REVIEW ARTICLE

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Autoimmune cytopenias in chronic lymphocytic leukemia: a growing challenge in targeted therapies?

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Abstract

As the world's population ages, the incidence of chronic lymphocytic leukemia (CLL) will continue to increase. CLL--related autoimmune cytopenias (AICs) are becoming a growing challenge in daily clinical practice. AICs occur in c.10% of CLL patients, and include autoimmune hemolytic anemia, immune thrombocytopenia, pure red cell aplasia, and autoimmune granulocytopenia. The complication can appear at any disease stage, both in treated and previously untreated patients. In some cases, AICs precede the diagnosis of the underlying disease. The diagnostic process of autoimmune complications is often difficult. First of all, however, it requires differentiation from bone marrow infiltration resulting from underlying disease progression. A properly established diagnosis has prognostic and therapeutic implications. Autoimmune cytopenias are more often associated with high-risk CLL (with 17p deletion, 11q deletion, wild--type variant of gene encoding immunoglobulin heavy chain variable region) and show a complex pathogenesis. CLL cells and the surrounding microenvironment are involved in autoimmune mechanisms. Treatment of AICs depends on CLL stage. In the case of isolated symptoms of AICs, without accompanying features of CLL progression, glucocorticosteroids or rituximab are recommended in the first line treatment. No response or a suboptimal response to treatment implies further therapeutic decisions. According to significant advances in the treatment of chronic lymphocytic leukemia, therapeutic strategies for autoimmune cytopenias also need to be optimized. The widespread introduction of ibrutinib, idelalisib, and venetoclax has highlighted the need for understanding the interplay between targeted therapies and AICs.

Key words: chronic lymphocytic leukemia, autoimmune hemolytic anemia, autoimmune cytopenias, targeted therapy

Acta Haematologica Polonica 2022; 53, 5: 316–325

Introduction

Chronic lymphocytic leukemia (CLL) is the most common malignancy of the lymphatic system among adults living in the Western Hemisphere. It accounts for 30–40% of all leukemias diagnosed in developed countries, with an incidence of 4.2/100,000 people annually and a male predilection. The mean age at diagnosis is in the range of 65–72 years [1].

The course of chronic lymphocytic leukemia is characterized by considerable heterogeneity: less than 30% of cases are stable forms, while about 15% of patients will experience a highly aggressive disease [2].

A widely known phenomenon in patients with CLL is the presence of profound immune disorders, which determines an increased risk of developing secondary neoplasms, opportunistic infections and autoimmune complications [3–7]. The latter is dominated by autoimmune hemolytic anemia, occurring in 7–10% of patients. Immune thrombocytopenia affects 1–5% of CLL patients. Pure red cell aplasia and immune neutropenia account for less than 1% of complications [8, 9]. Evans's syndrome, i.e.

the simultaneous occurrence of autoimmune hemolytic anemia (AIHA), immune thrombocytopenia (ITP) and sometimes autoimmune granulocytopenia (AIG), affects approximately 1% of patients.

The higher incidence of AIHA and ITP is correlated with the known adverse prognosis factors: wild-type form of immunoglobulin heavy chain variable region (IGHV) coding gene, unfavorable cytogenetic aberrations (i.e. del11q23, del17p13), *TP53* gene mutation, short lymphocyte doubling time (LDT), elevated beta$_2$-microglobulin levels, high ZAP-70 and CD38 expression, and advanced disease stage [10–18]. In addition, autoimmune cytopenias (AICs) are more common in patients who previously received multiple treatment lines. The above data suggests that autoimmune complications are not an independent risk factor associated with an unfavorable course of the disease. The lack of differentiation of cytopenia cause in the commonly used Rai and Binet classification system should also be emphasized [19, 20]. Patients with cytopenia resulting from autoimmune processes, rather than from massive bone marrow infiltration due to progression of the underlying disease, have a longer mean survival time [15, 21].

The unquestionable achievement of the last few years in terms of improving the effectiveness of CLL treatment is the introduction of ibrutinib, idelalisib and venetoclax to the widely used targeted therapy. However, the influence of modern molecules on autoimmune complications is not yet fully understood. The reasons include the exclusion of patients with active forms of AICs from clinical trials, and the small amount of data regarding autoimmune complications. Moreover, there are no guidelines for the management of AICs in patients undergoing targeted therapy.

The aim of this study was to analyze the available literature data on autoimmune cytopenia in CLL patients, with particular emphasis on AIHA, ITP and the role of targeted therapies.

Pathophysiology and diagnostics

Due to the very low prevalence of pure red cell aplasia (PRCA) and AIG, the majority of studies regarding the pathophysiology of autoimmune cytopenia have focused on AIHA and ITP. AICs are underpinned by numerous immune system dysfunctions. Most often, the humoral mechanism plays a key role, involving IgG polyclonal autoantibodies. Immunoglobulins produced by healthy B lymphocytes are directed against membrane antigens found on red blood cells (RBC), platelets (PLT) and granulocytes (G) [22–24]. Much less frequently, a clone of CLL cells produces IgM autoantibodies [25, 26]. The binding of autoantibodies to bone marrow precursor cells at various maturation stages, leading to impaired normal hematopoiesis, has also been described [22].

Table I. Criteria for diagnosis of autoimmune hemolytic anemia

Parameter	Description
Hemoglobin	≤11 g/dL, in absence of cytostatic treatment in previous month and no other possible etiology of anemia
Hemolysis indicators	Presence of at least one of: reticulocytosis, increased LDH activity, increased unconjugated (indirect) bilirubin, or decreased haptoglobin level
DAT	Positive direct antiglobulin test for IgG, complement component 3 (C3) and//or presence of cold agglutinins; after excluding other causes e.g. DHTR

LDH — lactate dehydrogenase; DAT — direct antiglobulin test; IgG — immunoglobulin G; DHTR — delayed hemolytic transfusion reaction

The role of cellular mechanisms in the pathogenesis of AICs has also been emphasized [27]. T lymphocytes seem to play an important role, as their balance is disturbed towards the domination of Th2-type response [28]. Additionally, the expansion of regulatory T lymphocytes (Treg) observed in CLL patients may be responsible for decreased antitumor response and impaired immune surveillance involved in autoimmune diseases [29, 30]. Another likely mechanism contributing to AICs induction is antigen presentation by malignant B lymphocytes, resulting in the activation of autoreactive T cells [31, 32].

In the case of PRCA, the possible cause of cytopenia involves T lymphocytes cellular mechanisms with secretion of proapoptotic cytokines that affect erythropoietic precursor cells [33, 34]. Moreover, the role of T lymphocytes seems to enhance the coexistence of PRCA and the expansion of large granular T lymphocytes (T-LGL) [35].

The diagnosis of AIHA is based on meeting all of the criteria set out in Table I [36, 37].

AIHA in CLL, like its idiopathic form, is most often associated with the presence of warm IgG autoantibodies, binding erythrocytes in vitro at 37 °C. Cold agglutinin disease (CAD) is mainly caused by IgM immunoglobulins, which react optimally with the cell membrane of red blood cells at 4 °C. The results of the DAT allow for the differentiation of the above-mentioned types of autoantibodies, although in sporadic cases it is possible to detect both classes of immunoglobulins at the same time in the so-called mixed type.

A negative result of direct antiglobulin test does not preclude the diagnosis of AIHA. There have been reports of patients with a diagnosis made despite a negative result with the presence of at least two laboratory indicators of hemolysis [15]. Negative DAT can be caused, inter alia, by insufficient sensitivity of the method used in the determination of small amounts of polyclonal antibodies or the presence of low affinity immunoglobulins. An isolated positive antiglobulin test result does not yet allow the

Table II. Criteria for immune thrombocytopenia diagnosis

Parameter	Description
Platelets	Sharp drop of <100 G/L with no other apparent reason, with normal bone marrow function (number of megakaryocytes measured by trephine biopsy within normal range or elevated)
Splenomegaly/treatment	No splenomegaly and no cytostatic treatment in previous month
Other probable causes	Exclusion of CMV, parvovirus B19, HIV, HCV, *Helicobacter pylori* infections, TTP, DIC, HIT

CMV — cytomegalovirus; HIV — human immunodeficiency virus; HCV — hepatitis C virus; TTP — thrombotic thrombocytopenic purpura; DIC — disseminated intravascular coagulation; HIT — heparin-induced thrombocytopenia

Table III. Criteria for pure red cell aplasia diagnosis

Parameter	Description
Hemoglobin	≤11 g/dL in absence of hemolysis
Reticulocytes	Reduction of absolute number of reticulocytes without coexistence of thrombocytopenia and neutropenia
Other probable causes	Exclusion of CMV, parvovirus B19, HIV, EBV infections; thymoma
Trephine biopsy	Absence of erythropoiesis precursors, possible defects in maturation of erythroid line

CMV — cytomegalovirus; HIV — human immunodeficiency virus; EBV — Epstein-Bárr virus

Table IV. Criteria for autoimmune neutropenia diagnosis

Parameter	Description
Neutrophiles	Isolated, persistent neutropenia <0.5 G/L
Treatment	No cytostatic treatment in previous eight weeks
Trephine biopsy	Absence of granulopoiesis precursors

diagnosis of autoimmune hemolytic anemia. In the study by Dearden et al., positive DAT occurred in 14% of patients, with a positive predictive value (PPV) of 28% [38]. Similarly, Quinquenel et al. indicated that the positive DAT rate in CLL patients was 14.8% [39], exceeding the value of 7–10% found in AIHA. In addition, a positive direct antiglobulin test is observed in patients with systemic lupus erythematosus, chronic infections, liver or kidney failure, and after administration of anti-thymocyte globulin (ATC) or intravenous immunoglobulins (IVIG).

In order to diagnose ITP, it is necessary to confirm all of the criteria set out in Table II [14, 15, 40].

The criteria for PRCA and AIG diagnosis are set out in Tables III and IV, respectively [40].

The diagnostics of immune cytopenia in CLL may be difficult. Anemia, thrombocytopenia, and elevated LDH activity are also seen during progression of underlying disease. For this reason, it is recommended to perform imaging tests (ultrasonography, computed tomography) in order to exclude progressive splenomegaly and lymphadenopathy. The concentration of haptoglobin, which belongs to the group of acute phase proteins (APPs), may be slightly decreased, or within the normal range, in the presence of inflammation. In addition to hemolysis, the causes of lower haptoglobin levels may also include liver failure and a recent transfusion of red cell concentrates (RCC). Massive bone marrow infiltration by the CLL clone and thus hematopoietic failure is accompanied by reticulocytopenia.

It is also necessary to exclude other causes of anemia, such as iron/vitamin B12/folic acid deficiency, bleeding, chronic kidney disease or chronic inflammation. Moreover, the demonstration of indirect hyperbilirubinemia may require differentiation from Gilbert syndrome, Crigler-Najjar syndrome, or hyperthyroidism. In patients previously treated with chemotherapy, especially with purine bases analogs or alkylating compounds, diagnostics of myelodysplastic syndrome is recommended in the case of cytopenia. There have also been reports of late-onset neutropenia following rituximab administration, an average of 77 days after the last dose of the drug [41].

Treatment

In clinical practice, the management of patients with AICs depends on the CLL stage (Figure 1). Isolated symptoms of AICs require immunosuppressive therapy first. A lack of response is an indication to initiate treatment of the underlying CLL, which is the immediate cause of AICs. Similarly, when autoimmune cytopenia is accompanied by indications for CLL treatment, appropriate therapy should be introduced [42].
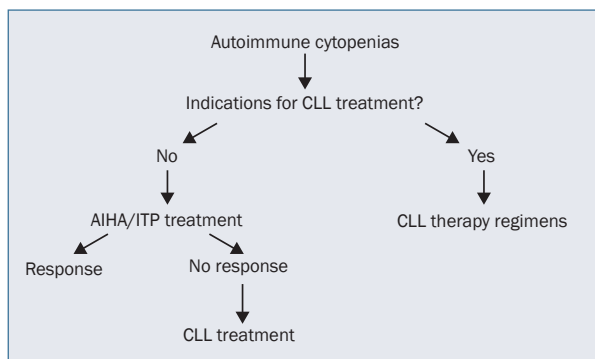
Figure 1. Algorithm of therapeutic management after autoimmune cytopenia diagnosis; CLL — chronic lymphocytic leukemia; AIHA — autoimmune hemolytic anemia; ITP — immune thrombocytopenia

Autoimmune hemolytic anemia

The current therapeutic strategies for AIHA in CLL are based on guidelines for primary forms treatment [36, 43]. Among others, this is due to frequent disqualification of patients with active, uncontrolled autoimmune cytopenia from prospective clinical trials.

The decision to start treatment is made individually, based on the analysis of several factors: the dynamics of development and the severity of anemia [mainly hemoglobin (Hg) <11 g/dL], the patient's age, comorbidities, and CLL stage. RCC transfusion is recommended when Hg level is <6 g/dL. This does not apply to elderly patients with ischemic heart disease, in whom transfusion is indicated in less severe anemia. The excessive supply of RBC should be avoided due to the risk of iron overload and alloimmunization [9]. In the case of CAD, transfusion of warmed RCC is required.

According to the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) 2018 recommendations, glucocorticosteroids (GCs) are the first line treatment of AIHA with the presence of warm antibodies [42]. Prednisone at a dose of 1 mg/kg bw/day is recommended for 3–4 weeks, followed by tapering off within 1–2 months [44, 45]. Moreover, therapy with either high-dose methylprednisolone (1 g single dose) [40, 44] or dexamethasone pulse (40 mg daily for 4 days) [43] is also possible. In the case of contraindications to GCs therapy, their intolerance, lack of response or the need to quickly inhibit massive hemolysis, IVIG is used at a dose of 1 g/kg bw/day for two consecutive days [40, 46]. Resistant forms are treated with rituximab (R) (four doses of 375 mg/m^2 weekly) with an overall response rate reported as 72–80% [47, 48]. If the above-mentioned regimens remain ineffective, other immunosuppressants can be considered (cyclophosphamide, azathioprine, cyclosporine, and mycophenolate mofetil).

Patients with progression of CLL or AIHA refractory to standard therapy require lymphoproliferation-oriented treatment, adjusted for biological state and comorbidities

[49]. Despite the significant AICs frequency in daily clinical practice, the data describing the effectiveness of particular chemotherapy regimens remains conflicting.

Historically, combination therapy with rituximab, cyclophosphamide and dexamethasone (RCD) or rituximab, cyclophosphamide, vincristine and prednisolone (R-CVP) has shown a satisfactory response rate (90–100%) lasting up to 24 months [50–52] Immunochemotherapy with bendamustine in combination with rituximab was effective in patients with AIHA and warm antibodies — overall response rate (ORR) reached 81%, with an average duration of 28.3 months [53]. A retrospective analysis of a small group of eight patients who received obinutuzumab for AIHA or ITP, showed a response to therapy in seven patients with a complete response (CR) rate of 50% [54]. A prospective, randomized trial would be necessary for a direct comparison of obinutuzumab and rituximab.

Patients with cold antibodies require different management, as standard immunosuppressants and chemotherapy are ineffective in most cases. However, the course of hemolysis is usually milder. The indication for treatment depends on RCC transfusions or symptomatic CAD. Rituximab is recommended in the first line (at the dose as above), with a response rate of 70–100% [55, 56]. A prospective, non-randomized clinical trial in 45 patients with primary CAD showed the effectiveness of combined immunochemotherapy with bendamustine and rituximab (BR) with 71% of responses [CR 40%, partial response (PR) 31%] and mean duration of response exceeding 32 months [57]. However, studies evaluating the effectiveness of this regimen in cold agglutinin disease complicating chronic lymphocytic leukemia are necessary.

Folic acid supplementation (1–5 mg/day) is indicated in all cases of symptomatic AIHA. Moreover, anticoagulant prophylaxis is recommended especially in patients hospitalized due to AIHA after splenectomy, in the absence of contraindications. Prevention of gastrointestinal bleeding, osteoporosis and *Pneumocystis jiroveci* infection should be considered in patients undergoing chronic steroid therapy [49]. It is worth emphasizing that treatment with rituximab reduces the need to repeat GCs therapy, which may be particularly beneficial in elderly patients with multiple comorbidities [58].

Immune thrombocytopenia

The treatment of ITP patients is similar to that of AIHA [59]. The indication for treatment initiation is thrombocytopenia <30 G/L or active bleeding. Prednisone (1 mg/kg bw/day) for 3–4 weeks with subsequent tapering off is used in the first line treatment. In a study comparing the effectiveness of high-dose pulses of dexamethasone and prednisone in the treatment of primary ITP, the ORR was 82.1% and 67.4% for dexamethasone and prednisone, respectively ($p = 0.044$) with a CR rate of 50.5% vs 26.8%, respectively

(*p* = 0.001) [60]. However, there is no data supporting this advantage in the treatment of secondary ITP. Resistance to steroid therapy, as during AIHA treatment, is an indication for IVIG, followed by rituximab and cyclosporin [59]. Thrombopoietin receptor agonists (eltrombopag, romiplostim) showed 80% effectiveness in 10 patients with ITP during CLL [61]. The duration of response in another study in patients with primary ITP and non-immune thrombocytopenia was at least nine months [62]. Rapid (within 1–3 weeks) increases in platelet counts have also been reported after treatment with romiplostim in patients refractory to standard ITP therapy [63, 64]. Due to the lack of data assessing the long-term efficacy and safety of drugs, the benefit of using thrombopoietin receptor agonists (TPO-RA) has been suggested e.g. in bridge therapy for splenectomy or other surgical procedures. Further studies on the use of TPO-RA in ITP treatment in CLL patients are necessary (the indication is currently not registered in Poland).

Pure red cell aplasia

The therapeutic regimen is similar to that of AIHA and ITP, including steroid therapy and IVIG. When the aforementioned methods are ineffective, cyclosporin A (effective combined treatment with prednisone or fludarabine and erythropoietin has also been described), cyclophosphamide or rituximab at a weekly dose of 375 mg/m^2 for four weeks can be considered [65].

Autoimmune granulocytopenia

Treatment of immune-related neutropenia is indicated when the neutrophil count is <0.5 G/L, or higher, if accompanied by bacterial or opportunistic infections. Due to the rarity of this complication, therapeutic recommendations including combination therapy with rituximab, cyclosporin A, and granulocyte colony-stimulating factor are based on case reports [66, 67].

The indications for splenectomy remain very limited, including AICs resistant to immunosuppressive therapy and those used in CLL [40, 65].

Autoimmune cytopenias as CLL treatment complication

The mechanisms responsible for the induction of autoimmune cytopenias during CLL treatment are not fully understood. Association of AICs with impaired Treg lymphocytes function and inverted CD4/CD8 ratio as a result of chemotherapeutic agents have been postulated [68, 69]. A significant incidence (11–23%) of AIHA during treatment with fludarabine (F) in monotherapy has been reported in both retrospective and prospective studies [38, 70, 71]. Among other purine bases analogs, cladribine was also associated with the development of AIHA in 22% of patients [72]. However, the data mainly concerned patients with advanced stages of CLL who had previously received multiple treatment lines. In addition, the risk of hematological autoimmune complications appears to be reduced with multi-drug regimens with cyclophosphamide (C) and/or rituximab. In the multicenter LRF CLL4 study, the percentage of patients who developed autoimmune hemolytic anemia during FC treatment (5%) was statistically significantly lower than in the group treated with C or F in monotherapy (12% and 11%, respectively, *p* = 0.01) [38]. In a prospective, randomized, phase III trial comparing the effectiveness of the FC and FCR regimens, in both groups AIHA occurred in 1% and <1% of patients, respectively [73]. In another analysis of 300 patients treated with the FCR regimen, the incidence of AIC was 6.5% (17 cases of AIHA and two of PRCA), thus not exceeding the percentage in the general population of CLL patients [74].

Novel drugs

Molecules from the group of Bruton's tyrosine kinase (BTK), phosphatidylinositol 3-kinase (PI3K) and B-cell lymphoma 2 (BCL2) inhibitors have clearly demonstrated significant efficacy in the treatment of chronic lymphocytic leukemia. The complex influence of targeted therapies on a patient's immune system has also been observed, which may be responsible for both the stimulation and inhibition of autoimmune mechanisms. Currently, an increasing number of CLL patients are receiving therapy with drugs from this group. It is important therefore to understand the interdependence of new molecules and AICs.

Ibrutinib, a BTK inhibitor, plays a role in controlling autoimmune mechanisms, possibly by influencing the activity of T lymphocytes and monocyte/macrophage compartment [75–77]. However, preliminary clinical reports have remained inconclusive and contradictory. There have been reports of refractory AICs successfully treated with ibrutinib [78–81], but also exacerbations of cytopenia after initiation of treatment with inhibitors [82, 83]. Rogers et al. [84] analyzed the data of 301 patients treated with ibrutinib in four clinical trials. A total of 26% of patients had a positive history of AICs before the initiation of therapy with a BTK inhibitor, with 22 of them receiving treatment for active AICs at study inclusion. 19/22 patients (86%) did not require further AIC-targeted therapy after an average of 4.7 months of ibrutinib treatment. The occurrence of *de novo* autoimmune cytopenia as a complication of ibrutinib treatment was described in 6/301 patients (2%). Data based on comprehensive analysis of the Phase III RESONATE study did not reveal new AICs cases [85], while retrospective real-world data (RWD) showed a low rate (6%) of autoimmune complications of BTK inhibitor (five cases of AIHA, three ITP, one PRCA, one AIG, and one aplastic anemia) and increased control of AICs occurring before drug initiation [86]. Moreover, the effective use of ibrutinib in the therapy of refractory PRCA (independence from RCC transfusion) and AIG

(sustained response after one treatment cycle) has been described in a series of two cases [87].

In 2019, the results of a study by Quinquenel et al. revealed an ORR of 92% among 25 AICs patients treated with ibrutinib (16 AIHA, five ITP, three Evans's syndrome, and one PRCA) [88]. Ibrutinib, in addition to inhibiting Bruton's kinase, has also been shown to be an inhibitor of interleukin-2-inducible T-cell (ITK). In this case, the immunomodulatory effect of the drug consists in blocking Th2 cells (T-helper) activation and shifting the response towards Th1 type, which is the desired effect in the treatment of autoimmune diseases [77]. Phase II trials are currently underway to evaluate the effectiveness of BTK inhibitors in the treatment of AIHA (NCT03827603), ITP (NCT03395210), and a wide range of other autoimmune diseases [89, 90].

Data regarding idelalisib's use in the treatment of AICs is very limited. This is partly due to the presence of known non-hematological autoimmune complications, i.e. liver, lung or intestinal inflammation, which have led to the avoidance of PI3K inhibitor use in patients with coexisting AICs [91]. However, a 95% effectiveness of idelalisib in combination with rituximab in the treatment of AICs in 19 French patients (12 AIHA, six ITP, and one Evans's syndrome) has been reported; all AIHA relapses occurred after the completion of treatment with PI3K inhibitor [88]. Moreover, in a phase III study evaluating the efficacy of idelalisib in the treatment of refractory/relapsed chronic lymphocytic leukemia, no autoimmune cytopenia was reported among the most common adverse events (defined as occurring with a frequency ≥15%), nor in a long-term follow-up [92].

Data on the efficacy of venetoclax in the treatment of AICs in patients with CLL has mainly been derived from case reports [93]. Despite the reporting of side effects in the form of AICs in studies evaluating the effectiveness of BCL2 inhibitor in CLL treatment, no analysis of this complication has been performed. In a Phase II study in patients with relapsed/refractory chronic lymphocytic leukemia with del (17p), AIHA and ITP were diagnosed in 8% and 5% of patients, respectively [94]. In the phase III MURANO study, among 194 patients with CLL randomized to venetoclax in combination with rituximab, in two patients the treatment was discontinued due to AIHA, and in one patient due to ITP [95]. The overall prevalence of AICs in this study has not been assessed, possibly due to the low complication rate.

In the largest retrospective analysis to date in 815 patients with chronic lymphocytic leukemia, Vitale et al. [96] showed that treatment with ibrutinib, idelalisib or venetoclax did not increase the incidence of AICs compared to the untreated patients. AICs were recorded as a complication in 1% of patients treated with ibrutinib, in 0.9% of patients treated with idelalisib, and in 7% of patients treated with venetoclax. Patients with possible complications in the form of autoimmune cytopenia (nine cases of AIHA, three

cases of ITP) achieved good responses to immunosuppressive therapy with glucocorticosteroids, R or IVIG. It should be emphasized that among patients with AICs developed during treatment with ibrutinib or venetoclax, the combination with anti-CD20 molecules was not initially used. Moreover, in a significant minority of cases, AICs were newly diagnosed, while more often they concerned patients with a positive history of autoimmune cytopenia before targeted therapy initiation. The onset of AICs during targeted therapy has been observed at various treatment stages. However, a late-onset complication has been associated with active progression of underlying disease or as occurring shortly before progression. Autoimmune cytopenias did not occur in patients who achieved complete remission.

The data demonstrates the efficacy of targeted therapy in the treatment of both CLL and concomitant AICs. The response rate among active or controlled autoimmune cytopenia in patients treated with ibrutinib, idelalisib and venetoclax was 85%, 75%, and 66%, respectively. Only in a few cases did autoimmune cytopenia remain stable or worsen. The apparent superiority of ibrutinib may be due to the smaller sample size and the shorter follow-up in the venetoclax cohort, and the less sustained disease control when idelalisib was used as a treatment.

In addition, autoimmune cytopenias occurring before the initiation of targeted therapy in analysis by Vitale et al. [96] were statistically significantly associated with severe hypogammaglobulinemia. This may reflect advanced disease stage itself, but might also indicate profound disturbances in the functioning of the patient's immune system.

Conclusions

Autoimmune cytopenias complicating the course of chronic lymphocytic leukemia occur in c.10% of CLL patients [9]. Differences in the reported frequencies of AICs in individual studies result, among others, from differences in the analyzed cohorts (e.g. restricted only to patients undergoing multiple treatment lines), different follow-up durations, and to the diagnostic difficulties described in this article.

The prognostic significance of autoimmune cytopenia remains highly questionable. The available data suggests an association of AICs with advanced stages of CLL and unfavorable prognostic factors, but the effect on overall survival has not been clearly established. Analysis of the cause of abnormal blood counts as an unfavorable prognostic factor showed a statistically significant relationship only in the group of patients with cytopenia that had resulted from bone marrow infiltration and not from immune-related mechanisms [21, 97].

The low risk of autoimmune cytopenia should not limit the use of targeted drugs. However, the lack of guidelines for AICs diagnosed during treatment with new molecules

remains a significant problem. Various protocols are used: dose reduction, temporal treatment interruption, as well as adding-on steroid therapy, IVIG or rituximab [96]. Currently, there is also no consensus as to which targeted therapy should be preferred in AICs treatment. This decision is most often based on the experience of the treating center [98].

An interesting issue requiring further analysis would appear to be the effect of combining targeted therapy with anti-CD20 molecules as a potential factor preventing or minimizing the risk of autoimmune cytopenia [99]. The authors of the CLL14 study analysis do not mention AICs among the side effects with an incidence of at least 1% [100].

The treatment of an increasing number of patients with ibrutinib, idelalisib and venetoclax, as well as the extended follow-up duration in individual clinical trials, has led to a continuous increase in the amount of data regarding the impact of targeted therapies on autoimmune cytopenias. This is increasingly likely to result in conclusive data in the near future.

Authors' contributions

JT-S — literature collection, manuscript writing. MJ — data check, critical revision. LG — conceived idea for manuscript, critical revision. All authors — final approval of manuscript.

Conflict of interest

None.

Financial support

None.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; uniform requirements for manuscripts submitted to biomedical journals.

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