Treatment options in chronic lymphocytic leukemia (CLL) – a Polish perspective

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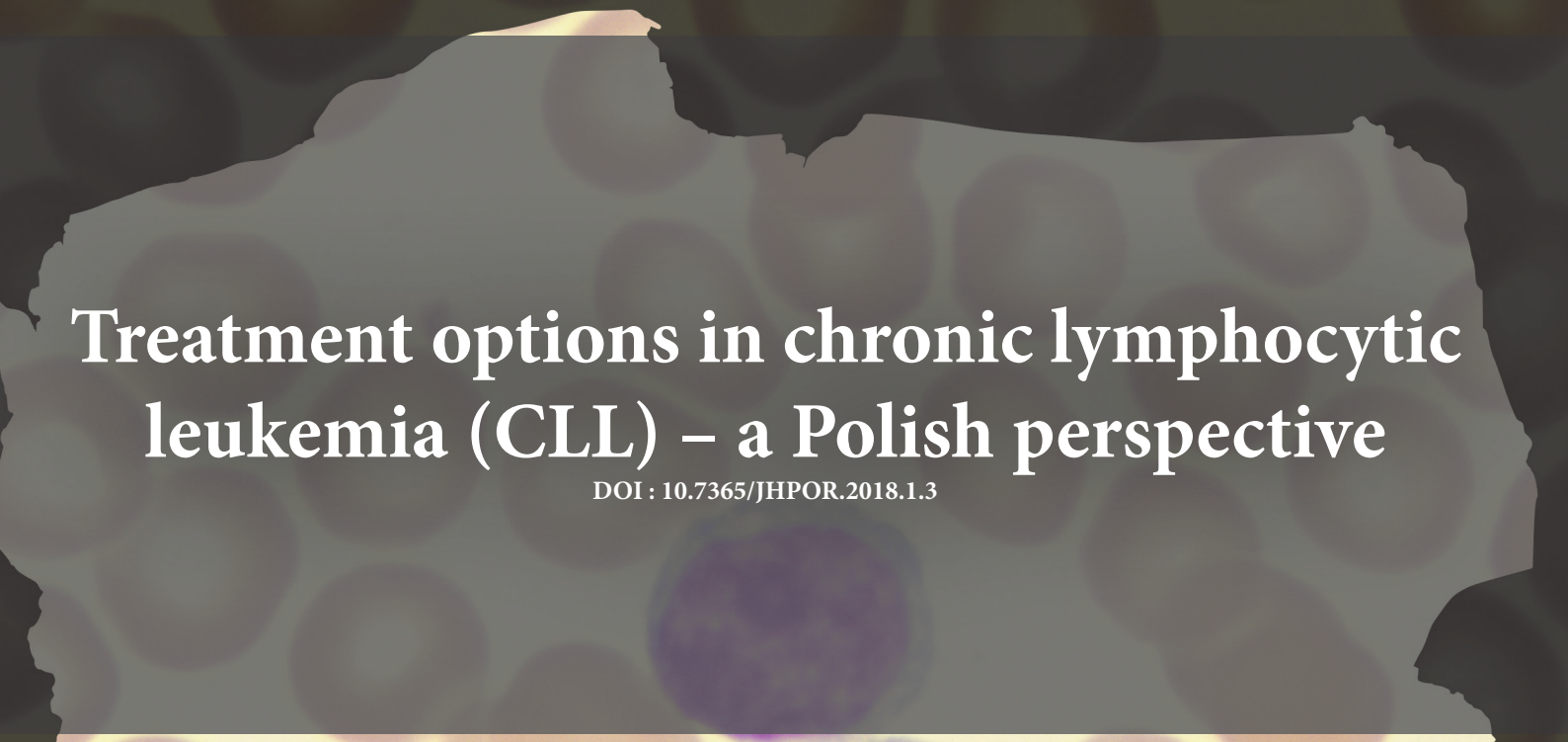

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Abstract

Chronic lymphocytic leukemia (CLL) is the most frequent type of leukemia among the elderly people in Western societies. CLL is genetically and molecularly heterogeneous disease that translates into clinical outcomes. Currently, the most unfavorable prognosis is associated with the presence of deletion of the short arm of chromosome 17 (del17p) and/or mutation of the TP53 gene (mTP53) that requires an individualized therapeutic approach. Allogenic hematopoietic stem cells transplantation (allo-HSCT) is still the only potentially curative treatment option in patients with CLL. Nevertheless, it is associated with high toxicity and treatment-related mortality. Therefore, it can be used only in selected patients, mostly young and fit without significant comorbidities. Moreover, allo-HSCT should be performed in patients who achieve disease remission. Recent advances in molecular biology have led to the better understanding of CLL pathophysiology and development of new targeted therapies. Recently developed and approved drugs such as new anti-CD20 monoclonal antibodies (obinutuzumab, ofatumumab), B-cell receptor inhibitors (BCRi) (ibrutinib, idelalisib) and B-cell lymphoma 2 (BCL-2) protein inhibitor (venetoclax) provide better clinical outcomes in CLL patients than previously used standard chemotherapy regimens. Most of those new drugs have been included in treatment algorithms described in Polish, European and global clinical practice guidelines. However, not all of them are available for Polish patients due to the lack of reimbursement, leaving them in the clinical unmet need state. This review summarizes recent advances in CLL treatment, focusing on the Polish perspective.

Introduction

Chronic lymphocytic leukemia (CLL, ICD-10 code: C.91.1) is the most common type of leukemia in adults in the Western hemisphere. According to IWCLL (International Workshop on CLL) criteria, the diagnosis of CLL requires the presence of B-lymphocytosis in the peripheral blood (≥5 x 109/L) sustained for at least three months.[1] Malignant B-lymphocytes coexpress CD-5, CD-19, CD-20, CD-23 antigens on the surface. At the same time, the level of expression of surface immunoglobulins CD-20 and CD-79b antigens is lower than in normal B cells. Clonal CLL cells express either kappa or lambda immunoglobulin light chains. In blood smear, malignant B-lymphocytes are characterized by small size, a narrow border of cytoplasm and dense nucleus without visible nucleoli with partially aggregated chromatin.[1–3]

Chronic lymphocytic leukemia is often associated with the presence of specific genetic mutations and aberrations which are detected in up to 80% of patients at CLL diagnosis.[4, 5] The most common aberration is deletion of the long arm of chromosome 13 (del13q), which is present in about 55% of CLL patients. Less frequent are deletions of the long arm of chromosome 11 (del11q) and trisomy of chromosome 12 (tri12), which occur in about 10–25% CLL patients.[6] Deletion of the short arm of chromosome 17 (del17p) is less frequent (5–8%) but carries the worst prognosis and it is associated with the resistance to standard chemotherapy used in CLL, such as purine analogs and alkylating drugs.[6, 7] Beside chromosomal aberrations, a set of specific somatic mutations correlating with adverse outcomes has been identified in NOTCH1, ATM, BIRC3, SF3B1, TP53 genes. TP53 mutation (mTP53) is often concomitant with del17p and is the primary cause of disruption of the TP53 cell pathway which results in inhibition of apoptosis in malignant cells. The prognostic impact of mTP53 is the same as del17p.[5, 8]

Clinical presentation and natural course of disease in CLL is highly heterogeneous. Nowadays, most patients at CLL diagnosis do not experience any clinical symptoms and the reason for the initiation of diagnostic procedure is an incidental discovery of lymphocytosis during routine blood examination. Among other patients first clinical signs of CLL include: lymphadenopathy, splenomegaly, fatigue, increased susceptibility to infections, or general symptoms, like fever, weight loss, night sweats.[8, 9] About 30% of CLL patients, needs no therapy and their overall survival is up to 20 years since the time of diagnosis. In other patients, clinical manifestation at the beginning is mild but disease progresses in time and ends with death up to 10 years from diagnosis. Some of the patients have an aggressive form of CLL, which results in death in 2–3 years from diagnosis.[8, 10]

Causes of CLL have not yet been fully described, however recent advances in molecular biology suggest that two major signal pathways engaged in survival, proliferation, and differentiation of lymphocytes B may play an important role in CLL pathogenesis (Figure 1). Two proposed mechanisms include enhancing the BCR signal pathway and altered expression of BCL-2 family proteins leading to increased survival of malignant cells due to disruptions of apoptosis. Furthermore, other intracellular factors like BAFF (B-cell Activating Factor), APRIL (A Proliferation-Inducing Ligand), TNF (Tumor Necrosis Factors) and cytokines are proposed to have an impact in CLL development.[11]

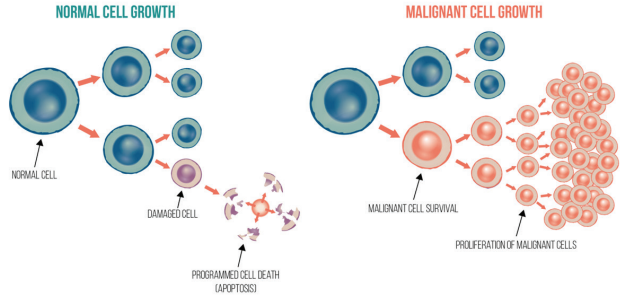

Figure 1. Normal and malignant lymphocyte B growth in blood (adapted from NCCN guidelines for patients 2016)[12]

Several factors may increase the risk of CLL which include age, ethnicity and family history.[8, 13] Progression of CLL is associated with several complications, such as infections, transformation into a more aggressive type of lymphoma, like diffuse large B-cell lymphoma (also called as Richter transformation) or Hodgkin lymphoma, secondary malignancies and autoimmune penias, such as autoimmune hemolytic anemia, immune thrombocytopenic purpura, pure red-cell aplasia or autoimmune neutropenia.[9, 14] All of the complications mentioned above may be the primary cause of premature death of CLL patients. Hence, an effective treatment of CLL is a significant challenge for healthcare professionals.

Epidemiology

World

CLL represents the most common type of leukemia among adults in the Western world, accounting for about 25–34% of all types of leukemias and about 70% of lymphocytic leukemias.[10, 15, 16] According to ORPHANET data, the prevalence of CLL is 1–5/10,000.[17] Estimated incidence rate reported by SEER (Surveillance, Epidemiology, and End Results Program), in 2015 in the US was 4.4/100,000. Around 20,940 new cases of CLL are expected in 2018 in the US according to SEER estimations, which represents 1.2% of all new cancer cases. According to SEER data, CLL is usually diagnosed among people between 65 and 74 years with median age 70 years at diagnosis. Incidence rates differ between sexes and races – men are 1.5–2 times more frequently affected than women and Caucasians are at higher risk of CLL than other ethnicities.[13]

In recent years prolongation of overall survival of CLL patients has been observed. Data obtained from the US SEER registry indicate that within three decades the percentage of 5-year survival increased by over 15 percentage points, from 67.5% in 1975 to 87% in 2010.[13] Similarly, in Northern Europe countries, this percentage increased by almost 8 percentage points in ten years, from 70.3% in 1997–1999 to 78.1% in 2006–2008.[18] One of the proposed explanation of this observed trend is the recent development of more effective therapeutic options and individualized approaches to CLL treatment. Due to the fact, that CLL mainly affects the elderly, improvement in overall survival can be explained also by the increased effectiveness of the treatment of comorbidities. Countries of Eastern Europe, including Poland, seem to be an exception of this general rule with the percentage of 5-year survival on approximately 54% in 2006–2008, which may be explained by limitations in the access to modern therapies and shorter average life expectancy in the general population.[18]

Poland

CLL prevalence and incidence rates are similar in Poland to those observed in Europe and in the US. Prevalence rate reported by the Polish Clinical Oncology Society (PTOK – Polskie Towarzystwo Onkologii Klinicznej) registry is about 4.2/100,000 per year.[9] Epidemiological research based on National Cancer Registry (KRN) data, recently published by Didkowska et al. in 2016, indicate that the number of new CLL cases doubled from 782 patients in 1999 to 1 749 patients in 2013. Thereby, standardized morbidity rate in general population increased from 1.4/100,000 in 1999 to 2.4/100,000 in 2013. In 2013 the median age at the time of diagnosis in Poland was 69 years (in men 68 years, in women 71 years). The highest morbidity rate was observed in men aged 60–79 years. Epidemiological data published by Didkowska et al. confirmed the general observation that CLL affects more frequently men than women, regardless of age. The highest value of the standardized morbidity rate was observed in men over 65 years and amounted to 27.5/100,000, while in women of the same age group it was 15,2/100,00.[19]

According to KRN data, CLL was the cause of death in 77% of all deaths in lymphocytic leukemias patients and 36% of all deaths in leukemias patients. The num-

ber of deaths due to CLL increased between 1999 and 2013, from 299 deaths to 604 deaths in men and from 217 deaths to 400 deaths in women. Analysis of mortality trends in this period indicates that standardized mortality rate increased over time in a general population and in the subpopulation of patients aged over 65 years. In 2006–2009, reported standardized 5–year survival rates were 55,8% in Polish men and 68,1% in women, which means that Polish patients' survival was poor in comparison with Northern Europe and the US data in similar periods (Chart 1).[19]

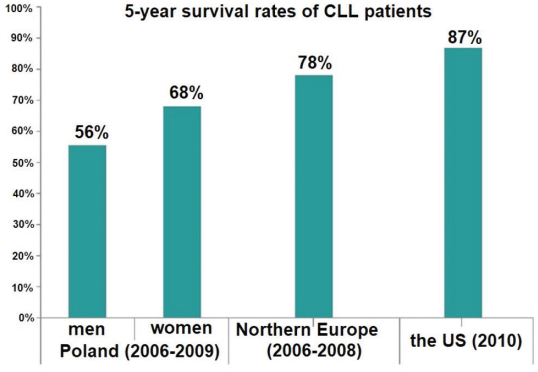

Chart 1. Comparison of 5-year survival rates of CLL patients in Poland, Northern Europe and US (based on EUROCARE-5, Didkowska 2016 and SEER)[13, 18, 19]

Prognosis

Since CLL is a heterogeneous disease, the accurate prognosis is an extremely difficult issue. Many variable factors need to be considered including findings in clinical assessment, biological factors and laboratory parameters like lymphocyte doubling time.[20] Widely applied in clinical practice Rai and Binet classifications are the most elementary scales which help to estimate CLL patients' survival. According to original series describing Rai and Binet classifications, median overall survival reported for patients in Rai stage 0 is about 150 months, while median survival of patients classified in Binet stage A is comparable to healthy age-matched controls.[20] Currently, del17p and/or mTP53 and IGVH mutational status, are thought to be the most relevant prognostic and predictive factors for patients with CLL. Clinical trials showed that most of the genetic abnormalities observed in CLL patients are associated with worse prognosis, however, there are few specific mutations which presence results in better patient's outcome than normal karyotype (Figure 2).[21]

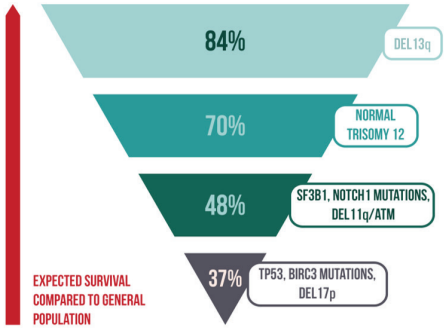

Figure 2. Expected survival of CLL patients calculated at ten years and compared to general population according to the cytogenetic status (adapted from Foà 2013)[21]

Del17p is associated with the worst clinical outcome of all recently identified chromosomal aberrations due to the resistance to standard chemoimmunotherapy regimens and early relapses. Estimated median overall survival for CLL patients with del17 ranges between 12–32 months.[4, 20] Recent studies have shown that del17p is not as rare as it used to be thought. Patients with de novo del17p mutations (3–8% of CLL patients) have a better prognosis and longer median overall survival, accounting to 4–5 years than patients with acquired del17p (30%), whose survival decreases significantly with median overall survival up to 1.5 years.[5, 6, 8, 22] Del17p usually coexists with TP53 gene mutation in the remaining allele of chromosome 17. Patients with both types of abnormalities have a notably worse outcome with shorter median overall survival and progression-free survival than patients with only del17p or mTP53. However, also isolated TP53 gene mutation is responsible for patient's poor prognosis. Standard first-line treatments for physically fit CLL patients are based on fludarabine in combination with cyclophosphamide and rituximab, however, carriers of del17p and/or mTP53 do not respond to these therapies.[5] Therefore, most of the efforts are focused on developing new promising targeted agents for del17p/mTP53 patients. Since BCR inhibitors have been approved and are commonly used, a novel prognostic factor, which is the response to BCRi treatment may also be considered. BCRi treatment withdrawal due to CLL progression is associated with worse prognosis than if it occurs due to adverse events.[23–25]

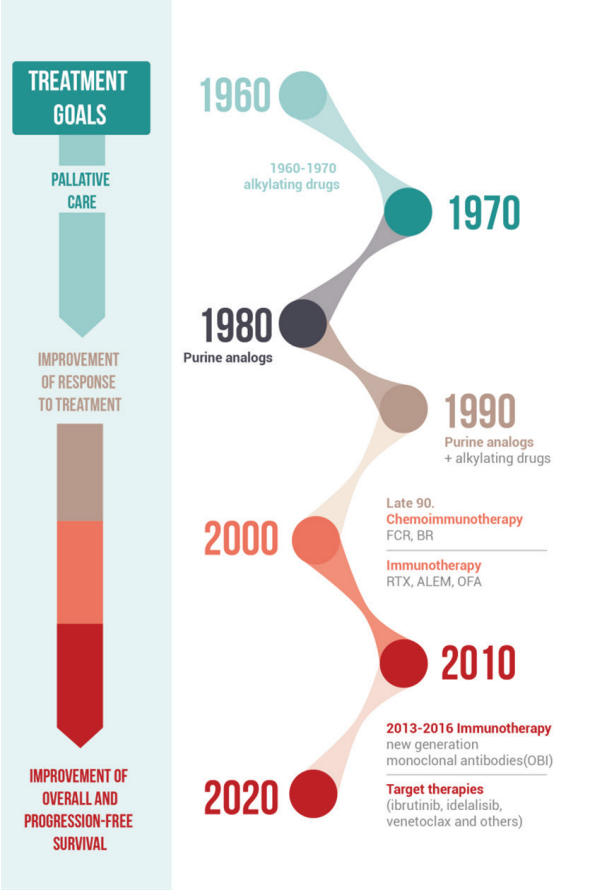

Figure 3. Progress in CLL treatment during last decades

ALEM – alemtuzumab; BR – bendamustine + rituximab; FCR – fludarabine + cyclophosphamide + rituximab; OBI – obinutuzumab; OFA – ofatumumab

Treatment

Therapeutic goals in treating CLL patients have gradually changed over the past decades. In the 1960s and 1970s, treatment dedicated to CLL was exclusively palliative with wide usage of alkylating drugs: mainly chlorambucil and much more rarely cyclophosphamide. The breakthrough in the treatment of CLL was the introduction of purine analogs, first as monotherapy, then in combination with cyclophosphamide (FC) which improved progression-free survival (PFS)[26–28] However, combining the FC regimen with anti-CD20 monoclonal antibody – rituximab (FCR) have demonstrated for the first time that prolonging patients overall survival (OS) is also possible.[29] Since then, this option has been considered as the gold standard in the treatment of patients with CLL, however according to clinical practice guidelines this therapy is recommended only to younger patients in a good general condition without major comorbidities. In physically fit patients, but older than 65 years and/or with infections in the previous history, BR (bendamustine, rituximab) should be considered.[30] Patients in a worse general condition and/or with significant comorbidities should be treated with less toxic chemoimmunotherapy regimens like chlorambucil combined with obinutuzumab (CLB+OBI), ofatumumab (CLB+OFA) or rituximab (CLB+RTX).[31–33] All of the therapeutic options mentioned above have limited efficacy in patients burdened with del17p and/or mTP53.[34, 35]

Currently, CLL remains incurable with conventional therapies and the main goal of the treatment is to prolong PFS and OS (Figure 3).[9, 34, 36] Allogenic hematopoietic stem cells transplantation is the only known, potentially curative treatment, however, due to its toxicity, this procedure is restricted only for selected patients with high-risk disease. The better understanding of CLL pathogenesis has enforced the development of new breakthrough molecules with tumor-specific activity. Among them, new generation monoclonal antibodies, B-cell receptor inhibitors (BCRi) including Bruton kinase inhibitors (BTKi) and PI3K-delta inhibitors, as well as inhibitors of anti-apoptotic BCL-2 protein may be distinguished (Figure 4). Currently, some of these agents have been already approved by regulatory authorities.

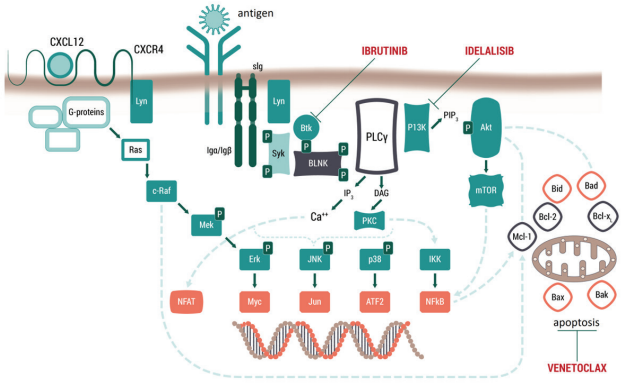

Figure 4. BCR signaling pathway and potentially relevant target points for novel therapeutic agents (adapted from Hallek 2015) [37]

Monoclonal antibodies

In 2010 and 2014 two new generation antibodies – ofatumumab (Arzerra®) and obinutuzumab (Gazyvaro®) have been registered in Europe. Both Ofatumumab (OFA) and obinutuzumab (OBI) are indicated in combination therapy in treatment-naïve CLL patients.[38, 39] Efficacy of both agents has been proven in clinical trials in which both agents were superior to already approved chemo- or chemoimmunotherapy regimens. In the CLL11 trial, combination therapy CLB with OBI resulted in improvement of responses rates and overall survival as compared to CLB monotherapy (ORR: 77.3% vs 31.4%, CR: 22.3% vs 0%; hazard ratio for death: 0.41 [0.23; 0.74], p = 0.002) and in prolongation of progression-free survival as compared to combination therapy CLB+RTX (median PFS:

26.7 vs 16.3 months).[40–42] Since the publication of CLL11 trial results, the combination of CLB and OBI has become a standard of first-line therapy in adult patients with comorbidities without del17p and/or TP53 mutation.[43] In the COMPLEMENT 1, trial OFA combined with CLB improved overall response rate (81% vs 69%) and progression-free survival (22,4 vs 13,1 months) compared to CLB monotherapy in treatment-naïve patients.[41, 43, 44] Safety and efficacy of OBI and OFA have not been compared directly in randomized trials yet, so according to the guidelines, treatment choice should be based on clinicians' experience, costs, patients' general condition and availability.[41] Because OFA has not been reimbursed in Poland yet, Polish CLL patients who qualify to combination therapy with CLB+monoclonal antibody anti-CD20, can be treated with RTX or OBI.[45]

B-cell receptor inhibitors

In 2014 two BCR inhibitors – ibrutinib (Imbruvica®) and idelalisib (Zydelig®) have been approved by EMA for marketing in EU countries. Ibrutinib (IBR), as an orally, irreversible BTK inhibitor, is indicated in both treatment-naïve and relapsed/refractory CLL patients. Clinical trials performed in CLL patients have shown that IBR was an effective agent in treating CLL patients burdened with del17p and/or mTP53 in the first and further lines of treatment.[46] The clinical benefit of IBR was confirmed in RESONATE and RESONATE-2 trials, which showed that IBR induced responses in all subgroups, regardless of age, previous treatment and the presence of adverse prognostic factors like del17p, del11q or unmutated IGHV. RESONATE-2 study, dedicated to untreated CLL patients aged above 65 years and lacking del17p showed greater efficacy of IBR compared to CLB, resulting in higher overall (86% vs 35%) and complete (4% vs 2%) response rates, superior progression-free (89% vs 36%) and overall survival (98% vs 85%) at 24 months.[41, 43, 47] In RESONATE study, previously treated CLL patients were randomized to either IBR or OFA monotherapy. Most of the patients had high-risk factors including del17p and resistance to purine analogues. Treatment with IBR showed greater efficacy in general study population as well as in del17p subgroup, resulting in significantly prolonged PFS and OS and higher ORR compared to OFA. At a median follow-up of 9.4 months, median progression-free survival was not reached in IBR group, while in OFA group PFS accounted to 5.8 months.[40, 41, 43, 48] Further evidence from RESONATE-17 confirmed safety and efficacy of IBR in relapsed/refractory CLL patients burdened with del17p resulting in high overall response (83%), progression-free (63%) and overall survival rates (75%) at a median follow-up of 27.6 months.[40, 41, 43, 49] IBR has been reimbursed in Poland in relapsed/refractory patients with the presence of del17 and/or mTP53 since September 2017. However, IBR is not reimbursed in relapsed/refractory CLL patients without del17p and/or mTP53 despite its proven efficacy in this subpopulation.[45]

Idelalisib (IDE) is an orally PI3K-delta inhibitor, which is indicated in combination with RTX or OFA for the treatment in CLL patients who received at least one prior therapy or in patients with the presence of del17p and/or mTP53 who are not eligible for any other therapy in first-line setting.[50] Promising clinical efficacy of IDE was observed in phase III randomized clinical trial in which patients were randomized to RTX treatment with either IDE or placebo (PLC). In Treatment with IDE+RTX improved patients' outcomes compared to PLC+RTX, resulting in better overall response (81% vs 13%), the overall survival rate at 12 months (92% vs 80%) and progression-free survival rate at 24 months (93% vs 46%). More than 40% were burdened with TP53 mutation and results observed in the subgroup of del17p and/or mTP53 patients were consistent with those observed in the whole study population.[40, 41, 43, 51] However, treatment with IDE was found to be associated with greater risk of opportunistic infections, especially Pneumocystis jirovecii pneumonia and cytomegalovirus infections, when IDE was used in combination with chemoimmunotherapy in CLL front-line therapy. In 2016 EMA published safety recommendations for healthcare professionals in which it advises adequate anti-infectious prophylaxis and monitoring of infections in patients treated with IDE.[52] IDE has not been reimbursed in Poland due to above safety concerns and other reasons, hence it cannot be an alternative treatment option instead of IBR in patients burdened with del17p and/or mTP53.[45]

Although BCR inhibitors produce durable remissions in the majority of CLL patients, the treatment is discontinued in some patients due to toxicity or treatment failure. Recent evidence suggests that relapses can be a result of acquired point mutations in the BTK receptor or its signal transduction mediator – PLCG2.[25] Hence, development of new agents in treating CLL is still needed. Some of them, like BCl-2 inhibitors, may be an alternative treatment option for these patients.

BCL-2 inhibitors

In 2016 first oral BCl-2 inhibitor – venetoclax (Venclyxto®) has been approved by EMA for the treatment of CLL patients in Europe. Venetoclax (VEN) induces cell apoptosis leading to rapid decrease of tumor mass. Venetoclax has two indications. The first one includes treatment of CLL patients with the presence of del17p and/or mTP53 who are unsuitable for or have failed BCRi, the second – treatment of CLL patients with the absence of above cytogenetic abnormalities in which both chemoimmunotherapy and BCRi therapy have failed.[53] Clinical benefits of VEN have been proven in two ongoing phase II clin-

ical trials: M14-032 and M13-982. Single-arm M13-982 trial has evaluated efficacy and safety of VEN in relapsed/refractory CLL patients with del17 and/or mTP53. Reported overall response rate in the entire cohort was 79% with complete response rate near to 8%.[53–57] In another single-arm M14-032 trial, heavily pretreated patients have been treated with VEN, regardless of the presence of del17p and/or mTP53. Results of this study confirmed that VEN is an effective treatment, resulting in high ORR and CR rate (65% and 9% respectively), as well as OS and PFS rates at 12 months (91% and 75% respectively). At a median follow-up of 14 months, median PFS was 25 months, while median OS was not reached. Consistent outcomes were observed in del17p and/or mTP53 patients in which ORR was 70%.[58–60] Due to its high efficacy in rapid tumor mass reduction, VEN treatment is associated with the risk of tumor lysis syndrome (TLS). Specific prophylaxis including a dose-titration schedule of VEN during first 5 weeks, adequate hydration, administration of anti-hyperuricemic agents and laboratory parameters assessment are implemented to prevent TLS and maintain the patients' safety.[53] Despite its proven clinical efficacy, VEN has not been reimbursed in Poland yet. It means that patients who failed or are not suitable for BCRi still have no effective treatment option.[45]

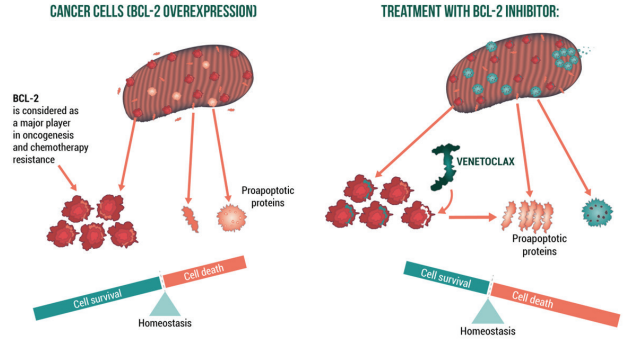

Figure 5. Mechanism of action BCL-2 inhibitor – venetoclax (based on Adams 2007)[61]

Other emerging therapies

Several agents are currently under development in variable phases of pre-clinical and clinical trials. Among BTK inhibitors, acalabrutinib have already been investigated in phase I–III trials and has shown promising results in CLL patients. Other BTK inhibitors studied in CLL include ONO-4059, BGB-3111 and spebrutinib – all of them showed acceptable tolerability in early phase clinical trials. Potentially clinically relevant PI3K inhibitors other than IDE include e.g. duvelisib, TGR-1202, copanlisib, buparlisib and acalisib.[7, 62] According to Clinical Trials database (clinicaltrial.gov), only four clinical trials are currently recruiting patients with CLL in Poland. In three of them, VEN is the investigational arms, either as a monotherapy or in a combination therapy (Table 1).[63]

Challenges in the treatment of CLL

The approval of novel therapies, such as BCR inhibitors, has raised new clinical challenges in CLL treatment. The most recent concern is the treatment of CLL patients who relapsed after BCRi.

Results from the multicenter clinical trial – RESONATE showed that about 40% of CLL patients relapse after IBR treatment within 3 years from the therapy initiation.[64] Results from recently published studies, performed in the post-BCRi population in clinical practice, indicate that estimated median survival of those patients ranges between 1 and 33 months, according to the reason of treatment's withdrawal. The shortest median survival is observed in patients with Richter transformation (median OS: 2–3 months), the longest in patients who discontinued treatment due to the toxicity (median OS: up to 33 months). Patients with CLL progression survive about 16–23 months (median OS), probably due to the possibility of the implementation of the next line of treatment.[65–68]

According to studies of Jain et al. (2017) and Mato et al. (2017) only some CLL patients receive next line of treatment after the BCRi failure.[65, 69] In the study of Mato et al., next line of treatment after BCRi failure was introduced in 167 of 316 patients (53%). The most frequent therapies included: alternative BCRi (21–22%), VEN (16%) and OBI (8%). Other therapies, mostly chemo(immuno) therapy regimens were used only in individual patients. Outcomes of this study demonstrated the highest efficacy of VEN with ORR of 74% and CR rate of 32%. However, treatment change from IDE to IBR was also effective in some patients. Chemoimmunotherapy showed far worse outcomes than the VEN therapy with overall response rate about 50% and complete response of 2% (Chart 2).[69] As reported by Mato et al. (2017) median PFS in patients after BCRi failure who were treated with chemoimmunotherapy was only 5 months (more information below).[69]

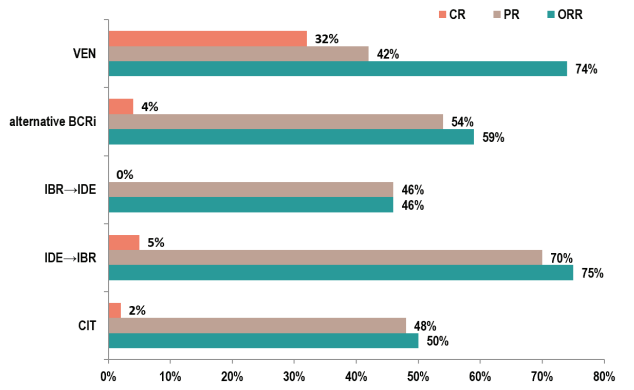

Chart 2. Response to the treatment in CLL patients after post-BCRi failure according to treatment (Mato 2017) [69]

ALEM – alemtuzumab; BR – bendamustine + rituximab; FCR – fludarabine + cyclophosphamide + rituximab; OBI – obinutuzumab; OFA – ofatumumab

Treatment availability in Poland

Despite the recent progress in developing novel high-effective targeted therapies, an availability of them is highly limited in Poland – only two have already been reimbursed (OBI, IBR), one of which to a limited extent (IBR)(Table 2).[45]

IBR is currently reimbursed only for relapsed/refractory CLL patients with the presence of del17 and/or mTP53, despite its high effectiveness in relapsed/refractory patients without these abnormalities. The lack of reimbursement of newly approved agents and significant delays in that process have a negative impact on the prognosis of patients with CLL. According to the comparison of recommended by the most recent European clinical guideline treatments and the Polish reimbursement status, not all of clinical CLL patients' needs are met (Figure 6).

Polish CLL patients with del17p and/or mTP53 who failed BCRi therapy, are currently condemned to ineffective treatments due to the lack of reimbursement of other than IBR alternative BCRi like IDE or BCL-2 inhibitor like VEN. Until recently, treatment with BCR inhibitors was not reimbursed in Poland, nevertheless, some Polish patients with CLL had the opportunity to obtain free therapy with IBR as part of the Early Accessibility Program (PCI-32765, JNJ54179060) Named Patient Program) carried out by Janssen-Cilag, in the years 2014-2015. Therapy with IBR was initiated in 240 patients with CLL/SLL. Data published by Iskierka-Jażdżewska et al. in 2017, regarding 165 patients covered by the program indicated that the percentage of patients withdrawing the therapy was 19%, and the main causes were adverse events (50%) and progression (38%).[70] The most recent data indicate that this overall percentage can reach even 31% of Polish CLL patients.[71] The same data indicates that Polish CLL patients after BCRi failure live extremely short – the median overall survival is 1.8 months (range 0.2-16.7).[70] According to the real world clinical data described above (Mato 2017), therapy with VEN might be an effective option for these patients. However, Polish CLL patients are currently deprived of this therapy, what is emphasized by Polish hematologists. According to the statement of Polish experts in the field of hematology, Polish clinicians "do not have (…) any effective treatment option in this clinical situation [progression of CLL due to rapid resistance to ibrutinib]".[72]

The participation of CLL patients in clinical trials might be an alternative solution for this deliberate issue, which is the restriction in the reimbursement of novel targeted therapies in Poland. Such method is recommended by European and Polish clinical practice guidelines, however number of clinical trials conducted in CLL patients in Poland happens to be scanty. As previously mentioned, Polish CLL patients can be recruited currently to only four multicenter clinical trials. Additionally, not all the patients fulfill the inclusion criteria and have enough motivation and strength for

Table 1. Currently recruiting or not yet recruiting trials in CLL with locations in Poland according to clinicaltrials.gov [63]

Study	Investigated population	Investigational arms	Enrollment	Locations	Phase	Study start date	
				No./No. in PL	Sites in PL		
NCT03328273	High-risk R/R CLL	AZD6738 +/-acalabrutinib	62	3/1	Cracow	I/II	Jan 2018
NCT02980731 (M15-889)	R/R CLL with del17p/mTP53 + or - and BCRi failure + or -	VEN	200	35/3	Chorzow, Lodz, Warsaw	III	Dec 2016
NCT02639910	R/R CLL with BCRi failure or unsuitable	MOR00208+VEN MOR00208+IDE	24	31/4	Cracow, Gdansk, Lublin, Opole	II	Nov 2016
NCT03462719	R/R CLL with del17p/mTP53 +	IBR+VEN CLB+OBI	200	86/6	Chorzow, Lodz, Lublin, Slupsk, Warsaw, Wroclaw	III	Apr 2018

R/R – relapsed/refractory

the participation in clinical trials. Hence, to satisfy the clinical unmet need in the selected high-risk, relapsed/refractory population of Polish CLL patients, novel approved targeted therapies with proven clinical safety and efficacy should be reimbursed as soon as possible.

Conclusions

Despite the recent advances in treating CLL, Polish patients with this disease have still limited access to breakthrough targeted therapies. A lot of efforts from clinicians, manufacturers and the Ministry of Health are still needed to improve Polish CLL patient's clinical outcomes.

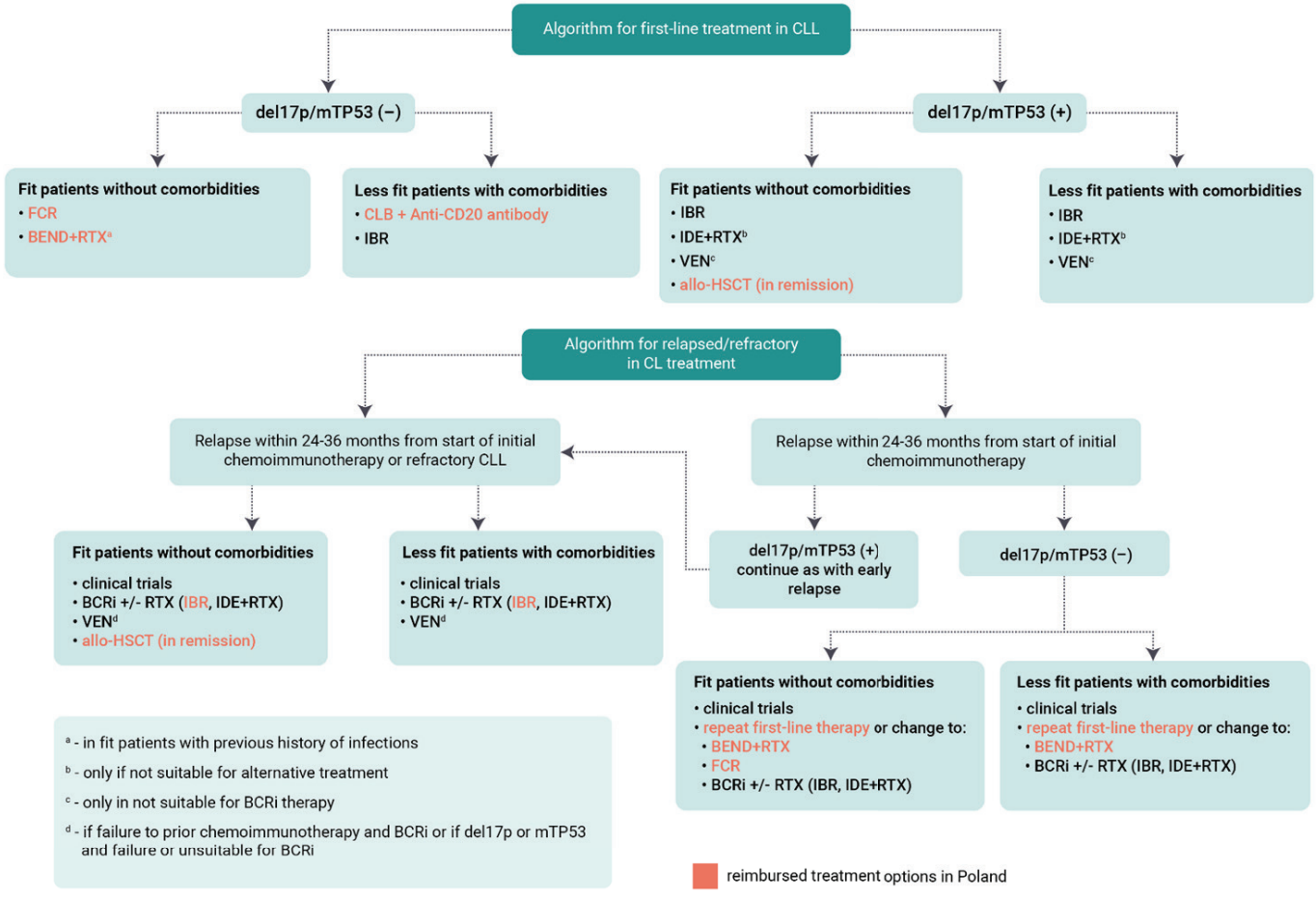

Figure 6. Treatment algorithm in treatment-naive and relapsed-refractory CLL patients according to ESMO guidelines (adapted from Eichorst 2015-2017)[31–33]

Table 2. The marketing authorization and the reimbursement status of novel agents therapies in Europe and Poland [31–34, 38, 39, 45, 46, 50, 53, 73–91]

Novel agents therapy	Marketing authorization in:			Clinical recommendations in:			Reimbursement in Europe in:			Reimbursement in Poland in:		
	CLL	del17p/mTP53	BCRi f/u	CLL	del17p/mTP53	BCRi f/u	CLL*	del17p/mTP53	BCRi f/u	CLL*	del17p/mTP53	BCRi f/u
Monoclonal antibodies anty-CD20												
Obinutuzumab	✓	X	X	✓	X	X	✓	NA	NA	✓	NA	NA
Ofatumumab	✓	X	X	✓	X	X	✓	NA	NA	X	NA	NA
BCR inhibitors												
Ibrutinib	✓	✓	X	✓	✓	✓	✓	✓	NA	X	✓	NA
Idelalisib	✓	✓	X	✓	✓	✓	✓	✓	NA	X	X	NA
BCl-2 inhibitors												
Venetoclax	✓	✓	✓	✓	✓	✓	✓	✓	✓	X	X	X

*✓– yes; X– no; f/u – failure/unsuitable; NA – not applied, *CLL – full coverage in CLL according to SmPC*

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