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Monitoring and Management of Toxicities of Novel B Cell Signaling Agents

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Abstract

Purpose review B cell signaling agents, including ibrutinib, idelalisib, and the BCL-2 inhibitor venetoclax have become an integral part of therapy for patients with non-Hodgkin's lymphomas. The toxicity profiles of these medications is distinct from chemoimmunotherapy. Here, we will review the mechanism of action of these drugs, their efficacy, and toxicity management.

Recent findings Ibrutinib use is associated with increased risk of atrial fibrillation and bleeding which can be managed using dose interruptions and modifications. Patients on idelalisib require close clinical and frequent laboratory monitoring, particularly of liver function tests to ensure there are no serious adverse events. Monitoring for infections is important in patients on both idelalisib and ibrutinib. Venetoclax requires close clinical and laboratory monitoring to prevent significant tumor lysis.

Summary Targeted B cell receptor therapies each have unique side effect profiles which require careful clinical monitoring. As we continue to use these therapies, optimal management strategies will continue to be elucidated.

Keywords Toxicity · Ibrutinib · Idelalisib · Venetoclax · Colitis · Pneumonitis · Opportunistic infections · Tumor lysis · Atrial fibrillation · Receptor signaling

Introduction

Recently, therapeutic treatment strategies for chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), and Waldenstrom's macroglobulinemia (WM) have been transformed by the introduction and subsequent FDA approval of two agents targeting the B cell receptor (BCR) (ibrutinib and idelalisib) and one targeting BCL2 (venetoclax). The toxicity profiles of these agents and their management are somewhat distinct from those of standard chemoimmunotherapy (CIT) combinations. Herein, we will review the mechanisms of action of BTK inhibitors, PI3 kinase inhibitors, BCL-2 inhibitors, efficacy, individual toxicity profiles, and the management of common treatment-associated toxicities.

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The B Cell Receptor

Antigenic stimulation of the extracellular domain of the B cell receptor initiates a signaling cascade responsible for B cell function and proliferation. This signal leads to recruitment of CD79a and CD79b leading to activation of spleen tyrosine kinase (SYK) and Lck/Yes novel tyrosine (LYN) kinase. SYK and LYN phosphorylate immunoreceptor tyrosine-based activation motifs (ITAMs) which activate Bruton's tyrosine kinase (BTK) and phosphatidyl inositol 3 kinase δ (PI3Kδ) [1]. Activated BTK phosphorylates and activates PLCγ2, causing release of intracellular calcium stores causing upregulation of transcription factors including NFκB leading to integrin activation, chemokine-mediated migration, and B cell proliferation [2]. B cell receptor signaling has been implicated in the pathogenesis of chronic lymphocytic leukemia through several mechanisms: it has been demonstrated that BCR/BTK signaling pathway is upregulated in CLL cells via ligand-dependent antigen-mediated pathways and ligand-independent autonomous pathways [3]. PI3Kδ which is predominately expressed on lymphocytes, is also

expressed on CLL cells [4, 5]. It is involved in BCR signaling and integrates signals from several cell surface receptors including integrins, CD40, CXCR4 [6, 7]. It plays a role in B cell chemotaxis and leads to upregulation of CLL chemokine secretion [2]. The identification of these pathways led to the development of targeted inhibitors of BTK and PI3K. Their efficacy and toxicity profiles are unique due to their on and off target effects.

Ibrutinib

Ibrutinib is a first in class, oral inhibitor of BTK. Ibrutinib is selective but has been shown to have off-target effects on other tyrosine kinases including interleukein-2-inducible T cell kinase (ITK), epidermal growth factor receptor kinase (EGFR), and T cell X chromosome kinase (TXK), as well as Tec family proteins other than BTK [8].

Byrd et al. performed a phase 1b/2 study in patients with relapsed/refractory CLL/SLL. Eighty-five patients were enrolled, with a median of 4 prior lines of therapy and were treated with either 420 or 840 mg daily of ibrutinib. The overall response rate (ORR) was 71% at both doses with 2% complete response (CR) [9, 10•]. PFS was 75% and OS was 83% at 26 months. Thirty-three percent of patients had deletion 17p and 36% had deletion 11q. These results were confirmed in the phase 3 RESONATE trial comparing ibrutinib versus ofatumumab in patients with relapsed/refractory CLL/SLL. Median PFS in the ofatumumab arm was 8 months and was not reached in the ibrutinib arm with HR 0.133 ($p < 0.001$), with 3-year PFS 59% [9, 11]. Ibrutinib was associated with 51% grade 3 or 4 adverse events reported as compared to 39% for ofatumumab. There was an increase in rates of atrial fibrillation in ibrutinib-treated patients as compared to ofatumumab. RESONATE 2 demonstrated similar progression-free survival and overall survival for upfront ibrutinib therapy compared to chlorambucil (PFS not reached vs. 18 months, HR 0.16 $p < 0.001$, OS at 24 months 98 vs. 85% HR 0.16 $p < 0.001$) [12]. Ibrutinib was well tolerated in the upfront setting, with diarrhea, fatigue, and cough being the most frequently reported adverse events (all grades). Patient-reported outcomes (PROs) were also improved in patients treated with ibrutinib, with patients reporting an increased time without symptoms and prolonged PRO quality-adjusted survival when compared to chlorambucil [13]. The HELIOS trial compared bendamustine/rituximab with and without ibrutinib and found improvements in PFS (not reached vs. 13.3 months) [14]. The addition of ibrutinib to bendamustine/rituximab was associated with 77% of patients in the ibrutinib/CIT and 74% of patients in the placebo/CIT group reporting grade 3 or 4 adverse events, most of which were consistent with the known toxicity profile of bendamustine/rituximab combination therapy (neutropenia, thrombocytopenia). Here, we will review the most common ibrutinib toxicities and their management (Table 1).

Atrial Fibrillation

The reported average incidence of atrial fibrillation in patients treated with ibrutinib in clinical trials is between 5 and 9% [9, 12, 14, 15•] with an incidence which may increase over time to up to 16% [16]. In a real-world analysis of kinase inhibitor therapy in patients with CLL, atrial fibrillation was the most common toxicity leading to ibrutinib discontinuation [17]. The mechanism for development of atrial fibrillation remains unclear, but it is possible that the off-target inhibition of BTK and TEC kinases which are also expressed on cardiac cells may alter the PI3KT-AKT signaling pathway which is cardioprotective during times of stress [18, 19].

A recent meta-analysis of four trials of patients treated with ibrutinib for CLL/SLL, mantle cell lymphoma (MCL) found a pooled incidence rate of 3.3 per 100 person years in patients receiving ibrutinib vs. 0.8 cases per 100 person years in pooled control arms [20•]. Pooled relative risk was 3.9 (CI 95% 2.0–7.5 $p < 0.0001$). Risk factors associated with developing atrial fibrillation included older age, male sex, a history of atrial fibrillation, and a history of pre-existing cardiac disease. Mato et al. evaluated a cohort of 183 treated ibrutinib patients to determine if pre-treatment variables could predict the development of atrial fibrillation [21]. Twenty patients (11.3%) developed atrial fibrillation after initiating therapy. Univariate analysis looked at predictors including age, baseline hypertension, diabetes, sex, and left atrial abnormality (LAA) on EKG. LAA was the only variable associated with the development of atrial fibrillation (OR 9.1 95% CI 2.2–37.3, $p = 0.02$) and had moderately high sensitivity and specificity (79 and 71%, respectively) [21].

Table 1 Recommended management strategies for common ibrutinib toxicities

Ibrutinib toxicity management

Toxicity	Management Gr 1 and Gr 2 toxicity	Management Gr 3 and Gr 4 toxicity
Atrial fibrillation	• Continue ibrutinib at current dose • Management of atrial fibrillation • Attempt to avoid CYP3A4 inhibitors and p-glycoprotein substrates	• Hold ibrutinib and initiate management of atrial fibrillation • Restart ibrutinib at current dose • If recurrence, hold ibrutinib, can re-challenge at lower dose
Bleeding	• Hold Ibrutinib until resolution	• Hold ibrutinib until bleeding resolution • Restart at lower dose
Arthralgias/ myalgias	• Continue ibrutinib	• Hold ibrutinib until toxicity resolution • Dose reduction not required

Currently, there are no standard guidelines for treatment of ibrutinib-induced atrial fibrillation. Thompson et al. examined the characteristics, management, and treatment outcomes of patients with ibrutinib-associated atrial fibrillation [15•].

In a multicenter, retrospective analysis, 56 patients with atrial fibrillation were identified: to manage atrial fibrillation, 51/56 patients were treated with rate control (38 patients received beta-blockers, 4 received calcium channel blockers) or antiarrhythmic therapy (19 patients received amiodarone, 4 patients received flecainide, 7 underwent cardioversion). Twenty-two of 56 patients stopped ibrutinib, 13/56 patients had a dose reduction, and 21/56 patient continued full-dose ibrutinib. Atrial fibrillation resolved in 35/56 (62%) of patients and subsequently recurred in 10/35 (28%) of these patients. Three of 56 patients experienced severe cardiac failure and 1 patient had an ischemic stroke. Eighty-two percent of patients received thromboembolism prophylaxis, 34% with antiplatelet agents (ASA, ASA/clopidogrel, ASA/clopidogrel/LMWH), and 48% with anticoagulants (warfarin, LMWH, DOAC). Eight of 56 (14%) patients had grades 3–4 bleeding, 5 of who were on thromboembolism prophylaxis (1 ASA, 1ASA/clopidogrel, 3 warfarin) [15•]. A review by Vronitkis et al. proposed an algorithm for the management of ibrutinib-associated atrial fibrillation [22]. Rate and rhythm control should be based on patient stability, with unstable patients requiring assessment by cardiology for potential cardioversion, and stable patients should receive appropriate rate or rhythm control. Close attention needs to be paid to possible drug interaction, and diltiazem, verapamil, and amiodarone should be avoided if possible. Stroke risk is determined using CHADS-VASC2 and bleeding risk with HAS-BLED calculation. If risk of thromboembolism outweighs risk of major bleed, an individualized patient decision can be made which includes (1) rhythm control and temporarily stopping ibrutinib while on anticoagulation; (2) treatment with rate control, anticoagulation, and switching from ibrutinib to another agent; (3) rate control, anticoagulation, and minimizing other medications associated with bleeding risk; and (4) rate control and continuing ibrutinib without using anticoagulation.

Current guidelines recommend interrupting therapy for ≥ grade 3 non-hematologic toxicity, with subsequent dose reductions upon repeated toxicity occurrence [23]. Dose reduction does not appear to have an effect on resolution of atrial fibrillation, though larger cohorts of patients are needed to fully evaluate this [15•]. Appropriate treatment of atrial fibrillation includes rate or rhythm control [24]. Ibrutinib is metabolized by CYP3A4, and concomitant use of CYP3A4 inhibitors (ex. diltiazem, verapamil, amiodarone) can affect serum levels, and concurrent use may require dose reduction of ibrutinib [25]. Ibrutinib also interacts with P-glycoprotein substrates (including digoxin, dabigatran), leading to increased serum drug levels which should be monitored [23]. If possible, alternative agents such a beta-blockers should be employed first if there are no other contraindications to their use. Consideration of anticoagulation should be based on patient's stroke risk using CHADS-VASC2 [26]. Patients on warfarin were excluded from phase III randomized control trials, and there we avoid warfarin use in patients given the lack of safety data for this combination. Other options for anticoagulation include direct oral anticoagulants (DOACs), while paying close attention to drug interactions with ibrutinib or LMWH.

Bleeding

In early phase clinical trials of ibrutinib in CLL and MCL, an increase in incidental, severe bleeding, including subdural hematomas and post-procedural bleeding was observed [10•, 27]. Four patients developed subdural hematomas in an early study in relapsed/refractory MCL. These were associated with trauma (falls, head trauma), and all four patients also had exposure to aspirin or warfarin preceding these events. Further analysis demonstrated that 55% of patients who experienced bleeding episodes of any grade were on concomitant antiplatelet/anticoagulants. Subsequently, patients on anticoagulation (vitamin K antagonists) were excluded from later phase clinical trials due to concern about increased bleeding risk. In the RESONATE trial, the most common bleeding AEs were grades 1–2 petechiae or ecchymoses (44 vs. 12% compared to ofatumumab). There were two episodes of major hemorrhage (grade 3 or higher) in the ibrutinib group and three in the ofatumumab arm [9]. Similar rates were also seen in RESONATE 2 with six episodes of bleeding reported, including four episodes of major hemorrhage (two CNS episodes). Three patients were on concomitant anticoagulation or antiplatelet at the time of event [9]. Eleven episodes of major hemorrhage were reported in the ibrutinib arm of the HELIOS trial, compared to 5 in the placebo arm. Six of 11 patients with major bleeding while on ibrutinib were on concomitant anticoagulation/antiplatelet agents [14].

BTK is involved in platelet signaling via GP1b (via von Willebrand factor) and GPVI (via collagen)-mediated platelet aggregation and adhesion [28]. The mechanism of increased bleeding risk remains unclear as patient's with X-linked agammaglobulinemia (congenital absence of BTK) do not have a higher risk of bleeding [29], indicating that bleeding may be related to a combination of the underlying disease as well as off-target drug effects. Lipsky et al. looked at patients treated with ibrutinib and evaluated platelet function and coagulation factors prior to and 4 weeks after treatment with ibrutinib. They demonstrated platelet aggregation was impaired when compared to healthy controls in response to both collagen and adenosine 5′-diphosphate (ADP) [30]. In vitro collagen-mediated platelet aggregation has been shown to be reversible once ibrutinib has been discontinued for 7 days [28, 31].

Recently, Caron et al. performed a systematic review and meta-analysis of observational studies and randomized control trial to determine the incidence rate of major bleeding and overall bleeding with ibrutinib as compared to treatment with other agents. Twenty-two manuscripts reported bleeding data on 2152 patients treated with ibrutinib (4 RCTs, 10 phase II studies, 3 prospective cohort studies, 5 retrospective cohort studies, 15 studies in patients with CLL, 4 in MCL, 2 in patients with Waldenstrom's macroglobulinemia) [32•]. Thirteen studies reported the incidence of overall bleeding, with pooled annual incidence of any bleeding event of 20.1 per 100 patient years (95% CI 19.1–22.1) with a pooled relative risk of 2.72 for patients treated with ibrutinib. (CI 95% 1.62–4.58 $p = 0.0002$) The pooled incidence of overall bleeding of patients treated with other therapies was 11.6 per 100 person years (95% CI, 9.1–14.4). The pooled incidence of major bleeding of 17 studies of patients treated with ibrutinib was 2.76 (95% CI, 2.07–3.53) per 100 patient years with a relative risk of 1.66 as compared to treatment with alternative therapies (CI 95% 0.96–2.85, $p = 0.07$) This study demonstrated that the overall rates of bleeding are increased with ibrutinib, and that there may be an increase in major bleeding, though this was not statistically significant [32•].

The incidence of bleeding in patients treated with concomitant antiplatelet agents (in particular ASA) and anticoagulants have recently been studied. Jones et al. retrospectively analyzed data from patients enrolled on two clinical trials to look at the frequency of treatment with concomitant anticoagulants and antiplatelet agents and their association with major bleeding. In 327 patients treated with ibrutinib for CLL, 11% received some treatment with concomitant anticoagulants and 34% with antiplatelet agents. The overall rate of major bleeding with ibrutinib (grade ≥ 3) was 2%. Of the 175 patients receiving anticoagulants or antiplatelet, the rates of major bleeding were 3% [33].

In the event of bleeding, ibrutinib should be held until resolution of bleeding episode [23]. Dose reduction is recommended in the event of clinically significant bleeding (grade 3 or higher). Dose reduction is not required for grade 1 or 2 bleeding, including ecchymoses and petechiae [23]. Given the increased risk of bleeding post-procedure, it is recommended to hold ibrutinib for 3 to 7 days prior and 3 to 7 days after invasive procedures [23, 34].

Arthralgias/Myalgias

Arthralgia and myalgias are a frequent grade 1–2 toxicity in patients treated with ibrutinib. In early trials, 27% of patients reported grade 1–2 arthralgias and 19% reported grade 1–2 muscle spasms [10•]. The frequency of these events has been observed across clinical trials [9, 35]. Importantly, arthralgias/myalgias are a common reason for ibrutinib discontinuation, occurring in 9/258 patients who discontinued therapy due to this toxicity/intolerance [36•]. In another large cohort study, the UK CLL Forum found that of 82/315 patients treated with ibrutinib required a dose reduction, with 4/82 patients requiring it for arthralgias/myalgias [37]. To our knowledge, there are no reports of effective therapies for this toxicity. Grades 3 and 4 arthralgias can be managed by a drug interruption as per label guidelines for management of non-hematologic toxicity. [23]. If arthralgias persist, ibrutinib can be dose reduced to mitigate toxicity, though there are no data to suggest that there is a relationship between dose level and toxicity.

Pneumonitis

Although it is a rare complication of treatment, several cases of ibrutinib-associated pneumonitis have been described. The largest case series by Mato et al. describes four cases of non-infectious pneumonitis associated with ibrutinib. Patients underwent extensive pulmonary work up including infectious work up, imaging, and bronchoscopy. Symptoms improved with discontinuation of ibrutinib and treatment with corticosteroids. One patient had recurrence of symptoms after resuming treatment with ibrutinib, and ibrutinib was permanently discontinued in three patients [38]. The mechanism of ibrutinib-associated lung toxicity remains unclear, though pulmonary toxicity has been observed in other target therapies, including idelalisib (~4%) [39•]. If pneumonitis is suspected, ibrutinib should be held while extensive pulmonary work up, including CT scans, infectious work up, and possibly bronchoscopy are performed. Treatment with corticosteroids should be started once infectious etiologies have been ruled out [38].

Opportunistic Infections

Opportunistic infections (OIs) not usually associated with patients with CLL and other non-Hodgkin's lymphoma have been reported since the approval of ibrutinib. A recent review by Chamilos et al. looked at the incidence of *Pneumocystis jirovecii* (PJP), *Cryptococcus neoformans*, and airborne filamentous fungi (*Aspergillus*, *Fusarium*, and *Mucorales*) in patients treated with ibrutinib [40]. Seven cases of *Cryptococcus neoformans*, 8 cases of PJP, 1 case of Histoplasmosis, 19 cases of invasive aspergillosis, 3 cases of mucormycosis, and 1 case of fusarium were described in patients with CLL, MCL Waldenstrom's macroglobulinemia, and primary CNS lymphoma. Infections occurred as early as 3 weeks into treatment and as far out as 23.6 months. Rogers et al. recently completed a retrospective cohort analysis of patients treated with ibrutinib at a single academic institution. They identified opportunistic infections in 23 of 566 patients treated. The most common OI was fungal infections, and most common of these was presumed Aspergillosis (9/23) [41]. Average duration of

ibrutinib exposure was 0.39 years. Cumulative incidence of OI was 2.3% at 6 months and increased to 4.7% at 5 years. They identified ≥ 3 lines of therapy, diabetes, and liver disease as independently associated with OI development. Of the patients, 44.9% received PJP prophylaxis, and 11.5% were on fungal prophylaxis with fluconazole. Tillman et al. performed a systematic review of infectious complications in patients on ibrutinib therapy (either single agent or in combination.). Twenty-nine full publications and 25 abstracts from 48 trail cohorts of patients treated for NHL (CLL, MCL, primary central nervous system lymphoma, Follicular lymphoma, WM, hairy cell leukemia, marginal zone lymphoma) were included in the analysis. They found 92% of trials reported infectious outcomes, with 56% of patients treated with single-agent ibrutinib and 52% treated with combination therapy experiencing one or more infections. Twenty-six percent of these were grade 3 or 4, with pneumonia accounting for 13% (single-agent treatment) and 8% (combination). Two percent of patients had grade 5 pneumonia which included cases of *PJP*, *Hisplasma*, *Crytococcus*, *Nocardia*, and *Aspergillus* [42]. Currently, routine prophylaxis for viral, PJP, or fungal infections is not recommended [23].

Acalabrutinib

Acalabrutinib is a second-generation, oral selective irreversible inhibitor of BTK. It does not irreversibly inhibit EGFR, TEC, and ITK [43], which are postulated to be responsible for many of the off-target effects of ibrutinib. In a phase 1/2 dose escalation study, Byrd et al. examined the safety and efficacy of acalabrutinib in patients with relapsed/refractory CLL. Sixty-one patients were treated and no dose-limiting toxicities were seen [43]. Patients on warfarin, medications associated with torsades de pointes, high-degree AV block, and significant QT prolongation were excluded. Of note, atrial fibrillation was not an exclusion criteria. At a median of 14.3 months of follow up, ORR was 95% which was seen across all dose cohorts. The most common adverse events observed were headache (43%, no grade 3 or 4 events), diarrhea (39%, grade 3 or 4 2%), weight gain (26%, grade 3 or 2%), and pyrexia (23%, grade 3 or 4 3%). Updated toxicity profile after median follow up of 19.8 months were similar with headache (46%), diarrhea (43%), and upper respiratory tract infections (28%) being most common. Less than five percent of patients experienced grade 3 and 4 AEs, the most common of which were neutropenia (11%) and pneumonia (10%). There were no grade ≥ 3 bleeding events, and the rates of atrial fibrillation were low (3% all grade, 2% grade 3 or 4) [44]. There are no clear patterns of toxicity and currently there are no formal management guidelines. Recently, acalabrutinib received FDA approval for treatment of relapsed mantle cell lymphoma [45] with approval for other indications including CLL pending further results of phase 2 and phase 3 trials.

Idelalisib

Idelalisib is a selective, oral phosphatidylinositol 3-kinase inhibitor (specifically PI3K p110δ) approved for use in combination with rituximab for patients with relapsed CLL and as a single agent for relapsed/refractory follicular lymphoma. There are four isoforms of the catalytic domains to PI3K: p110α, p110β, p110γ, and p110δ [46]. The gamma isoform has been implicated in T cell development and signaling, while the delta isoform is largely found on leukocytes [5]. Inhibition of p110δ has been shown to decrease downstream signaling of BCR, CXCR4, and CXCR5 leading to decreased activation of AKT, mTOR, and other pathways in preclinical studies [6, 7].

Furman et al. reported findings for patients treated with either 150 mg idelalisib plus rituximab vs. placebo plus rituximab in patients with relapsed/refractory CLL who were acceptable candidates for rituximab monotherapy [39•]. PFS was not reached in the idelalisib group and was 5.5 months in the rituximab plus placebo group (HR for progression 0.15, $P < 0.001$). Overall response rates were higher in the idelalisib group (81 vs. 13%, OR 29.92, $p < 0.001$) as was overall survival at 12 months (91 vs. 80% HR 0.28, $p = 0.02$). Idelalisib was associated with 91% adverse events reported in the treatment group vs. 94% in the rituximab group, with 56 vs. 48% of these being grade 3–4 events, respectively. Most common grade 3–4 toxicities in the idelalisib/rituximab group were hematologic (neutropenia, anemia, thrombocytopenia), transaminitis, and diarrhea. In a phase 2 study of 125 patients with relapsed indolent NHL, Gopal et al. demonstrated an ORR of 57% with a median duration of response of 12.5 months and median PFS 12.5 months [47]. Overall rates of adverse events were 82% with 54% grade 3–4 events reported. Most common grade 3–4 toxicities were diarrhea, neutropenia, and transaminitis. We will focus on the incidence and management of these common, often severe, toxicities (Table 2).

Colitis

One of the most frequent adverse events reported with idelalisib administration is diarrhea. Across clinical trials, 14–19% of patients have experienced grade 3–5 diarrhea and colitis [48]. Intestinal perforation occurred in 6 patients (of 1192 treated across phase1, 2, and 3 trials) [49•].

Diarrhea can be categorized into two groups: the first is typically self-limited, responds well to anti-motility agents, and occurs within the first 8 weeks of initiation of therapy (median time of 1.9 months) [49•]. The second type occurs

Table 2 Recommended management of common idelalisib toxicities

Idelalisib toxicity management		
Toxicity	Management Gr 1 and Gr 2 toxicity	Management Gr 3 and Gr 4 toxicity
Colitis (early: within first 8 weeks of treatment)	• Trial of loperamide • Infectious work up if persists • Hold idelalisib if persists > 3 days • Dietary modifications (low lactose diet) • Consider steroids if persistent	• Hold idelalisib • Initiate infectious work • Consider steroids if infectious work up negative • Can re-challenge at reduced dose if grade 3
Colitis (late:)	• Grade 1: trial of loperamide • Infectious work up if persists • Hold idelalisib if persists > 3 days • Dietary modifications (low lactose diet) • Consider steroids if persistent • Grade 2: Follow management for grade 3–4 toxicity	• Hold idelalisib • Initiate infectious work • Oral budesonide or IV corticosteroid therapy if infectious causes ruled out • Can re-challenge at reduced dose if grade 3
Pneumonitis	• Grade 1: continue idelalisib • Grade 2: follow management for grade 3–4 toxicity	• Hold idelalisib • CT chest imaging • Complete infectious work up including bronchoscopy • Initiate antimicrobials • Initiation of corticosteroids if bronchoscopy negative for infection
Transaminitis	• Continue idelalisib • Monitor LFTs weekly until resolution	• Hold idelalisib • Monitor LFTs weekly until resolution • Can restart idelalisib at lower dose and escalate • Permanently discontinue if LFTs ≥ 20 ULN

at a median time of 7.1 months after beginning treatment and responds poorly to anti-motility agents [49•, 50]. Across several clinical trials, there were 106 cases of ≥ grade 3 colitis requiring interruption of therapy. Seventy-one of these patients were re-challenged with reduced dose idelalisib, with 58% of patients able to continue on therapy. In the upfront setting, Thompson et al. noted that 7/40 patients developed severe colitis requiring cessation of treatment [51]. Histologic features of idelalisib-induced colitis [52] and enterocolitis [53] have been studied in patients with CLL and NHL. Typical findings include the presence of intraepithelial lymphocytosis, apoptotic crypt epithelial cells, and neutrophilic cryptitis [53].

Consensus guidelines have been created for the work up and management of early and late idelalisib-associated diarrhea [49•]. Management includes full infectious work up including stool culture, dietary modifications to eliminate potential trigger foods, and a trial of anti-motility agents if infectious work up is negative. For early-onset mild/moderate (grade 1–2) diarrhea, it is recommended to continue idelalisib at the current dose and monitor patient's symptoms weekly. For severe (grade 3), it is recommended to hold idelalisib until resolution of diarrhea and restart at a reduced dose of 100 mg BID. Corticosteroids can be used for patients with persistent diarrhea if infectious causes have been ruled out. Options include oral budesonide, oral prednisone, or IV methylprednisolone for patients unable to tolerate oral intake. Management of late diarrhea is similar to early, but grade 2 diarrhea should be treated with grade 3 management, including holding idelalisib, and steroid therapy if negative infectious work up. Idelalisib should be permanently discontinued for grade 4 diarrhea [49•].

Pneumonitis

Pneumonitis is a serious complication associated with idelalisib. Clinically, patients present with cough, dyspnea, hypoxia, fever, and are found to have interstitial infiltrates on chest imaging. The overall rate of pneumonitis is ~ 4% [48] as compared to 1% in patients treated on placebo arms of clinical trials. Across early clinical trials, there were 24 reported cases of pneumonitis, 19 of which were reported as serious adverse events (grade ≥ 3), with 3 fatalities reported [49•].

Patients with suspected idelalisib-induced pneumonitis should discontinue drug and undergo complete infectious work up, and if no improvement with appropriate antimicrobial therapy with a negative infectious work up, treatment with corticosteroids can be considered. If idelalisib-related pneumonitis is suspected, treatment should be permanently discontinued [48].

Transaminitis

Across clinical trials, 50% of patients experienced transaminitis. Most commonly, AST and ALT elevations occur in the first 12 weeks of therapy and are often reversible

with drug interruption. Sixteen percent of patients experienced ≥ grade 3 transaminitis. One fatal case was reported across clinical trials [49•]. Seventy-four percent of patients were re-challenged with idelalisib at a lower dose, but 26% of patients had recurrence of transaminitis even with dose reduction [49•]. Lampson et al. reported a higher incidence of immune-mediated hepatotoxicity in younger patients treated with idelalisib upfront [54]. While the mechanism has not been elucidated, liver biopsies demonstrated lymphocytic infiltrates on liver biopsies in patients treated with idelalisib, as well as an increase in proinflammatory cytokines CCL-3 and CLL-4 implicating an immune mechanism of damage [54].

Liver function tests should be monitored for every 2 weeks for the first 3 months of therapy, followed by monthly monitoring for up to 6 months on therapy. Monitoring can be performed every 1 to 3 months thereafter [48]. Patients can continue treatment with idelalisib with AST/ALT elevation up to 3–5× the upper limit of normal (ULN). If elevated, liver function tests should be monitored weekly until resolution of toxicity [48]. Treatment should be discontinued at levels 5–20× ULN, and idelalisib can be restarted at 100 mg twice daily once ALT/AST have normalized. In patients with AST/ALT elevations > 20× ULN, idelalisib should be permanently discontinued [48]. Dose adjustment is not required for patients with pre-existing hepatic dysfunction [55].

Opportunistic Infections

In a phase 3 study combining idelalisib with bendamustine/rituximab vs. bendamustine/rituximab, patients in the idelalisib arm were noted to have an increase in opportunistic infections as compared to placebo [56]. Specifically, four patients developed PJP pneumonitis with none reported in the placebo group. Thirteen (6%) of patients developed cytomegalovirus infections. A case report of biopsy-proven CMV gastroenteritis have also been described in patients treated with idelalisib/rituximab [57]. Patients should be started on Pneumocystis jirovecii (PJP) prophylaxis at treatment initiation [49•]. CMV serostatus should be checked prior to initiating therapy with idelalisib, and patients who are positive should have CMV antigen or quantitative polymerase chain reaction levels monitored [58].

BCL-2 Biology

The BCL-2 family proteins are responsible for the regulation of apoptosis. Bcl-2, MCL-1, and several other proteins act as anti-apoptotic signals promoting cell survival. BH3-sensitizer proteins BIM, BID, Bad, Puma, and pro-apoptotic proteins Bax and Bak act to promote apoptosis. In normal cells, these signals are balanced, but malignant cells can increase pro-survival signs by increasing levels of anti-apoptotic proteins like Bcl-2 [59, 60].

Venetoclax

Venetoclax is a specific, potent, oral inhibitor of BCL-2 ("BH3-mimetic") which induces apoptosis. It is approved for relapsed 17p deletion CLL [61]. It binds less avidly to other BCL-2 family proteins, including BCL-XL and BCL-w and has no measurable binding to MCL-1 [62] (which differs from prior BCL-2 inhibitors) [63–65]. One hundred sixteen patients with relapsed/refractory CLL were enrolled onto the phase 1 study, 56 to the dose escalation cohort, and 60 to the expansion. The ORR was 79%, and 20% of patients achieved a complete remission [66•]. In a phase 2 study, Stilgenbauer et al. demonstrated venetoclax effectively treats relapsed/refractory CLL patients with TP53 disruption. One hundred seven patients were enrolled, and 54/70 patients (77%) achieved a response compared to 40% based on historical controls ($p < 0.0001$) with 8% achieving a CR or CR with incomplete recovery of blood counts as assessed by an independent review committee [67•]. Venetoclax administration was altered in early protocols due to the incidence of tumor lysis syndrome, including two deaths [68].

Tumor Lysis

Tumor lysis syndrome (TLS) occurs in the setting of rapid lysis of malignant cells leading to release of potassium, phosphorous, and uric acid into the blood stream. Laboratory tumor lysis is defined by the presence of two or more of the following electrolyte abnormalities: hyperuricemia (uric acid > 8 mg/dl), hyperkalemia (> 6 mmol/l), hypocalcemia (corrected calcium < 7 mg/dl or ionized calcium < 1.12), hyperphosphatemia which occur within 3 days of starting or 7 days of completing chemotherapy. Clinical tumor lysis is defined by laboratory evidence of tumor lysis in combination with increased creatinine level, seizures, cardiac dysrhythmia, or death [69].

To mitigate the risk of TLS, clinical trials in CLL employed a weekly dose ramp-up period starting at 20 mg daily to allow for gradual tumor debulking. Subsequent weekly increases are to 50, 100, 200, and 400 mg/day. For patients at high risk of TLS (bulky disease defined at any lymph node ≥ 10 cm or lymph node ≥5 cm with absolute lymphocyte count ≥ 25×10^9/L, impaired baseline renal function), hospitalization is recommended [66•]. Prophylactic use of uric acid-reducing agents, potassium and phosphate-binding agents, and hydration are also employed. In the first treatment group in the phase 1 study, the first three patients treated with an initial dose of 200 mg demonstrated evidence of laboratory tumor

lysis, prompting a change in the study protocol to start therapy at 20 mg with close monitoring for tumor lysis and aggressive prophylaxis [61, 66•].

It is important to determine if patients are low, medium, or high risk for tumor lysis, and if they have any pre-existing laboratory abnormalities, particularly renal dysfunction or electrolyte abnormalities. Patients with all lymph nodes < 5 cm and absolute lymphocyte count (ALC) $< 25 \times 10^9$/L are considered low risk for TLS. Recommended prophylaxis includes allopurinol and 1.5–2 L of fluid hydration daily and monitoring to tumor lysis parameters pre-dose (initial and ramp up doses) and 6–8 and 24 h after 20 and 50 mg doses [61]. Dose ramp up can be performed as an outpatient. Patients with any lymph nodes between 5 and 10 cm or an ALC $\geq 25 \times 10^9$/L are at medium risk for TLS. Such patients should be started on allopurinol, drink 1.5–2 L of fluid daily, with consideration of additional IV fluids. Monitoring to tumor lysis parameters is performed pre-dose (initial and ramp up doses) and 6–8 and 24 h after 20 and 50 mg doses. If patients have a reduced GFR (CrCL< 80), inpatient management should be considered. Inpatient management is required for initial doses (20 and 50 mg) in patients who are high risk as defined by any lymph node ≥ 10 cm or any lymph ≥ 5 cm with an ALC $\geq 25 \times 10^9$/L. Prophylaxis should include allopurinol, rasburicase if patient uric acid level is elevated at baseline, oral fluid (1.5–2 L daily), and additional IVF at 150–250 cm^3/h [61]. CYP3A inhibitors p-glycoprotein inhibitors may increase venetoclax levels and can increase the risk of tumor lysis if used concurrently (Table 3).

If patients have any signs of laboratory TLS, venetoclax should be held. Venetoclax can be continued at the same dose if laboratory TLS resolves within 24–48 h. If these persist for > 48 h, drug should be resumed at a reduced dose once laboratory values normalize [61]. For clinical TLS, drug should be resumed at a reduced dose upon resolution of TLS event. Management of tumor lysis includes aggressive hydration, monitoring labs frequently to ensure stability, and electrolyte-specific management [61]. It is important to note that if patients develop an increase in potassium > 0.5 mmol/l above prior value, even if this is not elevated, patients should receive kayexylate. Furosemide (if patient is adequately hydrated) and calcium gluconate should be started if potassium is above the upper limit of normal, with insulin and sodium bicarbonate if patients are symptomatic (muscle cramps, weakness, paresthesias, nausea/vomiting, diarrhea). Phosphate binders should be started if phosphate is > 5.0 mg/dl. Rasburicase with aggressive IVF resuscitation should be administered if uric acid > 10 mg/dl or uric acid is > 8 mg/dl with a 25% increase from prior value and patients have an increase in Cr 0.3 mg/dl. Bicarbonate-based fluids should be avoided when giving rasburicase, as this can worsen calcium pyrophosphate precipitation [61]. Hypocalcemia (< 7 mg/dL) with associated symptoms can be managed with careful administration of calcium gluconate with appropriate cardiac monitoring. Elevations in creatinine require increase in IVF rate and close monitoring of all laboratory TLS parameters [61].

Neutropenia

Neutropenia is the most common grade 3 or 4 toxicity reported with venetoclax administration. In the phase 1 study, Roberts et al. reported 41% developed grade 3 and 4 neutropenia, though the rates of febrile neutropenia were lower (6%)

Table 3 Recommended management of venetoclax dose escalation

Venetoclax dosing			
	Low risk	Medium risk	High risk
Location	• Outpatient	• Outpatient • Consider inpatient if CrCl < 80 ml/min for 20 and 50 mg doses	• Inpatient
Fluids	• 1.5–2 L oral fluids	• 1.5–2 L • Consider additional IVF	• 1.5–2 L oral fluids • 150–200 cm^3/h IVF
Anti-hyperuricemics	• Allopurinol	• Allopurinol	• Allopurinol • Consider rasburicase if baseline uric acid elevated
Blood chemistry monitoring	• Pre-dose: initial and all ramp up doses • Post-dose: 6–8 h, 24 h post 20 and 50 mg doses	• Pre-dose: initial and all ramp up doses • Post-dose: 6–8 h, 24 h post 20 and 50 mg doses	• Inpatient (20 and 50 mg doses) pre-dose: initial and 50 mg • Post-dose: 4, 8, 12, 24 h after 20 and 50 mg • Outpatient (subsequent doses) pre-dose: before all ramp-ups • Post-dose: 6–8, 24 h after dose

Low risk: all lymph nodes < 5 cm and absolute lymphocyte count (ALC) $< 25 \times 10^9$/L. Medium risk: any lymph nodes between 5 and 10 cm or an ALC $\geq 25 \times 10^9$/L. High risk: any lymph node ≥ 10 cm or any lymph ≥ 5 cm with an ALC $\geq 25 \times 10^9$/L

[66•]. In the phase 2 trial, grade 3 or 4 neutropenia was reported in 40% of patients, with 23% of patients experiencing grade 4 neutropenia. Rates of febrile neutropenia were low and developed in five patients (5%). In both the phase 1 and phase 2 trials, grade 3 or 4 neutropenia were managed with either dose interruption or reduction, with or without granulocyte colony-stimulating factor [66•, 67•, 70]. It is currently recommended to interrupt venetoclax dosing for grade 3 neutropenia with signs of infection or fever, or grade 4 neutropenia, and to resume at same dose when at grade 1 or resolution of toxicity for the first occurrence. Patients can receive G-CSF support until neutropenia resolves and in clinical practice may require intermittent G-CSF support to maintain counts on dose-reduced venetoclax. Management of subsequent occurrences include interrupting treatment, use of granulocyte colony-stimulating factor if clinically indicated, and resuming drug at a lower dose at the resolution of neutropenia [61].

Conclusions

The BCR inhibitors, ibrutinib, and idelalisib and BCL-2 inhibitor venetoclax have demonstrated clinical efficacy in treatment-naïve and heavily pretreated patients with CLL and other NHL. All three drugs are overall well tolerated, though associated toxicities differ as compared to chemoimmunotherapy. For patients treated with ibrutinib, it is important to monitor for the development of arrhythmias, bleeding complications, and arthralgias/myalgias, as these toxicities often lead to treatment discontinuation. Colitis, transaminitis, and pneumonitis are common, but serious toxicities of idelalisib treatment, and require early intervention to prevent potentially fatal complications. Monitoring for tumor lysis and neutropenia allow for safe treatment with venetoclax, though dose modification and treatment interruption may be needed to safely administer therapy. Continued monitoring for the above toxicities allow for safe, effective treatment using these medications. Long-term safety data is not currently available but will help shape clinical practice in the future.

Compliance with Ethical Standards

Conflict of Interest Joanna Rhodes declares that she has no conflict of interest.

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Human and Animal Rights and Informed Consent This article contains studies with human or animal subjects performed by the authors.

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