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Immunological changes with kinase inhibitor therapy for chronic lymphocytic leukemia

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Abstract

Ibrutinib and idelalisib are kinase inhibitors that have revolutionized the treatment of chronic lymphocytic leukemia (CLL). Capable of inducing durable remissions, these agents also modulate the immune system. Both ibrutinib and idelalisib abrogate the tumor-supporting microenvironment by disrupting cell-cell interactions, modulating the T-cell compartment and altering the cytokine milieu. Ibrutinib also partially restores T-cell and myeloid defects associated with CLL. In contrast, immune-related adverse effects, including pneumonitis, colitis, hepatotoxicity, and infections are of particular concern with idelalisib. While opportunistic infections and viral reactivations occur with both ibrutinib and idelalisib, these complications are less common and less severe with ibrutinib, especially when used as monotherapy without additional immunosuppressive agents. This review discusses the impact of ibrutinib and idelalisib on the immune system, including infectious and auto-immune complications as well as their specific effects on the B-cell, T-cell and myeloid compartment.

Keywords

Lymphoid Leukemia; Signaling therapies; T-Cell Mediated Immunity; The Humoral Immune Response

Introduction

Immune dysregulation is a hallmark of chronic lymphocytic leukemia (CLL). Clinical manifestations such as an increased susceptibility to infections and autoimmunity are associated with morbidity and mortality. Chemoimmunotherapy frequently causes severe neutropenia, placing patients at even greater risk of infectious complications. Fludarabine, a backbone of chemoimmunotherapy regimens, can precipitate and exacerbate autoimmune hemolytic anemia. Kinase inhibitors that target growth and survival pathways in CLL cells are now approved for clinical use; however, the targeted kinases are also functionally

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important in normal immune cells. Herein, we will review the effects of the first two approved kinase inhibitors, ibrutinib and idelalisib, on the immunity of patients with CLL.

Infections

Infections are a well-recognized complication and a common cause of death in CLL. An important limitation of chemoimmunotherapy is the increased risk of infection. Ibrutinib is the first-in-class inhibitor of Bruton tyrosine kinase (BTK), a key member of the B-cell receptor (BCR) signaling pathway. In the frontline setting, infections occur at a lower rate with ibrutinib compared to chemoimmunotherapy (Table) [1, 2, 3, 4, 5]. When patients start ibrutinib, the risk of infections is highest during the first 6 months of therapy and then subsequently decreases [6, 7]. The distribution of infections is similar to CLL in general with the respiratory tract being the predominant site of infections [7]. Grade 3 pneumonia develops in 4% to 12% of patients treated with ibrutinib [8, 9].

Idelalisib, an oral inhibitor of PI3K δ , is approved, in combination with rituximab, to treat relapsed CLL. PI3K δ and BTK are interconnected in the BCR signaling pathway and both are essential for signal transduction [10]. Although no head-to-head comparison of idelalisib and ibrutinib has been reported, the rate of infections during treatment with idelalisib appears to be higher. Notably, grade 3 pneumonia occurred in 19% and 8% of patients in two phase 2 trials of idelalisib and rituximab in the upfront and salvage settings, respectively [11, 12].

As experience with ibrutinib and idelalisib grows, the risk of opportunistic infections is increasingly appreciated. Six trials of idelalisib combined with other drugs to treat CLL and indolent non-Hodgkin lymphoma were halted due to an increased incidence of death predominantly from opportunistic infections [14, 15]. In the phase 3 randomized trial of bendamustine and rituximab with idelalisib or placebo for previously treated CLL, patients receiving idelalisib had more pneumocystis jiroveci pneumonia (PJP, 2% versus 0%) and cytomegalovirus (CMV) infection (6% versus 1%) than those in the placebo group [16]. A retrospective analysis of over 2,100 patients in the idelalisib clinical development program also found an increased risk of PJP with the use of idelalisib [17]. Prophylaxis against PJP somewhat mitigated this risk, but it is hard to identify at-risk patients because neither CD4 count nor age was associated with PJP. PJP was also reported in 5 CLL patients after a median of 6 months on ibrutinib, 4 being treated in first-line [18]. Unlike the severe clinical picture seen in acquired immunodeficiency, the patients in this case series were either asymptomatic or only had mild symptoms of dyspnea and cough. Since ibrutinib is administered continuously until disease progression, the decision to start prophylaxis against PJP represents a long-term commitment and should be carefully discussed with patients. In our experience, ibrutinib-treated patients diagnosed with PJP respond clinically and radiologically to oral trimethoprim/sulfamethoxazole.

Aspergillus infections have also been a concern with ibrutinib use. In a study evaluating ibrutinib for the treatment of primary central nervous system (CNS) lymphoma, 2 of 18 (11%) patients died of aspergillus lung and CNS involvement on ibrutinib monotherapy and 7 of 16 (44%) patients developed lung and CNS aspergillus infection when ibrutinib was

combined with chemotherapy and corticosteroids. In addition, aspergillus brain abscesses were reported in 3 patients with CLL treated with ibrutinib and concomitant corticosteroids [19]. The high incidence of fungal infections with ibrutinib may be related to co-administration of steroids causing additional immunosuppression and the deleterious effects of ibrutinib on macrophage function [20].

Viral infection or reactivation has been problematic especially with idelalisib, contributing to increased CMV-associated fatalities in combination therapies as mentioned above [14, 15]. In addition, disseminated varicella zoster was reported in 2 patients on ibrutinib and 1 patient on idelalisib leading to death [21]. Both patients on ibrutinib were successfully treated with intravenous acyclovir followed by long-term valacyclovir suppression. Hepatitis B reactivation has also been reported in the literature after treatment of CLL with ibrutinib [22]. Finally, there is a case report of central nervous system (CNS) non-HIV associated immune reconstitution inflammatory syndrome after ibrutinib therapy for Richter transformation, thought to be triggered by latent CMV CNS infection [23].

Autoimmunity

Cytopenias

Another defining feature of immune dysfunction in CLL is autoimmunity, especially autoimmune cytopenia (AIC). During the course of their disease, 2 to 10% of patients develop autoimmune hemolytic anemia (AIHA) due to antibodies against autologous red blood cells [24, 25]. Treatment with fludarabine, advanced disease stage, unmutated immunoglobulin heavy chain variable (IGHV) gene, and adverse cytogenetic abnormalities have been associated with an increased risk of AIHA [26, 27]. Less commonly, immune thrombocytopenia, and rarely, pure red cell aplasia can occur.

Conflicting data exist regarding the risk of AIC in the context of ibrutinib therapy. On one hand, treatment-emergent AIC, including flares of preexisting AIC and less commonly, de novo AIC, have been reported [28, 29]. On the other hand, treatment with ibrutinib has also been associated with resolution of AIC and seroconversion to a negative direct antiglobulin test [28]. An important caveat is that most clinical trials of ibrutinib excluded patients with active AIC, which may distort the incidence of AIC relative to ibrutinib use in the community.

Organ manifestations

Autoimmune complications are a significant concern with the use of idelalisib. Grade 3 diarrhea, transaminitis and pneumonitis occurred in 7%, 8%, and 4% of patients receiving idelalisib and rituximab as salvage therapy [11, 12]. Surprisingly, these adverse events increased in frequency when idelalisib was used in first-line. In a phase 2 study of idelalisib and rituximab for previously untreated CLL, the rates of grade 3 colitis or diarrhea, transaminitis and pneumonitis were 42%, 23%, and 3%, respectively [13]. In addition to line of therapy, risk factors for immune-mediated adverse events are treatment naïve CLL, younger age and mutated IGHV status [30]. The role of T cells in the underlying pathophysiology will be discussed later in this review.

The safety profile appears to be different with novel PI3K δ inhibitors. Umbralisib is a dual inhibitor of PI3K δ and casein kinase under clinical investigation. In a phase 1 dose escalation study of umbralisib for relapsed or refractory lymphoid malignancies, grade 3 colitis and transaminitis occurred in 3% and 2% of patients, respectively [31]. No pneumonitis or opportunistic infections were observed.

B cells

B cells play a crucial role in humoral immunity, antigen presentation and secretion of co-stimulatory cytokines. The BCR is a membrane-bound structure responsible for antigen recognition in B cells. Signaling through the BCR provides essential trophic signals for normal B cells and CLL cells alike. BTK and PI3K δ are downstream members necessary for signal transduction. These intracellular kinases are inhibited by ibrutinib and idelalisib respectively resulting in swift and dramatic downregulation of BCR-regulated genes [32, 33]. Most research available to date has focused on the effects of ibrutinib and idelalisib on the malignant B cell compartment, whereas the impact of these drugs on healthy B-cells and humoral immunity remains relatively less studied.

Ibrutinib effects on B cells

BTK is critical for B-cell development and immunoglobulin synthesis. Patients with X-linked agammaglobulinemia (XLA), caused by loss-of-function germline mutations in *BTK*, lack mature B cells, have severely depressed immunoglobulin levels, and suffer from recurrent infections. Ibrutinib, which irreversibly inhibits BTK, exerts multiple effects on malignant CLL B cells, including (i) impairment of cell adhesion leading to transient lymphocytosis [34, 35], (ii) disruption of communication with the tumor-sustaining microenvironment [35], (iii) modest induction of apoptosis [36] and (iv) decreased cell proliferation (Figure Figure 1) [32, 37].

In contrast, ibrutinib does not recapitulate the severe B-cell impairment caused by genetic inactivation of BTK. Normal B cells derived from healthy volunteers have lower levels of BTK mRNA and BTK protein expression and are less vulnerable to ibrutinib mediated apoptosis than CLL cells in vitro [36]. Surprisingly, aspects of humoral immunity appear to be positively affected by ibrutinib therapy. A consistent increase in IgA has been observed across clinical trials of ibrutinib [6, 12]. The change in IgA appears to be clinically relevant – in a phase 2 study, patients with greater improvements in IgA developed fewer infections [38]. It is important to note however that although there was evidence of recovery of normal polyclonal B cells, they remained abnormal in number and subset composition. Furthermore, CLL patients on ibrutinib therapy can mount antibody responses to influenza vaccination, albeit the rate of detectable titers is less than in healthy individuals, but comparable to past reports on vaccine responses in CLL patients not treated with ibrutinib [39]. Influenza is a unique vaccine because it is given annually to patients who may have preexisting immunity from prior exposure or vaccination. Immunization against influenza could therefore trigger an anamnestic immune response rather than the development of de novo immunity. The non-malignant B-cell immune repertoire remains stable during ibrutinib therapy, suggesting the pool of antigen-experienced and antigen-naïve B cells are unaffected by treatment [40].

However, additional studies are required to investigate the immune response against neoantigens in patients on ibrutinib.

Idelalisib effects on B cells

The major effects of idelalisib on CLL B cells include (i) impairment of cell adhesion leading to transient lymphocytosis [12, 41] and (ii) loss of tumor protective microenvironment leading to induction of apoptosis (less pronounced than with ibrutinib) (Figure Figure 1) [42].

PI3K δ expression levels are comparable across healthy as well as CLL B cells, however PI3K activity is higher in CLL B cells [42, 43]. Similar to effects observed with ibrutinib, normal B cells appeared to be less susceptible to idelalisib induced apoptosis compared to CLL B cells in vitro, possibly related to higher PI3K δ activity in CLL B cells [42]. In terms of humoral immunity, idelalisib does not appear to impact serum immunoglobulin levels [41]. Recently, idelalisib was shown to increase somatic hypermutation and genomic instability via upregulation of B-cell specific activation-induced cytidine deaminase in normal and malignant B cells [44]. The clinical implications of this finding are currently unknown.

T cells

Tumor immune surveillance depends on a coordinated Th1-cell response that promotes cytotoxicity against emerging cancer cells. In CLL, the T-cell compartment is defective, fostering an environment that is both immunosuppressive and pro-tumor. The major T-cell abnormalities in CLL include skewing away from a Th1 dominant response towards a Th2 response, impaired immune synapse formation and chronic activation of T cells leading to pseudoexhaustion [45, 46, 47].

Ibrutinib effects on T cells

Clinically relevant doses of ibrutinib irreversibly inhibit interleukin-2-inducible kinase (ITK), a member of the Tec family kinases that are involved in the T-cell receptor signaling pathway [48, 49]. Most studies report a decrease in the number of circulating T cells during ibrutinib therapy, which appears to disrupt the crosstalk between CLL and T-cells [45, 50, 51]. In vitro and murine models have shown that while Th2 cells depend on ITK for TCR signal transduction, Th1 cells can be continuously activated in an ITK independent fashion via redundant resting lymphocyte kinase (RLK). Ibrutinib mediated ITK inhibition depletes Th2 T-cell signaling and polarizes T cells towards a Th1 predominant phenotype [48, 52]. This Th1 polarization is accompanied by an increase in Th1-mediated cytokines (IFN- γ) while Th2-mediated cytokines (IL-2, IL-4, IL-6, IL-10, TNF- α) are significantly reduced [36, 45, 48, 53]. It is noteworthy that conflicting data exists from ibrutinib-treated patients. Plasma levels of both Th1 and Th2 cytokines decreased during treatment with ibrutinib, while the ratio of these cytokines did not significantly change [51]. A different study found that the production of Th1 and Th2 cytokines after ex vivo stimulation of peripheral blood mononuclear cells were not affected by ibrutinib therapy [54]. The effect of ibrutinib on the differentiation of IL-17 producing Th17 cells remains unclear. One study demonstrated an increase in Th17 cells ex vivo [54], whereas a decrease in Th17 cells was observed in vivo in

CLL patients following ibrutinib administration [45]. In support of the latter, Th17 differentiation is markedly diminished in ITK-deficient mice [55]; and *in vitro*, ibrutinib inhibited differentiation of murine Th17 cells. Taken together, these data illustrate the difference between *in vitro* and *in vivo* effects of ibrutinib therapy on Th polarization and highlight the importance of correlative analyses in clinical trials.

Additionally, ibrutinib attenuates the expression of T cell activation and pseudoexhaustion markers (HLA-DR and CD39) on T cells, conceivably causing a shift toward healthier effector T cells [45]. The expression of immune checkpoint molecules, PD-1 and CTLA-4, on CD8+ T cells is also reduced in patients treated with acalabrutinib, a second generation selective BTK inhibitor that does not inhibit ITK, suggesting that at least some of the observed T-cell changes on ibrutinib are BTK-dependent [54]. In a study of 15 patients treated with ibrutinib alone or in combination with rituximab, treatment resulted in diversification of the T-cell receptor repertoire, which was associated with fewer infections and more complete remissions. However, interpretation of these data is limited by the small sample size and heterogeneous treatment administered [51].

Overall, ibrutinib mitigates immune dysregulation induced by CLL by affecting the polarization, signaling, receptor repertoire and cytokine secretion of T cells. Indeed, ibrutinib enhanced *ex vivo* expansion, *in vivo* proliferation, and clinical activity of chimeric antigen receptor (CAR) T-cell therapy for CLL [56]. The addition of ibrutinib to an anti-PD-L1 antibody also enhanced tumor shrinkage in mice bearing ibrutinib-resistant lymphoma, breast, and colon cancer [57]. Anti-PD1 blockade with pembrolizumab induced a clinical response in 4 of 6 patients (66%) with Richter's transformation and prior exposure to ibrutinib. The median OS after 11 months of follow-up was not yet reached compared to an expected OS of 4 months using standard chemotherapy in Richter's transformation of CLL previously treated with ibrutinib [58]. The *in vitro* activity of T-cell engaging CD19/CD3 bispecific antibodies against primary CLL cells from ibrutinib-treated patients is also better than the activity against treatment naïve samples [59]. Clinical trials investigating the combination of immunotherapy agents with ibrutinib in CLL are currently ongoing.

Idelalisib effects on T cells

Idelalisib does not appear to have a direct cytotoxic effect on T cells [42]. The absolute number of T helper cells or cytotoxic T cells in the peripheral blood did not significantly change during idelalisib treatment among clinical trial patients [41]. In terms of the influence on cytokine production, idelalisib seems to have an effect akin to ibrutinib in which it causes a decrease in the secretion of Th2 mediated inflammatory cytokines such as IL6, IL10, TNF α , as well as CD40L *in vitro* [42].

To address immune-related toxicities related to idelalisib use, there has been a focus on its effect on Treg cells. In PI3K δ inactivated mice inoculated with various solid tumor cancer cells, a decrease in Treg function allowed for a CD8+ T-cell mediated cytotoxic response that caused tumor shrinkage [60]. One potential consequence of decreased Treg function is autoimmunity and immune related adverse effects. PI3K δ inactivated mice are prone to develop potentially fatal autoimmune colitis [61, 62]. In humans, idelalisib is known to induce immune-related colitis, rash and hepatotoxicity. In patients experiencing idelalisib-

induced hepatotoxicity, the number of peripheral blood Treg cells were lower compared to patients who did not experience hepatotoxicity [30]. Additionally, histopathologic analysis of human subjects with idelalisib-associated colitis showed an increase in infiltrating CD8+ T-cells, reminiscent of GvHD [63].

In summary, idelalisib decreases the production of Th2-associated inflammatory cytokines and blunts Treg function, promoting a CD8+ cytotoxic T-cell response. The net effect may be improved anti-tumor immunity at the cost of more immune related adverse effects.

Myeloid compartment

Myeloid cells, in particular tumor associated macrophages (TAMs) and myeloid derived suppressor cells (MDSCs) are important in the pathogenesis of CLL [64, 65]. In vitro, TAMs support the survival of CLL cells by cell-cell contact and the secretion of immunosuppressive cytokines [66, 67]. MDSCs are immunosuppressive cells that are found at increased frequency in CLL patients compared to healthy individuals and are associated with shorter lymphocyte doubling time [68, 69, 70]. Both TAMs and MDSCs impair tumor immune surveillance via expansion of Treg cells and suppression of T-cell activation in CLL [64, 68, 71].

Ibrutinib effects on myeloid cells

Studies in mice have shown that BTK regulates the differentiation, function, and migration of myeloid cells [72, 73]. Neutrophils from patients with XLA are more susceptible to apoptosis due to the accumulation of reactive oxygen species [74]. These findings suggest that despite lower expression levels of PI3K δ in myeloid cells compared to lymphocytes [75], BTK-inhibition may exert independent effects on myeloid cells. In patients with CLL, ibrutinib disrupts direct cell-cell contact between macrophages and tumor cells in the bone marrow via decreased production of CLL cell- and macrophage derived chemokines (e.g. CCL3, CCL4, CXCL12 and CXCL13) [45, 76, 77]. In considering combination therapies with ibrutinib and anti-CD20 antibody, ibrutinib inhibits antibody-dependent phagocytosis of CLL cells by macrophages and polymorphonuclear cells, as well as antibody-dependent cell-mediated cytotoxicity and, through downregulation of CD20, complement-dependent cytotoxicity [78, 79, 80]. Ibrutinib may also affect macrophage function by impairing of Fc γ receptor function, thereby decreasing in Fc γ receptor mediated cytokine production [81].

Supplementary data on the effects of ibrutinib in myeloid cells is available in solid tumor mouse models. Ibrutinib treatment shifted macrophages toward a Th1-supportive phenotype and increased cytotoxic T-cell tumor infiltration in mice with pancreatic cancer [82]. Myeloid derived suppressor cells (MDSCs) suppress anti-tumor immunity and contribute to tumor progression. The function and frequency of MDSCs were reduced in solid tumor-bearing mice treated with ibrutinib [83]. However, these findings stand in contrast with earlier work showing that MDSCs counts were not affected by ibrutinib in mice with solid tumors [57]. Mouse models have also provided conflicting data regarding the importance of BTK and TEC in the survival and expansion of macrophages [84, 85].

Idelalisib effects on myeloid cells

Data about the effects of idelalisib on the myeloid compartment are scarce. To a lesser extent than ibrutinib, idelalisib inhibits multiple facets of antibody-mediated immune response, including antibody-dependent phagocytosis [78]. CLL cells treated with idelalisib in vitro also secrete less chemokines, CCL3 and CCL4, which may reduce the recruitment of macrophages to the tumor microenvironment [33]. In addition, PI3K δ inactivation decreases the number of MDSCs in a murine model of breast cancer. Whether and how idelalisib affects MDSCs has not been described [60].

Conclusion

With widespread use of B-cell receptor signaling inhibitors, it is becoming clear that these agents not only target tumor cells, but also more broadly impact the immune system. Ibrutinib and idelalisib disrupt support signals from the tumor microenvironment to CLL cells (Figure 2). The immune dysfunction associated with CLL appears to be partially improved with ibrutinib. In contrast, idelalisib inhibits Treg cells resulting in significant autoimmune organ complications. Increased susceptibility to opportunistic infections remains an issue, in particular with idelalisib; continued vigilance for opportunistic infections in patients on chronic therapy with BTK inhibitors is warranted. As combination strategies are being investigated to eradicate CLL, it will be important to balance synergistic effects against tumor cells with the interference with host immunity and the ensuing risk of autoimmune and infectious complications.

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CLL B-Cell

Ibrutinib	Idelalisib
Loss of adhesion and lymphocytosis	
Decreased tissue homing	
Loss of interaction with protective tumor microenvironment	
Modest apoptosis	Low-level apoptosis
Decreased proliferation	

Figure 1.
Summary of effects of ibrutinib and idelalisib on CLL B-Cells.

Figure 2.
Summary of effects of ibrutinib and idelalisib on B cells, T cells and myeloid cells.

Table.

Infectious Complications with Ibrutinib, Idelalisib and Chemoimmunotherapy.

	Ibrutinib	Idelalisib plus anti-CD1220 antibody	Chemo-immunotherapy	Comments
Pneumonia	Treatment naïve 4–6% [8, 9]	Treatment naïve 19% [13]	Treatment naïve 9–11% [1]	
	Relapsed disease 6–12% [6]	Relapsed disease 8–13% [12, 81]	Relapsed disease 5–13% [4, 5]	
Pneumocystis Jiroveci Pneumonia	5 case reports of grade 2 [17]	2–3% [18]		PJP prophylaxis recommended with ibrutinib treatment
Cytomegalovirus	1 case report [23]	Idelalisib combination trials were halted due to fatal PJP and CMV infections [14]		Antiviral prophylaxis recommended with ibrutinib treatment
Aspergillus	3 case reports of aspergillus brain abscesses [19]			Increased risk of CNS and/or lung infection observed in primary CNS lymphoma with ibrutinib +/- chemotherapy and steroids