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Review

Chronic lymphocytic leukemia and infection risk in the era of targeted therapies: Linking mechanisms with infections

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ABSTRACT

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia in the world. Patient with CLL are at particular risk for infections due to inherent disease-related immune dysfunction in addition to the effect of certain systemic therapies on the immune system. The advent of B-cell receptor (BCR) inhibitors such as ibrutinib and idelalisib has led to a practice change that utilizes these targeted agents in the treatment of CLL, either in place of chemoimmunotherapy (CIT) or in later line settings. In this paper, we review the pathophysiology of immune dysfunction in CLL, the spectrum of immunodeficiency with the various therapeutic agents along with prevention strategies with a focus on targeted therapies.

1. Introduction

Infections are a major source of morbidity and mortality in patients with chronic lymphocytic leukemia (CLL), accounting for 50–60% of all deaths [1]. They occur due to inherent immune dysfunction caused by the disease process, and in certain situations, due to immunosuppressive effects of treatment. The spectrum of infections has evolved over the last two decades with the introduction of purine analogues and monoclonal antibodies in the management of CLL. Furthermore, therapies targeting B-cell receptor (BCR) signaling have become a major component of the management of CLL after the U.S. Food and Drug Administration (FDA) approval of two oral kinase inhibitors (idelalisib and ibrutinib) in 2014 followed by a BCL2 inhibitor (venetoclax) in 2016. Clinical trials evaluating the efficacy of these therapies are typically not powered to detect differences in uncommon opportunistic infections (OIs) between arms. However, with the widespread use of these targeted therapies, OIs are increasingly recognized as an emerging source of morbidity and mortality [2].

In this review, we aim to summarize the available literature on immune dysfunction in CLL, infection risk with established therapies, and emerging infections with targeted therapies. We then discuss recommended strategies for prevention of infections in general and OIs in particular.

2. Inherent immune dysfunction in CLL

2.1. Complement activity & phagocytic defects

Decreased levels of components of the complement system are found in patients with CLL, and tend to be more common in advanced-stage CLL [3]. Approximately 38% of patients were deficient in one or more complement component in one study examining the effect of CD20 monoclonal antibody treatment efficacy. This deficiency correlated with reduced complement-dependent cytotoxicity [4]. Furthermore, Fust et al. [5] found that only abnormalities in the classical complement pathway were found in patients with CLL, with a reduction in mean C1 and C4 levels in > 50% of patients tested. However, no relationship has consistently been established between complement abnormalities and the risk of infection in patients with CLL.

Defects in phagocyte function have been reported in the form of digestive enzyme deficiencies in lymphocytes, monocytes, and neutrophils. These included b-glucuronidase, lysozyme, and myeloperoxidase, all of which normalize when the disease goes into remission [6].

2.2. Cell-mediated immunity

Defects in T cells, natural killer (NK) cells, and dendritic cells (DC) have been described in several in vitro studies. First, CLL cells appear to inhibit the interaction between activated T cells and normal B cells [7]. Second, in B-CLL but not SLL, impaired NK cell function with reduced activating receptor expression and transcriptional downregulation of

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several cytotoxic pathways has been described [8]. The NK-cell defect seems to be of clinical significance, as higher NK-cell numbers is seen in patients with early-stage disease and mutated IGHV genes, and higher cytolytic capacity is seen in patients with monoclonal B-lymphocytosis [9]. Third, DCs in patients with CLL appear morphologically and phenotypically immature (lacking the maturation marker CD83 and CD80) and unable to induce a significant proliferative response in allo-mixed lymphocyte reaction, with a reduced ability to release interleukin 12 and to drive a type 1T-cell response [10]. Moreover, CLL cells appear to express several inhibitory signals that have various effects on cell-mediated immunity; CD200 promotes differentiation of CD4+ T cells into T regulatory (Treg) cells, which express CTLA-4 (CD152), CD270 and PD-L1 (CD274) interact with their receptors CD160 and PD-1 (CD279), respectively, to inhibit T-cell activation and proliferation [9].

The impact of these defects on infection risk, and their reversibility with treatment of the disease is unclear. However, in clinical practice, reactivation of varicella zoster and attacks of herpes simplex virus do occur in patients with CLL who have not been treated with fludarabine-based chemotherapy, suggesting inherent defective cell-mediated immunity. Furthermore, second malignances are more common in CLL, particularly skin and virally induced cancers [11] underscoring a possible defect in immune surveillance.

2.3. Humoral immunity

The most studied immune defect in CLL is hypogammaglobulinemia. The incidence of a reduction in any immunoglobulin in CLL has been reported at approximately 46%–64% [12,13], and the reduction in the levels of IgG and IgA increases as the disease advances. In one study, an IgG level < 700 mg/dL at diagnosis was associated with a reduced survival [12]. Bacterial infection of the sinuses and respiratory tract is the most common site of infection in these patients, which may be related to deficiencies in serum IgA and IgG4, as well as defects in mucosal immune function [14]. However, there is no consistent correlation between immunoglobulin levels and the incidence of infection in patients with CLL. Freeman et al. reported a rate of clinically significant infection (defined as sepsis requiring intravenous antibiotics, lower respiratory tract infections, or recurrent sinobronchial disease) of 16% and a rate of IgG deficiency of 50% in a cohort of 150 patients [13].

Immunoglobulin VH (IGVH) mutational status may also have an impact on risk of infection [15,16]. In a retrospective review of 231 CLL patients, those with unmutated IGVH genes had a shorter time to first infection and higher infection-related mortality than patients with mutated IGVH genes (31 vs. 62 months, $p < .001$) [15]. However, the level of immunoglobulins was comparable between the two groups, as reported in two separate studies [15,16].

3. Therapeutic categories and microbial spectrum (Table 1)

3.1. Alkylators and purine analogues

Chlorambucil has been used for the treatment of CLL for decades. Most infections that occur with the use of chlorambucil are bacterial, usually affecting the respiratory tract [17]. Fludarabine, a purine analogue, have changed the spectrum of infectious complications seen in CLL patients due to T cell dysfunction. Results of one of the earliest studies using fludarabine and prednisone for CLL showed that CD4+ T cell levels were uniformly depressed from a median 1015/μL pretreatment to a median 159/μL after 3 months of fludarabine therapy [18]. This CD4+ T cell deficiency may last up to 1–2 years after completion of therapy [19]. The spectrum of infection seen with T-cell dysfunction includes Listeria, *Pneumocystis jirovecii* (*P. jirovecii*), Nocardia, Mycobacterial infections, and opportunistic fungal (Candida and Aspergillus) and viral (cytomegalovirus (CMV), varicella zoster virus (VZV), and herpes simplex virus (HSV)) infections. Herpesviruses are the most commonly seen infections with fludarabine therapy, followed by Listeriosis and *P. jirovecii*, seen in 7% of previously treated patients receiving fludarabine plus prednisone but only 1% of previously untreated patients [20,21].

Risk factors that increase the risk of infection include previous treatment for CLL, advanced disease, elevated β2-microglobulin levels, low serum albumin levels, and low neutrophil count [20]. When combining fludarabine with cyclophosphamide, another alkylator, in treatment naïve patients the rates of severe infections and OIs appear to be similar between the combination and the fludarabine arms [22]. However, the combination therapy utilizing chlorambucil as the alkylator resulted in significantly more infections [21], and this was also seen in previously treated patients receiving fludarabine and cyclophosphamide (26% had herpesvirus infections, 7% had fungal infections) [23]. Additionally, fludarabine induces more neutropenia than chlorambucil [24], but similar rates compared to alkylator and anthracycline-based regimens [25].

Bendamustine is a unique alkylator that can also deplete CD4+ and CD8+ T cells (Table 1) [26,27]. Bendamustine was compared to fludarabine and cyclophosphamide, both with rituximab, in treatment-naïve patients without del(17p) [28]. Severe infections (grade 3/4) were more commonly seen with fludarabine, cyclophosphamide and rituximab (FCR), especially in patients older than 65 years (47% vs. 26%). Although the combination of bendamustine and rituximab (BR) depletes both T- cells and B-cells the risk of OIs, especially *Pneumocystis jirvovecii* pneumonia (PJP), is not substantially increased and primary prophylaxis for PJP is not typically offered when using bendamustine [29].

Cladribine and pentostatin are two other purine analogues that result in prolonged quantitative abnormalities in T cell subsets. In several

Table 1
Class of therapy with corresponding immune dysfunction and potential infectious risks.

Class of therapy	Immune dysfunction	Infections
Alkylating agents (e.g. chlorambucil, cyclophosphamide, bendamustine)	Neutropenia Lymphopenia (T cell dysfunction)	Bacterial Fungal, if prolonged PJP Cryptococcus
Purine analogues (e.g. fludarabine, pentostatin)	Neutropenia Lymphopenia (T cell dysfunction)	Bacterial Fungal, if prolonged PJPCryptococcus
Anti-CD20 antibodies (e.g. rituximab, ofatumumab, obinatuzumab)	Lymphopenia (B cell dysfunction)	Bacterial Hepatitis B reactivation Viruses (e.g. enterovirus, JC virus)
Anti-CD52 antibody (i.e. alemtuzumab)	Lymphopenia (B and T cell dysfunction)	Viruses (e.g. CMV, HSV, VZV) Fungal PJP
BTK inhibitors (e.g. ibrutinib, acalabrutinib)	Lymphopenia (B cell dysfunction, possible T cell dysfunction)	Hepatitis B reactivation Fungal (Aspergillus, Cryptococcus) PJP
PI3K inhibitors (e.g. idelalisib)	Neutropenia Lymphopenia (B and T cell dysfunction)	Bacterial Fungal, if prolonged Viruses (e.g. CMV, HSV) Aspergillus PJP
BCL2 inhibitors (e.g. venetoclax)	Neutropenia Lymphopenia (B cell dysfunction)	Bacterial Viruses (e.g. enterovirus)

PJP: *Pneumocystis jirovecii* pneumonia; CMV: cytomegalovirus; HSV: herpes simplex virus; VZV: varicella zoster virus.