Case Report

THE DIFFERENT FACES OF CHRONIC LYMPHOCYTIC LEUKEMIA - TWO CLINICAL CASES

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Summary

Chronic lymphocytic leukemia is one of the most common types of leukemia affecting adults over 65 years of age [1]. The disease is a part of the so-called indolent lymphomas and has a variable clinical course, defined by many factors. In recent years, knowing better the pathogenetic mechanisms of the disease, significant advances in the treatment have been made [2]. Monoclonal antibodies, immunomodulators, tyrosine kinase inhibitors, anti-apoptotic Bcl-2 protein inhibitors have been approved for clinical practice. Nevertheless, the development of tumor resistance and recurrence of the disease remains a challenge for hematologists, biologists, and pharmacists. We present two clinical cases of patients of both age groups (young adults and adults), in whom treatment was started with a Bruton's tyrosine kinase (BTK) inhibitor, after inadequate response to immunochemotherapy (CIT).

Keywords: low doses Ibrutinib, lymphocytic leukemia, secondary cancer

Introduction

Chronic lymphocytic leukemia (CLL) belongs to the group of lymphoproliferative disorders, in which a significant number of patients are asymptomatic at diagnosis, and thus treatment is delayed [3]. The variable clinical course is related to many factors. Nowadays, these factors are divided into three large groups: patient-related factors, disease-related factors, and those associated with therapy [4]. A comprehensive risk assessment, based on the identification of prognostic and predictive factors, dividing CLL patients into different risk groups, allows the choice of an optimal therapeutic regimen. According to current treatment standards, patients with active or progressive disease, as well as these in advanced stage (C- Binet/ III-IV Rai), are indicated for treatment. In most algorithms, the treatment is based on a patient's age, comorbidities, and the molecular-genetic profile of the disease. Patients with deletion 17p / TP53 are indicated for treatment with tyrosine kinase inhibitors (TKI) or BH3-mimetic [5].

Case 1

A 75-year-old male, ex-smoker, with a negative family

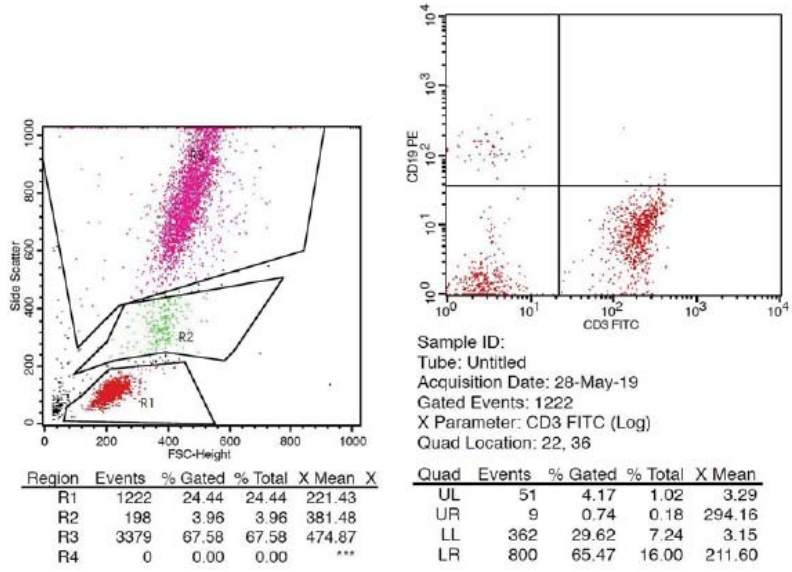
history for lymphoma or leukemia was diagnosed in 2014, with CLL on his first visit to the clinic of hematology. The results from the blood smear showed increased leukocyte count 70.7 X 10^9 / l, absolute lymphocyte count 37.8 X 10^9/ l, normal hemoglobin level, and platelet count. Flow cytometric analysis of peripheral blood was performed and abnormal B-lymphocytes expressing aberrant phenotype were detected CD19 (+) positive, CD5 (+) positive, CD20 (+) positive low expression, CD22 (-) negative, CD38 (-) negative, FMC7 (-) medium expression CD23 (+), CD200 (+) positive, CD49d negative). With fluorescent in situ hybridization (FISH) on interphase nuclei, 88% of cells were detected to have del (11) (q22). The test was negative for del (17) (p13). Based on the above laboratory tests and after a full-body scan (CT), the patient was staged at B-CLL-Rai/Binet A with B symptoms. Because of his concomitant diseases (arterial hypertension, ischemic post-infarction cardiomyopathy, post-percutaneous coronary intervention with stents of the left anterior descending artery, diabetes mellitus type II, cholecystectomy) and the patient's age, Rituximab therapy was initiated.

A year later, due to a significant enlargement of the peripheral lymph nodes and a feeling of breathlessness, a second-line therapy (Rituximab and Bendamustine) in conventional doses was started. The patient acquired a diffuse urticarial rash after the first Bendamustine infusion, this treatment was discontinued, and Rituximab plus Chlorambucil therapy was initiated. In March 2017, the patient was symptomatic, without changes in lymph node size, but grade III thrombocytopenia and moderate anemia were registered from the complete blood count (CBC). The radiological examination of the chest showed pleural effusion requiring thoracocentesis. A control FISH analysis was performed, and in 89% of the interphase nuclei del (11) (q22) was detected. Del (13) (q14) or the absence of the entire chromosome 13 was observed in 55% of cells. The anemia and thrombocytopenia were corrected with replacement therapy and erythropoietin. In May 2017, a control CT was carried out. It revealed data for lymph node enlargement, presence of ascites, and hydrothorax, which confirmed the progression of the disease. Laboratory tests showed leukocytosis (WBC) - 63.7X 10^9/ l; thrombocytopenia (Plt) - 80.0X 10^9/ l, erythrocytes (RBC) - 4.13 X 10^{12}/ l, hemoglobin (Hb)-133.0 g/l (hemoglobin values were compensated by erythropoietin and transfusions of erythrocyte concentrates), lymphocytes – 82%. Based on all of the results mentioned above, the presence of "bulky disease," performance status, and comorbidity (ECOG-2, CIRS-10), we commenced treatment with Ibrutinib - 3 tablets (420mg) daily. On the third day of treatment, the patient reported diarrhea, and the dose of Ibrutinib was reduced to one tablet a day. At the end of the second month of Ibrutinib treatment, based on the revised criteria of the IWG-CLL for the response to therapy, a physical examination, imaging, and laboratory investigations were performed. We also found a significant clinical improvement: lack of symptoms, ECOG-0, a reduction in peripheral lymphadenopathy, normal leukocyte count, absence of anemia, and thrombocytopenia.

One year later, there were no pathologically enlarged lymph nodes. Laboratory tests showed WBC- 6.7 X 10^9/ l ; RBC- 4.13 X 10^{12}/ l; Hb - 130.0g/l ; Ht - 0.382; MCV - 92.3; MCH - 31.6; MCHC - 342.0; Plt – 206 X 10^9/ l ; lymphocyte count - 50% The patient continued treatment at a dose of 1 tablet daily. Two years after the start of treatment with TKI, no chromosome aberrations were detected by IFISH analysis, along with a normal CT image. Full blood count was as follows: WBC- 6.8X 10^9/ l ;RBC- 4.15X 10^{12}/ l ;Hb - 124.0g/l; Plt - 190X 10^9/ l; lymphocytes 34%; monocytes - 6%; granulocytes - 60%. A flow cytometric analysis of peripheral blood did not detect B-lymphocytes expressing aberrant phenotype (Figure 1).

Case 2

A 30-year-old female was diagnosed with B-CLL in October 2010, upon visiting a hematologist with complaints related to swelling of her cervical and axillary lymph nodes. Three courses with Cyclophosphamide, Oncovin, Prednisolon (CVP) were conducted, and the patient was referred to a specialized hematology hospital for treatment. Laboratory tests were conducted in January 2011; the flow cytometric analysis identified a B-cell lymphoma population (51 G / l) expressing the phenotype CD19 (+), CD20 (+), CD22 (+), CD23 (+), which corresponded to CLL. The patient was staged in C - Binet.



Region	Events	% Gated	% Total	X Mean	X
R1	1222	24.44	24.44	221.43	
R2	198	3.96	3.96	381.48	
R3	3379	67.58	67.58	474.87	
R4	0	0.00	0.00	***	

Quad	Events	% Gated	% Total	X Mean
UL	51	4.17	1.02	3.29
UR	9	0.74	0.18	294.16
LL	362	29.62	7.24	3.15
LR	800	65.47	16.00	211.60

Figure1. Flow cytometric analysis of peripheral blood, two years after Ibrutinib therapy

Alemtuzumab treatment and search for a suitable donor was initiated. In April 2012, polyclonal hypergammaglobulinemia was found.

Subsequently, because of the presence of disease symptoms, the patient was treated by R-FCMprotocol(Rituximab,Cyclophosphamide, Mitoxantrone). Fludarabine was excluded due to the autoimmune phenomenon. As a result of treatment, a partial response was achieved. In 2013, because of generalized lymph node enlargement and extreme leukocytosis of 386 G / l, leukapheresis was performed with subsequent CIT, including Rituximab plus Bendamustine. In 2015, disease symptoms recurred, and treatment was reinitiated (R-CVP). Bone marrow biopsy showed significant involvement of bone marrow in the disease process. The cytogenetic analysis found no abnormality, and a FISH study did not identify a del (11) (q22). Serum electrophoresis was undertaken and IgM kappa + FLC kappa paraprotein (6.0%) 5.5 g / l was detected. CT showed generalized lymphadenomegaly. Hepato-splenomegaly was found with predominant splenomegaly. The direct Coombs test was highly positive. In 2016, CT showed extreme hepatomegaly and data on progression as compared to the previous CT study. Trepanobiopsy proved a nodular character of involvement and a significant increase of leukemic / lymphoma cells from CD20 + CD79a + CD5 + CD23 + B- cells. In about 20% of cells, del (17) (p13) was detected by FISH analysis. Del (11) (q22), del (13) (q14), and trisomy 12 were not found. Chemotherapy with Rituximab + Bendamustine was applied, but complete remission was not achieved. In June 2017, treatment with Ibrutinib was started with three tablets daily. In 2018, a control CT scan showed a reduction in organomegaly, and CBC results were in the normal range.

During the year, the patient complained of pain in the anal area, with a gradually developing anal fistula. In July 2019, a two-barrel sigmostomy was performed for removal of the passage. In November 2019, the patient was admitted to a clinic of surgery, presenting with pain and a wound in the gluteus region, which significantly had increased in size. CBC revealed moderate anemia, leukocytosis to 12 G/l, and thrombocytosis 558 G/l. Excision, necrectomy, fasciotomy, and biopsy were performed. Histological analysis showed the infiltration of soft tissue by G2-G3 squamous cell carcinoma with a trabecular and breeding growth pattern.

Discussion

The presented cases are of interest because of the difference in the clinical course of the disease in different age groups. According to most scientific reports, the age over 65 is an

unfavorable prognostic factor. Age is a limiting factor for intensive therapy. On the other hand, neoplasms are more common in the elderly. In the second clinical case presented, a second neoplasm was established after a long treatment period of the underlying disease with different therapeutic regimens. In recent years, secondary tumors have been reported in patients undergoing treatment with Ibrutinib [6]. However, there is no clear evidence of a correlation between the drug and the development of a second malignancy. Previous chemotherapy regimens that patients have received, the presence of del17p, and associated with this cytogenetic abnormality defining resistance to treatment [7], as well as impaired immunity, are all factors that may serve as a basis for the development of a neoplastic disease, regardless of age.

Ibrutinib belongs to the group of Bruton's tyrosine kinase (BTK) inhibitors. It was approved by the FDA for treatment of patients with B- CLL in 2014, a second-line therapy. Later, in 2016 Ibrutinib was approved as first-line therapy in the treatment for patients with B-CLL and presence of del17p [8]. Its mechanism of action is associated with selective inhibition of the enzyme activity of BTK and the resulting limitation of tumor growth and proliferation [9]. The standard dose administered to treat patients with B- CLL is 420mg daily (3 tablets, 140 mg), and the dose may be changed in case of adverse effects [10].

In the first case, chromosomal aberration del11q was identified by IFISH. According to the literature, it is associated with lymphadenomegaly [11]. Deletions affecting the ATM gene correlate with an unfavorable prognosis [9], although that del11q is not included as a prognostic factor in the international prognostic index (CLL-IPI). Due to age and concomitant diseases of the patient, he was treated with low doses of Ibrutinib, which proved sufficient to control the disease. Lisa S. Chen et al. reported good results and efficacy when using BTK at lower doses [12].

Conclusion

Although unspecified in clinical practice, doses of Ibrutinib could be tailored to a patient's condition, age, comorbidities, and clinical course of the disease. An association between the development of secondary neoplasia in patients with CLL undergoing BTC treatment is difficult to demonstrate due to the complex and not fully understood pathogenesis of the disease.

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