Incidence and management of toxicity associated with ibrutinib and idelalisib: a practical approach

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ABSTRACT

The use of novel B-cell receptor signaling inhibitors results in high response rates and long progression-free survival in patients with indolent B-cell malignancies, such as chronic lymphocytic leukemia, follicular lymphoma, mantle cell lymphoma and Waldenström macroglobulinemia. Ibrutinib, the first-in-class inhibitor of Bruton tyrosine kinase, and idelalisib, the first-in-class inhibitor of phosphatidylinositol 3-kinase δ, have recently been approved for the treatment of several indolent B-cell malignancies. These drugs are especially being used for previously unmet needs, i.e., for patients with relapsed or refractory disease, high-risk cytogenetic or molecular abnormalities, or with comorbidities. Treatment with ibrutinib and idelalisib is generally well tolerated, even by elderly patients. However, the use of these drugs may come with toxicities that are distinct from the side effects of immunochemotherapy. In this review we discuss the most commonly reported and/or most clinically relevant adverse events associated with these B-cell receptor inhibitors, with special emphasis on recommendations for their management.

Introduction

Recently, a new class of drugs has been introduced for the treatment of various B-cell malignancies, including chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma, follicular lymphoma, mantle cell lymphoma, marginal zone lymphoma and Waldenström macroglobulinemia. These drugs inhibit Bruton tyrosine kinase (BTK) or phosphatidylinositol 3-kinase (PI3K), key components of the B-cell receptor signaling pathway that is crucial for proliferation, survival and homing of malignant B cells.[1-6] They are highly effective with respect to induction of remission and prolongation of progression-free survival compared to standard therapies in patients with relapsed or refractory disease, high-risk disease (e.g. CLL with deletion of 17p) or elderly or comorbid patients unfit for immunochemotherapy. Ibrutinib is currently approved for the treatment of mantle cell lymphoma in patients who have received at least one prior therapy, CLL, Waldenström macroglobulinemia [United States Federal Drug Agency (FDA), European Medicine Agency (EMA)] and marginal zone lymphoma (FDA), and idelalisib is approved for previously treated CLL in combination with rituximab and for follicular lymphoma and small lymphocytic lymphoma in patients who have received at least two prior therapies (FDA, EMA).[7-13]

Ibrutinib covalently inhibits BTK, which is essential for B-cell homeostasis. Genetic loss of BTK, as occurs in X-linked agammaglobulinemia, results in the absence of B cells and hypogammaglobulinemia.[14] Inhibition of BTK in malignant B cells induces diminished proliferation, decreased survival and impaired adhesion and migration of the malignant B cells to their growth-promoting microenvironment.[1-4] Idelalisib is a reversible inhibitor of PI3Kδ. PI3K is a cytoplasmic tyrosine

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kinase involved in various signaling pathways, most importantly activating the AKT/mTOR pathway. The δ isoform is ubiquitously expressed in leukocytes. Inhibition of PI3Kδ induces disruption of interactions between malignant B cells and their microenvironment.

The use of these drugs comes with side effects that are uncommon for immunochemotherapy-based regimens, and in this review an overview is given of their nature and management. Richter transformation is not discussed extensively as it is not an adverse event, although it is important to be aware that Richter transformation is occasionally observed during treatment with B-cell receptor inhibitors.[15,16]

We performed extensive searches in PubMed and screened published abstracts of the American Society of Hematology, the European Hematology Association and American Society of Clinical Oncology from 2014 up to January 2017 using the search term 'ibrutinib' or 'idelalisib'. We incorporated reports of clinical trials, real-world analyses, meta-analyses, original articles about mechanisms of action or resistance, and articles on specific side effects of interest. Information from clinical trials was used either from the most recent publication, or, when appropriate, from earlier reports in the case that the required details were only given there.

Ibrutinib

The currently approved daily dose is 560 mg for patients with mantle cell lymphoma and 420 mg for those with CLL/ small lymphocytic lymphoma and Waldenström macroglobulinemia.[9,11,17-19] Ibrutinib has also been combined with the anti-CD20 monoclonal antibodies rituximab or ofatumumab[10,20] and with bendamustine plus rituximab in clinical trials.[21,23]

Ibrutinib is often associated with asymptomatic lymphocytosis upon initiation of treatment. Lymphocytosis has been recognized to be inherent to its mechanism of action, as ibrutinib disrupts integrin-mediated adhesion and homing of malignant B cells to the lymphoid microenvironment, and does not require any specific management even when persistent for months.[24]

Drug interactions, dose and discontinuation

Ibrutinib is metabolized by CYP3A4, and concomitant use of a CYP3A4 inhibitor (e.g. antifungal azoles, macrolides and diltiazem) or CYP3A4 inducer (e.g. rifampicin or carbamazepine) has been demonstrated to have profound effects on serum ibrutinib levels in healthy volunteers.[25] Ibrutinib can also increase the levels of P-glycoprotein substrates (e.g. digoxin, dabigatran).[26]

It has not been definitively established that dose (or serum level) affects tolerability, but two observations suggest that it does. The first observation is the higher discontinuation rate due to adverse events in CLL patients on a higher dose (840 mg/day) than those on the current standard dose of 420 mg/day, although the cohorts were rather small [4/34 (12%) *versus* 2/51 (4%)].[27] The second observation is that patients who experienced inacceptable toxicity were able to continue ibrutinib treatment after dose reduction without progression-free survival being affected.[28,29]

It seems safe to discontinue ibrutinib for at least 8-14 days without this affecting progression-free survival, e.g. in the case of invasive procedures (see section on bleeding).[29,30] Dose reduction because of adverse events allows the continuation of ibrutinib without affecting progression-free survival.[28,29]

The discontinuation rate because of adverse events in prospective studies with ibrutinib monotherapy increased over time to 20% after a median time on study of 46 months.[31] The incidence of dose modification in two real-world analyses was 19% and 26% (median follow-up of 17 and 16 months, respectively).[29,32] The reported incidence of permanent discontinuation varied greatly in real-world experience: two studies reported 11% and 18% discontinuation rates due to adverse events (median follow-up 10 and 16 months)[29,33] and one reported a 51% discontinuation rate due to adverse events (median follow-up 17 months).[32] The most frequent reasons for discontinuation or dose reduction varied between the studies and included, in alphabetical order: arthralgia, atrial fibrillation (AF), bleeding, second malignancy, general debility, infection and pneumonitis.[29,32,33]

Fatal adverse events have been reported in 1-9% of patients on single-agent ibrutinib.[8,9,19,33-35]

Bruising and clinically relevant bleeding

Incidence and severity

Safety concerns on the combination of ibrutinib and anticoagulant/antiplatelet (AC/AP) therapy were raised by the company during the first trials. The concerns were based on the observation of incidental severe bleeding, including subdural hematomas and post-invasive procedural bleeding, although precise information on the number of patients and concomitant AC or AP therapy was not released.[9,11,27] The observed bleeding events subsequently led to the exclusion of patients on vitamin K antagonist therapy in trials and the strong recommendation to avoid combining ibrutinib with vitamin K antagonists outside clinical trials.[8,10,21,36] Additionally, it was advised to withhold ibrutinib 3-7 days before and after invasive procedures depending on the bleeding risk.[11,26] *In vitro* studies demonstrated a collagen-dependent platelet activation defect and absent adherence to von Willebrand factor in 7/14 patients after starting ibrutinib, of whom five had bruising.[37] Intriguingly, however, another study found that the platelet function assay already showed impaired aggregation at baseline in 22/85 tested patients, i.e. before starting ibrutinib, with the proportion increasing to 41/85 after starting ibrutinib.[38] After initiation of ibrutinib treatment, this study also found inhibition of collagen-induced platelet aggregation, whereas the ADP-induced platelet aggregation improved on ibrutinib therapy. None of the 99 patients in these two studies had major bleeding. These preclinical and clinical findings all raised interest in reporting the incidence and severity of bleeding in patients on ibrutinib.

With the abovementioned restrictions and precautions, lower grade (<3) bleeding (mainly ecchymosis and petechiae presenting during the first 6 months) occurred in 28% of 50 patients unequivocally reported not to be on simultaneous AP or AC therapy.[9] A systematic review of four randomized controlled trials confirmed an increased incidence of any grade bleeding, with a 2.93-fold increase (P=0.03) in the ibrutinib compared to the control arms. The relative risk of major bleeding was 1.72 in the ibrutinib compared to the control arms (P=0.07).[39] The addition of ibrutinib to bendamustine-rituximab did not result in a

higher incidence of any grade or major bleeding.[40]

Grade ≥3 bleeding occurred in 2-4% in the studies unambiguously reporting on patients not on concomitant AP or AC therapy (11/392)[9,41,42] which seems to be of a similar magnitude as observed in treated patients before the targeted therapy era (6%/year).[43] The rate of major hemorrhagic events (grade ≥3 and intracranial bleeding) was similar (3.8%) among the 287 patients treated with ibrutinib and bendamustine-rituximab, without a difference between patients on or not on concomitant AP or AC treatment.[21]

The incidence of major bleeding in patients simultaneously treated with AP, but not AC, treatment was 2.5% (8/318).[33,41,42,44] This is comparable to the 2.2-2.7% risk of major bleeding per year in patients treated with long-term, low-dose aspirin (up to 325 mg) and is of the same magnitude as that in patients on aspirin and clopidogrel (3.7%).[45,46]

The incidence of major bleeding was 3.2% (2/62) in patients being concomitantly treated with AC [mainly low-molecular-weight heparin or directly acting oral anticoagulants (DOAC)], but not AP.[33,41,42,44] In the report with the highest number of patients on concomitant DOAC therapy and detailed information on bleeding incidence, none of the 15 patients developed major bleeding.[47] The 3.2% risk of major bleeding among patients on concomitant AC therapy is within the range reported for long-term vitamin K antagonists (3.1%-3.4% per year) or DOAC (2.1%-3.6% per year) treatment for AF.[48-50] As only a few patients had received vitamin K antagonists concomitantly with ibrutinib in the referenced studies, it is uncertain whether co-treatment with a vitamin K antagonist may result in a higher risk of major bleeding.

Experience with ibrutinib in combination with both AP and AC treatment is limited. Major bleeding was reported in 10/48 patients (21%).[41,42,44] This incidence seems higher than that reported for dual/triple AP and AC therapy in patients not on ibrutinib treatment (2.6%-14%),[46,51,52] despite the possibility that major bleeding in patients on ibrutinib is overestimated due to the low number of patients.

Management

The clinically most relevant issues are summarized in Figure 1.

Although grade 1 bruising is very frequent, it does not need to be considered a precursor of major bleeding, nor should bruising lead to ibrutinib discontinuation as in the vast majority of patients it will not advance beyond grade 1 severity and will disappear spontaneously.

The concomitant use of either AP or AC with ibrutinib does not increase the risk of major bleeding, based on the limited follow-up currently available, and does not, therefore, require any specific precautions. Nonetheless, the need for AP or AC therapy should be reconsidered in every case, particularly since it is not unusual that the indi-

Table 1. Adverse events reported during ibrutinib use.

	Previously untreated [19, 62]	Previously treated [8, 9, 11, 20, 34, 65, 92]
Total (number)	165	730
Diarrhea, any grade	42-68	29-82
Grade ≥3	4-13	0-7
Fatigue, any grade	30-32	21-98
Grade ≥3	1-3	2-4
Arthralgia, any grade	16-23	17
Grade ≥3	0	0-1
Bleeding, any grade	NR	10-50
Grade ≥3 *	4	6-8
AF, any grade	6	4-14
Grade ≥3	1	2-12
Neutropenia, any grade	16	16-48
Grade ≥3	10-17	0-11
Anemia, any grade	16-19	16-48
Grade ≥3	0-6	0-16
Thrombocytopenia, any grade	13	17-52
Grade ≥3	2-3	4-13
Infection, any grade	NR	70-78
Grade ≥3	10	24-28
Febrile neutropenia, any grade	2	3
Pneumonia, any grade	NR	10-20
URTI, any grade	17-26	16-28
Cataract, any grade	NR	3

Values represent percentages of patients affected. AF: atrial fibrillation, URTI: upper respiratory tract infection, NR: not reported.

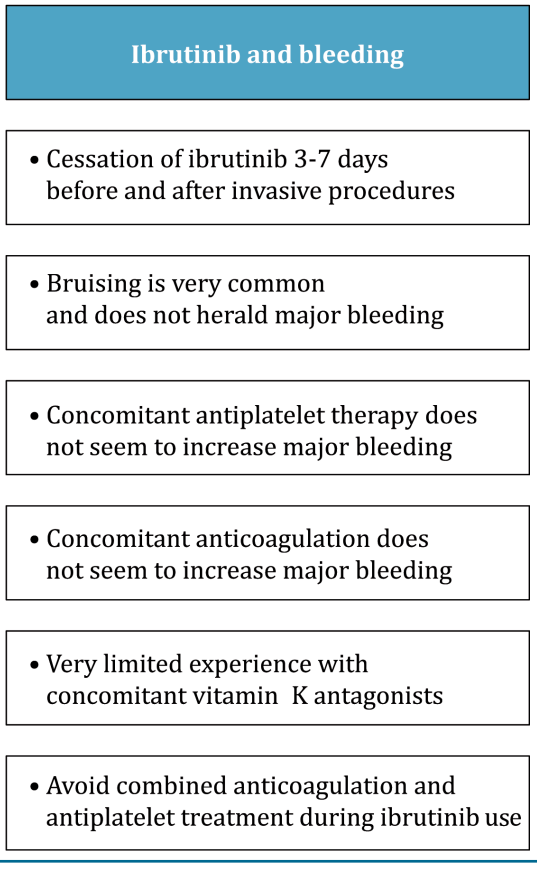

Figure 1. Summary of relevant issues relating to bleeding and anticoagulation during ibrutinib treatment.

cation has expired. As experience with concomitant vitamin K antagonists is almost absent, and because of the warnings in the early days, patients should switch to either low-molecular-weight heparin or a DOAC. If dual or triple therapy with AP and AC is required, alternative antineoplastic therapy should be considered, when available, because of the high risk of major bleeding.

In the event of severe bleeding ibrutinib should be interrupted, although there is no evidence about the efficacy of ibrutinib interruption. However, since temporary discontinuation does not compromise progression-free survival, it seems rational in these cases.

In line with safety measures in clinical trials, perioperative withdrawal of ibrutinib for 3-7 days should be considered for invasive procedures, although interruption may not always be necessary if mechanical hemostasis is feasible. *In vitro* studies showed that platelet aggregation is fully restored within 5-7 days after ibrutinib cessation, which coincides with the time of physiological platelet restoral.[37,53] In the case of serious bleeding, platelet transfusion should be considered even in the absence of thrombocytopenia. As platelet transfusion is expected to be most effective after the ibrutinib half-life interval, repeated platelet transfusions ≥3 hours after the last ibrutinib dosage may be considered, although no evidence is available to support this strategy.

Atrial fibrillation

Incidence and severity

The incidence of AF was 9% with a median time on ibrutinib of 46 months.[31] A meta-analysis of four trials with a median follow-up of 26 months found an incidence of AF of 3.3/100 person-years in patients receiving ibrutinib, and 0.8 in the non-ibrutinib-treated patients.[54] The latter incidence is in the same range as that found in 2444 non-ibrutinib-treated patients (1/100 person-years).[55] In both ibrutinib- and non-ibrutinib-treated patients, older age, male sex, a history of AF, hypertension and pre-existing cardiac disease increased the likelihood of developing AF.[40,55] In a retrospective analysis of 56 AF events during ibrutinib treatment 42% of the patients had grade 3-4 AF (i.e. symptomatic or requiring urgent treatment) and AF was paroxysmal in 64%.[47]

Ibrutinib treatment also results in an increased incidence of ventricular arrhythmia, which was estimated to be 2/100 person-years *versus* 0 in non-ibrutinib-treated CLL patients in the randomized clinical trials.[56]

Management

Based on currently available information, it cannot be recommended to withhold ibrutinib when AF develops because this does not seem to result in a higher resolution rate of the AF,[47] but does compromise progression-free survival and overall survival (see above). Likewise, dose reduction does not alter the resolution rate of AF.[47] Given the observation that once AF has developed ibrutinib withdrawal does not change its course, appropriate treatment of AF should be started as would be done in non-ibrutinib-treated patients. The pharmacological interactions with P-glycoprotein substrates (e.g. digoxin, dabigatran), CYP3A4-inhibiting anti-arrhythmic drugs (e.g. verapamil, amiodarone) and certain DOACs (e.g. apixaban, rivaroxaban) should be taken into account (see section on pharmacokinetics).[25,57-59] If AC therapy is indicated based on the risk of stroke (CHA_2DS_2-VASc score) and bleeding (HAS-BLED score),[60,61] a DOAC is preferred over a vitamin K antagonist because of the above-mentioned considerations (see section on bleeding) and because of the favorable risk-benefit profile of DOACs in AF patients (Figure 2). Dual or triple AC and AP therapy with concomitant ibrutinib should be avoided, and in these cases alternative anti-lymphoproliferative disease treatment is encouraged.

Hypertension

Incidence and severity

The incidence of grade ≥3 hypertension requiring medical treatment among patients on ibrutinib therapy increased over time to 26% after 46 months.[7,31] After initiation of antihypertensive medication, dose reduction or discontinuation of ibrutinib due to hypertension was not reported to be necessary.[19,62]

Management

Blood pressure should be monitored regularly, especially since hypertension may be co-causal for the development of AF. Hypertension should be managed as usual. The dose of ibrutinib does not need to be reduced nor does the ibrutinib need to be discontinued.

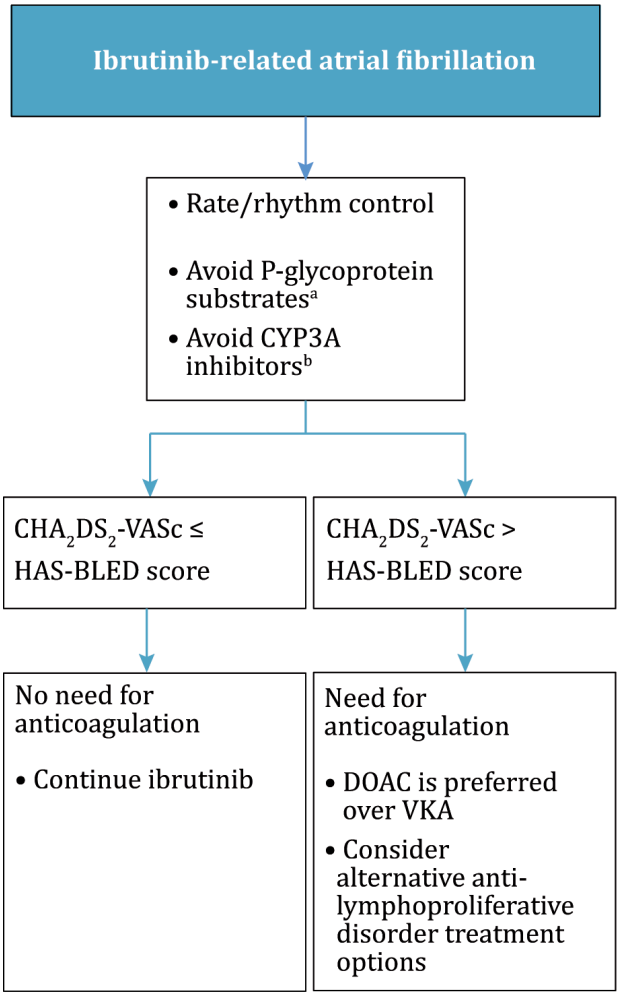

Figure 2. Flowchart for management of atrial fibrillation during ibrutinib use. [a]e.g. digoxin [b]e.g. verapamil, diltiazem. DOAC: directly acting oral anticoagulants; VKA: vitamin K antagonists.

Severe infections

Incidence and severity

Grade ≥3 infections occurred in 10-13% of 60 treatment-naïve patients[7,62] and 24-52% of 407 relapsed/refractory patients on ibrutinib monotherapy.[7-9] Addition of ibrutinib to bendamustine-rituximab did not lead to an increased incidence of severe infections, as the exposure-adjusted incidence of severe infections was 2.3 per 100 patient-months in both groups.[21,40] Improved IgA levels (>50% over baseline) are associated with a decreased risk of infection.[63]

Infection prophylaxis with intravenous immunoglobulin administration that had been started before ibrutinib therapy was stopped in 55% of the patients with relapsed/refractory CLL.[7] Of note, although IgG levels remained stable during initial therapy, IgG levels declined after 12 months of ibrutinib.[27,63]

Five cases with PCR-evidence of *Pneumocystis jiroveci* pneumonia (PJP; all grade ≤2) were found in one cohort of 96 patients,[64] although no other studies reported PJP in ≥1% of their patients.[9,63,65]

Management

For patients on ibrutinib presenting with fever or other signs of infection a thorough work-up should be started to identify the focus and etiological microorganism, including opportunistic pathogens. Treatment of bacterial infections should be based on local resistance patterns. The estimated low incidence of PJP during ibrutinib treatment does not justify PJP prophylaxis.[66]

Hematologic complications

Incidence and severity

Grade ≥3 neutropenia occurred in 10-17% of the patients on ibrutinib monotherapy, usually in the initial months of therapy.[8,9,11,19,31,34] Grade ≥3 anemia and thrombocytopenia each occurred in approximately 5% of the patients.[7,8,19,34] Ibrutinib did not increase the incidence of cytopenias when added to bendamustine-rituximab.[21]

Management

Dose reduction because of cytopenia has been reported in some patients (with unknown benefit), as has the use of growth factors. Discontinuation of ibrutinib because of cytopenia has seldom been judged necessary.

Autoimmune cytopenia

Autoimmune cytopenias that needed treatment before starting ibrutinib may resolve completely, while in some patients a temporary flare or first episode has been observed.[67,68] Autoimmune cytopenias could typically be managed with continuation of ibrutinib and temporary addition of standard immunosuppressive treatment (e.g. glucocorticoids, rituximab).[68]

Diarrhea

Incidence and severity

Diarrhea has been frequently reported in patients on ibrutinib, but its severity rarely exceeds grade 1.[7,8,10,19,62,69] It occurs most often during the first 6 months of treatment,[70] and its median duration is 20 days.[7]

Management

Diarrhea is usually self-limiting, and antimotility drugs are only occasionally required.[7,9] Dose reduction or discontinuation of ibrutinib because of diarrhea has rarely been necessary.[7-9] Beneficial effects of reducing the dose of ibrutinib in combination with antimotility drugs have occasionally been reported.[7,8] However, prolonged discontinuation of ibrutinib (>8-14 days) is not recommended.[29,30]

Rash

Incidence and severity

Rash occurs frequently and is generally classified as grade 1 or 2.[8,10,21,62,69]

Management

Rash often recovers spontaneously without any specific treatment. Pruritic rash may require topical corticosteroid therapy and oral histamines. Treatment interruption was

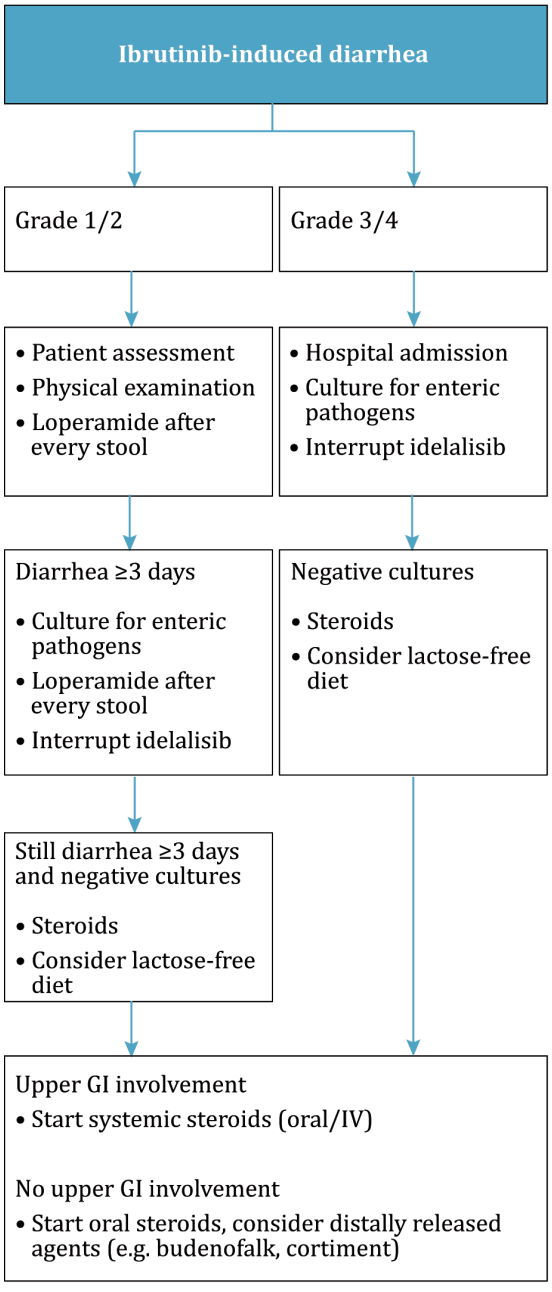

Figure 3. Flowchart for management idelalisib-induced diarrhea. GI: gastrointestinal tract. IV: intravenous.

judged necessary in some patients only, but ibrutinib dose-reduction or discontinuation has not been reported for this rash.

Hair and nail alterations

Hair alterations were described in 26% of 66 patients during ibrutinib therapy.[71] The hair changes were characterized by softening and straightening. Brittle fingernails or splitting of the nails developed in 67%, usually at 6 months after starting ibrutinib, which is consistent with the growth time of nails.

There is only anecdotal evidence that biotin supplementation resulted in some benefit.[71]

Cataract

Although animal studies initially raised concern over an increased incidence of cataract formation during ibrutinib treatment, the observed cataract rate in serial ophthalmological examinations in clinical trials in 506 patients was similar to that observed in the age-matched population.[27,72-74]

Idelalisib

The approved dosage of idelalisib is 150 mg twice daily. In Europe, idelalisib is currently approved in combination with rituximab for patients with CLL and as monotherapy for patients with relapsed/refractory follicular lymphoma. Asymptomatic lymphocytosis is frequently seen at the beginning of idelalisib treatment in CLL and small lymphocytic lymphoma, with no need for specific management.

Drug interactions, dose and discontinuation

Dose reductions of concomitant CYP3A4 substrates may be needed, since the main metabolite of idelalisib is a potent CYP3A4 inhibitor.[75] Strong CYP3A4 inducers (e.g. rifampicin) can decrease idelalisib levels.[75]

In phase I-II trials, 9-20% of the patients discontinued treatment because of adverse events.[13,76-78] A phase III CLL trial (n=110) reported treatment discontinuation because of adverse events in 8% of the patients.[12] Serious adverse events, most commonly pneumonia, fever and febrile neu-

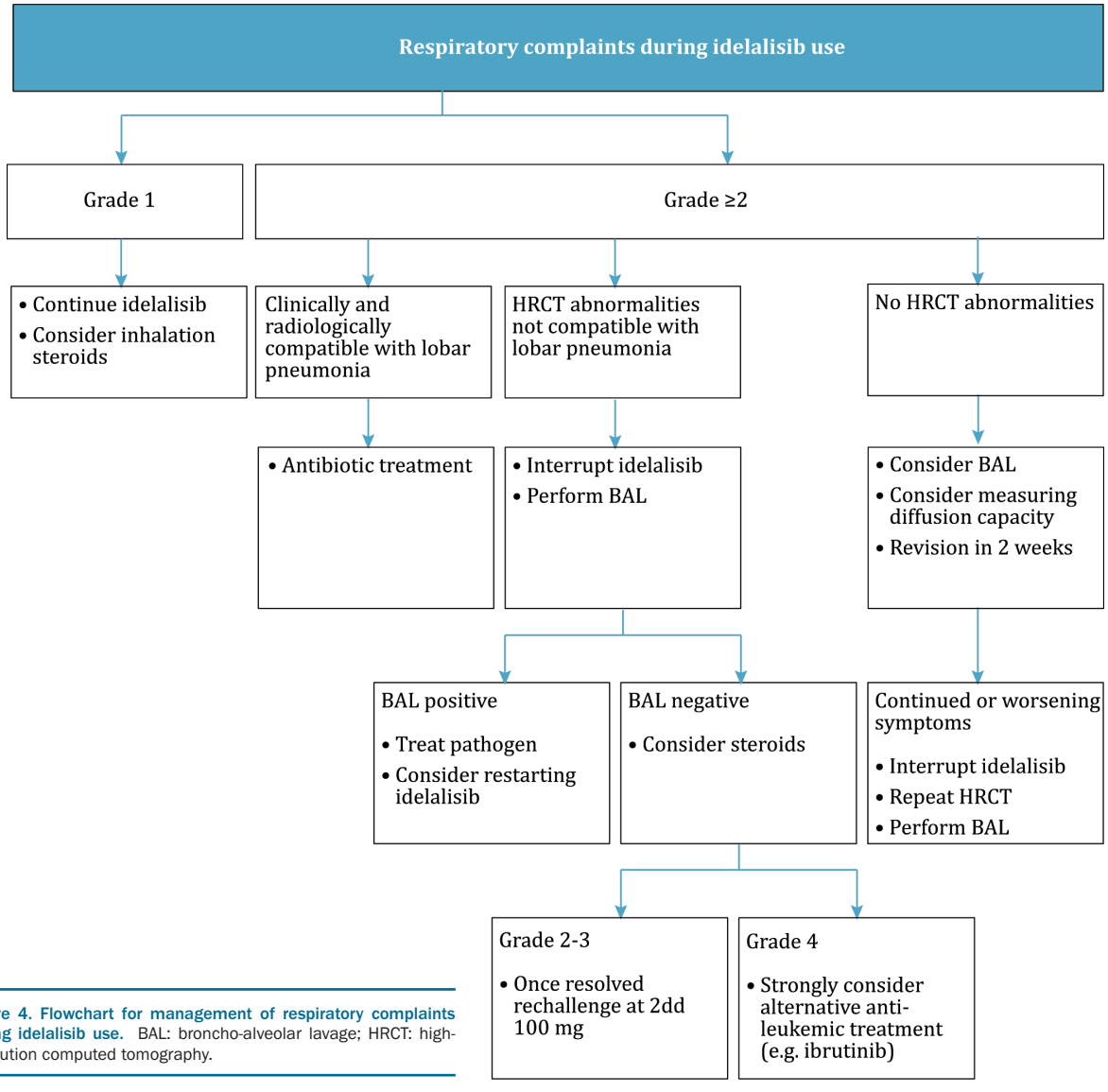

Figure 4. Flowchart for management of respiratory complaints during idelalisib use. BAL: broncho-alveolar lavage; HRCT: high-resolution computed tomography.

tropenia, occurred in 40% of the patients. Of note, in a trial of idelalisib in combination with rituximab in treatment-naive patients the discontinuation rate due to adverse events was considerably higher, at 45%, mainly due to a higher incidence of diarrhea and/or colitis and pneumonitis.[79] Potential explanations include the addition of rituximab, although the rate of adverse events appears higher than in other trials of idelalisib and rituximab, and the fact that patients were previously untreated,[2] and thus had a more intact immune system, together with histopathological findings supporting the hypothesis that these adverse events resulted from an autoimmune mechanism.[35,80-82] Fatal non-progression adverse events have been reported in 3-8% across trials.[13,76-79] It is of note that published data on long-term safety of idelalisib treatment are lacking, as the median follow-up time in the published trials ranges from 3.5 to 9.7 months only.[12,13,76,78]

Results of a recent planned interim analysis of three ongoing randomized idelalisib trials pointed towards decreased overall survival in the idelalisib arms. The fatal adverse events observed were mostly of an infectious nature, including opportunistic infections, specifically PJP and cytomegalovirus infections, and were more commonly seen in the idelalisib study arms, which led to a major drug warning by Gilead.[83] Following completion of an EMA review, the benefit-risk balance of idelalisib in combination with rituximab for the treatment of relapsed CLL, including patients with 17p deletion or *TP53* mutation, and idelalisib monotherapy for the treatment of refractory follicular lymphoma remained positive albeit with the strong recommendation to implement safety measures, specifically PJP prophylaxis and regular cytomegalovirus monitoring.

Table 2. Adverse events reported during idelalisib use.

	Previously untreated [79]	Previously treated [12, 13, 76-78]
Total (number)	64	393
Diarrhea and/or colitis, any grade	64	14-43
Grade ≥3	42	4-18
Fatigue, any grade	31	24-36
Grade ≥3	0	2-3
Cough, any grade	33	13-29
Grade ≥3	2	0-4
URTI, any grade	NR	14-20
Grade ≥3	NR	0
Pneumonia, any grade	28	11-22
Grade ≥3	19	6-20
Pneumonitis, any grade	3	2
Grade ≥3	3	2
AST and/or ALT increased, any grade	67	24-60
Grade ≥3	23	2-20
Neutropenia, any grade	53	30-57
Grade ≥3	28	10-43
Anemia, any grade	23	23-37
Grade ≥3	3	2-11
Thrombocytopenia, any grade	14	17-30
Grade ≥3	2	5-17
Febrile neutropenia, any grade	5	3-11

Values represent percentage of patients affected. URTI: upper respiratory tract infection; AST: aspartate transaminase; ALT: alanine transaminase; NR: not reported.

Diarrhea

Incidence and severity

Diarrhea can occur at any time after initiation of idelalisib and its incidence is higher in treatment-naïve patients (42%)[79] than in patients with relapsed/refractory disease (4-18%).[12,13,76,77] Diarrhea that occurs within the first 8 weeks of idelalisib use is usually grade 1-2 (i.e. an increase in stools of up to six stools per day over baseline).

Late-onset diarrhea is generally grade ≥3, with a median time to onset of 7.1 months and there are no accompanying symptoms such as cramps, blood or mucus.[82,84] Colonoscopy shows macroscopic, in some cases ulcerative, colitis, and histology shows lymphocytic colitis in combination with characteristic epithelial cell apoptosis and neutrophilic cryptitis.[82] Idelalisib-induced intestinal perforation is rare (<0.5%).[84]

Although a definitive underlying mechanism for idelalisib-associated diarrhea is unknown, PI3Kδ inhibition has been associated with immune dysregulation resulting in inhibition of regulatory T cells and increased damage via $CD8^+$ cytotoxic T cells.[35,79-81]

Management

Management of grade 1-2 diarrhea with antidiarrheal agents is usually successful (see Figure 3).[82,84] Corticosteroids can be prescribed for ongoing grade 1-2 diarrhea with negative cultures. In patients without upper gastrointestinal tract involvement (e.g. nausea, vomiting), distally released oral corticosteroids may be considered (i.e. budesonide). In a small series of duodenal biopsies in patients with idelalisib-induced diarrhea (n=8), villous blunting and increased intra-epithelial lymphocytes were observed; thus a lactose-free diet may be worth consideration.[85]

In patients with grade ≥3 diarrhea, or grade 2 diarrhea that is unresolved after 24-48 h, it is advisable to interrupt idelalisib treatment and to start oral or intravenous corticosteroids. The median time to resolution of diarrhea after idelalisib interruption ranged from 1 week to 1 month in various trials. Interruption of idelalisib and concurrent initiation of oral budesonide in 23 patients with grade 3 diarrhea led to resolution in all cases after a mean of 12 days.[84]

Rechallenge was attempted in 71 patients with grade 3 idelalisib-related diarrhea (out of 106); and 58% were reported to be able to continue idelalisib, although no information on the duration of continuation was provided.[84]

Pneumonia and pneumonitis

Incidence and severity

Infectious pneumonia is common during idelalisib use with a reported incidence of approximately 20% (n=292); the majority of cases are grade ≥3.[12,76,77,79] PJP has been reported in a small number of patients on idelalisib treatment, including a few fatal cases.[12] Non-infectious pneumonitis was seen in 3% (n=760) mainly during the first 6 months of idelalisib therapy, and was usually severe, with some fatal cases.[84] Clinical symptoms include coughing, dyspnea and fever progressing over weeks. Various abnor-

malities are observed with computed tomography, including ground-glass opacities, consolidation and pleural effusion.[86]

Management

If patients present with respiratory complaints clinically and radiologically compatible with lobar bacterial pneumonia, empiric antibiotic treatment should be started promptly. Interruption of idelalisib is not routinely advised, since idelalisib is not presumed to cause bacterial pneumonia and no beneficial effects of idelalisib interruption or dose reduction have been reported.

In patients with grade ≥2 respiratory complaints and no clear bacterial pneumonia or lack of clinical response to empiric antibiotic treatment, high-resolution computed tomography should be performed. In the presence of imaging abnormalities incompatible with lobar pneumonia, broncho-alveolar lavage should be performed to exclude infectious causes, which would require markedly different treatment, and idelalisib should be interrupted while awaiting the results of culture of the lavage fluid, as treatment continuation may be fatal in idelalisib-induced pneumonitis (see Figure 4). In the absence of high-resolution computed tomography abnormalities, pulmonary function testing, including oxygen diffusion capacity, may be considered and inhaled steroids could be prescribed.

When pneumonia is excluded and pneumonitis is highly suspected, individual reports have described beneficial effects of corticosteroids in addition to cessation of idelalisib.[84,86] Among 13 patients with pneumonitis who were rechallenged with idelalisib (out of 24), two-thirds were able to continue idelalisib.[87] Idelalisib should not be reintroduced if the idelalisib-induced pneumonitis was life-threatening

Almost all cases of PJP occurred in patients not receiving PJP prophylaxis, which prompted the EMA to recommend PJP prophylaxis for up to 2 to 6 months after treatment discontinuation, depending on concurrent immunosuppressive drug use and neutropenia.[83,88]

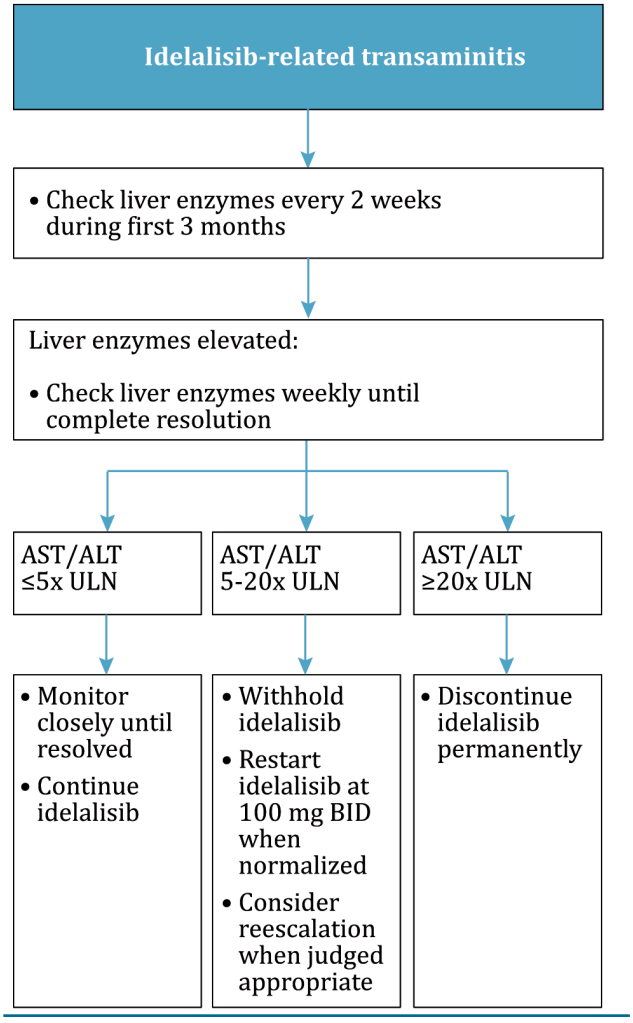

Figure 5. Flowchart for management of transaminitis during idelalisib treatment. AST: aspartate transaminase; ALT: alanine transaminase; ULN: upper limit of normal; BID: *bis in die*.

Hepatotoxicity

Incidence and severity

Hepatotoxicity is most often seen during the first 3 months of idelalisib treatment and is characterized by an elevation of alanine transaminase (ALT) and aspartate transaminase (AST) blood levels. The incidence of ALT and AST elevations of any grade is 50%, with grade ≥3 increases occurring in 16%.[84,87] Among 1192 patients treated in idelalisib clinical trials, one fatal case (<0.1%) of hepatoxicity occurred in a patient treated with idelalisib and ofatumumab.[84] Hepatotoxicity was more prevalent in younger, previously untreated patients.[85,79] The median time to onset of grade ≥3 ALT/AST elevations was 1.4 months.

Management

ALT and AST should be monitored frequently, especially in the first months of treatment. If hepatotoxicity occurs, the liver enzymes should be monitored every week until it is resolved (Figure 5). Idelalisib treatment can be continued if ALT/AST elevations three to five times the upper limit of normal (ULN) occur, with close monitoring of the liver enzymes. Idelalisib should be discontinued if ALT and AST elevations reach 5-20 times the ULN. Idelalisib can be reinitiated at a lower dose of 100 mg twice daily when ALT and AST levels have returned to normal. If ALT and AST elevations do not recur at the idelalisib dose of 100 mg twice daily, re-escalating the idelalisib dose to 150 mg twice daily can be considered at the discretion of the treating physician. After dose interruption, the elevations in liver enzymes are reversible in the majority of patients and do not recur after reinitiating idelalisib at a lower dose.[89] Idelalisib should be permanently discontinued if ALT/AST levels reach more than 20 times the ULN.[84,90]

Idelalisib is well-tolerated in patients with pre-existing moderate or severe hepatic impairment.[91] Therefore, dose adjustment beforehand is not necessary in patients with prior hepatic impairment, and it is advised to monitor patients as described above.

Hematologic complications

Incidence and severity

Neutropenia is common during the first months of idelalisib treatment. Any grade neutropenia occurs in 44-57%

of the patients, with the neutropenia being grade 3-4 in 23-43%.[12,76,77] Across trials, GM-CSF was administered to 16-25% of the patients, whereas dose reduction was rarely judged necessary (1%) and the drug was withheld in <0.05% because of neutropenia.[84] Anemia occurred in 23-37% (grade 3: 3-11%) of the patients during idelalisib reatment. Similarly, thrombocytopenia occurred in 17-30% (grade 3: 5-17%).[12,13,76,77]

Management

Blood counts should be monitored frequently during the first months of idelalisib treatment. In the case of persistent neutropenia, temporary growth factor support can be considered.

Rash

Incidence and severity

Any grade rash was reported in 10-22% of patients with relapsed or relapsed/refractory disease, with grade ≥3 rash occurring in 0-2%.[12,77] The reported frequency of rash was considerably higher in treatment-naïve patients at 58% (grade 3: 13%).[79]

Management

If serious cutaneous reactions occur during idelalisib treatment, the drug should be discontinued. The efficacy of antihistamines or steroids has not been described.

Conclusion

Novel B-cell receptor inhibitors have been shown to be effective in the treatment of indolent B-cell malignancies. Ibrutinib and idelalisib, the first two approved B-cell receptor pathway inhibitors, are administered orally and continuously. Their use results in high response rates and long progression-free survival even in patients with high-risk, relapsed or refractory disease.

Clinical trials have shown acceptable safety profiles of these drugs. Nonetheless, both agents have toxicity profiles that are different from those of immunochemotherapy (Figure 6). Moreover, the safety profile of ibrutinib is clearly distinct from that of idelalisib and this should be taken into consideration when making individual treatment decisions. During ibrutinib treatment, bleeding and AF can pose especially complex treatment dilemmas, whereas diarrhea, pneumonitis and ALT/AST elevations are challenging during idelalisib treatment. Appropriate management and awareness of these adverse events is especially important in the light of continuous use of B-cell receptor inhibitors.

Practical recommendations for the clinic

Ibrutinib

- Grade 1 bruising is frequent but harmless
- Antiplatelet or anticoagulation (DOAC or LMWH) therapy appears safe
- Avoid combined antiplatelet and anticoagulation therapy
- Withhold ibrutinib 3-7 days before and after invasive procedures
- Check for atrial fibrillation regularly
- Hypertension may occur even later during therapy
- Check blood counts regularly during first months

Idelalisib

- PJP prophylaxis and regular CMV monitoring are mandatory
- Take diarrhea seriously and handle according to Figure 3
- Be aware of the low but potentially life-threatening risk of pneumonitis
- Check liver enzymes in the first 3 months and handle elevations according to Figure 5
- Check blood counts regularly during first months

Figure 6. Recommendations for the clinic summarizing important toxicity-related issues during therapy with ibrutinib or idelalisib. DOAC: directly acting oral anticoagulants; LMWH: low-molecular-weight heparin; PJP: *Pneumocystis jiroveci* pneumonia; CMV: cytomegalovirus.

Continued monitoring of toxicity associated with B-cell receptor inhibitors is essential and should be preferably reported using common terminology (i.e. Common Terminology Criteria for Adverse Events). This is particularly important for long-term safety data, as they are currently largely absent. Mechanistic insights and increased experience will likely lead to improved management strategies for the prevention of serious complications.

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