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Case Report

Ibrutinib for Richter syndrome?

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Abstract. Chronic lymphocytic leukemia (CLL), the most frequent form of leukemia in Western countries, is characterized by the clonal proliferation and accumulation of neoplastic B lymphocytes in the blood, bone marrow, lymph nodes, and spleen. The median age of patients at diagnosis is 65 years, with only 10 to 15 percent under 50 years of age. In evolution, Richter transformation significantly alter the patient's prognosis Even the kinetics of tumor progression by pathological accumulation of lymphocytes is slow, cytogenetic abnormalities have been found that appear with disease progression, deletion 17p13 was detected in a small percentage of patients. The aim of this paper was to highlight that this anomaly associated with a Richter transformation may predict treatment failure and decreased survival duration, even if the patient has carried out multiple lines of chemotherapy. Ibrutinib treatment was initiated, but the disease relapse by the therapy resistance, the outcome resulting in patient death.

Key Words: chronic lymphocytic leukemia, 17p deletion, Richter syndrome, ibrutinib.

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Introduction

In the paper of Tsang et al (2015), in which the physicians from the Mayo Clinic in the United States described the efficacy of ibrutinib in treatment of Richter syndrome (RS). RS represents the transformation of a chronic lymphocytic leukemia (CLL) into an aggressive lymphoma, usually a diffuse large B-cell lymphoma (DLBCL), occurring in 1-10% of the CLL patients (Parikh et al 2013).

Case presentation and literature review

The Hand-Choi algorithm based on immunohistochemistry staining (Choi et al 2009) has proven that most of the DLBCL transformations in CLL patients are activated B-cell subtypes, as is the case of both the Mayo Clinic patients and the patient from Cluj Napoca (IOCN patient). Most Richter syndrome DLBCL will appear on a background of clinical and genetic features of the CLL, like an advanced Rai stage, ζ-associated protein-70+, CD38+, CD49d+, as well as somatic mutations of the CLL B lymphocyte such as del17p13.1 or del11q23.1 (Rossi et al 2001). Tsang et al have (2015) reported a series of 4 cases of Richter syndrome successfully treated with ibrutinib. This drug is a covalent inhibitor of Bruton's tyrosine kinase that has recently been approved by the United States Food and Drug Administration (FDA) for the treatment of CLL or small lymphocytic lymphoma, in patients in high risk of a poor outcome, at it had an improved progression-free survival, overall survival and response rate in comparison with ofatumumab (Byrd et al 2014). Patient no.4 in Tsang's report, who had almost identical characteristics as ours is shown in Table 1. The most important characteristics shared in these 2 patients is 17p deletion, a key element in the progression from CLL to DLBCL, but in our case ibrutinib did not have the results expected. In our case the CLL was refractory to most chemotherapy regimens. The first line of CLL therapy was the same in both cases, but the second and third line administered wereFCR (fludarabine, cyclophosphamide, rituximab) and R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), as according to Leporrier et al (2001) and Wierda et al (2005). As the patient did not respond to any of the available therapy options, we decided to administer ibrutinib. But soon after, the disease progressed to a DLBCL, treated with R-CHOP combination chemotherapy as according to the Phase I Clinical Trials Program of The University of Texas MD Anderson Cancer Center in Houston, USA (Tsimberidou et al 2013). A positron emission tomography (PET)/CT was used for a check-up in order to assess the status of the patient. No regions with high standardized uptake values (SUV) were noticed. Thus, the RS might be linked to ibrutinib administration, whose effects had little or no effect of the clinical evolution of the patient. Our results come in contradiction to Tsang et al (2015), that state that this small molecule has great potential for a novel therapeutic approach for treating RS and propose future therapies based on ibrutinib, either as monotherapy or various combination chemotherapy regimens. It is true that the RESONATE clinical trial in which ibrutinib was proven to be superior to ofatumumab in treating chemotherapy-refractory CLL or small lymphocytic lymphoma (SLL), seven out of the 391 patients developed a RS (Byrd et al 2014), as was out case. Of particular interest are patients with deletion of 17p13.1, that have a poor response to chemotherapy (Byrd et al 2013).

Patient's characteristics	Mayo Clinic patient	IOCN patient
At the time of CLL diagnosis		
Age, years	71	60
Sex	female	male
WBC x 10^9/ L	19.6	18.2
Hemoglobin, g/dL	12	10.1
Platelet count x 10^9/ L	218	186
B2 microglobulin, mg/ dL	N/A	N/A
Rai stage	I	II
IGHV mutation status	unmutated	unmutated
ZAP-70 expression > 20%	yes	yes
CD49d expression > 30%	yes	yes
CD38 expression > 30%	no	yes
FISH	del 17p	Del 17p
CLL therapy	1. bendamustine and rituximab. 2. everolimus and alemtuzumab. 3. methylprednisolone and ofatumumab. 4. methylprednisolone and alemtuzumab.	1. bendamustine and rituximab. 2. FCR (fludarabine, cyclophosphamide, rituximab). 3. R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone). 4. methylprednisolone and ofatumumab. 5. Ibrutinib
Time from last CLL therapy to RS diagnosis (months)	<1	<1
At the time of DLBC diagnosis		
Age, years	74	63
WBC x 10^9/ L	2.6	3.1
Hemoglobin, g/dL	9.8	12.3
Platelet count x 10^9/ L	169	185
LDH, U/L (normal: 111-222 U/L)	466	382
RS prognosis score	3 (high intermediate)	3 (high intermediate)
Type of biopsy specimen	Bone marrow aspirate and biopsy	Bone marrow aspirate and biopsy
Subtype (GCB vs ABC)	ABC	ABC
MYC rearrangement by FISH	negative	negative
EBV status	negative	negative
Initial therapy for RS	none	R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)
Ibrutinib dose, mg per day	420	420
Concomitant therapy with ibrutinib	none	none
Duration of ibrutinib therapy, months	10.8	13.1
Best response achieved	PR	PD
Status at most recent follow-up	Progressive CLL	death occurred during R-CHOP chemotherapy

Bruton's tyrosine kinases (BTK) are important in activating key pathways in cell survival in CLL, as Akt, extracellular signal-regulated kinases (ERK) and nuclear factor kappa light chain enhancer of activated B-cells (NF-κB) (Craxton et al 1999), all inhibited by ibrutinib. Still, disease relapse and therapy-resistance occurs as levels of BTK phosphorylation are much higher in CLL in comparison with normal B lymphocytes, consistent with an aberrant B-cell receptor (BCR) pathway activation. Thus, despite ibrutinib administration, BTK will directly promote cell proliferation in CLL, as proven by Cheng et al (2014) in BTK transfection and know-down experiments.

Conclusions

Molecular biology of RS should be further investigated in relation with tyrosine kinase inhibitors, with a special focus on the clonal evolution of the malignant B lymphocyte before various clinical trials be started in order to assure the best therapeutic

option for patients diagnosed with various lymphoproliferative disorders.

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Abbreviations

EBV- Epstein-Barr virus
FISH - fluorescence in situ hybridization
IGHV - immunoglobulin heavy chain genes
LDH - lactate dehydrogenase
N/A - not available
PD - progressive disease
PR - partial response
WBC - white cell blood count
ZAP-70 - zeta chain associated protein kinase 70

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