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Successful treatment of "accelerated" chronic lymphocytic leukemia with single agent ibrutinib: A report of two cases.

John Xie [a], Albert Jang [a], Andrew Vegel [a], Yasmin Hajja [b], Yara Mouawad [b], Ali Baghian [b], Bachir Berbari [b], Janet L. Schmid [c], Francisco Socola [b], Hana Safah [b], Nakhle S. Saba [b,*]

[a] Deming Department of Medicine, Tulane University School of Medicine, New Orleans, Louisiana, USA
[b] Section of Hematology and Medical Oncology, Deming Department of Medicine, Tulane University School of Medicine, New Orleans, Louisiana, USA
[c] Department of Pathology, Tulane University, New Orleans, LA

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ABSTRACT

"Accelerated" chronic lymphocytic leukemia/small lymphocytic lymphoma (A-CLL) is a rare histological variant of CLL/SLL, which tends to exhibit an aggressive clinical behavior compared to CLL. Due to the rarity of A-CLL (<1% of all cases), the optimal management remains ill-defined. We report two cases of A-CLL from our institution, in which both relapsed following initial chemoimmunotherapy regimens. Both patients were treated with single agent ibrutinib, a Bruton's tyrosine kinase inhibitor (BTKi), and achieved rapid, deep and durable responses. With the absence of clear guidance on A-CLL treatment, BTKi agents should be considered in the frontline treatment of A-CLL.

Introduction

Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) is the most common adult leukemia in the Western world, characterized by accumulation of clonal CD5+ *B*-lymphocytes in blood, bone marrow and lymphatic systems [1]. Cell proliferation in CLL/SLL occurs mostly in hallmark proliferation centers (PCs) within the lymph node [2-4]. These PCs can be seen in lymph nodes and comprise a mixture of small lymphocytes, prolymphocytes and paraimmunoblasts. Prolymphocytes are small to intermediate in size with condensed chromatin and small nucleoli. Paraimmunoblasts are larger cells with dispersed chromatin, a prominent central eosinophilic nucleolus and expanded cytoplasm. The PC may show increased expression of Ki-67, as well as c-Myc, E2F, Notch-1 and cyclin-D1, highlighting its role in tumor proliferation [5]. The two major histological categories of CLL involve either typical CLL or transformation into diffuse large B-cell lymphoma (DLBCL), also known as Richter's transformation (RT). However, there exists a subtype of CLL characterized by expanded and confluent PCs with elevated proliferation indices termed "accelerated" chronic lymphocytic leukemia/small lymphocytic lymphoma (referred to as A-CLL hereafter), which was initially described by Pugh and colleagues in 1988 [5,6].

A-CLL is a histological diagnosis, defined by Gine et al. on the basis of PC size and proliferative activity, requiring at least one of three morphologic criteria: 1) expanded proliferation centers (broader than a 20x microscopic field), 2) increased mitotic activity (>2.4 mitotic figures per PC) or 3) high Ki-67 index (>40% per PC) [7]. A-CLL is a rare disease entity, as it represents less than 1% of all reported cases of CLL. However, it is likely to be underdiagnosed, as tissue biopsy is not usually indicated in the work-up of CLL. A-CLL should be suspected in cases of rapidly enlarging adenopathy. It should also be considered in any relapsed or refractory cases. Lymph node biopsy would be warranted in these scenarios to achieve accurate diagnosis (and to rule out RT). This is especially paramount when one considers that A-CLL and RT have been shown to differ in terms of treatment and prognosis. Unfortunately, no specific radiographic or laboratory findings have been shown to be specific for A-CLL.

A-CLL appears to have features of both typical CLL and RT to suggest that A-CLL is an intermediate subtype. Typical CLL/SLL have either small or absent PCs, along with low mitotic activity and Ki-67 index (<40%) in their PCs [7]. Richter's transformation (RT) is marked by a proliferation of large cells that may include paraimmunoblasts, though most frequently resemble centroblasts and immunoblasts, and shows more diffuse Ki-67 expressing cells that are not confined to the PCs [8,9].

* Corresponding author: Associate Professor of Clinical Medicine, Section of Hematology & Medical Oncology, Tulane University School of Medicine, 1430 Tulane Ave, code#8578, New Orleans, LA 70112, Office: 504-988-6234.
E-mail address: nsaba@tulane.edu (N.S. Saba).

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A-CLL retains the immunophenotypic features expected of typical CLL as well, including CD5+, CD23+, and FMC7- [10]. Proliferation centers of both typical CLL and A-CLL show stronger expression of CD20, CD23, CD71, and IRF/MUM1 [11]. RT may show variable alterations of the CLL/SLL profile, including those associated with poor prognosis such as diminished CD52 or increased CD38 and ZAP-70.

A-CLL has been shown to exhibit an aggressive clinical behavior associated with a worse prognosis than typical CLL. The Gine et al. study reported a median overall survival of 34 months from diagnosis, compared to 76 months in typical CLL, using a front-line treatment that consisted of various chemoimmunotherapy (CIT) regimens [7]. Notably, no Bruton's tyrosine kinase inhibitor (BTKi) agents were used. In this study, LDH levels in A-CLL were more elevated than typical CLL, but not as high as RT (mean values ± SD in IU/L: 455±194 in CLL, versus 543±198 in A-CLL, versus 820±538 in RT; $P = 0.008$). Beta-2 microglobulin was also more frequently elevated (>2.3 mg/dl) in A-CLL than CLL, but comparable to RT (70% of cases elevated). In terms of immunoglobulin heavy chain (IGVH) mutational status, 7 out of the 7 cases checked in A-CLL were unmutated (100%). Fluorescence in situ hybridization (FISH) analysis showed no differences in the distribution of unfavorable cytogenetic features (17p and 11q deletions) among the three groups. However, others have reported that CLL with expanded PCs on morphology (as seen in A-CLL) were more likely to carry 17p and 11q deletions, *TP53* mutation, and complex karyotype [11-13].

Ibrutinib has transformed the landscape of CLL therapy in both frontline and relapsed setting after showing survival advantage to chemoimmunotherapy (CIT) [14,15]. In contrast, the role of ibrutinib in RT remains unclear, with some anecdotal reports suggesting potential short-term efficacy [16-18]. The use of ibrutinib in A-CLL is even murkier, with no published data available. This lack of knowledge was recently highlighted by Allan et al. acknowledging the need for data to determine whether A-CLL behaves more like typical CLL or RT in the era of targeted therapy, particularly BTKi [18].

Here, we report two relapsed/refractory cases of A-CLL/SLL with a short-lived remission following CIT, treated with ibrutinib resulting in rapid and deep clinical responses. To the best of our knowledge, the treatment of A-CLL with ibrutinib has not been reported.

Case presentations

CASE 1: A 65-year-old male initially presented with an enlarging right-sided cervical mass and fatigue. Physical exam was remarkable for a firm, fixed, non-tender right lower neck mass, in addition to several palpable lateral neck lymph nodes. Initial labs were unremarkable, including lymphocyte count and lactate dehydrogenase. Positron emission tomography/computed tomography (PET/CT) identified a 4.7 × 2.9 cm right-sided cervical mass with a maximal standardized uptake value (SUV) of 8.1, in addition to other mildly enlarged and PET-avid cervical, axillary, and mediastinal lymph nodes. Right cervical mass excision demonstrated effaced nodal architecture by a diffuse atypical lymphoid population of intermediate-sized cells expressing CD5, CD23, CD20, CD79a, and Bcl-2 while negative for BCL6, cyclin-D1, CD3, CD10, CD15, CD30 and EBER-ISH. The lymphoid population showed inconclusive light chain expression. Increased prolymphocytes and paraimmunoblasts were observed within expanded PCs along with a Ki-67 of 30% per PC. FISH study for the presence of rearrangement involving BCL6, MYC, or IGH/BCL2 was negative, though 3 copies of MYC and loss of BCL6 were seen in a subset of cells. Flow cytometry of the peripheral blood showed a small clonal B-cell population (< 2% of lymphocytes) consistent with the above immunophenotype. Bone marrow biopsy and aspirate revealed 5–10% involvement by the same B-cell clone. FISH analysis for NHL panel was negative for the presence of BCL6, ATM, IGH, and p53. Thus, a diagnosis of small lymphocytic lymphoma with increased prolymphocytes and scattered immunoblasts, sharing features with A-CLL was made based upon the expanded PCs within the microscopic fields. Six cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) were successfully administered resulting in partial remission (PR). Four months following completion of treatment, the patient reported enlarging right cervical adenopathy. PET visualized enlargement of cervical mass now measuring 10.5 × 7.5 × 4.7 cm with maximal SUV of 4.1 (Deauville score of 4) extending into the right paravertebral space, along with increased size and activity in lymph nodes of the chest and pelvis. Ibrutinib was instituted at an oral dose of 420 mg daily, resulting in decreased size and activity of lymph nodes seen on the 3-month follow-up PET/CT which included the right neck lymph node conglomerate measuring 4.4 × 2.5 × 3.3 cm with maximal SUV of 2.1 (Deauville score of 2). This decrease is consistent with PR in the absence of bone marrow (BM) reassessment. LN size continued to improve clinically for the next 12 months. Adverse events included occasional grade 1 visual disturbances. Ibrutinib-induced lymphocytosis was noted initially, as the absolute lymphocyte count (ALC) increased from 1.5×10^9 cells/L at baseline to 5.1×10^9 cells/L after one month of treatment before trending down over the course of 6 months. His-A-CLL was still in clinical remission at his last clinic visit 20 months from the start of ibrutinib, after which he was lost to follow-up.

CASE 2: A 63-year-old male who initially presented with lymphocytosis was diagnosed with CLL based upon initial flow cytometry of peripheral blood showing a clonal population of B-lymphocytes expressing CD5 (dim), CD19, CD20, CD22, CD23, CD38, and CD79b with lambda restriction. FISH analysis showed trisomy 12. His-stage was Rai I at presentation without any indication to start therapy; thus, surveillance monitoring was initiated. Three years later, he presented with increased shortness of breath and fatigue over a two-week period. His-physical exam was notable for reduced breath sounds in the left lower lobe, consistent with a left pleural effusion that was confirmed with a chest X-ray. A thoracentesis drained 1300 mL of exudative pleural fluid with evidence of CLL. During the follow up period for his pleural effusion, flow cytometry of the blood was repeated at another hospital and again illustrated CLL with B-lymphocytes expressing CD5, CD19, CD20, CD22, CD23, CD43, CD52, FMC7, and 11% showing positivity for CD38. No surface light chain was detected. Several weeks following that flow cytometry, he returned to clinic with unexplained fatigue and weight loss for which treatment was indicated. His-CLL stage was still Rai I at that time. Rituximab was administered weekly for eight weeks resulting in improvement of symptoms. A follow-up CT scan showed persistent but stable cervical and supraclavicular lymphadenopathy. He continued to be observed with regular clinic visits over the following months. Two years following rituximab, he developed rapidly enlarging adenopathy and shortness of breath. CT scan revealed multiple enlarged lymph nodes in the neck, chest, abdomen, and pelvis with the largest nodes noted as a subcarinal node measuring 2.9 × 3.3 cm, a portacaval node measuring 5.9 × 8.3 cm, a mesenteric node measuring 2.7 × 4.1 cm, and a left obturator node measuring 2.8 × 4.4 cm. Splenomegaly was also noted with a spleen measurement of 14.1 cm on CT scan. No LN or bone marrow biopsies were done at that time. Due to his splenomegaly, his CLL was upstaged to Rai II. He then received two cycles of bendamustine and rituximab, which was discontinued due to persistent neutropenia. A restaging CT showed PR. He then continued to be monitored with observation as an outpatient. Three years later, he developed worsening bilateral supraclavicular adenopathy, splenic enlargement to 16.7 cm and lymphadenopathy. The largest lymph nodes included a 2.7 × 2.1 cm right level IV cervical node, a 4.7 × 3.0 cm right axillary node, a 3.5 × 2.0 cm left periaortic node and a 2.3 × 1.8 cm mesenteric node. A lymph node biopsy demonstrated an effaced architecture with atypical lymphoid infiltrate composed of small lymphocytes and a preponderance of paraimmunoblasts and prolymphocytes within large and expanded PCs with a Ki-67 of 40% per PC. On immunostains, atypical lymphocytes expressed CD5 (weak), CD20, CD79a, PAX-5, CD29, CD43, and BCL2. There was partial expression of Bcl-6 (weak), and cyclin-D1 was occasionally observed in PCs. Repeat flow cytometry again showed malignant cells expressing CD5, CD19, CD20, CD22, CD23, CD38, CD45 and lambda light chain restriction, and negative for CD10

and FMC7. He was then diagnosed with A-CLL based on histologic and immunophenotypic findings. Ibrutinib 420 mg orally was started once daily. Ibrutinib-induced lymphocytosis was difficult to determine in this case as his ALC was 26.7×10^9 cells/L before treatment, and his follow-up ALC 6 weeks later was 6.3×10^9 cells/L. Follow up imaging illustrated decrease in same nodes as above with sizes of the right IV cervical node measuring 2.5 × 1.9 cm, the right axillary node measuring 3.0 × 2.1 cm, the left periaortic node measuring 2.0 × 1.6 cm, and the mesenteric node measuring 1.5 × 0.9 cm. These decreases led to a sum of the products of dimension (SPD) of 50.4%. He continued to have a decreased ALC of 4.1×10^9 cells/L as compared to ALC before ibrutinib treatment, hence a PR with lymphocytosis. He experienced no major side effects while on ibrutinib. He passed away due to other comorbidities roughly 3 years after starting ibrutinib with continued stability of his CLL.

Discussion

In this article, we present cases of two elderly men with relapsed/refractory A-CLL which was poorly responsive to CIT. Following continued progression of disease and symptoms, ibrutinib, a BTKi, was started. Both patients illustrated a good response to therapy with PR. Although the second patient had died near the median reported for A-CLL in the Gine et al. study[7], it is noted that his cause of death was due to his other comorbidities as his CLL was stable at the time of death. These cases suggest that ibrutinib is an effective option in A-CLL and should be trialed as a frontline therapy.

As an intermediate between CLL and RS in terms of immunophenotype, A-CLL also exhibits a similar response pattern. The resistance of A-CLL to CIT is comparable to the effect of CIT in RS. High-intensity chemotherapy has generally failed to provide satisfactory complete remission rates and median survival time of under 12 months for patients with RS [19]. Rossi et al. suggests that outcomes are improved in RS with CIT when de novo molecular features are acquired in the transformed clone, with a median overall survival of 62.5 months (clonally unrelated) versus 14.2 (clonally related) [20]. Patients with A-CLL, however, harbor preserved clonal relationships in PCs and peripheral blood and therefore likely to be relatively chemotherapy refractory [7]. Furthermore, deletion 17p, which is associated with A-CLL, has also been known to have a low response rate to conventional chemotherapy [9]. Notably, ibrutinib does not appear to be effective for RS, in contrast to A-CLL/SLL. In a single-center study, median survival in patients with RS receiving ibrutinib was under 18 months [21].

The potential for ibrutinib to be used as a frontline therapy in A-CLL should not be surprising, given its continually expanding field of use in the treatment of CLL/SLL within the past decade. Ibrutinib is an oral, irreversible inhibitor of BTK, indicated to treat treatment naïve and relapsed/refractory CLL including those with 17p deletion. Multiple trials confirmed the superiority of ibrutinib-based therapy to CIT, including BR and FCR [22-24]. Future prospective studies are needed to validate the efficacy of ibrutinib in A-CLL. However, in the era of BTKis, A-CLL will likely continue to be underdiagnosed, as A-CLL is a histologic diagnosis and lymph node biopsy is not typically done in CLL, especially when the disease is well-controlled.

Beyond the use of ibrutinib as a potential therapy for A-CLL, other therapeutic options mirror those for CLL. The B-cell lymphoma 2 (Bcl-2) inhibitor venetoclax is now considered a backbone in CLL therapy and could potentially be a reasonable option for A-CLL, albeit absence of data. On the other hand, drawing from current experience with RT, checkpoints inhibitors could also be a viable option in A-CLL.

Conclusion

Based on available survival data, A-CLL/SLL represents an aggressive histologic variant of CLL/SLL that manifests with rapidly enlarging adenopathy. These patients should receive a lymph node biopsy for further investigation. The lymph node may show expanded PCs without DLBCL transformation, which would be indicative of A-CLL. A-CLL responds poorly with chemoimmunotherapy. However, patients may achieve long-term clinical stability and improved performance status with BTKi monotherapy, and akin to CLL, this should be considered first-line treatment in A-CLL.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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