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Review

# Management of adverse effects/toxicity of ibrutinib

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ABSTRACT

Bruton tyrosine kinase signaling (BTK) is critical step for B-cell development and immunoglobulin synthesis. Ibrutinib is an orally bioavailable bruton tyrosine kinase inhibitor (BTKi) and forms an irreversible covalent bound to BTK at the Cysteine-481 residue. Ibrutinib has been approved by FDA for the treatment of mantle cell lymphoma, chronic lymphocytic leukemia, Waldenstrom's macroglobulinemia, marginal zone lymphoma and chronic graft-versus-host disease in allogeneic stem cell transplantation. Ibrutinib is generally well tolerated drug with rapid and durable responses but has some side events. The most common side effects are diarrhea, upper respiratory tract infection, bleeding, fatigue and cardiac side effects. These events are generally mild (grade I–II). However atrial fibrillation (AF) and bleeding are important and may be grade III or higher side effects require strict monitoring. Here side effects of ibrutinib have been summarized and important considerations in the management of these adverse events have been reviewed.

## 1. Introduction

Bruton tyrosine kinase signaling (BTK) is critical step for B-cell development and immunoglobulin synthesis. BTK is important for B-cell receptor signaling pathway. This pathway has essential role in the proliferation, survival, migration, and homing of normal and malignant B cells. Ibrutinib has marked clinical benefit in the treatment of several B cell malignancies. This drug irreversibly inhibits BTK pathway and makes significant impacts on malignant B cells. These effects are coordinated by (1) impairment of cell adhesion leading to transient lymphocytosis (Wang et al., 2013), (2) disruption of communication with tumor microenvironment (Wang et al., 2013), (3) modest induction of apoptosis (Dreyling et al., 2016) and (4) decreased cell proliferation (Byrd et al., 2013; Rozman and Montserrat, 1995).

Ibrutinib is an orally bioavailable BTKi and forms an irreversible covalent bound to BTK at Cysteine-481 residue (Herman et al., 2011; Honigberg et al., 2010). However, its binding profile is not restricted to BTK and it inhibits other kinases including interleukin-2-inducible T-cell kinase (ITK), tec protein tyrosine kinase (TEC), BMX and epidermal growth factor receptor (EGFR) (Cheng et al., 2014).

Ibrutinib has been approved by FDA for the treatment of mantle cell lymphoma (MCL) at 2013 (Wang et al., 2013), for chronic lymphocytic leukemia (CLL) at 2014 (Byrd et al., 2013), for Waldenstrom's macroglobulinemia (WM) at 2015 (Treon et al., 2015) and for marginal zone lymphoma (Noy et al., 2017) and chronic graft-versus-host disease in allo-HCT at 2017 (Miklos et al., 2017).

Ibrutinib is generally well tolerated drug with rapid and durable responses but has some adverse events. The most common side effects are diarrhea, upper respiratory tract infection, bleeding, fatigue and cardiac side effects (Tang et al., 2017). These events are generally mild (grade I-II). However AF and bleeding are important and may be severe. Grade ≥ III side effects require strict monitoring. Here side effects of ibrutinib have been summarized and important points in the management of these adverse events have been reviewed.

### 1.1. Cutaneous side effects

#### 1.1.1. Incidence

Cutaneous manifestations have been reported in 2–27% of patients treated by ibrutinib. The most common cutaneous side effects are rash, petechiae and bruising (Byrd et al., 2013, 2014; Wang et al., 2013; O'Brien et al., 2014; Treon et al., 2015). Two distinct rash subtypes have been reported. Some are nonpalpable, largely asymptomatic petechial rash and the others are palpable and eruption is characterized by pruritic, nonblanching, violaceous papules. These clinically mimick leucocytoclastic vasculitis (Iberri et al., 2018). Rash is generally mild (grade I–II) (Iberri et al., 2018; Byrd et al., 2014; Burger et al., 2014; Chanan-Khan et al., 2016; O'Brien et al., 2014; Farooqui et al., 2015). Severe allergic drug reactions, including lip tingling and tongue swelling have been reported in cases with grade III cutaneous rash (Iberri et al., 2018).

#### 1.1.2. Management

Depends on the presence of palpable rash and its severity. Palpable

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purpuric rash has an earlier onset and shows variable clinical presentation. Generally patients are successfully treated with topical corticosteroid therapy. Oral anti-histamines, and systemic corticosteroids are used in cases with severe rash and temporary interruption of ibrutinib may be useful. Almost all patients are able to receive ibrutinib at optimal dose and dose reductions are necessary only in some cases (Iberri et al., 2018; de Weerdt et al., 2017).

### 1.2. Hair and nail toxicities

#### 1.2.1. Incidence

Hair and nail toxicities have been reported in 26% and 66% of the patients, respectively. Hair changes are characterized by softening and straightening. Nail changes are brittle fingernails or splitting. These changes are seen usually 6 months after ibrutinib treatment. This time is compatible with growth time of nails. Biotin supplementation may be useful (Bitar et al., 2016).

### 1.3. Bleeding

#### 1.3.1. Incidence

It has been reported increased rates of bleeding, including subdural hematomas, gastrointestinal bleeding, and hematuria in early clinical trials (Byrd et al., 2013; Wang et al., 2016). After these events clinicians have more attention to bleeding problems. Overall bleeding rate has been found as 20.8 per 100 patient-years in observational and randomized controlled studies (Caron et al., 2017). The incidence of bleeding in cases with ibrutinib has been compared with other therapies in two randomized controlled studies; the incidence of overall bleeding has been found as 11.6 per 100-patient years and pooled relative risk of any bleeding with ibrutinib has been found as 2.72 (Caron et al., 2017). An important problem in these analyses are definition, grading and the severity of bleeding and also drug interruptions. The relative risk of major bleeding in cases treated by ibrutinib as compared with other therapies has been found as between 1.66 (Yun et al., 2017).

In clinical trials, ibrutinib has been found to be associated with approximately 50% risk of bleeding, and the majority of these events are grade I-II bleeding (petechiae and contusion) (Byrd et al., 2015; Wang et al., 2015; Farooqui et al., 2015; Jaglowski et al., 2015). The rate of major bleeding (grade ≥III) has been reported between 1 and 10% in major trials (Table 1). However to analyze the bleeding events in cases treated by ibrutinib is complex due to the frequent use of anticoagulant (AC) and/or antiplatelet (AP) drugs. An analysis from two studies (PCYC-1102 and RESONATE) it has been found that the use of anticoagulant (11%) and antiplatelet agents (34%) was 11.5 and 34%, respectively and 3% of this population had major bleeding events (Byrd et al., 2013; Byrd et al., 2014; Jones et al., 2017). Most of these events have been reported in early period of ibrutinib treatment (within 3–6 months of therapy) and only 1% of the patients discontinued drug (Jones et al., 2017). The incidence of major bleeding in cases simultaneously receiving AP and AC (mainly low molecular weight heparin or direct oral anticoagulants) therapy were 2.5% and 3.2%, respectively (Winqvist et al., 2016; Jones et al., 2017). Major bleeding has not been reported in a study covering 15 cases receiving direct oral anticoagulants simultaneously with ibrutinib (Thompson et al., 2016). There is limited data about the major bleeding in cases receiving AC and AP combination with ibrutinib and has been reported as 21% (10/48) which is higher than patients treated by AP and AC combinations (2.6–14%) without ibrutinib (Jones et al., 2017; Mock et al., 2018). There is no sufficient data about the bleeding risk in cases using vitamin K antagonists with ibrutinib.

#### 1.3.2. Pathogenesis

BTK plays a role in platelet signaling through glycoprotein (GP) 1b and GPVI, which mediate platelet aggregation and adhesion through von Willebrand factor and collagen. However, the effect of BTK inhibition on platelet function and bleeding risk is not clear. Patients with X-linked agammaglobulinemia do not have increased bleeding despite a congenital absence of functional BTK and this point suggest that bleeding associated with ibrutinib is not a simple event and can not be defined by this pathway alone (Oda et al., 2000). CLL itself induces platelet dysfunction by impairing both adenosine diphosphate (ADP) and collagen-mediated platelet dysfunction (Lipsky et al., 2015). Platelets express both BTK and TEC which help to activate platelet aggregation by regulating phospholipase C2 downstream of the collagen receptor GPVI (Atkinson, 2003). Ibrutinib shows potent antiplatelet effects due to inhibition of collagen and von Willebrand factor-dependent platelet functions downstream of GPVI. The degree of reduction of in vitro collagen-mediated platelet aggregation in ibrutinib-treated patients has been found to be correlated with bleeding, which is reversible following addition of untreated platelets and drug discontinuation (Levade et al., 2014; Kamel et al., 2015). Platelet function and coagulation factors at baseline and 4 weeks after initiation of ibrutinib therapy have been evaluated by Lipsky et al. It has been found that lower factor VIII and von Willebrand factor activity suggest the reduced platelet function and the increased risk of bleeding before ibrutinib therapy as compared with healthy controls. On the other hand platelet aggregation has been found to be impaired in cases with CLL and response to both collagen and adenosine 59-diphosphate agonists have been found to be decreased in ibrutinib-treated and treatment-naive patients as compared with normal controls. It has been found that inhibition in collagen-induced platelet aggregation and ADP induced platelet aggregation improve with ibrutinib therapy. These findings suggest the underlying disease effect on platelet aggregation. Although ibrutinib therapy reduces platelet aggregation with collagen response to adenosine 59-diphosphate improves over time on therapy. Bleeding events decrease after 6 months of ibrutinib therapy and this is probably associated with improved disease control with ibrutinib (Lipsky et al., 2015). Defects in GPVI and integrin aIIbb3 may cause unstable thrombus formation and this may contribute to bleeding (Bye et al., 2015). These may be the underlying mechanisms for bleeding tendency in cases treated by ibrutinib.

Although grade I bruising is very frequent, it is not a predictor of major bleeding, and bruising is not the sign of ibrutinib discontinuation in these cases, because they disappear spontaneously. However in case of severe bleeding ibrutinib should be interrupted. In vitro studies showed that platelet aggregation is fully restored within 5–7 days after ibrutinib cessation and this time is compatible with physiological

**Table 1**
Rate of major bleeding from ibrutinib trials.
Reprinted from Tang PCS, 2017 Table 3.

| Trial | Study design | Major bleeding (> grade III) |
|---|---|---|
| Chanan-Khan (HELIOS) | Randomized controlled study | 4% |
| Byrd et al., 2015 | Phase II single arm | 8% |
| Barr (Resonate 2) | Randomized controlled study | 6% |
| Byrd (Resonate) 2015 | Randomized controlled study | 1% |
| Wang et al., 2015 | Phase II single arm | 6% |
| Dreyling et al., 2016 | Randomized controlled study | 10% |

platelet restoration (Levade et al., 2014; Kamel et al., 2015) In the case of serious bleeding, platelet transfusion should be considered even in the absence of thrombocytopenia. Because platelet transfusion is expected to be effective after the ibrutinib half-life interval, repeated platelet transfusions ≥3 h after the last ibrutinib dose must be considered. However there is no evidence supporting this strategy (de Weerdt et al., 2017). In cases treated by ibrutinib and clinically relevant bleeding, ibrutinib product monograph proposes one tablet dose reduction but it is not known the effect of this strategy for underlying hematologic disorder and subsequent bleeding event (Janssen, Imbruvica product monograph 2016). On the other hand indications and dosages of anti-thrombotic drugs are important. Another important point is the co-incidental use of nonsteroidal anti-inflammatory drugs and herbal supplements. Special attention must be paid for CYP3A4 inhibitors. Because these inhibitors increase the serum level of ibrutinib and cause increased toxic effects. Supportive therapy must be initiated and contributing factors for bleeding must be reviewed and also ibrutinib must be withheld until resolution of the bleeding in cases with major bleeding. Decision to re-start for ibrutinib is associated with ongoing bleeding risk and underlying disease status. It must not be forgotten that ibrutinib must be withhold 3–7 days before invasive procedures (Caron et al., 2017; Treon et al., 2015; de Weerdt et al., 2017). Although concomitant use of either AC or AP with ibrutinib does not increase the risk of major bleeding the need for AC/AP therapy must be reconsidered in every case and switch must be done to low molecular weight heparin or direct oral anticoagulants if patient is receiving vitamin K antagonists. There is no special precaution in cases planned AC/AP therapy however alternative anti-neoplastic treatment must be considered in cases requiring AP/AC combination (de Weerdt et al., 2017).

#### 1.3.3. Choice of anticoagulant

There is a paucity of safety data regarding the optimal choice of anticoagulation in ibrutinib treated patients who develop AF with elevated embolic stroke risk. Most of the ibrutinib trials prohibit the concurrent use of warfarin following observations of major hemorrhage in patients using warfarin (McMullen et al., 2014). The United States and European regulatory agencies provide contradictory recommendations regarding the concomitant use of ibrutinib and warfarin. Concomitant warfarin use is contraindicated by European Medicines Agency but is acceptable by FDA (FDA, 2015; European Medicines Agency, 2017). Another important dilemma is the anti-platelet drug use to prevent late stent thrombosis in cases performed percutaneous coronary stent placement. A minimum of 12 months of dual anti-platelet therapy (DAPT: aspirin and clopidogrel/ticagrelor) is necessary in cases performed drug-eluting coronary stent implantation while 2–4 weeks of DAPT is sufficient in cases performed bare metal stents (Fihn et al., 2012). These are important points in cases treated by ibrutinib and requiring coronary stent placement. Key points in cases using ibrutinib associated bleeding have been shown in Table 2.

### 1.4. Cardiac side effects

#### 1.4.1. Atrial fibrillation (AF)

*Incidence*. AF is important in cases treated by ibrutinib, because the most common reason for ibrutinib discontinuation is AF among treatment-related toxicities (Mato et al., 2016). Discontinuation rate has been reported as high as 32% (Jain et al., 2016, 2017; Maddocks and Jones, 2016) and AF is associated with increased risk of stroke, cardiomyopathy and mortality (Thompson et al., 2016; Fauchier et al., 2016). It has been found higher incidence of AF in a meta analysis in ibrutinib treated patients as compared with non-ibrutinib treated patients (3.3/100 person-years vs 0.8) (Leong et al., 2016). AF incidence in first 18 months is 3–7% and increases to 9–16% at longer follow up (Tang et al., 2017; Brown et al., 2017; O'Brien et al., 2014; Byrd et al., 2015; Burger et al., 2015; Leong et al., 2016; Wang et al., 2015). In a retrospective analysis, prevalence of AF has been found as 6.1% in 2292 newly diagnosed patients on ibrutinib without prior history of AF (Shanafelt et al., 2017). Median time to AF has been found as around 4 months (Tang et al., 2017).

*Pathogenesis*. Ibrutinib has arrhythmogenic potential but mechanism of AF development is not clear. QTc prolongation which is an important cardiac side effect in many of the tyrosine kinase inhibitors used in clinical practice has not been reported (Loury et al., 2013). As mentioned above AF is an important complication in cases treated by ibrutinib but AF is not seen in patients with X-linked agammaglobulinemia (XLA), a primary immunodeficiency disease characterized by BTK deficiency secondary to BTK gene mutations. There is evidence of crosstalk between BTK and TEC and the PI3K–Akt pathway (Qiu and Kung, 2000). Ibrutinib causes downregulation of the PI3K-Akt signaling pathway which may be involved in the molecular mechanism of ibrutinib-induced AF and reduced signaling in this pathway in the heart can lead to an increased susceptibility to AF (Pretorius et al., 2010). BTK and TEC transcripts have been found in human heart tissue, and increased expression has been identified in patients with AF, which may suggest the cardioprotective role in the heart in preventing both AF and stress-induced cardiomyopathy (McMullen et al., 2014). This point suggests that other kinases play a role in pathogensis of ibrutinib related AF (Stewart et al., 2001). It has also been shown that ibrutinib triggers abnormal action potentials and increases late sodium current in cultured cardiomyocytes and leads to enhanced automaticity (Yang et al., 2015).

*Risk factors for AF and severity of this adverse effect*. Older age (≥65), male sex, hypertension and history of pre-existing cardiac disease and AF, diabetes mellitus, valvular heart disease and p mitrale have been found as main risk factors in the development of AF in cases treated by ibrutinib (Shanafelt et al., 2017; Mato et al., 2017). Table 3 shows the risk factors for AF in cases treated by ibrutinib. Grade III-IV AF has been found in 42% and paroxismal AF has been found in 64% of the cases in a retrospective analysis of 56 ibrutinib treated cases with AF (Brown et al., 2017; Thompson et al., 2016).

#### 1.4.2. Management of AF

Most of the AF events are grade III and requires reduction of ibrutinib dose or discontinuation of the drug or to use anticoagulation (Tang et al., 2017; Brown et al., 2017). Generally it is not recommend to stop therapy. Because the probability of conversion of AF to sinus rythm after discontinuation of the ibrutinib is low. On the other hand to stop therapy causes worse survival rates in cases treated with ibrutinib. However available data about the reversion of ibrutinib-induced AF is

**Table 2**
Key points in cases using ibrutinib associated bleeding.
Adapted from de Weerdt I, 2017 Figure 1.

- Bruising is very frequent and does not predictive for major bleeding
  - Ibrutinib must be stopped 3–7 days before and after invasive procedures
  - Concomitant anti-platelet therapy does not increase major bleeding
  - Experience is limited in cases using concomitant vitamin K antagonist
  - Combined anti-coagulation and anti-platelet drugs must be avoided in cases • treated with ibrutinib

**Table 3**
Risk factors for AF in cases treated by ibrutinib.

- Older age (≥65),
  - Male sex,
  - AF history,
  - Hypertension
  - Pre-existing cardiac disease
  - Diabetes mellitus,
  - Valvular heart disease
  - p mitrale

variable (Thompson et al., 2016). Some authors prefer to use beta blockers for patients with ibrutinib-induced A. Because the majority of anti-arrhythmic agents are pro-arrhythmic in nature. Electrical cardioversion may be an important strategy in cases with symptomatic, persistent or permanent AF not responding to beta blockers (Tang et al., 2017).

The choice of anticoagulants in cases ibrutinib related AF is not clear enough. However pharmacologic interactions between ibrutinib and P-glycoprotein substrates (digoxin and dabigatran), CYP3A4-inhibtor anti-arrythmic drugs (verapamil and amiodarone) and direct oral anticoagulants (apixaban, rivaroxaban) must be carefully considered and patients must be informed for possible drug interactions and also monitored strictly (de Zwart et al., 2016; de Jong et al., 2015; Scheers et al., 2015). Special caution must be exercised due to potential clinically significant drug–drug interactions. Ibrutinib is predominantly metabolized by hepatic cytochrome P450 3A4 (CYP3A4) and to a lesser extent with CYP2D6. Co-administration of CYP3A4 inducers or inhibitors can cause significant drug–drug interactions, which may alter the toxicity and efficacy of the medications (Scheers et al., 2015; de Jong et al., 2015). Even though both apixaban and rivaroxaban are substrates of CYP3A4, the clinical relevance of co-administration of both substrates is not established, unless there is possibility of enzyme saturation (which is uncommon for this group of drugs).

Aspirin has been found as an effective and safe choice. Direct oral anticoagulant is preferred choice over vitamin K antagonists if a patient requires anti-coagulant based on risk of stroke according to CHA2DS2-VASc score and bleeding according to the HAS-BLED score (Vrontikis et al., 2016; Kirchhof et al., 2016). A personalized, risk-adapted approach should be taken in selecting an anticoagulant: these are HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio) for patients receiving warfarin or HAS-BED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, elderly, drugs/alcohol) for treatment naive patients (Poli et al., 2017; Lip and Lane, 2016; Lip, 2012). Factor Xa inhibitors may be the preferred choice for anticoagulation in the elderly patients with multiple comorbidities. Conversely, it is feasible to continue warfarin for patients receiving warfarin with stable INR prior to commencement of ibrutinib (Chai et al., 2017). Although evidence is not clear, it may be reasonable to lower the dose of ibrutinib in patients who develop bleeding manifestations while on concurrent anti-coagulation. Concurrent administration of CYP3A4 inhibitors in this instance may lead to clinically significant bleeding (Tang et al., 2017).

Various anti-coagulants (most commonly low-molecular-weight heparin) and anti-platelet agents have been used in trials with acceptable bleeding risk (Jones et al., 2017). Direct oral anti-coagulants may be the preferred therapy of choice due to the easy administration and reduced major and fatal bleeding compared to warfarin. In a meta-analysis and systematic review of clinical trials performed in non-cancer settings, direct oral anti-coagulants significantly reduce the rate of major bleeding (relative risk 0.72) and fatal bleeding (relative risk 0.53). In the absence of similar trials performed in cancer settings, it may not be unreasonable to extrapolate this data to ibrutinib treated patient population (Chai-Adisaksopha et al., 2014).

Ibrutinib-related AF does not significantly increase the risk of major thrombo-embolic events such as transient ischemic attack or stroke with apropriate cardiac treatment. However ideal anti-coagulation and optimal monitoring of these cases are not clear. Dual or triple anti-coagulant and anti-platelet therapy with concomitant ibrutinib should be avoided, and in these cases alternative anti-lymphoproliferative disease treatment is encouraged (de Weerdt et al., 2017). Key points in cases treated by ibrutinib associated bleeding have been shown in Table 4.

**Table 4**
Key points in cases using ibrutinib associated atrial fibrillation.
Adapted from de Weerdt I, 2017 Figure 2.

- Rate and rythm must be controlled strictly
  - The use of The use of P-glycoprotein substrates and CYP3A inhibitors must be avoided
  - There is no need for anti-coagulation in cases CHA2DS2-VASc ≤ HAS BLED score
  - Anti-coagulation is necessary in cases CHA2DS2-VASc > HAS BLED score.
  - Direct anti-coagulants are preferred over vitamin K antagonists or alternative anti-neoplastic strategy must be considered

#### 1.4.3. Sudden cardiac deaths and ventricular arrhythmias

Ibrutinib treatment is associated with increased incidence of ventricular arrhythmias. Ventricular arrhythmias are an uncommon but dangerous side effect of ibrutinib therapy. The estimates of its frequency may be artificially low, as most trials have reported sudden deaths at home of unknown cause, which may represent the additional ventricular arrhythmias. Estimated risk of ventricular events are estimated as 2/100 person-years versus 0 in non-ibrutinib-treated CLL patients in the randomized clinical trials (Lampson et al., 2017; Tomcsanyi et al., 2016). Sudden death is another important adverse event in cases treated with ibrutinib. It has been reported 11 cases of ventricular arrhythmias including ventricular tachycardia and ventricular fibrillation and six cases of sudden cardiac deaths in a retrospective review of FDA Adverse Event Reporting System (FAERS) from 2013 to 2015. In a pooled data of published clinical trials, the incidence rates of sudden cardiac death has been found as 788 events per 100,000 person-years for patients receiving ibrutinib as compared to 200–400 events per 100,000 person years for the age-matched general population (Lampson et al., 2017). In conclusion, what should we do in the clinic? First, we must remember the risk–benefit ratio of ibrutinib. Patients should be informed about the rare, but real risk of ventricular arrhythmias, and symptoms of palpitations, dizziness, and syncope must be considered carefully and investigated with electrocardiogram as well as longer term cardiac rhythm monitoring to exclude the possibility of ventricular arrhythmias (Tam and Brown, 2018).

### 1.5. Hypertension

#### 1.5.1. Incidence

Hypertension risk has been found to be increased with the increased use of ibrutinib and grade III hypertension may be detected as high 25%. In one study, 29% of patients without AF required new anti-hypertensive medications, and 89% of patients with de novo AF developed Grade III hypertension. This may suggest that patients with a predilection to worsening hypertension while on ibrutinib may also be at increased risk for developing AF (Byrd et al., 2015; Yun et al., 2017).

#### 1.5.2. Management

Hypertension may trigger the occurrence of AF and for this reason blood pressure must be monitored regularly. There is no special approach for these cases and usual therapeutic drugs are effective. All patients should have baseline ECG evaluation to document normal cardiac rhythm. Repeated ECGs should be performed during treatment if the patient mentions symptoms of unexplained palpitations, tachycardia, or irregular heart rhythms. Urgent cardiology consultation is recommended if AF is discovered.

### 1.6. Infectious complications

#### 1.6.1. Incidence

Incidence and severity of infectious episodes increase in cases with relapsed refractory cases (Byrd et al., 2015; Byrd et al., 2014; Wang et al., 2015) as compared with untreated cases: up to 52% vs 10%, respectively (Wiestner, 2015; O'Brien et al., 2014). Addition of bendamustine-rituximab to single agent ibrutinib does not increase the risk of severe infections (Chanan-Khan et al., 2016). IgA levels increase in

cases treated by ibrutinib while IgG levels do not change over time (Sun et al., 2015; Byrd et al., 2013). Intravenous immunoglobulin prophylaxis could be stopped in a study covering relapsed/refractory CLL cases (Byrd et al., 2015). Data about the incidence *Pneuomocystis jiroveci* pneumonia (PJP) is not clear and may be seen as high as 5% and also atypical PJP infections have been reported. Asymptomatic pulmonary infiltrations, chronic cough and dyspnea are frequent and atypical clinical presentation may delay the diagnosis (as long as 24 months) and treatment of PJP infection. CD4 count and serum IgG levels have not been found to be decreased. These results suggest that PJP infection is associated with BTK inhibition. If confirmed, this association could result in significant changes in surveillance and/or prophylaxis, possibly extending to other BTK inhibitors. This trial was registered at www.clinicaltrials.gov as #NCT01500733 and #NCT02514083. Diagnostic procedures are bronchoalveolar lavage, and PCR for PJP; direct flourescence antibody test has been found to be diagnostic in only one of 5 cases (Ahn et al., 2016; Wang et al., 2015; Sun et al., 2015; O'Brien et al., 2014).

Fungal infections especially invasive aspergillosis are another problem in cases treated with ibrutinib. A study covering 33 cases with fungal infections has been presented; 27 of them had invasive aspergillosis and 40% had serebral localization. About half of these patients had contributing factors for fungal infections including neutropenia, corticosteroid use, and combined immuno-chemotherapy. An important point is the early onset, with median 3 months, of these infections (Ghez et al., 2018). A survey reported from France included 33 cases with invasive fungal infection; 27 had aspergillosis, 4 had disseminated cryptococcosis, 1 mucormycosis and pneumocystis and central nervous system involvement and again early onset have been found to be remarkable in this report (85% at 6 months) (11/27) (Rogers, 2018). However risk of fungal infection decreases with longer exposure of ibrutinib with an increase in IgA level and this point requires further studies (Sun et al., 2015). Fig. 1 shows the mechanism of increased risk infectious complications in cases treated with ibrutinib.

#### 1.6.2. Management

Fever and signs of infection in a case treated by ibrutinib should alert the clinician for infections including opportunistic infections and these must be treated according to the isolated microorganisms. Oral therapy is effective for the treatment of PJP infection (de Weerdt et al., 2017; Ahn et al., 2016). Patients must be followed up for especially early onset invasive fungal infections and cerebral localizations (Ghez et al., 2018).

### 1.7. Risk of hepatitis B virus (HBV) reactivation in patients treated with ibrutinib

HBV reactivation is an important problem in cases treated by targeted drugs and especially in countries which HBV infection is endemic. HBV reactivation has been reported in two cases treated by ibrutinib followed by DFCI between 2010 and 2016 among 412 patients. Twenty one of these cases had evidence of past HBV infection who are risk of reactivation and cumulative incidence of HBV reactivation has been found as 9.5% in cases with HBV reactivation risk while 0.5% among cases without reactivation risk and the median duration of ibrutinib use was 9.5 months (1–49 months) (Hammond et al., 2018). Life-threatening HBV reactivation has been reported by Herishanu et al. Flare has been found 6 weeks after discontinuation of ibrutinib which may be compatible with recovery of immune system (Herishanu et al., 2017). Ngoma reported a case of occult HBV reactivation in a case when receiving ibrutinib (de Jesus Ngoma et al., 2015). For these reasons HBV reactivation must be considered and prophylaxis must be considered in cases with past HBV infection.

### 1.8. Hematologic complications – cytopenias

#### 1.8.1. Incidence

Grade ≥3 anemia, neutropenia and thrombocytopenia develop in 5%, 10–17% and 5%, respectively in cases treated by ibrutinib monotherapy. Ibrutinib related hematotoxicity is generally at the early months of therapy (Byrd et al., 2015; Byrd et al., 2014; Wang et al., 2015; Dreyling et al., 2016; Treon et al., 2015; O'Brien et al., 2014). It has been reported that addition of bendamustine-rituximab to ibrutinib does not increase the incidence of hematologic side effects (Chanan-Khan et al., 2016).

#### 1.8.2. Autoimmune cytopenias

Autoimmune cytopenias requiring therapy may resolve completely with ibrutinib but addition of standard immunosuppressive drugs such as glucocorticoids and rituximab to ibrutinib may be necessary in some cases showing flare of autoimmune phenomenon (Rogers et al., 2016; Vitale et al., 2016).

#### 1.8.3. Management

Toxicity of ibrutinib diminishes over time; especially grade ≥3 cytopenias, fatigue, infections, and adverse events leading to discontinuation (Byrd et al., 2015). Dose reduction due to hematologic toxicities have been performed but there is no evidence of the efficacy of this strategy. Growth factor using may be advised, but discontinuation of ibrutinib due to cytopenias are not frequent (de Weerdt et al., 2017).

### 1.9. Diarrhea

#### 1.9.1. Incidence

Diarrhea is a frequent side effect in cases treated by ibrutinib but severity is not high and self-limiting. It occurs most frequently in the first six months of the therapy and median duration is generally 20 days (Byrd et al., 2015; Byrd et al., 2014; Burger et al., 2014; Burger et al., 2015; O'Brien et al., 2014; Farooqui et al., 2015).

#### 1.9.2. Management

Anti-motility drugs only are necessary due to self-limiting nature of diarrhea (Byrd et al., 2015; Wang et al., 2015). Dose reduction and/or discontinuation due to ibrutinib associated diarrhea is not necessary except in rare occasions and prolonged discontinuation (> 14 days) is not recommended (Forum, 2016; Barr et al., 2017). Table 5 shows rules for management of ibrutinib induced diarrhea.

## 2. Drug interactions, dose and discontinuation

Ibrutinib is rapidly absorbed after oral administration, and eliminated with a mean peak plasma concentration (Cmax) of 1–2 h, and a half-life of around 4–6 h. It is primarily metabolized by cytochrome P450 (CYP3A) to PCI-45227. Erythromycin is a moderate CYP3A inhibitor while voriconazole is a strong CYP3A inhibitor and a moderate and weak inhibitor of CYP2C19 and CYP2C9 enzymes. Erythromycin is an inhibitor of CYP3A. Clearance of ibrutinib is mediated by the CYP3A enzyme and its systemic exposure is significantly increased when co-administered with CYP3A inhibitors. It has been shown that co-administration of ketoconazole (strong CYP3A inhibitor) with ibrutinib increased Cmax and area under the concentration (AUClast) of ibrutinib by 29 and 24 fold, respectively (de Jong et al., 2018). Pharmacokinetic (PK) simulations predicted that co-administering ibrutinib with erythromycin or voriconazole increases the systemic exposure of ibrutinib by 7.5- and 9.1-fold, respectively (de Zwart et al., 2016). For this reason co-administration of ibrutinib with strong or moderate CYP3A inhibitors should be avoided, if co-administration is necessary, ibrutinib dose should be reduced or interrupted (de Jong et al., 2018). Combining ibrutinib with other moderate inhibitors that are less potent than

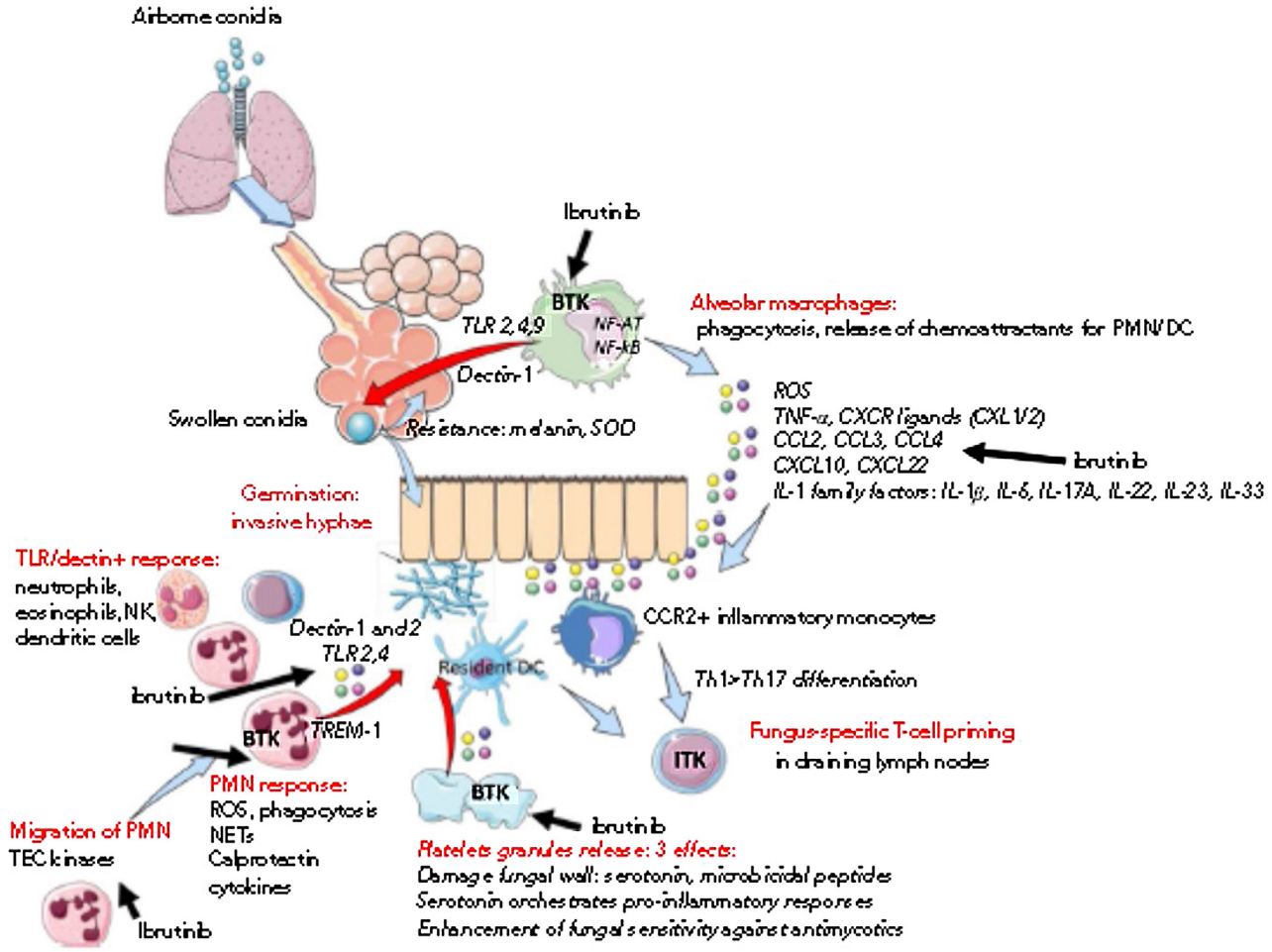


**Fig. 1.** Pathogenetic points for ibrutinib induced fungal infections. Abbreviations: DC, dendritic cells; NETs, neutrophils extra-cellular traps; PMN, polymorphonuclear neutrophils; ROS, reactive oxygen species; SOD, superoxyde dismutase; Th, T helper.
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**Table 5**
Management of ibrutinib induced diarrhea.
Adapted from de Weerdt I, 2017 Figure 3.

| Ibrutinib induced diarrhea | |
|---|---|
| Grade I/II | Grade III/IV |
| • Patient assessment<br>• Physical examination<br>• Loperamide after every stool<br><br>Diarrhea ≥3 days<br>• Culture for enteric pathogens<br>• Loperamide after every stool<br>• Interrupt ibrutinib<br>Still diarrhea ≥3 days<br>• Steroids<br>• Consider lactose-free diet<br>Upper gastrointestinal involvement<br>• Start systemic steroids (Oarl/Intravenous)<br>No upper gastrointestinal involvement<br>• Start oral steroids, consider distally released agents (budenofalk, cortiment) | • Hospital admission<br>• Culture for enteric pathogens<br>• Interrupt ibrutinib<br>Negative cultures<br>• Steroids<br>• Consider lactose-free diet |

erythromycin, such as fluconazole or verapamil or inhibitors used at lower doses, may result in exposures lower than those obtained with 560 mg ibrutinib alone. Thus, a dose reduction to 280 mg may be more appropriate with some moderate inhibitors to avoid under-dosing patients with B-cell malignancies. Indeed, per European summary of product characteristics approved for ibrutinib, a dose reduction to 280 mg is recommended in patients receiving moderate inhibitors for the duration of the inhibitor used with close monitoring for toxicity. It has been demonstrated that ibrutinib 140 mg with voriconazole or erythromycin provides exposure within the clinical range for patients with B-cell malignancies (de Jong et al., 2018).

Ibrutinib is metabolized by CYP3A4 and can increase the levels of P-glycoprotein substrates such as digoxin and dabigatran which are frequently used in older cases with CLL (de Weerdt et al., 2017; Prescribing information). For this reason concomitant use of CYP3A4 inhibitors especially azoles, macrolides and diltiazem increase the serum level of ibrutinib while CYP3A4 inducers such as rifampicin or carbamazepine can decrease the levels of ibrutinib (de Zwart et al., 2016).

## 3. The modifications and discontinuation rates due to adverse events

The dose modifications have been found to be necessary in 19–26% of the cases with a median follow up of 1.5 years (Forum, 2016; Mato et al., 2017). Up to one fifth of the patients discontinued the drug due to adverse events in prospective studies with ibrutinib monotherapy (O'Brien et al., 2014). In real World experiences discontiuation rates were found between 11 and 50% (Byrd et al., 2013; Winqvist et al., 2016; Mato et al., 2017). The most frequent reasons for discontinuation or dose reduction have been found to be variable between the series and these side effects were atrial fibrillation, bleedi ng, general debility,

arthralgia, infection especially pneumonitis and secondary malignancy (Forum, 2016; Mato et al., 2017; Winqvist et al., 2016). Up to 10% of the cases had fatal adverse events (Byrd et al., 2014; Wang et al., 2015; Burger et al., 2015; Dreyling et al., 2016; Lampson et al., 2016).

## Conflict of interest

There is no conflict of interest.

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