ACTA MEDICA TRANSILVANICA December27(4):8-10
Online ISSN 2285-7079

EVOLUTION FEATURES OF A PATIENT WITH CHRONIC LYMPHOCYTIC LEUKEMIA

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Keywords: *chronic lymphocytic leukemia, infection, second neoplasia, cytogenetics*

Abstract: *Chronic lymphocytic leukemia is still an incurable blood and bone marrow disease, but with a long and indolent rate of evolution. We present the case of a 56-year old male patient who was diagnosed with chronic lymphocytic leukemia, not requiring treatment. After 4 years of monitoring, his illness progressed with massive lymph nodes so we started treatment with chemotherapy. Due to several life-threatening respiratory infections, we needed to discontinue the treatment, but finally we managed to administer all the chemotherapy cycles. The patient relapsed several times and now he receives treatment with Ibrutinib. If the patient develops resistance to this inhibitor of Bruton's tyrosine kinase, treatment with Venetoclax remains a future therapeutic option.*

INTRODUCTION

Chronic lymphocytic leukemia is a blood and bone marrow neoplasia, characterized by an accumulation of B lymphocytes in the bone marrow, lymphoid organs and peripheral blood.(1) Chronic lymphocytic leukemia represents 25-30% of all cases of leukemia, and is the most common form of leukemia found in adults. The incidence of the disease is higher among men compared to women with a sex ratio of 2:1.(2)

The causes of chronic lymphocytic leukemia remain unknown but it is well known that the disease affects mostly white man, middle-aged or older. Although chronic lymphocytic leukemia has been known to be a disease that mainly affects the elderly, the latest data from the literature have shown an increased incidence among younger patients, so that one-third of newly diagnosed patients are under 55 years of age.(3)

Epidemiological studies have shown a familial susceptibility of about 5-10% to lymphoid malignancies.(4)

Literature data show that the risk of first-degree relatives of patients with chronic leukemia to develop a similar malignancy, increases up to 7 times more compared to the general population.(5) Chronic lymphocytic leukemia is a disease with a slow progression rate, therefore some people never need treatment.(6)

Chemotherapy remains the treatment of choice, plus immunotherapy and new molecules such as Bruton tyrosine kinase inhibitors- Ibrutinib (7,8), BCL 2 inhibitors such as Venetoclax (9) and PI3K inhibitor- Idelalisib.(10)

Although some patients do not achieve hematologic remission, they may survive for a long time. Autologous stem cell transplantation has not been shown to bring therapeutic benefits to patients with CLL (11) and allogeneic haematopoietic stem cell transplantation (such as CAR T cell therapy) has very limited indications.(12)

CASE REPORT

We present the case of a 56-year old male patient known since 2007 to be suffering from chronic lymphocytic leukemia, which presented only as leukocytosis and lymphocytosis at the time of diagnosis and not requiring treatment. He was only monitored by regular blood tests.

In 2011, at his medical visit, he presented with cervical and axillary lymphadenopathy blocks, but the liver and spleen could not be clinically examined due to abdominal fat.

A CT-scan was performed which showed multiple lymphadenopathy blocks in the cervical, axillary, submandibular, supraclavicular, mediastinal, abdominal and celiac regions, and homogeneous hepatosplenomegaly.

Paraclinical laboratory investigations show the following changes: Leukocytes-56.000/mm^3, Lymphocytes-7.180/mm^2, Hemoglobin-14.4 g/dL and Platelets-139.000/mm^3.

Due to disease progression, we decided to start chemotherapy. The first chemotherapy regimen (Fludarabine 50 mg/day 3 days, Cyclophosphamide 400 mg/day 3 days and Mitoxantrone10 mg) was well tolerated, but after a few weeks the patient had high fever (40^{0}C) and chills, but no lymphadenopathy or hepatosplenomegaly.

Biologically, the patient presented pancytopenia with Leukocytes 1840/mm^3, Hb 11,9 g/dl and Platelets 74.000/mm^3. He received antibiotics, antifungal, corticosteroid, granulocyte colony-stimulating factor and the evolution has been favorable.

The following 3 cycles of chemoimmunotherapy with Fludarabine, Cyclophosphamide and Rituximab were well tolerated, but after two months the patient presented again with fever, nasal obstruction, rhinorrhea, coughing and an inflammatory biological syndrome. Cytostatic treatment was delayed due to infection and antibiotics were administered again. We mention that none of the biological cultures taken could isolate any germ explaining the patient's repeated infections.

The patient finished 6 courses of chemotherapy and between April 2012 and January 2016 did not present for any periodic hematological examinations.

The patient returned in January 2016 with massive lymphadenopathy blocks in the neck and axillary region, as well as swallowing disorders.

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Article received on 12.09.2022 and accepted for publication on 20.12.2022

The labs showed: Leukocytes 90450/mm^3 and the bone marrow aspirate revealed a hyperplasia cell lineage with lymphoid lymphocytes between 60 and 83%. The bone marrow biopsy and flow cytometry confirmed the diagnosis of relapsed chronic lymphocytic leukemia. Due to financial reasons, we could not perform cytogenetic tests at diagnosis.

Cytostatic treatment was started again, but after the first cycle the patient presented a life-threatening infectious episode with severe pulmonary manifestations and candidemia.

A pulmonary tuberculosis and aspergillosis infection was excluded, but again we could not isolate a germ responsible for the infectious syndrome. However, the patient responded well to antibiotics and antifungal treatment.

Also, after a skin biopsy taken from the upper back, the patient was diagnosed with a second neoplasia – a malignant melanoma.

He continued with 6 cycles of chemotherapy with FCR regimen, but at the end of the treatment his CT-scan was reevaluated and a disease progression was revealed. Therefore we decided to start a new treatment with Ibrutinib 420 mg/day. After one week of treatment there was a 70% reduction of the lymphnodes and the lymphocytes increased from 7300/mm^3 to 24680/mm^3. This adverse reaction may persist up to 8 weeks after starting treatment.

Cytogenetic tests were made and the results showed: an IGHV unmutated status, undetected 17p deletion and TP53 sequencing. The patient continued with Ibrutinib and his lymphocytes in November 2018 were 9920/mm^3, but the lymph nodes began to grow again.

DISCUSSIONS

Chronic lymphocytic leukemia is the most common form of leukemia found in adults (13), diagnosed around the age of 70, being considered a disease of the elderly most patients living even 10 years after diagnosis.(14)

However, we observe from clinical practice a decrease in the age at diagnosis, as is the case of our patient.

Many patients have no early symptoms, therefore they go to the doctor when they experience symptoms such as: night sweats, weight loss, frequent infections, enlarged lymph nodes, even fever.

The most common complications of the disease are: frequent infections (especially in the respiratory tract), increased risk of other cancers particularly melanoma and cancer of the lung, immune deficiency syndrome and the possibility of the disease transforming into a more aggressive form of disease (Richter's syndrome).

Chronic lymphatic leukemia is a hematological pathology, which in recent years along with multiple myeloma, has seen the greatest progress in terms of therapeutic options available to clinical practice.

Until recently, the standard treatment of CLL was represented by the chemotherapy regime (Fludarabine, Cyclophosphamide) in combination with immunotherapy - Anti CD20 Ac (Rituximab).(15)

Although this type of therapy has not been abandoned, more and more patients diagnosed with CLL benefit from the new therapeutic agents, whose action is carried out at the level of small enzymatic or protein molecules.

Among them we mention BTK inhibitors, BCL-2 inhibitors and Pi3K inhibitors. Likewise, anti-CD20 monoclonal antibodies (Rituximab) are still widely used in monotherapy or in combination with new therapeutic agents.

Although it is considered to be an indolent disease, in some cases the rapid evolution towards progression can be quite important both from a clinical and biological point of view.(6)

This evolution may be due to the patient's genetic status, which may present the mutation of the TP53 gene, the deletion of 17p or unmutated IGHV status.(16)

All these genetic anomalies give the patient a worse response to the standard chemotherapy treatment.

The introduction of therapy with Bruton tyrosine kinase inhibitors (Ibrutinib, Acalabrutinib) represented a new perspective regarding the treatment management of patients with CLL, in fact personalized genetic therapy depending on the patient's mutational status.(17)

Another therapeutic target that was approved in patients with relapsed or refractory CLL was Pi3K inhibitors (phosphoinositide 3-kinase) in the combination of Idelalisib with Rituximab (10) or with Ofatumumab.(18)

The newest approved therapeutic agent is Venetoclax, an antiapoptotic BCL2 inhibitor, which acts on leukemic cells causing their apoptosis. It can be used both in the first line of treatment and in relapsed CLL cases.(19,20)

Although remarkable progress has been made in recent years regarding the personalized genetic therapy of patients suffering from CLL, according to the criteria of the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) the treatment will be initiated only when the patient presents with active hematological disease.(6)

Our patient was diagnosed with CLL with leukocytosis and lymphocytosis 11 years ago at the age of 45, and for 4 years he did not require treatment. He was only monitored by regular blood tests.

During chemotherapy the patient experienced complications such as: severe pulmonary infections (some life-threatening) and the development of a second malignancy. He received in total 12 cycles of chemotherapy, immunotherapy and he is currently receiving treatment with an inhibitor of Bruton's tyrosine kinase.

In spite of the multiple cycles of chemo- and immunotherapy administered since re-starting treatment, the patient only responded partially, even suffering moments of relapse.

If the patient develops resistance to its treatment with Ibrutinib, treatment with Bcl-2 inhibitors (Venetoclax) remains a future therapeutic option.

With recent progress in medicine, there is an increased desire to eradicate the minimal residual disease in chronic lymphocytic leukemia.(21)

With all the remarkable therapeutic regimens available in recent years even in our clinical practice, CLL remains an incurable disease, requiring new clinical trials, and not least the reevaluation of the benefit of stem cell allotransplantation as a method of curative treatment of the disease.(22)

CONCLUSIONS

CLL can be diagnosed through routine blood screening but more often when symptoms occur.

Patients with early-stage chronic lymphocytic leukemia does not require treatment sometimes even for a long period of time.

Patients with no mutation in the IGHV have a more unfavorable prognosis than patients with IGHV-mutated CLL.

The disease is not curable and its evolution can be indolent or aggressive.

Within ASH in December 2018 were published the conclusions of a study that showed superior results of treatment with Ibrutinib + Rituximab versus classical scheme FCR in terms of progression-free survival and overall survival.

The leading cause of death in CLL remains the severe respiratory infections due to a weakened immune system.

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