

Durable Response to Venetoclax Monotherapy in Richter's Syndrome: A Case Report and Review of Literature

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Abstract

In 2017, 20,110 people in the United States were diagnosed with chronic lymphocytic leukemia (CLL). Of these patients, 5-15% will ultimately undergo Richter's syndrome (RS), a transformation to a more aggressive lymphoma, most commonly diffuse large B-cell lymphoma (DLBCL) type. Particularly when the transformation is clonally related, prognosis is poor in these individuals with a median survival of only 5 - 14 months. This is an area of unmet need, and as such, the benefits of novel approaches with targeted therapies should be explored. Our patient is a 70-year-old female who was diagnosed with CLL in 2010. In 2016, she presented to her general practitioner with new B symptoms and leukocytosis. Cytogenetics on peripheral blood was notable for known trisomy 12 (52.8% of cells) and new 17p deletion (93.4% of cells). She received five cycles of ofatumumab with complete resolution of systemic symptoms but mixed response on interim computed tomography (CT) scan with ensuing rise in her white blood cell (WBC) and lactic acid dehydrogenase (LDH). A positron emission tomography (PET) scan had disproportionate uptake in the porta hepatis lymph nodes and subsequent lymph node biopsy confirmed transformation. She was started on R-CHOP chemotherapy but tolerated it very poorly. She was transitioned to venetoclax monotherapy in April 2017 and achieved a partial response by CT and bone marrow biopsy. This has been maintained over the last 12 months allowing the patient to travel and maintain a high quality of life. While the pathogenesis to RS is poorly understood, there have been several studies to identify tumor genetic changes predisposing to transformation. Of the proposed factors, a review of the literature consistently suggests *p53* tumor suppressor gene mutation and/or 17p deletion to be associated with RS. Venetoclax is a selective BCL-2 inhibitor that is now approved for CLL patients with 17p deletion. This case serves as an example encouraging the use and study of novel agents such as venetoclax alone or in combination with traditional regimens or other novel agents to mitigate the poor prognosis of 17p deletion associated

RS. Further research, however, is required to clarify the pathogenesis of RS and identify optimal treatment strategies.

Keywords: Chronic lymphocytic leukemia; Richter transformation; Venetoclax

Introduction

In 2017, 20,110 people in the United States were diagnosed with chronic lymphocytic leukemia (CLL) [1], and of these patients, 5-15% ultimately undergo Richter's syndrome (RS) [2, 3] at a transformation rate of about 0.5% per year [4]. RS is the development of high-grade non-Hodgkin's lymphoma (NHL), with diffuse large B-cell lymphoma (DLBCL) being the predominant type of RS, occurring in up to 90% of all cases [5]. While the pathogenesis to RS is ultimately poorly understood, there have been several studies to identify predisposing risk factors and/or tumor genetic predisposition to transformation. Multiple features are associated with higher risk of RS including polymorphisms in BCL-2 and CD38, advanced Rai stage > stage III at CLL diagnosis, biologic characteristics of the CLL B cell, and the type of chemotherapy used to treat the CLL [4]. Particularly when the transformation is clonally related, prognosis is poor in these individuals with a median survival of only 5 - 14 months with poor depth and duration of response to standard therapeutic options [4, 6]. Currently, national guidelines suggest treatment regimens traditionally designed for *de novo* DLBCL with consideration for allogeneic stem cell transplantation for appropriate transplant candidates with chemotherapy sensitive disease. However, since the median age at diagnosis of CLL is 70 years [1], many patients are in fact not considered appropriate candidates for allogeneic stem cell transplantation. As such, consideration of novel approaches with targeted therapies that can induce durable remission is an attractive option.

Case Report

Our case describes a 70-year-old female with a history of small lymphocytic lymphoma (SLL)/CLL diagnosed from a biopsy of the left supraclavicular node in October 2010. Bone marrow biopsy revealed 75-80% infiltration with CLL/SLL with fluorescence *in situ* hybridization (FISH) analysis 40% positive for trisomy 12. Imaging showed involvement in the neck, axilla, chest,

Manuscript submitted December 21, 2018, accepted February 15, 2019

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doi: <https://doi.org/10.14740/jh473>

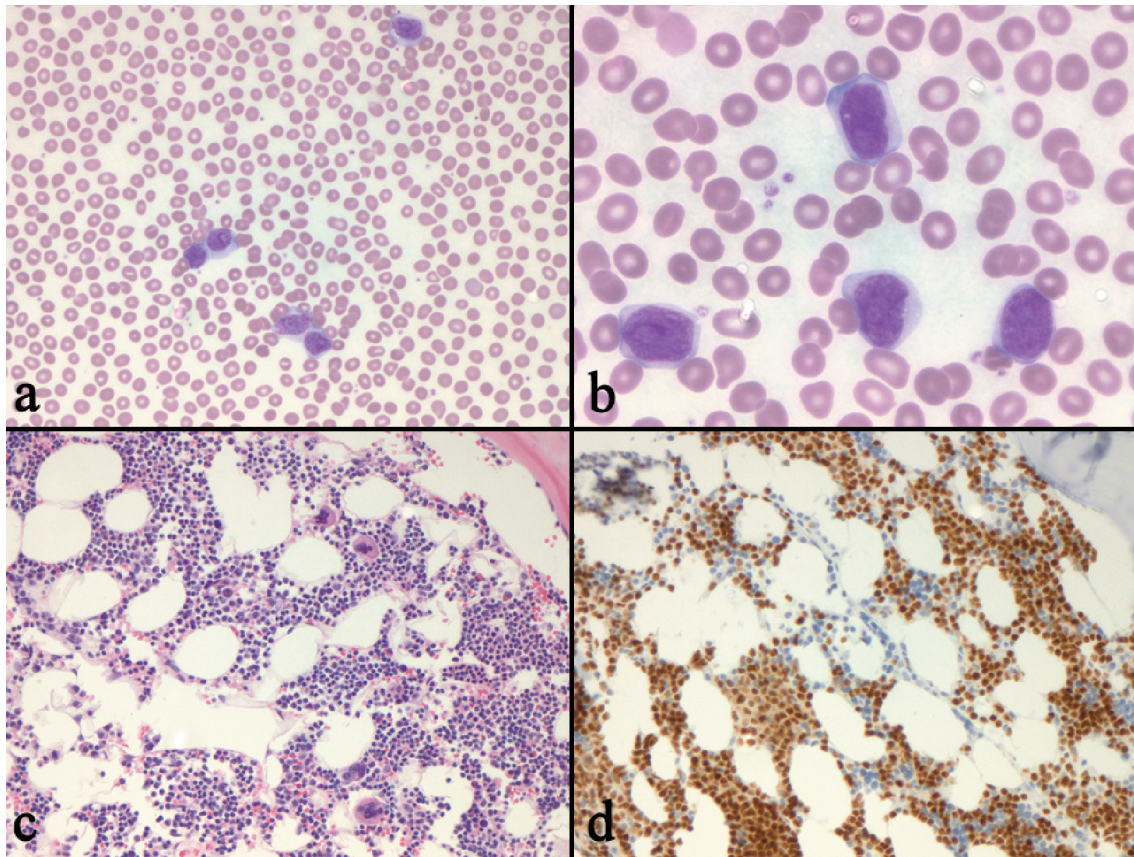


Figure 1. Bone marrow biopsy revealing persistent CLL with transformation to DLBCL. (a) Peripheral blood cells contained “blastoid” appear to be large lymphocytes with moderate amounts of cytoplasm and irregular nuclei ($\times 200$). (b) The cells have large, irregularly shaped nuclei with fine nuclear chromatin, and prominent nucleoli ($\times 400$). (c) The bone marrow biopsy shows an interstitial infiltrate of small to medium sized lymphocytes ($\times 200$). (d) PAX-5 immunostain of the marrow biopsy highlights the interstitial infiltrate ($\times 200$). CLL: chronic lymphocytic leukemia; DLBCL: diffuse large B-cell lymphoma.

abdomen, and groin. She completed six cycles of bendamustine and rituximab by April 2011, and achieved complete remission.

In June 2016, she presented to her primary care physician (PCP) with B symptoms and was found to have significant increase in leukocytosis (peak white blood cell (WBC) count was 162,350 and peak absolute lymphocyte count (ALC) was 139,960). FISH studies on peripheral blood was notable for known trisomy 12 (52.8% of cells) and new 17p deletion (93.4% of cells). Imaging revealed progression of the disease; and patient then received five cycles of ofatumumab with complete resolution of systemic symptoms but mixed response on interim computed tomography (CT) scan. WBC and lactic acid dehydrogenase (LDH) continued to rise, so a bone marrow biopsy was done which showed persistent chronic lymphocytic leukemia involving 30% of the marrow space and decreased myelopoiesis with Richter’s transformation evident in the peripheral blood (Fig. 1). A positron emission tomography (PET) scan had disproportionate fluorodeoxyglucose (FDG) uptake in the porta hepatis lymph nodes and subsequent lymph node biopsy confirmed transformation to DLBCL.

In March 2017, she was started on the first round of R-CHOP chemotherapy, which was complicated by multiple hospital admissions with fevers and confusion. CT scan follow-

ing the first cycle showed mixed response. Due to intolerance of the chemoimmunotherapy, she was started on venetoclax in April 2017. The patient achieved partial response by CT, which has been maintained since then allowing the patient to maintain a high quality of life.

Discussion

With the advent of novel targeted agents, better understanding of the biology and molecular pathways leading to a disease state is essential for selection of optimal therapy as well as accurate prediction of outcome. While the pathogenesis to RS is poorly understood, there have been several studies to identify tumor genetic changes predisposing to transformation. Chigrinova et al [2] studied CLL patient samples of patients with a previous history of CLL, patients in the CLL phase of RS, patients that have undergone RS to DLBCL, patients without transformation, and patients with *de novo* DLBCL. They found that half of the RS cases (30/60) involved TP53 inactivation and/or *CDKN2A* loss along with *MYC* activation. The next most common group occurring in a third of the cases, was those with presence of trisomy 12 [2], which is followed by the

acquisition of *NOTCH1* mutations. *NOTCH1* mutations are mutually exclusive from *MYC* oncogenic activation supporting the finding that *NOTCH1* directly stimulates *MYC* transcription [3]. Literature showed a more consistent correlation with patients with a *p53* tumor mutation and/or 17p deletion and predisposition for RS [2-4, 6, 7].

Venetoclax is BCL-2 specific BH3 mimetic that is now approved for CLL patients with 17p deletion. BH3 mimetics such as navitoclax and venetoclax are agents that help trigger apoptosis by acting as antagonists of BCL-2. High levels of BCL-2 are present in multiple hematologic malignancies including CLL, mantle cell lymphoma, and in up to one-third of DLBCL [8]. Inactivation of *TP53* for example can lead to increase in BCL-2 pro-survival proteins or impaired regulation of BH3-only proteins [9], which affects the anti-proliferative effect of chemotherapies [2-4, 6, 7]. The majority of RS-DLBCL patients have a disruption in *TP53* so it's important for targeted therapies to act independently of this gene, which venetoclax is able to do [10].

A phase I trial of venetoclax in relapsed/refractory CLL showed promising results with an overall response rate of 79% and complete remission in 20% of the patients [8]. Further studies are now being done to investigate venetoclax use in other hematologic malignancies. Recently, a phase I trial with venetoclax was recently done in 106 patients with relapsed or refractory non-Hodgkin's lymphoma. Only three patients had laboratory evidence of tumor lysis syndrome (TLS), but all had a high tumor burden to begin with and in general, the drug was well tolerated. Out of the 106 patients, seven patients had RS/DLBCL and three out of seven of those patients had an overall response but none achieved complete response [11].

Trials are underway studying venetoclax with other chemotherapy and targeted therapeutic agents. One trial published in 2017 that studied ibrutinib and venetoclax in relapsed, refractory CLL patients suggests possible synergy between the two chemo-immunotherapy agents [12]. Clinical trials exploring chemo-immunotherapy-venetoclax are already underway (NCT03054896) as well. Further research, however, is required to clarify the pathogenesis of RS and identify optimal treatment strategies. This case serves as an example encouraging the use and study of novel agents such as venetoclax alone or in combination with traditional regimens or other novel agents to mitigate the poor prognosis of 17p deletion associated RS. Studies using combination of venetoclax with other novel agents are also looking at the possibility of defined duration of therapy in patients who achieve deep remission. This may also apply to patients with RS.

Acknowledgments

We thank the patient for allowing us to share the details of her case.

Financial Disclosure

No disclosure. Publication fee was paid by the Division of Hematology, Oncology and Cell Therapy at Rush University

Medical Center.

Conflict of Interest

Parneswaran Venugopal is a consultant for Bayer and AbbVie pharmaceuticals. Brett Mahon is the director of Pathology for Tempus Laboratories and has equity interest. He is a consultant for AbbVie. Revathi Kollipara and Kelly Szymanski have no disclosures.

Informed Consent

The patient has provided verbal consent for preparation of this case report.

Author Contributions

Authors Kollipara, Szymanski and Venugopal contributed to the manuscript of the project. Author Mahon provided the images and description of Figure 1.

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