Clinical Cancer Research

Comprehensive Safety Analysis of Venetoclax Monotherapy for Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia

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Abstract

Purpose: The oral BCL-2 inhibitor venetoclax is an effective therapy for patients with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL), including disease with high-risk genomic features such as chromosome 17p deletion [del (17p)] or progressive disease following B-cell receptor pathway inhibitors.

Patients and Methods: We conducted a comprehensive analysis of the safety of 400 mg daily venetoclax monotherapy in 350 patients with CLL using an integrated dataset from three phase I/II studies.

Results: Median age was 66 years and 60% had del(17p). Patients had received a median of three prior therapies (range: 0–15); 42% previously received ibrutinib or idelalisib. Median duration of exposure to venetoclax was 16 months (0–56). In the pooled analysis, the most common adverse events (AE) of any grade were diarrhea (41%), neutropenia (40%), nausea (39%), anemia (31%), fatigue (28%), and upper respiratory tract infection (25%). The most common grade 3/4 AEs were neutropenia (37%), anemia (17%), and thrombocytopenia (14%). With the current 5-week ramp-up dosing, the incidence of laboratory TLS was 1.4% (2/166), none had clinical sequelae, and all of these patients were able to ramp-up to a daily dose of 400 mg. Grade 3/4 neutropenia was manageable with growth factor support and dose adjustments; the incidence of serious infections in these patients was 15%. Ten percent of patients discontinued venetoclax due to AEs and 8% died while on study, with the majority of deaths in the setting of disease progression.

Conclusions: Venetoclax as a long-term continuous therapy is generally well tolerated in patients with R/R CLL when initiated with the current treatment algorithm. *Clin Cancer Res; 24(18); 4371–9. ©2018 AACR.*

Introduction

The treatment landscape for chronic lymphocytic leukemia (CLL) has evolved rapidly over the last several years with the advent of highly effective and well-tolerated oral agents that target two key regulatory mechanisms for CLL cell survival: B-cell receptor signaling and the intrinsic pathway of apoptosis. The B-cell leukemia/lymphoma-2 (BCL-2) protein family, whose actions can be inhibited by a class of drugs called BH3 inhibitors, controls the intrinsic apoptosis pathway (1). Navitoclax, an earlier, less selective BH3 mimetic drug, which targets three antiapoptotic proteins (BCL-2, BCL-X_L, and BCL-w), showed promising antitumor activity in relapsed CLL (2, 3), but induced dose-limiting thrombocytopenia due to on-target inhibition of BCL-X_L, a protein now known to be critical for platelet survival (4).

A second-generation BH3 mimetic, venetoclax, is a potent, orally bioavailable small-molecule inhibitor that is highly selective for BCL-2, with much lower affinity for BCL-X_L (5). Venetoclax induces objective response in 80% of patients with relapsed/refractory (R/R) CLL, independent of risk factors such as chromosome 17p deletion [del(17p)] and/or *TP53* mutation (6–8). Complete remissions are observed in 16%–20% of patients, with minimal residual disease (MRD) negativity in 5%–27% of patients as measured by flow cytometry in peripheral blood or bone marrow (6, 7, 9). The early development of venetoclax in CLL was notable for a risk of tumor lysis syndrome (TLS), with two deaths, including one after an initial 50 mg dose and one after a 1,200 mg dose (6, 10). Subsequent modifications to the protocols such as TLS risk stratification, prophylaxis, and monitoring, as well as starting with a lower

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Translational Relevance

Venetoclax is a once-daily, orally bioavailable inhibitor of BCL-2 that is approved for treatment of patients with previously treated CLL. Venetoclax induces objective responses in 80% of patients with relapsed/refractory (R/R) CLL, independent of risk factors such as chromosome 17p deletion. With increased use of venetoclax in clinical practice, we report on a *post hoc*–integrated safety analysis of venetoclax monotherapy at the approved 400 mg daily dose in 350 patients enrolled in three phase I or II studies. The most common toxicities of venetoclax in R/R CLL were mild gastrointestinal symptoms and transient, uncomplicated neutropenia. Tumor lysis syndrome at initiation was observed in some of the initial patients but this risk was subsequently mitigated by risk-adapted prophylaxis, monitoring and stepwise dose ramp-up to 400 mg/day. Venetoclax was generally well tolerated in patients with R/R CLL when initiated with the current treatment algorithm. Our study will help to inform the optimal management of patients with CLL receiving venetoclax.

initial dosing at 20 mg with subsequent dose ramp-up were introduced to mitigate this risk of TLS.

Venetoclax is approved in the United States for patients with CLL who have received at least one previous therapy (11). In the European Union and other areas, venetoclax has been approved for patients who are unsuitable for, or who have not responded to, B-cell receptor signaling pathway inhibitor (BCRi) therapy and for those without del(17p) or *TP53* mutation who have not responded to chemoimmunotherapy and BCRi therapy (12). Investigation in other CLL patient populations and in combination studies are ongoing (13). As venetoclax is used more widely worldwide, a more comprehensive understanding of the safety profile is needed to inform optimal management of patients initiating therapy and receiving long-term treatment at the approved 400 mg daily dose. Here, we report on an integrated safety analysis of venetoclax monotherapy across 350 patients with CLL enrolled across three phase I/II studies.

Patients and Methods

Integrated dataset

This integrated safety analysis used a data cutoff of November 28, 2016. Patients with CLL were included in the analysis if they were treated with venetoclax monotherapy on the phase I M12-175 (first-in-human; $n = 67$; NCT01328626ref. 6), phase II M13-982 [del(17p); $n = 158$, of whom 153 were previously treated; NCT01889186; ref. 7)], or phase II M14-032 (patients with disease that had progressed during or after prior ibrutinib or idelalisib; $n = 125$; NCT02141282; refs. 14, 15) studies. After dose ramp-up, all patients received venetoclax 400 mg once daily. Patients included in this analysis were assigned to receive 400 mg daily ventoclax (patients in the phase I study assigned to the 400 mg dose cohort and all patients enrolled in the two phase II trials) and received at least one dose of venetoclax during ramp-up. Patients received treatment until disease progression (PD), unacceptable toxicity, or study discontinuation, and were followed for survival after discontinuation.

Oversight of clinical studies

Protocols for the clinical studies were designed by the sponsors (AbbVie and Genentech) in collaboration with investigators, and approved by institutional review boards at each participating site. Studies were conducted according to the Declaration of Helsinki and the International Conference on Harmonization (ICH) for Good Clinical Practice. All patients provided written informed consent.

Patients

Adult patients were enrolled if they had R/R CLL requiring treatment based on 2008 iwCLL criteria (16). Key patient enrollment criteria are mentioned in the Supplementary Data.

Venetoclax dosing

Most patients included in this analysis started venetoclax at 20 mg daily for 1 week followed by ramp-up over 5 weeks to 50, 100, and 200 mg weekly to the target 400 mg dose, which is the label-recommended dose for CLL (Fig. 1). Patients in the main cohort of M13-982 ($n = 107$) initiated venetoclax with a single-test dose of 20 mg on day 1 followed by 50 mg for the rest of the first week and then ramped up to 400 mg over 4 to 5 weeks (7).

Tumor lysis syndrome prophylaxis and monitoring

In addition to following the ramp-up dosing schedule, TLS prophylaxis and laboratory monitoring were also required. All patients received hydration and oral uric acid–reducing agents starting at least 48 hours prior to the first venetoclax dose. Most patients at low risk for developing TLS (all lymph nodes <5 cm in the largest diameter on CT imaging and ALC $<25\times10^9$/L; ref. 17) were treated in an outpatient setting with less intensive monitoring; the initial group of patients in the M13-982 and M12-175 studies were enrolled under more stringent monitoring and were hospitalized at the first 20-mg and 50-mg doses. Patients at medium risk (any lymph node $\geq$5 cm to <10 cm or isolated ALC $\geq25 \times 10^9$/L) received intravenous hydration (1.5–2 L) on the days of first 20-mg and 50-mg doses and hospitalization was considered at treating physicians' discretion for patients with CrCl < 80 mL/minute, as reduced renal function could hamper a patient's capacity to handle fluid load and biochemical fluctuations. Patients with the highest risk of experiencing TLS (any lymph node $\geq$10 cm in the largest diameter; or lymph node $\geq$5 cm and ALC $\geq25\times10^9$/L) were hospitalized the day

Figure 1.

Venetoclax dosing schedule in CLL. On the basis of the current venetoclax dosing protocol, patients started venetoclax once daily at 20 mg for 1 week followed by a gradual ramp-up to 400 mg over 5 weeks.

prior to the first 20-mg and 50-mg doses for closer monitoring. They received intravenous hydration (150–200 mL/hour as tolerated) and rasburicase (for patients with elevated uric acid or per investigator discretion), and were hospitalized until at least 24-hour postdose laboratory chemistry values were reviewed by the investigator and confirmed to be normal. For patients initiating treatment in the outpatient setting, laboratory monitoring at each dose level occurred within 72 hours prior to the first dose, and at 0, 8, and 24 hours postdose. For hospitalized patients, laboratory monitoring occurred on admission the night before the first dose at 20 mg and 50 mg, and at 0, 4, 8, 12, and 24 hours postdose, with subsequent monitoring performed in an outpatient setting if feasible.

Safety assessments

Adverse events (AE), including serious AEs (SAE), were defined according to ICH guidelines (ICH E2A). Laboratory abnormalities and changes in vital signs were considered AEs only if they resulted in discontinuation from treatment, necessitated therapeutic medical intervention, met protocol-specified criteria, and/or per investigator discretion. Severity of AEs was based on the NCI Common Terminology Criteria for Adverse Events v4.0 (18).

Statistical analysis

Subgroup analyses of the integrated dataset were evaluated for patients with the specific high-risk disease features of del(17p) CLL and/or PD during or after prior BCRi therapy (ibrutinib, idelalisib, or investigational BCR-targeting agents). These subgroups were not mutually exclusive and some patients had both features and are included in the analysis of each of these subsets. While modifications were made over time to the dose ramp-up schedule for initiating venetoclax, the overall safety was not different between the 4- and 5-week ramp-up schedules. Evaluations of TLS included a subset of 166 patients who received venetoclax, following the current recommended dosing regimen (Fig. 1) and TLS prophylaxis, and monitoring recommendations to evaluate the effectiveness of TLS management among patients who were treated according to current guidelines (11, 12) As MedDRA version 17.1 has a single preferred term of TLS, all events were reviewed and categorized as laboratory-only or clinical TLS

Table 1. Patient demographics and baseline clinical characteristics

		Subgroups of interest	
	All patients ***N* = 350**	**del(17p) CLL** ***n* = 211***	**Prior BCRi** ***n* = 148***
Male, *n* (%)	238 (68)	137 (65)	102 (69)
White, *n* (%)	326 (94)	199 (95)	136 (92)
Age, median (range), years	66 (28–85)	66 (29–85)	66 (28–85)
CLL/SLL, *n* (%)	342 (98)/8 (2)[a]	211 (100)	146 (98)/2 (1)
TP53 mutation, *n/N* (%)	141/297 (48)	124/178 (70)	46/140 (33)
Unmutated *IGHV*, *n/N* (%)	137/181 (76)	80/102 (78)	77/99 (78)
Prior no. of therapies,[b] median (range)	3 (1–15)	3 (1–15)	4 (1–15)
Prior therapies, *n* (%)			
Fludarabine	229 (65)	136 (65)	87 (59)
Bendamustine	149 (43)	87 (41)	63 (43)
Alkylating agents	247 (71)	153 (73)	94 (64)
Medical history of cytopenias (within 6 months of first venetoclax dose), *n* (%)			
Neutropenia	52 (15)	49 (23)	8 (5)
Thrombocytopenia	106 (30)	59 (28)	71 (48)
Anemia	150 (43)	74 (35)	82 (55)
G-CSF support at study entry	46 (13)	31 (15)	17 (12)
ECOG performance status, *n/N* (%)			
0	140 (40)	85 (40)	49 (33)
1	187 (54)	111 (53)	87 (59)
2	20 (6)	15 (7)	11 (8)
Missing	3	0	1
Bulky nodes, *n* (%)			
One or more nodes ≥5 cm	172 (49)	103 (49)	64 (43)
One or more nodes ≥10 cm	48 (14)	26 (12)	17 (12)
ALC $\geq 25\times10^9$/L, *n* (%)	126 (39)	93 (44)	43 (30)
CrCl ≥60 mL/minute	274 (78)	160 (76)	117 (79)
TLS risk category,[c] *n/N* (%)			
Low	61/166 (37)		
Medium	59/166 (36)	NA	NA
High	46/166 (28)		

Abbreviations: ALC, absolute lymphocyte count; BCRi, B-cell receptor pathway inhibitors (ibrutinib, idelalisib, or investigational compounds); CrCl, creatinine clearance; ECOG, Eastern Cooperative Oncology Group performance score; G-CSF, granulocyte-colony stimulating factor; NA, data not evaluated for subgroups; SLL, small lymphocytic lymphoma; TLS, tumor lysis syndrome.

*Subgroups include patients across all three clinical studies. The 211 patients with del(17p) CLL and 148 patients who received prior BCRi are not mutually exclusive and do not add up to the 350 patients included in the overall integrated dataset.

[a]Eight patients with SLL were included in the M12-175 study.

[b]Does not include 5 patients who were treatment naïve and received venetoclax in the M13-982 study.

[c]A total of 115 patients were included in the TLS analysis set and included only those patients who received venetoclax per the 5-week dose ramp-up schedule with current protocol TLS prophylaxis and monitoring measures. Risk categories were defined as: Low, all lymph nodes ≤5 cm and ALC $<25\times10^9$/L; medium, any lymph node ≥5 cm to <10 cm or ALC $\geq25\times10^9$/L; and high, any lymph node ≥10 cm or lymph node ≥5 cm and ALC $\geq25\times10^9$/L.

based on more specific published criteria (19). All statistical analyses were performed with SAS software, version 9.4.

Results

Patient demographics and baseline characteristics

Across studies, 350 patients were enrolled from June 2011 through November 2016. The median age was 66 years (range: 28–85), 60% had del(17p) CLL, and 48% had *TP53* mutation. Patients had received a median of 3 prior therapies (0–15), including 42% who had received prior BCRi (Table 1).

Overview of safety profile

Mean and median durations of exposure to venetoclax were both 16 months (0–56) at data cutoff, with 202 (58%) patients having received treatment for more than 1 year. The safety profile of venetoclax was indistinguishable for patients with del(17p) CLL and/or patients who had received prior BCRi versus all patients (Table 2; Supplementary Table S3). The most common any-grade AEs were mild gastrointestinal events (diarrhea, 41% and nausea, 39%) and cytopenias (neutropenia, 40%; anemia, 31%; and thrombocytopenia, 21%). In general, nearly all patients ($n = 323$) had an AE of any grade during the dose ramp-up period and the number of patients with onset of new AEs reduced with time on venetoclax (Supplementary Table S4). The most common AEs reported in in ≥5% of patients with first onset after 1 year on therapy included upper respiratory tract infection (12%), diarrhea (9%), pneumonia (7%), nausea (6%), bronchitis (6%), nasopharyngitis (6%), and hypertension (6%). The majority of these events were reported as grade 1 or 2 in severity.

The most common AEs assessed by the investigator as having a reasonable possibility of being related to venetoclax treatment in

Table 2. Summary of AEs while on venetoclax or up to 30 days posttreatment

		Subgroups of interest	
Event, *n* (%)	**All patients *N* = 350**	**del(17p) CLL *n* = 211[a]**	**Prior BCRi *n* = 148[a]**
Any grade AE	343 (98)	207 (98)	144 (97)
Common any grade AEs (≥10% of all patients)			
Diarrhea	145 (41)	85 (40)	57 (39)
Neutropenia	141 (40)	83 (39)	54 (37)
Nausea	137 (39)	71 (34)	57 (39)
Anemia[b]	109 (31)	62 (29)	57 (39)
Fatigue	99 (28)	52 (25)	41 (32)
Upper respiratory tract infection	86 (25)	44 (21)	26 (18)
Thrombocytopenia	74 (21)	46 (22)	34 (23)
Cough	63 (18)	32 (15)	29 (20)
Headache	62 (18)	37 (18)	23 (16)
Pyrexia	60 (17)	35 (17)	20 (14)
Constipation	56 (16)	26 (12)	22 (15)
Vomiting	55 (16)	31 (15)	23 (16)
Hyperkalemia[c]	52 (15)	34 (16)	27 (18)
Hyperphosphatemia[c]	48 (14)	25 (12)	21 (14)
Peripheral edema	47 (13)	25 (12)	24 (16)
Hypocalcemia[c]	41 (12)	19 (9)	26 (18)
Pneumonia	40 (11)	25 (12)	14 (10)
Back pain	39 (11)	23 (11)	15 (10)
Abdominal pain	37 (11)	17 (8)	12 (8)
Dizziness	37 (11)	18 (9)	13 (9)
Dyspnea	37 (11)	24 (11)	21 (14)
Grade 3/4 AEs	274 (78)	164 (78)	108 (73)
Common grade 3/4 AEs (≥10% of all patients)			
Neutropenia	128 (37)	76 (36)	47 (32)
Anemia	60 (17)	33 (16)	33 (22)
Thrombocytopenia	49 (14)	30 (14)	23 (16)
SAEs	181 (52)	114 (54)	64 (43)
Common SAEs (≥2% of all patients)			
Pneumonia	24 (7)	17 (8)	9 (6)
Febrile neutropenia	17 (5)	9 (4)	10 (7)
Pyrexia	12 (3)	9 (4)	2 (2)
Autoimmune hemolytic anemia	10 (3)	8 (4)	2 (2)
AEs leading to[d]			
Dose reduction	45 (13)	26 (12)	16 (11)
Dose interruption	120 (34)	67 (32)	45 (30)
Discontinuation	35 (10)	23 (11)	14 (10)
Death	15 (3)	10 (5)	9 (6)

Abbreviation: BCRi, B-cell receptor pathway inhibitors (ibrutinib, idelalisib, or investigational compounds).

[a]Subgroups include patients across all three clinical studies. The 211 patients with del(17p) CLL and 148 patients who received prior BCRi are not mutually exclusive and do not add up to the 350 patients included in the overall integrated dataset.

[b]Includes the Medical Dictionary for Regulatory Activities (MedDRA) preferred term "anemia" and does not include events of autoimmune hemolytic anemia.

[c]The majority of laboratory changes reported as AEs occurred during the dose ramp-up period: 26/52 events of hypokalemia, 46 of 48 events of hyperphosphatemia, and 39 of 41 events of hypocalcemia.

[d]Excludes those due to disease progression.

≥10% of patients were neutropenia (33%), nausea (25%), diarrhea (24%), fatigue (15%), thrombocytopenia (13%), anemia (12%), and hyperphosphatemia (10%). The most common AEs reported as grade 3 or higher, and assessed by the investigator as having a reasonable possibility of being related to venetoclax were cytopenias: neutropenia (30%), thrombocytopenia (8%), and anemia (7%).

Venetoclax was dose reduced or interrupted for AEs in 45 (13%) and 120 (34%) patients, with the most common reason for dose adjustment being neutropenia. New AEs requiring dose adjustments became less frequent with longer time on therapy (Supplementary Table S4).

Thirty-five (10%) patients discontinued venetoclax due to AEs (Supplementary Table S5). Twenty-nine patients died while on study, including 14 due to PD (9 of these patients never achieved objective response, while 5 had previously achieved partial response). The remaining deaths were due to septic shock ($n = 4$, including 1 due to *Corynebacterium* and 1 *Klebsiella*), multiorgan failure ($n = 2$), small-intestine obstruction, viral pneumonia, hemorrhagic stroke, liver failure, cardiopulmonary failure, general physical health deterioration, multiple myeloma, respiratory failure, and AE not specified (1 each). Median time to death related to PD was 5.1 months (1–27.5) and for deaths for other reasons was 1.5 months (0.1–13.5).

The rates of AEs, including grade 3/4 AEs, serious AEs, and AEs leading to venetoclax reduction, interruption, or discontinuation did not differ among subgroups, including del(17p) CLL or prior BCRi treatment (Table 2) as well as when evaluated among patients <75 or ≥75 years of age (data not shown).

Tumor lysis syndrome

Among all 350 patients included in this integrated analysis, 11 had TLS events reported on venetoclax, of whom 6 patients received venetoclax by prior dosing schedules (e.g., ramp-up starting at a higher starting dose or over 4 weeks to the target dose). To assess the dosing schedule now utilized outside of clinical trials, TLS was also evaluated in 166 patients who initiated venetoclax using the current 5-week ramp-up (Fig. 1) and received TLS prophylaxis and monitoring as per current recommendations (11, 12). Of these 166 patients, 61 had low TLS risk, 59 medium risk, and 46 high risk (Table 1). At baseline, 151 (91%) patients received allopurinol, 135 (81%) had intravenous hydration, and 45 (27%, majority with high TLS risk) received rasburicase. During the 5-week ramp-up, most patients were managed with intravenous hydration (81% at the 20-mg dose of venetoclax). Additional intervention (phosphate binder and potassium binder) to correct laboratory abnormalities was utilized in 4% at the 20-mg dose of venetoclax and 1% of patients at subsequent doses. Five of 166 patients (3%) were reported by investigators as having TLS, and one of these patients experienced two events (Supplementary Table S6). None of these events met Howard criteria (19) for clinical TLS, and only two (1.2%) met criteria for laboratory TLS, one due to decreased calcium and increased phosphate levels, and the other due to increased phosphate and uric acid levels. All TLS-related events occurred during ramp-up, with one that occurred the day after dosing at 200 mg, 3 occurred at the end of the week during scheduled assessments for the next dose ramp-up, and the last event occurred on day 3 following 200 mg (patient presented with fever, chills, and nausea; Supplementary Table S6). Venetoclax dosing was interrupted for 4 of these patients, and all were able to resume dosing to reach 400 mg.

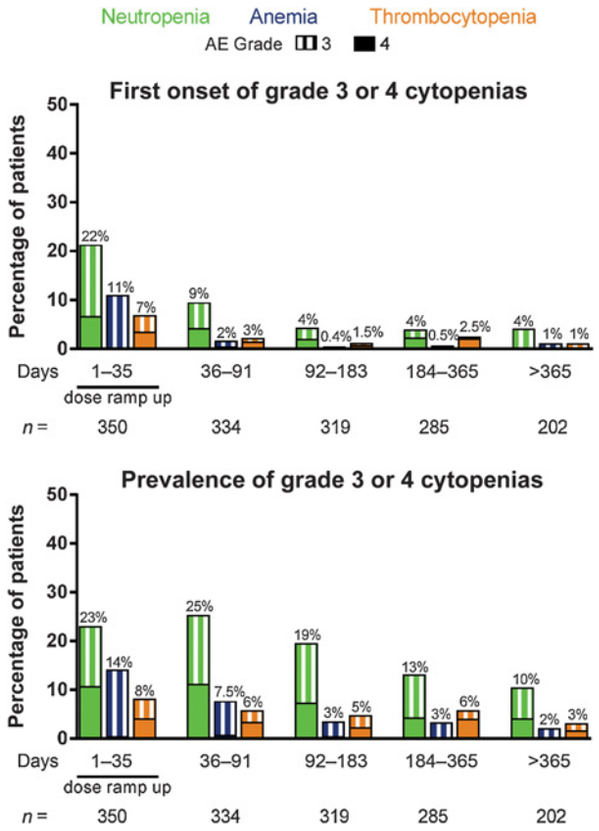

Figure 2.

First onset and prevalence of grade 3 or 4 cytopenias. During the dose ramp-up period, patients started at 20 mg daily with weekly increases over 5 weeks to the target 400 mg daily dose of venetoclax. Some patients took longer than 5 weeks to ramp up but AEs are included in the 1- to 35-day interval. Patients received 400 mg daily venetoclax during subsequent time intervals. The intervals and number of patients evaluated during each interval are shown below the *x*-axis. The number of patients per time interval reduced with time on venetoclax due to discontinuations or disease progression. Thus, those included after 1 year ($n = 202$) were the patients who were able to tolerate venetoclax long term. Most cytopenias occurring between 184 and 365 days on therapy were in the context of disease progression. Analysis of first onset over time counted an event for a patient only for the time interval for the onset of first occurrence. If a patient experienced more than one event of the same preferred AE term, then only the first occurrence was included. Analysis of prevalence over time counted a patient in every time interval for which an AE was present. If a patient had a recurrence of the same preferred AE term, the recurrent event was also counted in every time interval for which the AE was present.

The investigator-reported laboratory TLS events were observed in 0 of 61 patients with low TLS risk, 1 of 59 (1.7%) with medium risk, and 4 of 46 (8.7%) with high risk. Single laboratory abnormalities consistent with Howard criteria (19) were seen throughout the ramp-up period, most commonly in patients with medium and high tumor burden (Supplementary Table S7).

Hematologic toxicity

First onset of most hematologic AEs occurred during the ramp-up period, and incidence of new hematologic AEs was low after the first 3 months of treatment (Fig. 2). Over time, onset of new

Table 3. Cytopenias reported during venetoclax monotherapy or up to 30 days posttreatment

Event, *n* (%)	All patients *N* = 350	Subgroups of interest: del(17p) CLL *n* = 211[a]	Subgroups of interest: Prior BCRi *n* = 148[a]
Neutropenia	141 (40)	83 (39)	54 (37)
Grade 3/4	128 (37)	76 (36)	47 (32)
SAE	6 (1.7)	5 (2)	2 (1.4)
Leading to dose reduction	17 (5)	13 (6)	4 (3)
Leading to dose interruption	14 (4)	10 (5)	4 (3)
Leading to discontinuation	1 (0.3)	0	0
Anemia[b]	109 (31)	62 (29)	57 (39)
Grade 3/4	60 (17)	33 (16)	33 (22)
SAE	5 (1.4)	3 (1)	1 (0.7)
Leading to dose reduction	1 (0.3)	0	1 (0.7)
Leading to dose interruption	1 (0.3)	0	0
Leading to discontinuation	0	0	0
Thrombocytopenia	74 (21)	46 (22)	34 (23)
Grade 3/4	49 (14)	30 (14)	23 (16)
SAE	6 (1.7)	5 (2)	2 (1.4)
Leading to dose reduction	3 (0.9)	2 (0.9)	0
Leading to dose interruption	8 (2)	5 (2)	3 (2)
Leading to discontinuation	2 (0.6)	2 (0.9)	0

Abbreviation: BCRi, B-cell receptor pathway inhibitors (ibrutinib, idelalisib, or investigational compounds).

[a]Subgroups include patients across all three clinical studies. The 211 patients with del(17p) CLL and 148 patients who received prior BCRi are not mutually exclusive and do not add up to the 350 patients included in the overall integrated dataset.

[b]Includes the Medical Dictionary for Regulatory Activities (MedDRA) preferred term "anemia" and does not include events of autoimmune hemolytic anemia.

grade 3/4 cytopenias decreased (e.g., 26% of patients experienced grade 3/4 neutropenia during dose ramp-up vs. 4% with first onset after 1 year on venetoclax). In addition, ongoing or recurrent events decreased over time or resolved with further treatment (Fig. 2).

Baseline grade 1/2 neutropenia was reported for 15% of patients prior to initiating venetoclax and 13% of all patients received G-CSF within 6 months of study entry. Neutropenia was the most common AE leading to venetoclax dose adjustments (Table 3), and was largely managed by supportive care measures, including G-CSF for 41% of all patients (75% of patients with grade 3/4 neutropenia). One-third (106 of 350) of patients received G-CSF during dose ramp-up and this number decreased over time such that 11% (22 of 202) of patients received G-CSF beyond 1 year of treatment. Grade 4 neutropenia was reported in 86 (25%) patients, and median time to first event was 25 days (2–491), with only 1 patient who discontinued study due to grade 4 neutropenia.

On the basis of risk factors for neutropenia identified in the literature associated with impaired hematopoietic stem cell reserve, cumulative prior therapy, disease-related marrow suppression (20), and investigator experience, an exploratory *post hoc* multivariate analysis to identify factors associated with development of grade 3/4 neutropenia with venetoclax was conducted (see Supplementary Data for details). A decision rule was derived for predicting grade 3/4 neutropenia while on venetoclax. Patients were identified as high risk if they had Binet stage C and screening neutrophil count $<5.64\times10^9$/L or Binet stage A/B and screening neutrophil count $<2.46\times10^9$/L. Patients were low risk if they had Binet stage C and screening neutrophil count $\geq5.64\times10^9$/L or Binet stage A/B and screening neutrophil count $\geq2.46\times10^9$/L. The analysis showed that patients with the highest risk for neutropenia had 83% rate of grade 3/4 neutropenia on venetoclax compared with 46% for those patients considered low risk (OR: 5.865).

On venetoclax, 109 (31%) patients experienced anemia, with half of these being grade 3/4. Of patients with grade 3/4 anemia, 48% had history of prior anemia, 1.6% prior AIHA and/or had received packed cell transfusion within 4 weeks of initiating venetoclax. Also, four grade 3/4 events of anemia occurred in the setting of PD. Five cases of anemia were considered SAEs (Table 3). Venetoclax dose reduction or interruption due to anemia occurred for 1 patient each, and no patients discontinued due to anemia. Grade 3/4 anemia events were mainly observed in the initial 3 months of treatment, with few new onset grade 3/4 anemia events in patients who continued venetoclax and a decrease in prevalence of events over time. An increase in hemoglobin levels over time was also observed (Supplementary Fig. S1). Collectively, this suggests an improvement in preexisting anemia as patients continue to be on venetoclax.

AEs of AIHA were reported in 17 (5%) patients; 14 were grade 3/4, and 10 were SAEs. Median time to first AE of AIHA was 2.6 months (0.07–12.4). Upon medical review of SAEs, 3 cases had documented preexisting AIHA. Most AIHA cases were manageable by medical intervention (blood transfusion, corticosteroids, intravenous immunoglobulin, and concomitant rituximab) and dose adjustments [reductions ($n = 2$) and/or interruptions ($n = 4$)]. There were two discontinuations due to AIHA.

Thrombocytopenia was reported for 74 (21%) patients, with 14% grade 3/4 events (Table 3). One-third of patients who experienced thrombocytopenia on venetoclax had a prior history of thrombocytopenia due to marrow infiltration or immune thrombocytopenia purpura (ITP). Thrombocytopenia required dose reduction for 3 patients and dosing interruption for 8 patients, with 2 patients discontinuing venetoclax due to thrombocytopenia. Grade 4 thrombocytopenia was reported in 44 (13%) patients, and median time to first event was 35 days (1–674); none resulting in major bleeding events. Of patients with grade 3/4 thrombocytopenia, six events occurred in the setting of PD. Hematologic laboratory parameters were stable over time on venetoclax (Supplementary Figs. S1 and S2), even for patients with advanced stage disease (Supplementary Fig. S1).

Infections

Infections of any grade occurred in 251 (72%) patients, with the most common being upper respiratory tract infection (25%), pneumonia (11%), nasopharyngitis (10%), and urinary tract infection (10%). A total of 77 (22%) patients had an infection of grade 3 or higher, at an average exposure-adjusted rate of 2.1 per 100 patient months. Pneumonia ($n = 24$, 7%) was the most common grade 3/4 infection and 23% of infections were considered SAEs (Supplementary Fig. S3 provides incidence and prevalence of serious infections). An exploratory *post hoc* multivariate analysis was performed to identify factors associated with the development of serious infections on venetoclax (see Supplementary Data for details). Of a number of baseline factors evaluated in the model, the analysis showed that patients with prior fludarabine exposure had a higher rate of serious infections on venetoclax than those patients who had not received prior fludarabine (33% vs. 13%, respectively; OR: 2.353; $P = 0.004$).

Of 157 patients with grade 3/4 neutropenia/decreased neutrophil count, 15% had concomitant serious infections; a causative association of neutropenia and concomitant infection could not

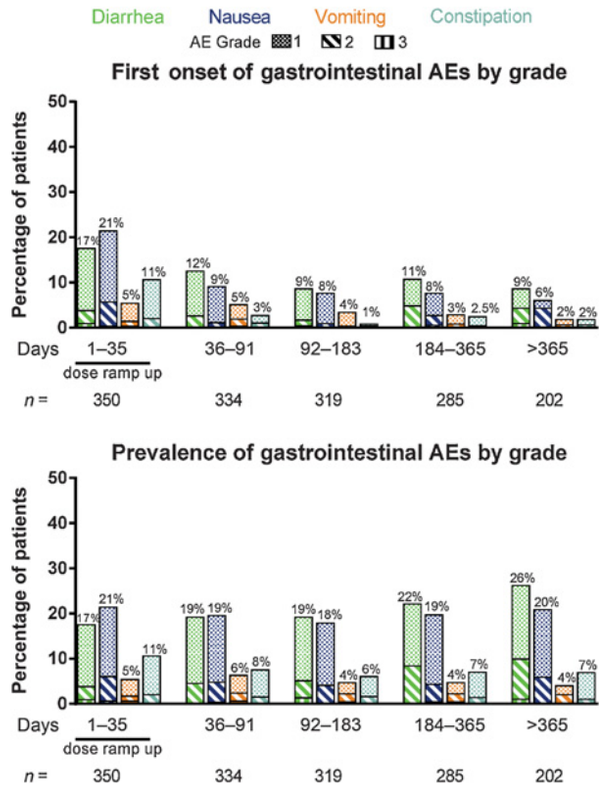

Figure 3.

First onset and prevalence of gastrointestinal toxicities. During the dose ramp-up period, patients started at 20 mg daily with weekly increases over 5 weeks to the target 400 mg daily dose of venetoclax. Some patients took longer than 5 weeks to ramp up but AEs are included in the 1- to 35-day interval. Patients received 400 mg daily venetoclax during subsequent time intervals. The intervals and number of patients evaluated during each interval are shown below the *x*-axis. The number of patients per time interval reduced with time on venetoclax due to discontinuations or disease progression. Thus, those included after 1 year ($n = 202$) were patients who were able to tolerate venetoclax long term. Analysis of first onset over time, counted an event for a patient only for the time interval for the onset of first occurrence. If a patient experienced more than one event of the same preferred AE term, then only the first occurrence was included. Analysis of prevalence over time counted a patient in every time interval for which an AE was present. If a patient had a recurrence of the same preferred AE term, the recurrent event was also counted in every time interval for which the AE was present. No gastrointestinal AEs grades 4 or higher were reported.

be established due to presence in many patients of preexisting grade 3/4 neutropenia before starting venetoclax.

Of note, opportunistic infections were reported in 11 patients (3.1%), and included oral candidiasis ($n = 2$), *Aspergillus* pneumonia (2), *Pneumocystis jirovecii* pneumonia (2), ocular toxoplasmosis, nocardiosis, herpes pharyngitis, herpes zoster multidermatomal, and candida esophagitis (1 each). Median time to opportunistic infection was 4.5 months (0.3–22). Two patients with pneumonia and one with herpes zoster infection had serious opportunistic infections that occurred at 2.2 and 2.2 months after initiating venetoclax, respectively. One of these patients had two separate serious events of pneumonia and interrupted venetoclax during each episode, with dosing resumed at a lower 300-mg dose. The patient with herpes zoster infection also interrupted venetoclax and resumed dosing at 400 mg. There were no deaths related to opportunistic infections.

Gastrointestinal adverse events

On venetoclax, 263 (75%) patients experienced gastrointestinal AEs, with grade 1 diarrhea (26%) and nausea (28%), being the most common. Grade 2 diarrhea was reported in 13% of the patients and grade 2 nausea in 11%. Grade 3 diarrhea, nausea, vomiting, and constipation were reported in 9, 3, 4, and 1 patients, respectively; most events occurred during the first year of therapy and no grade 4 events were reported. Grade 3 events were all transient [median length of event of 5 days (1–29)] and no patients had more than one such event. Onset of new gastrointestinal AEs was highest during dose ramp-up and decreased with time; however, low-grade gastrointestinal events typically persisted over time for patients who initially experienced these AEs (Fig. 3). Venetoclax dose reductions or interruptions due to gastrointestinal AEs occurred in 4 (1%) and 23 (7%) patients, respectively. One patient with irritable bowel syndrome at study entry discontinued venetoclax due to persistent grade 2 diarrhea and vomiting.

Discussion

As venetoclax use in clinical practice is increasing worldwide, a detailed analysis of its toxicity profile is important to help clinicians safely and effectively administer the drug. On the basis of our analysis across these 3 early-phase venetoclax monotherapy studies, most patients experienced an AE of any grade during dose ramp-up, with the onset and severity of new AEs decreasing over time; however, low-grade gastrointestinal toxicity was persistent in the subset of patients who initially experienced these events. Venetoclax required infrequent dose adjustments, suggesting that it can be well tolerated as a chronic therapy within the timeframe currently analyzed (up to nearly 5 years).

TLS is an important identified risk and was observed in early development of venetoclax prior to the implementation of a comprehensive TLS mitigation strategy. Our data from this integrated safety analysis demonstrate that TLS risk can be effectively mitigated with standardized ramp-up dosing and risk-adapted prophylaxis and monitoring. This TLS mitigation scheme includes a lower 20-mg starting dose, gradual dose ramp-up over 5 weeks, and close laboratory monitoring, along with TLS prophylaxis (e.g., oral or intravenous hydration and oral uric acid–reducing agents; ref. 11). In 166 patients managed using the current dosing algorithm and TLS prophylaxis, six TLS cases were reported by investigators in 5 patients, of which only 2 (1.2%) met Howard criteria for laboratory TLS; none were clinical TLS.

A comprehensive review of clinical and laboratory data across TLS analysis sets was conducted to explore whether a categorical definition based on tumor burden alone would be predictive of patients at risk for TLS with venetoclax. We found that TLS risk with venetoclax is multifactorial with similar risk factors as those identified for other highly active anticancer agents. Although high tumor burden (as indicated by ALC and lymph node size) is a key risk factor, other factors may play a role (i.e., renal function, prior TLS, and ability to adequately deliver hydration). Thus, TLS risk with venetoclax treatment is a continuum characterized by increasing risk with increased

tumor volume and/or presence of other comorbidities or risk factors. By assessing tumor burden, following TLS prevention recommendations, and strict adherence to the dose ramp-up scheme outlined in the drug label (11), TLS risk is minimized, allowing safe ramp-up to a 400 mg daily dose.

BCL-2 is now recognized to be important for the survival of neutrophil precursors (21), potentially explaining why neutropenia was the most common AE requiring intervention on venetoclax. Patients with R/R CLL typically have significant disease bone marrow infiltration and in many cases also display persistent myelosuppression from prior chemoimmunotherapy. As such, it is not surprising that the rates of neutropenia in CLL tend to be substantially higher that those seen in other non-Hodgkin lymphomas, where lower neutropenia rates were seen even when venetoclax doses as high as 1,200 mg once daily were evaluated (22). In CLL, the onset of neutropenia was most common during dose ramp-up, and incidence decreased with time on therapy. This temporal pattern is likely due to both improved CLL disease control on effective therapy, and in some cases may also reflect marrow recovery from prior myelosuppressive chemotherapy. Although the incidence of new onset neutropenia decreased over time, its prevalence at lower grade remained relatively stable in patients on venetoclax for over 1 year. Growth factor support with or without dose adjustments effectively mitigated the clinical sequelae, with the risk of infections or fever being low; the overall rate of infections (adjusted exposure rate of 2.1 per 100 patient months) and types of infections were in the range of what would be expected for a group of heavily pretreated patients with CLL. A total of 11 (3.1%) patients had opportunistic infections on treatment, with no deaths reported. The percentage of opportunistic infections reported here on venetoclax is similar to 4.1% (23 of 566) of patients who developed an opportunistic infection on ibrutinib monotherapy or in combination across hematologic malignancies (73.7% had CLL) based on experience from a single academic center (23). One-third of patients experienced anemia while on venetoclax, with most of these patients having a history of anemia prior to starting therapy. The prevalence of anemia decreased over time and mean hemoglobin levels increased over time.

The BCL-2/BCL-X_L inhibitor navitoclax led to a predictable, dose-dependent thrombocytopenia due to on-target inhibition of BCL-X_L in platelets (3). We hypothesized that as a more specific BCL-2 inhibitor, with >100-fold functional selectivity for BCL-2 over BCL-X_L (5), venetoclax would not induce similar effects. While the rate of all-grade thrombocytopenia was 19%, 31% of the patients who experienced thrombocytopenia on venetoclax had a history of thrombocytopenia due to marrow infiltration or ITP, and the onset of thrombocytopenia decreased over time with an improvement in platelet counts seen in patients who continued to receive venetoclax. Moreover, only 2 patients discontinued venetoclax due to thrombocytopenia, both in the setting of advanced disease with prior thrombocytopenia. These data support our hypothesis that unlike navitoclax, venetoclax does not induce dose-dependent thrombocytopenia.

A limitation of our study is that the early-phase clinical trials included in this integrated analysis were not randomized and did not include control or placebo groups, though the safety profile of venetoclax appears to be consistent across the different trial populations. Furthermore, it should be noted that our analysis focuses on patients with R/R CLL, and it cannot be assumed that our findings will apply to first-line CLL patients treated with venetoclax, although the safety profile of venetoclax in early data from an ongoing first-line study of venetoclax plus obinutuzumab (CLL14, NCT02242942) look promising (24).

Overall, venetoclax demonstrated a manageable safety profile in R/R CLL at the approved dose and schedule of 400-mg once daily. Given its favorable safety profile in the setting of CLL and its ability even as monotherapy to induce deep remissions in patients with high-risk R/R CLL, venetoclax is now being explored in several combination studies with agents selected to avoid overlapping toxicities, including mAbs, chemotherapy, and other novel agents (10, 24, 25). Such approaches hold promise as the field strives to develop highly effective, well-tolerated, time-limited regimens with the potential to achieve long-term disease-free survival with improved quality of life for patients with CLL.

Disclosure of Potential Conflicts of Interest

M.S. Davids reports receiving commercial research grants from Genentech, Pharmacyclics, and TG Therapeutics, and is a consultant/advisory board member for AbbVie, Roche/Genentech, Pharmacyclics, Janssen, Gilead, Astra-Zeneca, MEI Pharma, and TG Therapeutics. M. Hallek reports receiving commercial research grants and speakers bureau honoraria from, and is a consultant/advisory board member for AbbVie, Roche/Genentech, Janssen, and Gilead. A.W. Roberts reports receiving commercial research grants from AbbVie, Janssen and Servier, and holds ownership interest (including patents) in the Walter and Eliza Hall Institute, which receives royalties related to Venetoclax. J.F. Gerecitano is an employee of AbbVie. S.Y. Kim is an employee of and holds ownership interest (including patents) in AbbVie. J. Potluri is an employee of AbbVie. A. Best is an employee of and holds ownership interest (including patents) in AbbVie. M.E. Verdugo is an employee of AbbVie. P. Hillmen reports receiving commercial research grants from AbbVie, Janssen, Pharmacyclics, and Gilead, reports receiving speakers' bureau honoraria from AbbVie, Janssen, and Roche, is a consultant/advisory board member for AbbVie. J.F. Seymour reports receiving speakers' bureau honoraria from AbbVie, Roche, and Celgene, and is a consultant/advisory board member for AbbVie, Celgene, Roche, Janssen, and Takeda. No potential conflicts of interest were disclosed by the other authors.

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