decrease of lymph node and spleen size and therefore can be attributed to mobilization of CLL cells from tissue compartments into peripheral blood [44]. Other inhibitors of BCR signaling pathways showed a similar increase of lymphocytes in peripheral blood upon treatment. For pretreated patients with CLL and mantle cell lymphoma (MCL), ibrutinib is already approved by the FDA. For untreated elderly CLL patients, a current trial also shows high safety and efficacy [45].

The phosphoinositide 3-kinase (PI3K) inhibitor idelalisib, another agent targeting the BCR signaling pathway, has been shown to be efficacious in CLL. Although the detailed mechanism is only partly understood in CLL, activated PI3K is associated with nuclear factor-kappa-B (NFκB) activation and expression of B-cell lymphoma (BCL)-XL and Mcl-1, both of which mediate inhibition of pro-survival pathways [46]. Additionally, PI3K inhibition reduced chemotaxis of CLL cells into protective tissue microenvironments so that the malignant cells are more amenable to chemotherapy [47]. In 51 pretreated patients of a phase I study, idelalisib was administered in combination with rituximab or bendamustine or both. ORRs were similar in the rituximab-idelalisib arm compared with more intensive idelalisib combination therapies (78% vs. 82% and 87%) [48]. This result led to a placebo controlled phase III study in relapsed CLL patients without the option of further chemo(immuno)therapy due to comorbidities, decreased renal function, or myelosuppression. The ORRs were 81% in patients who received rituximab and idelalisib vs. 13% for rituximab monotherapy. Notably, after 12 months of follow-up, idelalisib-rituximab-treated patients had a significantly improved OS (hazard ratio (HR) = 0.28, $P = 0.02$) and PFS (HR = 0.15, $P < 0.001$). This is striking as severe adverse events were quite similar with both treatments and most adverse events were of grade 1-2 [49]. Among these side effects, pyrexia, chills, and diarrhea were more often observed in the PI3K inhibitor arm. Interestingly, rituximab-idelalisib treated patients with *TP53* mutation or 17p deletion had a similar PFS in comparison to patients without these high-risk abnormalities [50]. FDA and European Medicines Agency (EMA) approval of this treatment option for CLL is expected in 2014.

Inducers of cell death

Impairment of programmed cell death (apoptosis) is of importance in the pathogenesis of hematopoietic malignancies in general and CLL in particular [51]. ABT-199 is an orally bioavailable antagonist of the anti-apoptotic protein BCL-2 by mimicking the BH3 domain (thus termed a BH3-mimetic), thereby inducing cell death. In contrast to its precursor ABT-263, ABT-199 has a similar effect on BCL-2 but a strongly reduced inhibition of BCL-XL. This results in a decreased side effect of thrombocytopenia [52]. Application of ABT-199 is followed by a dramatic reduction of CLL cells within 12 hours. In a phase I/II study, this resulted in tumor lysis syndrome in five patients with one attributed death. This led to an adjustment of the dosing schedule to a so-called "ramp-up" approach at treatment initiation in the ongoing phase I/II studies. ABT-199 administered as monotherapy in 56 high-risk CLL patients resulted in an

ORR of 84%. Interestingly, efficacy seems to be independent of TP53 function, as 17 cases with a deletion of 17p had similar response rates (82%) [53,54]. Major side effects besides tumor lysis syndrome were diarrhea (46%), neutropenia (43%; four cases with grade IV), and fatigue (34%). ABT-199 is currently in clinical development in CLL as monotherapy in combination with antibodies and chemotherapy.

Summary

The era of chemotherapy as the mainstay of CLL treatment is not over yet, as treatment with FCR, BR, and Clb +obinutuzumab is still the gold standard in the first-line treatment situation, depending on the patient's fitness. However, a broad range of novel agents with different mechanisms of action have entered clinical trials and have already proven not only their efficacy but also a favorable safety profile. New drugs targeting specific molecular features like ibrutinib, idelalisib, or ABT-199 are tested at present, and their advent is very likely to change the treatment paradigm of CLL which is relying on chemoimmunotherapy. The combination of chemotherapy, CD20 antibodies and these novel compounds is currently a frequently selected approach in clinical trials. However, for many CLL patients who are elderly and unfit, monotherapy with these agents appears an attractive perspective, due to their striking efficacy and good tolerability. Another approach is a sequential administration of the novel drugs as maintenance therapy, depending on the presence of risk factors or MRD positivity after induction therapy. In contrast to ibrutinib and idelalisib, ABT-199 results in a dramatic reduction of tumor burden within a few hours of dosing and therefore is more similar to a classic induction therapy with a perspective for MRD negativity. Several studies are under way to investigate the efficacy of combinations of these novel compounds targeting a range of pathogenic principles. These approaches very likely in the near future will change not only our therapeutic strategies but also the current risk factors for treatment failure and will hopefully pave the way to a cure for CLL.

Abbreviations

ADCC, antibody-dependent cell-mediated cytotoxicity; BCR, B-cell receptor; BR, bendamustine and rituximab; BTK, Bruton's tyrosine kinase; Clb, chlorambucil; CLL, chronic lymphocytic leukemia; CMV, cytomegalovirus; FCR, fludarabine, cyclophosphamide and rituximab; FDA, US Food and Drug Administration; IGHV, immunoglobulin heavy-chain variable region gene; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PI3K, phosphoinositide 3-kinase.

Disclosures

The authors declare that they have no disclosures.

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