Atypical Infections in Chronic Lymphocytic Leukemia and Mantle Cell Lymphoma Patients Treated with Ibrutinib

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Abstract

Ibrutinib is an oral Bruton’s tyrosine kinase inhibitor with clinical efficacy in several B cell malignancies. In a pooled analysis of clinical trials evaluating ibrutinib, grade 3-4 infections were reported in 14% of patients. We screened consecutive patients on ibrutinib therapy for chronic lymphocytic leukemia (CLL) or mantle cell lymphoma (MCL) for infectious complications. Patients were hospitalized with documented infections uncommon to this patient population including Legionella pneumonia, Campylobacter bacteremia and fatal progressive multifocal leukoencephalopathy (PML). All patients received prior therapies for CLL/MCL. Immunological evaluation of these patients demonstrated immunoglobulin depression and profound lymphopenia with severe depletion in both B and CD4 T cell counts, suggesting defects in both humoral and T cell mediated immunity. This data support a broader immunosuppressive effect for ibrutinib than initially anticipated. While responding patients may show later recovery of B cell function, profound immunosuppression may occur at earlier treatment time points, particularly in previously treated patients. Closer patient monitoring during the first months of ibrutinib therapy may be desirable.

Keywords: Ibrutinib; Infection; Innate immunity; Progressive multifocal leukoencephalopathy

Introduction

Ibrutinib is an oral inhibitor of the Bruton’s tyrosine kinase (BTK) enzyme [1], which is predominantly expressed in B lymphocytes, and is a major downstream mediator of signaling through the B cell receptor (BCR). Ibrutinib has shown clinical efficacy in several B cell malignancies including chronic lymphocytic leukemia (CLL) [2-4], mantle cell lymphoma (MCL) [5] and Waldenström macroglobulinemia (WM) [6], both as a single agent and in combination with chemotherapy and immune therapies. Recently approved for these indications by both the FDA and EAMA, being the first drug that targets the BCR and the relative ease of oral delivery, it is expected to move into earlier treatment lines within the next few years.

Patients with lymphoproliferative neoplasms suffer from dysregulation of the immune system, predisposing them to a wide range of infections. Treatment of lymphoproliferative neoplasms is often associated with infectious complications, mainly during periods of severe neutropenia. Inherent humoral immunosuppression in CLL, depletion of normal B cells with monoclonal antibodies and the cellular immunosuppression related to treatment with nucleoside analogues further increase the risk of infections in patients with indolent B cell malignancies, in particular after several lines of treatment. Recurrent infections with encapaculated bacteria are common in both untreated as well as treated CLL, Staphylococcus aureus and various gram-negative enteric pathogens predominate during periods of neutropenia, while Herpes simplex and Varicella-zoster infections are associated with prior nucleoside analogue treatment. Fungal infections are encountered less often [7]. In a pooled analysis of clinical trials evaluating ibrutinib, grade 3-4 infections were reported in 14% of patients resulting in death in 2% [8]. The frequency of grade ≥ 3 infections in ibrutinib treated CLL patients (n=132, median follow-up=3 years) was recently reported to be greater in relapsed refractory patients (51%) compared to treatment naive patients (13%) [9]. The spectrum of infections included upper and lower respiratory tract infection, urinary tract infections, cellulitis, bacteremia, gastroenteritis, Clostridia and Staphylococcal infections. Treatment discontinuation due to infection was reported in 9% of patients in an analysis of 308 patients participating in four sequential ibrutinib trials [10]. Reported here is a series of CLL and MCL patients treated with ibrutinib who developed infections seen uncommonly in these diseases including Legionella pneumonia, Campylobacter bacteremia and progressive multifocal leukoencephalopathy (PML). Clinical and Immunological evaluation of these patients suggests that ibrutinib may target cells of the innate pathway in addition to suppressing B lymphocytes function, thus supporting it has a broader immunosuppressive effect that should be taken into account using this drug.

Patients and Methods

Consecutive patients receiving single agent ibrutinib therapy between April 2014 and July 2016 at the Institute of Hematology, Assaf Harofe Medical Center, were screened for documented infectious complications. Data were collected from patients’ medical records. The study was approved by the institutional review board.

Results

Ibrutinib was approved by the Israeli health authorities and reimbursed for limited indications in January 2015 but has been available via companionate use since March 2014. In the screened time...
period, we identified four patients treated with ibrutinib for either CLL (n=3) or MCL (n=1) who were hospitalized with an identified infection. All were tested negative for HIV. Baseline characteristics of hospitalized patients are provided in Table 1. Ibrutinib was given as 2nd and 3rd line of therapy in 1 and 3 patients, respectively. Median treatment duration with ibrutinib prior to infection was 5 (range 1-23) months, and the median dose immediately prior to hospitalization was 420 mg/day (range 420 mg/day-560 mg/day). Two patients were on preventive Intravenous Immunoglobulin (IVIG) treatment due to recurrent infections (infected bronchiectasis and recurrent sinusitis each in one) with the last infusion given 26 and 17 days prior to infection, respectively. Immunoglobulin (Ig) levels and immunophenotype of peripheral blood mononuclear cells (PBMC) are provided in Table 2. Serum Ig levels were reduced in three out of four patients prior to initiation of ibrutinib therapy and further decreased during treatment. All four patients had total white blood cell counts and absolute neutrophil counts within the normal range while on ibrutinib treatment. Three patients demonstrated marked lymphopenia with absolute CD4 counts below normal range in all four patients. CD4/CD8 ratio was significantly low in all four patients, with absolute CD4 counts ranging between 48 and 418 cells/microliter and half of them being below 200 cells/microliter. Patient characteristics and immunological profile for two additional patients on ibrutinib therapy, who did not develop infection, are provided in Table 3. Both received ibrutinib as second line therapy, for CLL/SLL and MCL each in one patient, respectively. These patients had less severe lymphopenia, with normal B cell (CD19+) and T cell (CD3+) count and only mildly depleted NK cells and CD4/CD8 ratios.

**Discussion**

We report on uncharacteristic, opportunistic infections in a cohort of previously treated patients with lymphoproliferative neoplasms receiving single agent ibrutinib. Infections appeared at a median of 5 months after starting ibrutinib, and were manageable in three out of four patients, allowing resumption of ibrutinib therapy after control of the infectious episode. Patients with infections had low immunoglobulin levels, as well as profound lymphopenia of both CD4 T and B lineages and decreased NK cell counts.

The atypical infections documented in our patients are characteristic of immunocompromised hosts, and suggest impaired cellular, rather than humoral immune depression. Two of our patients had documented Campylobacter bacteremia. Campylobacter infections are endemic in Israel, which has one of the highest incidence rates reported among industrialized countries [11]. Campylobacter infection in immunocompetent individuals is generally restricted to the intestine, with bloodstream infection occurring in less than 1% of cases.

### Table 1: Characteristics of study patients.

| Patient number | Age (years)/Gender | Hematological diagnosis | Comorbidity | Prior treatments | Infection | Outcome |
|----------------|--------------------|-------------------------|-------------|-----------------|----------|---------|
| 1              | 80/male            | CLL                     | IHD         | Obinutuzumab-chlorambucil | Campylobacter jejuni bacteremia | Alive   | ibrutinib treatment continued |
| 2              | 67/male            | CLL                     | ESRD (dialysis) | FCR, BR         | Legionella pneumonia          | Alive   | ibrutinib treatment continued, dose reduction |
| 3              | 53/female          | MCL                     | HTN         | R-CHOP/R-DHAP    | Campylobacter coli bacteremia | Alive   | ibrutinib treatment continued |
| 4              | 58/female          | CLL                     | Hypothyroidism | FCR, BR         | PML                  | Death   |         |

| Patient number | Hematological diagnosis | Comorbidity | Prior treatments | Infection | Outcome |
|----------------|-------------------------|-------------|-----------------|----------|---------|
| 1              | CLL                     | IHD         | Obinutuzumab-chlorambucil | Campylobacter jejuni bacteremia | Alive   |
| 2              | CLL                     | ESRD (dialysis) | FCR, BR         | Legionella pneumonia          | Alive   |
| 3              | MCL                     | HTN         | R-CHOP/R-DHAP    | Campylobacter coli bacteremia | Alive   |
| 4              | CLL                     | Hypothyroidism | FCR, BR         | PML                  | Death   |

### Table 2: Immunological results of study patients.

| Immunoglobulins g/L | Patient number | Prior | During | Prior | During | Prior | During | Prior | During |
|---------------------|----------------|-------|--------|-------|--------|-------|--------|-------|--------|
| IgG                 |                | 6.61  | 3.36   | 23    | 22.8   | 6.03  | 0.67   | 3.72  | 4.12   |
| IgM                 |                | 1.18  | <0.17  | 0.7   | 0.24   | 0.22  | <0.17  | <0.17 | <0.17  |
| IgA                 |                | 0.43  | 0.3    | 17.2  | 7.21   | 1.08  | <0.06  | 0.49  | 0.14   |
| WBC K/µL            |                | 6.3   | 3.2    | 31.6  | 6.4    | 7.3   | 4      | 106   | 2.3    |
| ANC K/µL            |                | 4.5   | 12.6   | 2.2   | 5.2    | 5.4   | 17.6   | 5.7   | 3.5    |
| ALC K/µL            |                | 0.9   | 0.8    | 28    | 2.2    | 1     | 0.4    | 99    | 0.7    |
| CD19 %/number K/µL |                | 0     | 29/0.64| 0     | 0      | 2/0.01|        |       |        |
| CD3 %/number K/µL  |                | 780.6 | 57/1.25| 90/0.36| 89/0.62|        |       |       |        |
| CD4 number cells/µL |                | 192   | 418    | 48    | 250    |        |       |       |        |
| CD3-CD56+ %/number K/µL | | 4.0/0.53 | 2/0.044| 3/0.01 | 5/0.035|        |       |       |        |
| CD4/CD8             |                | 0.48  | 0.54   | 0.15  | 0.57   |        |       |       |        |

1 Normal IgG 7-16 g/L, IgM 0.4-2.3 g/L, IgA 0.7-5 g/L

2 Normal IgG 6.5-16 g/L, IgM 0.7-4 g/L, IgA 0.5-3 g/L

3 percent from total lymphocyte count.

WBC: White Blood Count; ANC: Absolute Neutrophil Count; ALC: Absolute Lymphocyte Count.
ANCs, Absolute Neutrophil Count; ALCs, Absolute Lymphocyte Count.

Some of these infections, Campylobacter bacteremia and Legionella pneumonia were reported here for the first time. PML has recently been linked to ibrutinib therapy and our report adds one more case to the growing number of reported cases [14]. However, our case is the first report of a confirmed PML in a patient receiving ibrutinib. In conclusion, we present a series of previously treated CLL/MCL patients, diagnosed with atypical infections early in the course of ibrutinib treatment. Some of these infections, Campylobacter bacteremia and Legionella pneumonia were reported here for the first time. PML has recently been linked to ibrutinib therapy and our report adds one more case to the growing evidence of this association. Immunological data for these patients supports impairment of cellular immunity characteristic of such infections. We believe that along with its very significant efficacy in B cell malignancies, ibrutinib may have a broader immunosuppressive effect than initially anticipated, particularly in the first months of therapy and in previously treated patients. As the drug becomes more widely available and moves into earlier lines of therapy, it is important to be aware of such infections and to develop strategies to mitigate them.

### Table 3: Characteristics of patients without infection

| Patient number | 1 | 2 |
|----------------|---|---|
| Age (years)/Gender | 82/female | 81/male |
| Hematological diagnosis | CLL/SLL | MCL |
| Comorbidity | None | HTN |
| Timing of analysis | Prior to ibrutinib | During ibrutinib | Prior to ibrutinib | During ibrutinib |
| Immunoglobulins g/L | IgG | IgM | IgA |
| CD19 %/number K/µL | 66/3.1 | 10/0.08 | 24/0.31 |
| CD3 %/number K/µL | 27/1.27 | 82/0.66 | 37/0.48 |
| CD4 number cells/µL | 924 | 269 | 351 |
| CD3-CD56+ %/number K/µL | 7/0.33 | ND | 3/0.04 |
| CD4/CD8 | 0.67 | 0.93 | 1.35 |

### Systematic Review

A recent systematic review of Ig levels in treatment naïve (n=52) and relapsed/refractory (n=32) CLL patients treated with single agent ibrutinib was reported [19]. Compared with baseline values IgG levels decreased significantly 12 and 24 months after initiating ibrutinib, were unchanged at 6 months, IgM levels increased transiently at 6 and 12 months and IgA levels increased significantly at 6 months of treatment, and thereafter. Importantly, the rate of infections in this report was higher in the first 6 months of therapy, with lower infection rates on long term treatment correlating with the increase in IgA. This is in line with our data, demonstrating low Ig levels in patients with infections, at median 5 months ibrutinib therapy. In addition to its effect on B cells, data suggest that ibrutinib also modulate T cell, macrophage and NK cell function. IL2 inducible kinase (ITK), a member of the Tec kinase family, shares significant homology with BTK, and is inhibited by ibrutinib. Inhibition of ITK specifically depresses Th2 CD4 cells with preservation of Th1 and CD8 activity [20]. Inhibition of BTK activation in macrophages is associated with decreased phagocytic activity, which may enhance susceptibility to infection [21]. NK cells express both BTK and ITK, and their inhibition was associated with decreased innate immune responses to the TLR3 ligand, reduced expression of IFN-γ, perforin, and granzyme-B and decreased cytotoxic activity [22]. Although we did not specifically test cellular immune cell functions, all four patients with infection demonstrated significantly depressed CD4 counts and low NK cell counts. Interestingly, Ahn et al. recently reported an increased rate of Pneumocystis jirovecii pneumonia in previously untreated CLL patients on single-agent ibrutinib [23]. Infections occurred at a median of 6 months on ibrutinib, and were not associated with decreased IgG or CD4 T cell levels. The differences in types of infection and T cell number in our report compared to the prior report could be partially explained by prior treatments given in our cohort. Hemodilysis in one of four patients, could also have contributed to the risk for infection in that case. In conclusion, we present a series of previously treated CLL/MCL patients, diagnosed with atypical infections early in the course of ibrutinib treatment. Some of these infections, Campylobacter bacteremia and Legionella pneumonia were reported here for the first time. PML has recently been linked to ibrutinib therapy and our report adds one more case to the growing evidence of this association. Immunological data for these patients supports impairment of cellular immunity characteristic of such infections. We believe that along with its very significant efficacy in B cell malignancies, ibrutinib may have a broader immunosuppressive effect than initially anticipated, particularly in the first months of therapy and in previously treated patients. As the drug becomes more widely available and moves into earlier lines of therapy, it is important to be aware of such infections and to develop strategies to mitigate them.
to explore the full spectrum of its effects on the immune system and develop strategies to decrease the risk of serious infections with this agent.

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