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Ibrutinib, a Bruton's tyrosine kinase inhibitor, a new risk factor for cryptococcosis

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Abstract

Purpose. Invasive fungal diseases and especially *Cryptococcus neoformans* infections are increasingly reported in patients with hematological malignancies receiving ibrutinib, a Bruton's tyrosine kinase inhibitor.

Patients and method. We reported three additional cases and reviewed 16 previous published cases together with cases from the international pharmacovigilance database.

Results. Patients were mainly treated for chronic lymphocytic leukemia. Cryptococcosis mostly occurred during the first six months (66%) and especially the first two months (44%) of treatment. Clinical presentation is often pulmonary (68%) and the outcome is usually favorable despite ibrutinib continuation.

Conclusion. Clinicians must be aware of this infection in patients with hematological malignancies on ibrutinib.

Infections are common complications in patients with chronic lymphocytic leukemia (CLL) and can be related to both the disease (hypogammaglobulinemia, defect in cellular immunity, complement activity, and neutrophil function) and the treatment. Cryptococcosis is a relatively rare fungal disease accounting for 5.2% of all invasive fungal infections (IFIs) according to a 10-year population-based analysis published a few years ago [1]. Although cryptococcosis has been historically associated with HIV infection, its incidence has progressively decreased in high-income countries due to effective antiretroviral therapy and immune restoration, while an increased incidence is observed in the seronegative population [1]. The largest cohort studies of IFIs during CLL reported an incidence around 2%, from 1.4% to 4% [2,3]. A recent review reported infections during ibrutinib treatment for 56% of patients, mostly pneumonia with many cases related to opportunistic pathogens. Infectious events were grade 3-4 for 20% to 26% of patients and grade 5 for 2% of patients [4].

Ibrutinib is a Bruton's tyrosine kinase inhibitor that has been recently approved for the treatment of refractory CLL, mantle cell lymphoma, and Waldenström macroglobulinemia, and underlined as a new risk factor for IFI [5].

We report on surveillance data of cryptococcosis from our tertiary university hospital and our two regional hospitals. Sixteen cryptococcosis cases were diagnosed between 2013 and 2016 (four probable and 12 proven cases, according to the European Organization for Research and Treatment of Cancer/Mycosis Study Group [EORTC/MSG] criteria), among which five occurred in patients with hematological malignancies of which three received ibrutinib therapy.

Considering the increasing number of cryptococcosis in patients receiving ibrutinib reported in the literature, we reviewed all cases published to date in the literature to warn physicians about this emerging risk factor.

The main characteristics of our three patients and of the 16 reported cases are summarized in Tables 1a and 1b.

Most patients received ibrutinib for CLL (12/19). Although most of them had previously received other immunosuppressive drugs, none had developed previous opportunistic infections.

Neutrophil count was available for 10 patients; only three had mild neutropenia (from 0.98 to 1.2 G/L). When available, gamma globulin level ranged from 2.5 to 8.9 g/L (n=6) with levels below 5 g/L for three patients out of six. Cryptococcosis occurred at a median of 9.5 years after hematological disorder onset. The median duration between initiation of ibrutinib and diagnosis of cryptococcosis was five months. Eight cases out of 19 occurred within the first two months of treatment and only four cases (22%) after six months of ibrutinib therapy. The clinical presentation was pneumonia in 13/19 patients and meningoencephalitis in eight patients. Ten patients presented with disseminated cryptococcosis (involvement of ≥ 2 sites). Blood cultures were positive in five patients and CSF cultures in six patients.

One patient had a negative serum cryptococcal antigen despite a positive blood culture. Two patients also had negative CSF antigens while CSF cultures were positive.

Our three patients died of unrelated causes (pyelonephritis-related septic shock, *Pseudomonas aeruginosa* bacteremia-related septic shock, and sudden unexplained coma) between one and eight months after the cryptococcosis diagnosis. Two other deaths were reported in the literature cases and occurred within the first month after diagnosis of cryptococcosis. Ibrutinib was maintained in 7/13 patients and it did not seem to be associated with unfavorable outcome. Dose reductions were mainly performed because of interactions with fluconazole.

Searching for additional cases with Vigilyse™ in VigiBase® (the World Health Organization's global individual case safety report pharmacovigilance database) in March 2019, we identified 51 cases. Some of the published cases, including ours, might have been already declared in this database. The mean age of patients was 67.8 years. The median duration between ibrutinib introduction and cryptococcosis onset was four months (n=15) with a duration from 1 to 47 months. Ibrutinib was prescribed for CLL in 78% of cases (n=36).

Cryptococcal infections are classically triggered by a defect in cell-mediated immunity, mostly lymphopenia, though humoral immunity also seems to be important. X-linked immunodeficient mice, which possess a

mutation leading to a defective Bruton's tyrosine kinase, have very high fungal burden after experimental challenge with *C. neoformans* and fungal dissemination to the brain, suggesting that treatments aiming at blocking the function of Bruton's tyrosine kinase could result in a high risk of cryptococcosis [6]. In stark contrast, IFIs are very rare in patients with X-linked agammaglobulinemia with Bruton's tyrosine kinase deficiency, probably because of a residual Bruton's tyrosine kinase activity of myeloid cells [7]. It has also been suggested that ibrutinib could affect caspase recruitment domain homologs CARD9 and CARD11, both essentials to control the propagation of fungal infection in the brain [8]. Yet, the pathogenesis of disseminated cryptococcosis in patients receiving ibrutinib could also be related to a reduced accumulation by macrophages of glucuronoxylomannan, the major component of the capsular polysaccharide of *Cryptococcus neoformans*, triggered by tyrosine kinase inhibitors. This could lead to a negative interaction between glucuronoxylomannan, an essential virulence factor of the yeast, and binding sites on cells that are central to host resistance [9]. Taken together, experimental studies suggest a specific interaction between the Bruton's tyrosine kinase inhibitor ibrutinib and *Cryptococcus neoformans* that could explain the increased risk in patients with hematological malignancy receiving this new agent. Our series of three cases over a short period, along with previous publications, emphasizes the need to consider cryptococcosis as one of the major infections complicating ibrutinib therapy. Although cryptococcosis usually occurs within the first two months of ibrutinib, our experience clearly shows that the disease can also occur at a later stage. In addition, a recent analysis of small-molecule kinase inhibitors revealed that IFIs are emerging complications of drugs targeting immune signaling pathways [5].

The dose of ibrutinib was not associated with infection risk in a recent study [10]. Risk factors associated with IFI during ibrutinib treatment seemed to be more than three prior treatment regimens and neutropenia. One would expect that larger indications of these new drugs might lead to an increased risk of IFI including cryptococcosis in the near future, as recently outlined [5]. Clinicians should be aware of the emerging risk of cryptococcal infections in patients with lymphoproliferative disorders receiving ibrutinib, especially during the first months of treatment.

Disclosure of interest

The authors report no conflict of interest.

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JB wrote the article. FM, FR, PLP, and DB critically revised the article. JB, FM, TG, BM, ML, MM, and DB managed the patients. JM performed the search in VigiBase.

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Table 1a. Patients characteristics and clinical symptoms at presentation

	Sex	Age	Hematological disease	Time to diagnosis of cryptococcosis (y)	Duration of ibrutinib treatment (m)	Fever	Meningoencephalitis	Pulmonary involvement	Other
1*	M	67	CLL	2	6	Yes	No	Yes	Mediastinal adenopathy
2*	M	79	CLL	9	15	Yes	No	Yes	NA
3*	F	78	CLL	10	2	No	Yes	Yes	-Polyadenopathy - Subcutaneous collection - Pleural effusion
4 (11)	F	76	CLL	15	NA	Yes	No	No	Skin ulceration
5 (12)	F	68	CLL	2	1	Yes	No	Yes	NA
6 (13)	M	88	Lymphoplasmacytic lymphoma	17	1	Yes	Yes	Yes	Mediastinal lymph nodes
7 (13)	M	54	CLL	5	1	Yes	No	Yes	NA
8 (14)	F	74	Waldenström macroglobulinemia	10	2	Yes	Yes	No	Skin abscess
9 (15)	M	62	CLL	NA	2	Yes	Yes	No	NA
10 (16)	M	74	Mantle cell lymphoma	NA	5	No	No	Yes	NA
11 (17)	M	66	CLL	11	5	Yes	Yes	No	NA
12 (17)	M	73	CLL	4	2	Yes	No	Yes	NA

13 (10)	M	70	CLL		NA	5	NA	NA	Yes	NA
14 (10)	M	52	Follicular lymphoma		NA	3.5	NA	NA	Yes	NA
15 (10)	M	61	CLL		NA	7.3	NA	NA	Yes	NA
16 (18)	M	70	Mantle cell lymphoma		NA	5	Yes	Yes	No	NA
17 (18)	M	78	Mantle cell lymphoma		11	24	Yes	Yes	No	NA
18 (19)	M	79	Diffuse large B-cell lymphoma		0.16	1.5	Yes	No	Yes	Pleural effusion
19 (20)	M	83	CLL		9	48	Yes	Yes	Yes	NA

*: this study, CLL: chronic lymphocytic leukemia, m: months, NA: not available, y: years

Table 1b. Mycological findings, management, and outcome

Mycological findings		Cryptococcal antigen titer at diagnosis		Antifungal therapy	Ibrutinib	Outcome (d from cryptococcosis)
Positive culture site(s)		Serum	CSF			
1*	Blood	1/16	Negative	- FCZ 800 mg 14d - FCZ 400 mg 6w	Maintained	Death (39)
2*	Broncho-alveolar lavage	1/64	Negative	- FCZ 800 mg 5d - FCZ 400 mg 7m	Maintained	Death (239)
3*	CSF and subcutaneous collection	1/160	1/60	- L-AMB + 5-FC 30d - L-AMB+5-FC+FCZ 800 mg 35d - FCZ 800 mg	Stopped	Death (144)
4 (11)	Skin biopsy	NA	Negative	- FCZ 400 mg	NA	Complete resolution
5 (12)	Blood	Negative	Negative	- L-AMB + 5-FC 2w - FCZ	Maintained	Complete resolution
6 (13)	Lymph node biopsy and CSF	1/40	Negative	- L-AMB + 5-FC 2w - FCZ	Stopped	Complete resolution
7 (13)	BAL, blood, and CSF	NA	Negative	- L-AMB + 5-FC 2w - L-AMB + FCZ 2w	Stopped	Death (approximately 1 month)

- FCZ						
8 (14)	Skin biopsy and CSF	1/10	NA	- L-AMB	NA	Death (few days)
9 (15)	CSF and blood	1/2048	1/8,192	- L-AMB + 5-FC 6w - FCZ 400 mg	Maintained	Complete resolution
10 (16)	None	Negative	NA	- FCZ	NA	Partial resolution (150)
11 (17)	None	NA	Positive	- L-AMB + 5-FC 2w - FCZ	Maintained reduction	with Complete resolution
12 (17)	BAL	Positive	Negative	- FCZ 200 mg 6m	Maintained reduction	with Complete resolution
13 (10)	None	1/320	NA	- FCZ	NA	Complete resolution
14 (10)	Lung biopsy	1/160	NA	- FCZ	NA	Complete resolution
15 (10)	None	1/160	NA	- FCZ	NA	Complete resolution
16 (18)	None	1/64	1/2	- L-AMB + 5-FC 2w - FCZ	Stopped	Complete resolution
17 (18)	None	NA	Positive	- L-AMB + 5-FC 2w - FCZ	Stopped	Complete resolution
18 (19)	Pleural fluid	1/40	Negative	- L-AMB + 5-FC 4d - FCZ 400 mg 12m	Stopped	Partial resolution
19 (20)	Blood, CSF	1/1024	1/1028	- L-AMB + 5-FC 2w - FCZ	Maintained reduction	with Complete resolution

*: this study, 5-FC: flucytosine, BAL: bronchoalveolar lavage, CSF: cerebrospinal fluid, d: days, FCZ: fluconazole, L-AMB: liposomal amphotericin B, NA: Not available, w: weeks, m: month

For our cases, cryptococcal antigen detection has been determined using CrAg Lateral Flow Assay (IMMY, Inc., Norman, DK)