Invasive aspergillosis related to ibrutinib therapy for chronic lymphocytic leukemia

Benjamin Arthurs, MD a, b, *, Kathy Wunderle, MD b, Maylee Hsu, MD c, Suil Kim, MD, PhD a, b

a Division of Pulmonary & Critical Care Medicine, Veterans Affairs Portland Health Care System, Oregon Health & Science University, 3710 SW US Veterans Hospital Rd, Portland, OR 97239, United States
b Department of Medicine, Veterans Affairs Portland Health Care System, Oregon Health & Science University, 3710 SW US Veterans Hospital Rd, Portland, OR 97239, United States
c Department of Pathology, Veterans Affairs Portland Health Care System, Oregon Health & Science University, 3710 SW US Veterans Hospital Rd, Portland, OR 97239, United States

* Corresponding author. 3181 SW Sam Jackson Park Rd, Mail Code UHN67, Portland, OR 97239, United States.
E-mail address: arthurs@ohsu.edu (B. Arthurs).

ARTICLE INFO
Article history:
Received 2 January 2017
Received in revised form 15 March 2017
Accepted 19 March 2017

Keywords:
Aspergillus
Invasive aspergillosis
Ibrutinib
Bruton's tyrosine kinase
Chronic lymphocytic leukemia

ABSTRACT
We report a case of invasive pulmonary aspergillosis in a patient taking ibrutinib, a Bruton's tyrosine kinase inhibitor used to treat refractory chronic lymphocytic leukemia. We hypothesize that ibrutinib promoted this infection by suppressing innate immune responses against Aspergillus. Clinicians should be aware of potential Aspergillus infections in patients treated with this drug.

© 2017 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction
Ibrutinib is a novel anti-cancer drug recently approved for the treatment of refractory chronic lymphocytic leukemia (CLL) [1] and other B-cell cancers [2,3]. Ibrutinib selectively inhibits Bruton's tyrosine kinase (BTK), a key enzyme that promotes the survival and proliferation of normal B cells and CLL cells downstream of B-cell receptor activation [4]. Treatment with ibrutinib has not been previously reported to promote invasive Aspergillus infections in non-neutropenic patients.

2. Case report
A 62-year-old man was admitted to our hospital with three weeks of non-productive cough, dyspnea, fatigue, and anorexia. He had started ibrutinib six weeks prior to admission for relapsed CLL. He was retired and lived in western Oregon. He reported no exposure to tobacco, dust, birds, or other animals. His tuberculin skin test was negative prior to initiation of ibrutinib. On examination, the patient was afebrile (36.7 °C); pulse was 66/min; BP was 82/52 mm Hg; respiratory rate 16/min; and oxygen saturation 96% on room air. Cardiopulmonary examination was normal. Laboratory investigations revealed anemia (Hgb 5.0 g/dL), leukocytosis (21.2 x 10^3/μL), decreased platelets (140 x 10^3/μL), and an normaleutrophil count (1.91 x 10^3/μL). Serum chemistries were notable for a sodium of 129 mmol/L, chloride of 97 mmol/L, bicarbonate of 17 mmol/L, urea nitrogen of 26 mg/dL, and creatinine of 1.2 mg/dL.

Computed tomography scan of the lung showed multifocal upper lobe centrilobular nodules, patchy consolidations with air bronchograms, and small areas of cavitation (Fig. 1A), findings that were not present prior to ibrutinib initiation. Bronchoscopy revealed endobronchial masses in the lingula and right upper lobe (Fig. 1B). Biopsy of the masses showed necrotic mucosa containing septate fungal hyphae with acute angle branching.
consistent with *Aspergillus* (Fig. 1C). Bronchoalveolar lavage (BAL) was performed in the right middle lobe. BAL fluid grew *Aspergillus fumigatus* and showed no evidence of acid-fast bacilli or nocardia. BAL galactomannan was positive.

The patient was treated with voriconazole and ibrutinib was briefly discontinued. The patient developed hypercalcemia suspicious for relapsed CLL and ibrutinib was resumed at a lower dose. Serial chest radiographs showed resolution of the multifocal consolidative opacities and nodules over the subsequent two months. The patient’s CLL continued to progress despite additional chemotherapy and he died five months after starting ibrutinib.

### Table 1

| Organism | Description | Clinical Course |
|----------|-------------|-----------------|
| **Aspergillus** |
| Phase 3 trial [13] | Two patients with bronchopulmonary aspergillosis | Ibrutinib discontinued. |
| Follow-up of phase 2 trial [14] | One patient with “extensive aspergillosis” after two months of treatment with ibrutinib AND rituximab. | Patient one: ibrutinib discontinued, infection resolved. Patient two died. Patient three: critically ill, outcome unspecified. Patient died. |
| Case series [15] | Three patients with invasive aspergillosis and CNS involvement within two months of starting ibrutinib AND corticosteroids. | |
| Case report [16] | One neutropenic patient with multifocal pneumonia due to invasive aspergillosis and mucormycosis after seven months of ibrutinib therapy. | |
| **Cryptococcus neoformans** |
| Phase 2 trial [17] | One patient with “cryptococcal infection.” | Ibrutinib discontinued, infection resolved. Therapy resumed at lower dose with fluconazole prophylaxis. |
| Phase 1b-2 trial [1] | One patient with cryptococcal pneumonia. | Patient one: ibrutinib discontinued, infection resolved. |
| Case report [18] | One patient with disseminated infection without CNS involvement. | |
| Case series [19] | Two patients with disseminated infection with CNS involvement within one month of starting ibrutinib. | Patient one: ibrutinib discontinued, infection resolved. Patient two died. |
| **Pneumocystis jiroveci** |
| Phase 2 trial [17] | One patient with “pneumocystis infection.” | Ibrutinib continued, pneumonias resolved with oral antibiotics. Ibrutinib continued without prophylaxis in three patients without recurrent infection. |
| Case series [20] | Five patients with PJP pneumonia after 2–24 months of therapy despite CD4 > 500. Estimated incidence 2 cases/100 patient-years. | |
| **Histoplasma** |
| Phase 2 trial [17] | One patient with “histoplasmosis infection.” | Ibrutinib continued, infection resolved. |
| **Fusarium solani** |
| Case report [21] | One patient with disseminated infection, fever, and multiple skin abscesses after six weeks of treatment. | Ibrutinib continued, infection resolved. |
| **Other** |
| Follow-up of phase 1b-2 trial [14] | One patient with extensive fungal pneumonia after 20 months of treatment. | Ibrutinib discontinued, patient died. |

### 3. Discussion

Members of the genus *Aspergillus* are ubiquitous fungi that grow in soil. *Aspergillus* spores are regularly inhaled, but the fungi have almost no ability to invade hosts with adequate neutrophil and macrophage phagocyte function [5]. While CLL is characterized by defects in humoral immunity and T-cell function, phagocyte function is relatively preserved in CLL and invasive aspergillosis is uncommon [6]. Eventually, most CLL patients experience neutropenia, the most important risk factor for invasive aspergillosis, because of bone marrow involvement or myelosuppressive chemotherapy. However, the patient in this case was not neutropenic on presentation and had no clinical or radiographic evidence of pneumonia prior to receiving ibrutinib, suggesting that ibrutinib promoted invasive aspergillosis in this case.
In patients receiving ibrutinib for refractory CLL, invasive Aspergillus infection has been reported only in those who were neutropenic or receiving concomitant rituximab or corticosteroids (see Table 1). The patient we describe had impaired immunity due to CLL itself and related to his prior treatment for CLL with fludarabine and rituximab, and he was neutropenic in the months prior to starting ibrutinib. However, he was not neutropenic when ibrutinib was initiated or when he presented to hospital and he had not received additional immunosuppressive therapies. We hypothesize that ibrutinib promoted invasive pulmonary aspergillosis in this case via suppression of BTK in macrophages and neutrophils. As ibrutinib becomes more widely used in B-cell cancers, clinicians in this case via suppression of BTK in macrophages and neutrophils. In turn, BTK has been reported to be an essential part of the inflammasome [11], a protein complex that converts pro-IL-1beta into mature IL-1beta in response to Aspergillus infection [12]. Thus, there is growing evidence that BTK plays an important role in innate immune responses against Aspergillus.

Conflict of interest

None.

References

[1] J.C. Byrd, R.R. Furman, S.E. Coutre, I.W. Flinn, J.A. Burger, K.A. Blum, B. Grant, J.P. Sharman, M. Coleman, W.G. Wierda, J.A. Jones, W. Zhao, N.A. Heereema, A.J. Johnson, J. Suhbunthering, B.Y. Chang, F. Clow, E. Hedrick, J.J. Buggy, D.F. James, S. O'Brien, Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia, N. Engl. J. Med. 369 (2013) 32–42.

[2] S.P. Treon, C.K. Tripas, K. Mead, D. Warren, G. Varma, R. Green, K.V. Argypoulou, G. Yang, Y. Cao, L. Xu, C.J. Patterson, S. Rodig, J.L. Zehnder, J.C. Astor, N.L. Harris, S. Kanan, I. Ghozrial, J.J. Castillo, J.P. Laubach, Z.R. Hunter, Z. Salman, J. Li, M. Cheng, F. Clow, T. Graef, M.L. Palmob, R.H. Advani, Ibrutinib in previously treated Waldenström's macroglobulinemia, N. Engl. J. Med. 372 (2015) 1430–1440.

[3] M.L. Wang, S. Rule, P. Martin, A. Goy, R. Auer, B.S. Kahl, W. Jurcza, R.H. Advani, E. Romaugera, M.E. Williams, J.C. Barrientos, E. Chmielowska, J. Radford, S. Stilgenbauer, M. Dreyling, W.W. Jestezdyczak, P. Johnson, S.E. Spurgen, L. Li, L. Zhang, K. Newberry, Z. Ou, N. Cheng, B. Fang, J. McGrey, F. Chen, J.L. Buggy, B.Y. Chang, D.M. Bouque, L.A. Kunkel, K.A. Blum, Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma, N. Engl. J. Med. 369 (2013) 507–516.

[4] R.M. Young, L.M. Staftit, Ibrutinib treatment of CLL: the cancer fights back, Cancer Cell 26 (2014) 11–13.

[5] A. Schaffner, H. Douglas, A. Braude, Selective protection against conidia by mononuclear and against mycelia by polymorphic phagocytic fungi in resistance to Aspergillus. Observations on these two lines of defense in vivo and in vitro with human and mouse phagocytes, J. Clin. Invest. 69 (1982) 617–631.

[6] S. Tsiodras, G. Samonis, M.J. Keating, D.P. Kontoyiannis, Infection and immunity in chronic lymphocytic leukemia, Mayo Clin. Proc. 75 (2000) 1039–1054.

[7] K. Fieler, A. Sandriš, G. Terszowski, E. Kokai, T.B. Feyerabend, L. Bullinger, H.R. Rodewald, C. Brunner, Neutrophil development and function critically depend on Bruton tyrosine kinase in a mouse model of x-linked agammaglobulinemia, Blood, 117 (2011) 1329–1339.

[8] A. Mangha, A. Khare, V. Vineet, N.N. Panday, A. Mukhopadhyay, B. Ravindran, V. Bal, A. George, S. Rath, Pleiotropic consequences of Bruton tyrosine kinase deficiency in myeloid lineages lead to poor inflammatory responses, Blood 104 (2004) 1191–1197.

[9] K. Strijbis, F.C. Tafesse, G.D. Fairin, M.D. Witte, S.K. Dougan, N. Watson, E. Spooner, A. Esteban, V.K. Vyas, G.R. Fink, S. Grinstein, H.L. Ploegh, Bruton's Tyrosine Kinase (BTK) and Vav1 contribute to Dectin-1-dependent phagocytosis of Candida albicans in macrophages, PLoS Pathog. 9 (2013) e1003446.

[10] S. Herbst, A. Shah, M. Mazon Moya, V. Marzola, B. Jensen, A. Reed, M.A. Birell, S. Sajo, M. Mostowy, S. Shaunak, D. Armstrong-James, Phagocytosis-dependent activation of a TLR9-BTK-calcineurin-NFAT pathway co-ordinates innate immunity to Aspergillus fumigatus, EMBO Mol. Med. 7 (2015) 240–258.

[11] M. Itó, T. Shichita, M.A. Okada, R. Komine, Y. Noguchi, A. Yoshimura, R. Morita, Bruton's tyrosine kinase is essential for NLRP3 inflammasome activation and contributes to ischaemic brain injury, Nat. Commun. 6 (2015) 7360.

[12] R. Karki, S.M. Man, R.K. Malireddi, P. Gurung, P. Vogel, M. Lamkanfi, T.D. Kanneganti, Concerted activation of the AIM2 and NLRP3 inflammasomes orchestrates host protection against Aspergillus infection, Cell Host Microbe 17 (2015) 357–368.

[13] J.C. Byrd, J.R. Brown, S. O'Brien, J.C. Barrientos, N.E. Kay, N.M. Reddy, S. Coutre, C.S. Tam, S.P. Mulligan, U. Jaeger, S. Devereux, P.M. Barr, R.R. Furman, T.J. Kipps, F. Cymbalista, C. Pocock, P. Thornton, F. Caligaris-Cappio, T. Robak, J. Delgado, S.J. Schuster, M. Montillo, A. Schuh, S. de Vos, D. Gill, A. Bloor, C. Dearden, C. Moreno, J.J. Adams, C. Fardis, J. McGreyer, F. Clow, D.F. James, P. Hillmen, Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia, N. Engl. J. Med. 371 (2014) 213–223.

[14] P. Jain, M. Keating, W. Wierda, Z. Estrov, A. Ferrajoli, N. Jain, B. George, D. James, H. Kantarjian, J. Burger, S. O'Brien, Outcomes of patients with chronic lymphocytic leukemia after discontinuing ibrutinib, Blood 125 (2015) 2062–2067.

[15] R. Ruchlemer, R. Ben Ami, T. Lachish, Ibrutinib for chronic lymphocytic leukemia, N. Engl. J. Med. 374 (2015) 1593–1594.

[16] N. Kreinicz, J. Bejar, A. Polliausk, T. Tadmor, Severe pneumonia associated with ibrutinib monotherapy for CLL and lymphoma, Hematol. Oncol. (2017), http://dx.doi.org/10.1159/2016.2062.

[17] M.L. Wang, K.A. Blum, P. Martin, A. Goy, R. Auer, B.S. Kahl, W. Jurcza, R.H. Advani, E. Romaugera, M.E. Williams, J.C. Barrientos, E. Chmielowska, J. Radford, S. Stilgenbauer, M. Dreyling, W.W. Jestezdyczak, P. Johnson, S.E. Spurgen, L. Zhang, L. Baher, M. Cheng, D. Lee, D.M. Bouque, S. Rule, Long-term follow-up of MCL patients treated with single-agent ibrutinib: updated safety and efficacy results, Blood 126 (2015) 739–745.

[18] K. Okamoto, L.A. Proia, P.L. Demarais, Disseminated cryptococcosis in a patient with chronic lymphocytic leukemia on ibrutinib, Case Rep. Infect. Dis. (2016), http://dx.doi.org/10.1155/2016/4642831.

[19] J.A. Messina, E.K. Maziarz, A. Spec, D.P. Kontoyiannis, J.R. Perfect, Disseminated cryptococcosis with brain involvement in patients with chronic lymphocytic leukemia malignancies on ibrutinib, CIDIS (2016), http://dx.doi.org/10.1001/2015.7462.

[20] I.E. Ahn, T. Jerussi, M. Farooqui, X. Tian, A. Wiestner, J. Gea-Banacloche, Atypical Pneumocystis jiroveci pneumonia in previously untreated patients with CLL on single-agent ibrutinib, Blood 126 (2015) 1940–1943.

[21] T.S. Chan, R. Aur-Yeung, C.S. Chiu, S.C. Wong, Y.L. Kwong, Disseminated fusarium infection after ibrutinib therapy in chronic lymphocytic leukemia, Ann. Hematol. (2017), http://dx.doi.org/10.1007/s00277-017-2944-7.