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AUTOIMMUNE CYTOPENIA IN CHRONIC LYMPHOCYTIC LEUKEMIA: DIAGNOSIS AND TREATMENT

Yu.L. Yevstakhevych, Ya.I. Vyhovska, I.Y. Yevstakhevych, O.Y. Vyhovska, N.V. Pelenyo, M.M. Semerak, V.L. Novak, V.E. Loginsky*

State Institution "Institute of Blood Pathology and Transfusion Medicine", National Academy of Medical Sciences of Ukraine, Lviv 79044, Ukraine

The aim **of the study was to determine peculiarities of the distribution, diagnosis and development of immune cytopenias in patients with chronic lymphocytic leukemia (CLL) and to evaluate the efficacy of the different therapeutic approaches.** ***Materials and Methods*****: Treatment response and survival of 83 patients with CLL complicated by immune cytopenia (IC) were analyzed. Treatment schedules in 58 medicated patients included corticosteroids; chemotherapy (COP, CHOP regimens), immunotherapy (rituximab alone), immunochemotherapy (rituximab-containing regimens — R-COP, R-CHOP). Twenty-five patients underwent splenectomy.** ***Results*****: The use of corticosteroids, as the first line of treatment, resulted in short-term remission in most patients. Chemotherapy was effective in a half of CLL patients, but duration of the remission did not exceed 32 months in CLL associated with autoimmune hemolytic anemia and immune thrombocytopenia. After rituximab monotherapy (10 patients) the stable remission was reached in 60% of the patients with median relapse-free survival of 40 months. Rituximab containing chemotherapy (22 patients) caused the long-term remission in 72% of the patients with median relapse-free survival of 76 months. Splenectomy performed in 25 patients with CLL complicated by IC was effective in 70% of the patients. The outcome of splenectomy depends on IC entity. The best response was registered in associated immune thrombocytopenia (median overall survival 118 months), the worst — in Fisher — Evans syndrome (15 months).** ***Conclusions*****: The treatment of patients with CLL complicated by ICs should be individualized. For CLL patients without significant enlargement of lymph nodes and spleen, low lymphocytosis, associated with autoimmune hemolytic anemia or immune thrombocytopenia, the monotherapy with rituximab is optimal. In case of occurrence of autoimmune hemolytic anemia, immune thrombocytopenia or Fisher — Evans syndrome in CLL patients with enlargement of lymph nodes, spleen, significant lymphocytosis, the use of R-COP or R-CHOP schemes, 4–6 courses, is the most effective. Splenectomy is indicated in patients with massive splenomegaly, the resistance to medication, recurrent relapses after adequate therapy.**

Key Words**: chronic lymphocytic leukemia, autoimmune hemolytic anemia, immune thrombocytopenia, Fisher — Evans syndrome, rituximab, chemotherapy, splenectomy.**

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Chronic lymphocytic leukemia (CLL) is the most frequent type of leukemia with the standardized incidence rate of 4.0 per 100 thousand of population per year. However, the CLL incidence increases with age. CLL complications include immune cytopenias (IC): autoimmune hemolytic anemia (AIHA), immune thrombocytopenia (ITP), a combination of hemolysis and thrombocytopenia (Fisher — Evans syndrome — FES) [1–4]. The rare complications involve immune neutropenia (IN) and partial red-cell aplasia (PRCA). Diagnosis of the associated ICs frequently is complicated [1]. The ICs should be differentiated from cytopenias caused by bone marrow failure or hypersplenism, since they require different therapeutic approaches. The causes and clinical consequences of IC in CLL patients have not been elucidated in details. Nevertheless, such complications may affect significantly the outcome in CLL patients.

The aim of the study was to determine peculiarities of the distribution, diagnosis and development of IC in patients with CLL and to evaluate the efficacy of the different therapeutic approaches.

MATERIALS AND METHODS

In 1986–2018, we observed 83 patients with CLL complicated by ICs who were diagnosed and treated at the Departments of Hematology, General and Hematologic Surgery, and Polyclinics of the State Institution "Institute of Blood Pathology and Transfusion Medicine" (Lviv) and at the Lviv City Communal Clinical Hospital № 5. Among them there were 51 males 40–78 years old (median age 63.5) and 32 females 42–76 years old (median age 65.6). Compliance of the study with bioethical standards was approved by the Ethics Committee of the State Institution "Institute of Blood Pathology and Transfusion Medicine" (Lviv), protocol № 39, December 10, 2019. All patients provided their consent to the participation in the study.

The diagnosis of CLL was established taking into account clinical symptoms as well as results from diagnostic procedures, including cytomorphology, immunophenotyping, cytogenetics and immunohistochemistry, if available. The diagnosis was confirmed in all the patients by immunophenotyping (before

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*Correspondence: E-mail: msemerak@ukr.net
Abbreviations used: AIHA – autoimmune hemolytic anemia; CLL – chronic lymphocytic leukemia; CHOP – cyclophosphamide, doxorubicin (hydroxyl daunorubicin), vincristine, prednisolone; COP – cyclophosphamide, vincristine, prednisolone; DAT – direct antiglobulin test; FES – Fisher – Evans syndrome; IC – immune cytopenia; IN – immune neutropenia; ITP – immune thrombocytopenia; OS – overall survival; PRCA – partial red-cell aplasia; R-CHOP – rituximab, cyclophosphamide, vincristine, doxorubicin, prednisolone; RFS – relapse-free survival; R-COP – rituximab, cyclophosphamide, vincristine, prednisolone.

2002 — by manual method, thereafter — by flow cytometry) according to Matutes score system [5]. Immunophenotypic profile of the leukemic lymphocytes was characterized as monoclonal B-cell population $CD5^+$, $CD19^+$, $CD22^{low/-}$, $CD23^+$, $SmIg^{low}$, $CD79b^-$.

AIHA was diagnosed on the basis of two criteria: clinical evidence of hemolysis and presence of antibodies directed against red blood cells (RBCs). Clinical signs of hemolysis were rapid development of anemia, icterus, indirect bilirubinemia, reticulocytosis and maintained RBC lineage in the bone marrow. Anti-RBC antibodies were demonstrated by positive direct antiglobulin test (DAT), presence of warm or cold agglutinins.

ITP has been displayed by hemorrhagic syndrome, thrombocytopenia and sufficient amount of megakaryocytes in the bone marrow. Because of absence of a sensitive and specific test for antithrombocytic antibodies, ITP remains a diagnosis of exclusion, in lack of another likely explanation for the thrombocytopenia [1]. FES was characterized by simultaneous manifestations of immune hemolysis and thrombocytopenia, provided preserved RBC and megakaryocyte lineages in the bone marrow. PRCA and IN were diagnosed on the results of clinical, hematologic, immunologic and bone marrow findings. Table 1 shows the distribution of CLL patients according to the IC type.

58 patients underwent medicamentous therapy, 25 patients underwent splenectomy. The following treatment schemes were used: COP (cyclophosphamide, vincristine, prednisolone); CHOP (cyclophosphamide, doxorubicin (hydroxyl daunorubicin), vincristine, prednisolone); R-COP (rituximab, cyclophosphamide, vincristine, prednisolone), R-CHOP (rituximab, cyclophosphamide, vincristine, doxorubicin, prednisolone). Splenectomy had been performed by standard surgical technique after appropriate vaccination.

Treatment response was evaluated by overall (OS) and relapse-free (RFS) survival calculated by the Kaplan — Meier method. Cox's *F*-test and chi-square test were used to compare survival in treatment groups of the patients.

RESULTS

Table 1 demonstrates that the absolute number of AIHA, ITP and FES cases in males exceeds that in females. This is apparently related both to larger total number of male CLL patients in our study and higher CLL incidence in men.

Table 1. Distribution of CLL patients according to IC type

IC type	Men	Women	Total
AIHA	22	16	38
ITP	17	9	26
FES	11	4	15
IN	0	1	1
PRCA	1	2	3
Total	51	32	83

Table 2 shows the peripheral blood values in patients with CLL complicated by ICs who underwent conservative therapy.

The warm antibodies (positive DAT), titer from 1:8 to 1:2048, were detected in 21 patients with AIHA and 10 patients with FES. One patient showed high titer of cold antibodies (1:8000) (cold antibodies hemolytic anemia). IC in those patients was not related to previous treatment. DAT-positive anemia in 5 patients with AIHA and in one with FES may be attributed to both the underlying CLL and preceding treatment: one of them developed the recurrent hemolysis after fludarabin, 2 patients with AIHA and 1 patient with FES got hemolysis secondary to treatment with chlorambucil, in 2 patients AIHA occurred after COP medication.

IC is known to be the reason for therapy initiation in patients with CLL. The corticosteroids serve as a first-line standard. The treatment of all patients was started with prednisolone at a dose of 1 mg/kg of body weight, which commonly resulted into the short-term remissions. In view of AIHA development, five patients underwent treatment according to COP scheme and four patients underwent treatment according to CHOP scheme. The therapy has proved to be effective in five patients — a remission up to 34 months was observed. Other patients showed no significant response to treatment.

Better outcomes were observed with inclusion of rituximab into the scheme. Ten patients, in view of AIHA with prolonged hemolysis, underwent treatment according to the scheme with rituximab inclusion: four patients underwent treatment according to R-COP scheme, and six patients underwent treatment according to R-CHOP scheme. Nine patients after 4–6 courses of R-COP or R-CHOP developed long-term remissions (time of follow-up 12–68 months). Only one patient appeared to be resistant to treatment according to R-CHOP scheme and died.

Combination chemotherapy according to COP or CHOP regimens was prescribed for 3 CLL patients with associated ITP; remission lasting for 18 and 32 months developed in 2 patients. Rituximab-containing regimens (R-COP, R-CHOP) were used in 5 patients with associated ITP; remission which continued from 6 to 55 months occurred in 4 patients. One patient showed no response to the treatment.

No response to corticosteroid treatment was found in patients with CLL complicated by FES. Thereafter, 2 patients were treated by CHOP regimen with short-

Table 2. Pretreatment peripheral blood values in CLL patients complicated by ICs

Complication	Hemoglobin (g/L)	Red blood cells ($\cdot 10^{12}$/L)	White blood cells ($\cdot 10^9$/L)	Lymphocytes (%)	Platelets ($\cdot 10^9$/L)	Reticulocytes (‰)	Bilirubin μmol/L
AIHA	71	2.35	102	83	195	73.5	44.5
	[55–88.5]	[1.8–3.05]	[31.5–189]	[74.5–96]	[146–236]	[52–113]	[31–80]
ITP	119	4.0	46.5	74	20		
	[108–135]	[3.8–4.0]	[12–74]	[66–81]	[17–49]		
FES	52	1.7	155	95.5	59	29	37
	[49–86]	[1.4–2.7]	[181–225]	[93–96]	[14.5–82]	[14–88]	[16–46]

Note: The median values are given, the lower and upper quartiles are shown in the brackets.

term efficacy, and 6 patients underwent treatment with rituximab inclusion — R-COP (2 patients) and R-CHOP (4 patients). Remission in 3 patients continued 9–24 months, and others 3 patients have also shown response to treatment, however, the remission was short-term and the patients died in 4, 8 and 24 months after the treatment.

Generally, 10 CLL patients with IC (4 patients with AIHA, 5 patients with ITP, and one patient with FES) were treated by rituximab monotherapy (375 mg/m^2 once a week; 4 infusions). Those patients had no significant enlargement of lymph node, liver and spleen, WBC values ranged between 10 • 10^9/L and 83 • 10^9/L. Response to the treatment has been observed in 8 patients. However, one patient developed remission which lasted for less than 7 months, remained 95% CD38$^+$ cells and 88% cells with del(11q). In one more patient ITP relapse occurred after 9 months. The remission in other 6 patients is still lasting (time of follow-up 22–34 months). In one of them remission was accompanied by decreasing β_2 microglobulin value to 2.48 mg/L, number of CD38$^+$ cells to 6% and cells with del(11q) to 21%.

Table 3 shows blood count findings of patients with ITP prior to and after monotherapy with rituximab. Platelet values in all patients with ITP after rituximab monotherapy increased substantially.

Survival outcomes of CLL patients with IC treated by rituximab monotherapy (10 patients) and rituximab+chemotherapy (22 patients) are presented in Fig. 1. The median RFS for patients on rituximab monotherapy was 40 months, and for 22 patients on rituximab + chemotherapy — 76 months. Nevertheless, RFS rate is not significantly different between these treatment strategies (Cox's *F*-test $p = 0.301$).

To evaluate prognostic significance of IC types, we analyzed OS rate of CLL patients with associated AIHA, ITP and FES (Fig. 2). All the patients previously were medicated because of IC and/or CLL. In 15 patients with ITP, the cumulative proportion of surviving patients (OS) for 133 months (71.4%) was significantly higher than in the group of 29 patients with AIHA (28.5%, $p = 0.001$), and the cumulative proportion of surviving patients for 104 months (71.4%) was significantly higher than in the group of 10 patients with FES (10.5%, $p = 0.0004$). The median OS time for 10 patients with FES was 75 months, and for 29 patients with AIHA, it was 80 months ($p = 0.163$). In the group of 15 patients with ITP, median OS was not calculated since an actual survival rate was above 0.5.

Splenectomy has been performed in 41 patients with CLL, in 25 (60.1%) of them the disease was complicated by IC. Among them, there were 11 patients with ITP, 9 patients with AIHA and 5 patients with FES; 17 men 40–72 years old and 8 women 42–61 years old. Marked splehomegaly, reduced hemoglobin and RBC level (HGB — 50–80 g/L, RBC 1.6–2.9 • 10^{12}/L), reticulocytosis — 20–290 ‰, hyperbilirubinemia (bilirubin 40–84 μmol/L), and positive DAT were observed in all patients with CLL complicated by AIHA. In two patients AIHA was accompanied by occasional hemolytic crises. Splenectomy proved to be effective for 8 patients with CLL complicated by AIHA: the abdominal pressure syndrome caused by splenic enlargement was neutralized, the hemolysis ended, and hemoglobin level normalized. 1 patient died immediately after the surgery due to cardiovascular failure. 2 to 5 year survival was registered in 44% of patients, 1 patient has been living for 221 month. The median OS after splenectomy in patients with CLL complicated by AIHA was 32 months (Fig. 3).

Table 3. Peripheral blood values of patients with CLL complicated by ITP prior to and after monotherapy with rituximab

Time of examination	Hemoglobin	WBC (• 10^9/L)	PLT (• 10^9/L)
Prior to receiving	130	16.0	21
treatment	[105–137]	[10.8–35.0]	[19–82]
After administra-	121	12	128
tion of rituximab	[110–137]	[7–18.5]	[127–132]

Note: The median values are given, the lower and upper quartiles are shown in the brackets.

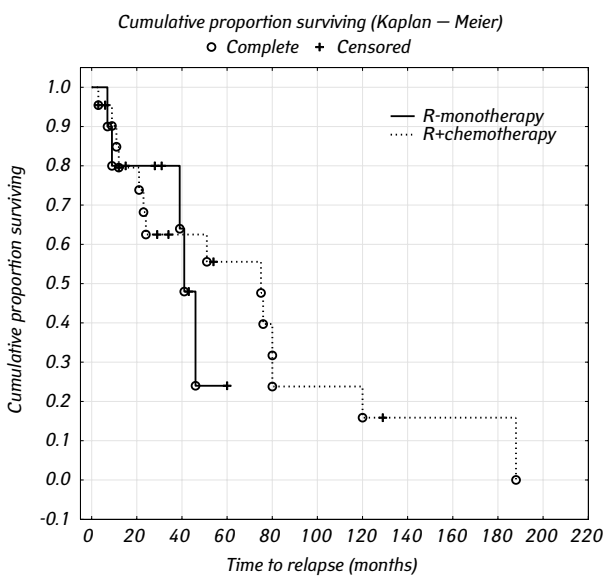

Fig. 1. RFS in CLL patients treated by rituximab monotherapy and rituximab + chemotherapy. Cox's *F*-test $p = 0.301$

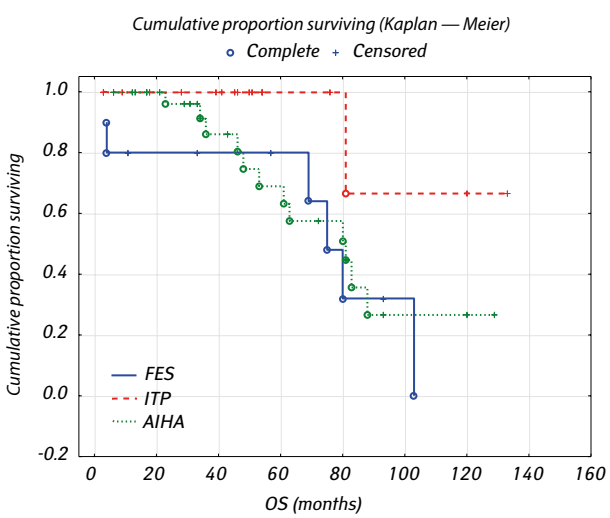

Fig. 2. OS in medicated CLL patients depending on the immune complication entity. Chi-square = 5.09, df = 2, $p = 0.079$; AIHA *vs* ITP — Cox's *F*-test $p = 0.001$; AIHA *vs* FES — Cox's *F*-test $p = 0.163$; ITP *vs* FES — Cox's *F*-test $p = 0.0004$

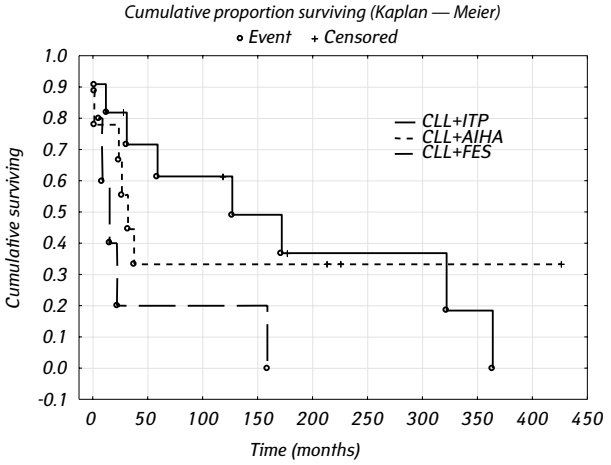

Fig. 3. OS in CLL patients with immune cytopenia after splenectomy. Chi-square = 3.62, df = 2, $p = 0.16$; AIHA *vs* ITP — Cox's *F*-test $p = 0.84$; AIHA *vs* FES — Cox's *F*-test $p = 0.14$; ITP *vs* FES — Cox's *F*-test $p = 0.029$

Eleven patients with CLL complicated by ITP underwent splenectomy. All patients had significantly reduced platelet counts ($< 50 \cdot 10^9$/L) without stable effect of conservative therapy (corticosteroids, thrombopoietin agonists) prior to the surgery. Splenomegaly with abdominal pressure syndrome was an additional indication for the surgery. In 5 patients with ITP, the spleen removal was accompanied by major bleedings caused by perisplenic adhesions and regional portal hypertension. Splenectomy proved to be effective for 8 (73%) patients with the platelet count having increased to 186.0–537.0 $\cdot$ 10^9/L after surgery and normalized within 2-3 weeks. Three patients showed no response to splenectomy, the platelet count did not significantly increased. The postoperative complications occurred in 2 patients: one patient was diagnosed with a subphrenic abscess, and another patient had splenic vein thrombosis. The patients' condition stabilized after appropriate treatment. Three patients died within 12 months after splenectomy due to disease progression. The survival for 24–67 months was observed in 6 patients and 2 patients survived for 117 and 361 months after splenectomy (Fig. 3).

5 patients with CLL complicated by FES underwent splenectomy. All these patients developed thrombocytopenia (platelet value from occasional to $68.0 \cdot 10^9$/L), warm-antibody AIHA, splenomegaly with abdominal syndrome and resistance to corticosteroids and chemotherapy. One patient developed acute cardiovasculare failure during postoperative period which was successfully cured. While analyzing the long-term outcomes of splenectomy, it has been defined that the median OS was only 15 months.

As shown in Fig. 3, the longest OS after splenectomy can be achieved in CLL patients with associated ITP (median OS 118 months), the shortest — in patients with FES (median OS 15 months; $p = 0.029$). Patients with AIHA (median OS 32 months) revealed intermediate OS duration. Postoperative mortality after splenectomy in the CLL patients with IC was 4%.

DISCUSSION

Autoimmune phenomena are commonly seen in B-lymphoproliferative disorders, especially in CLL. The pathophysiological mechanisms of the association between the malignant disorders and the ICs are not completely understood, although several theories have been proposed [1].

The ICs frequency rate in patients with CLL pursuant to data reported ranges between 4.3% and 9.7%. The most frequent complication of CLL is AIHA — in 5–10% of patients [2], in 7% of patients [3, 4], less frequent is ITP — in 1–5% of patients [2, 6]. The most frequent IC entity in cohort of the 58 examined CLL patients was AIHA (45.8%). The significant amount of reported cases of IC in CLL is associated with administration of alkylating agents [7, 8]. The IC cases are more frequently related to usage of purine nucleosides [8], single IC cases were described after treatment with bendamustine [9] and ibrutinib [10]. In presented series of the examined patients, 6 (10.3%) developed IC related to the medication: AIHA with severe hemolysis arose in 2 of them after treatment with chlorambucil, in 2 more patients immediately after COP course, in one patient after fludarabin treatment and in one patient FES occurred post treatment with chlorambucil. The cause of IC in other CLL patients has been connected with subsequent B-cell malignancy. In CLL associated with AIHA, polyclonal warm IgG antibodies produced by nonmalignant B cells have been found to be the culprit antibodies [1].

Corticosteroids are considered to be the first-line therapy according to diagnostic and treatment standards for CLL as well as in case of IC complication. Response to the treatment is observed in 1/3 of patients [2] or to 52% of patients [6].

Corticosteroids, intravenous immunoglobulins and monotherapy with rituximab are recommended as a first-line therapy for the IC occurred in CLL patients in the latest references [1, 11]. Corticosteroids as a first-line therapy in the examined patients resulted in a short-term remission of IC. If corticosteroids proved to be ineffective, it was recommended to prescribe vincristine, cyclophosphamide or undergo a combined chemotherapy according to COP or CHOP regimens.

The effectiveness of rituximab in treatment of CLL complicated by IC has been recently substantiated [12–14]. The rituximab monotherapy is recommended in standard dose 375 mg/m^2 intravenously once a week for 4 weeks [14, 15]. The long-term remission is observed in 60% of patients with CLL complicated by AIHA as reported [16]. Better efficacy is reached with combination of rituximab and chemotherapy: rituximab, cyclophosphamide, dexamethasone regimen [17–20] or R-COP regimen [21].

According to our observation, treatment by COP or CHOP courses results in the short remission of the IC, and only in 18% of the patients remission lasted during 3–4 years after the treatment. Better outcomes were observed when applying the rituximab

monotherapy, effective in 69% of the patients with remission lasting from 22 to 34 months. Combination treatment according to R-COP or R-CHOP schedules led to a long-lasting remission in 91% of the treated patients.

Splenectomy is recommended in case of ineffectiveness of the conservative treatment. As reported, 35% of the patients respond to corticosteroids, 54% of them respond to chemotherapy, and 70–75% — to splenectomy [6, 11, 22]. A 10-years follow-up of 233 patients with CLL complicated by ITP who underwent splenectomy showed that 88% of the patients respond to splenectomy, just as 77% of the patients exhibited complete response to medication [23]. Our observations showed that median post-splenectomy OS in patients with AIHA was 32 months, and in patients with ITP — 118 months. Unsatisfactory results of splenectomy were observed in CLL patients with associated FES. The mean OS time of the patients was only 15 months (Fig. 3). Splenectomy is indicated for CLL patients with marked splenomegaly: great tumor mass is removed, the hemolysis is reduced in cases with AIHA, and platelet values increase in cases with ITP. One of post-splenectomy complications is the development of the overwhelming post-splenectomy infection syndrome. All patients shall be vaccinated against capsulated bacteria 10–14 days prior to splenectomy for prevention of overwhelming post-splenectomy infection syndrome.

Considering our observations as well as reference data, it can be concluded that treatment of patients with CLL complicated by IC should be individualized. When IC occurred at early stages of the disease, absence or moderate lymphadenopathy and spleen enlargement, low lymphocytosis, preserved RBC and megakaryocyte lineages in bone marrow, the most effective treatment is rituximab monotherapy (a dose of 375 mg/kg of body weight — 4 injections with a week interval). In CLL patients with associated IC, enlarged lymph nodes, spleen, high lymphocytosis, the most relevant is treatment according to R-COP or R-CHOP regimens depending on the patient's age. Splenectomy is recommended for the patients with marked splenomegaly, resistant to the treatment or with recurrent IC.

In CLL staging systems, anemia and thrombocytopenia independently of the origin define a diagnosis of the late stages of CLL (III, IV according to Rai and C according to Binet). However, the nature of the cytopenia is not considered. The late stages of CLL are predictably assessed as adverse, with a short-term survival. Considering the difference of survival rate of the patients with immune and metaplastic cytopenias [7, 24, 25], we believe it would be appropriate to indicate the origin of cytopenia as "I" (immune) or "M" (metaplastic) when determining the stage III and IV according to Rai, and C according to Binet.

Further studies in a larger number of patients are required in order to decide which treatment strategies would be more benefitial for CLL patients with associated IC.

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