bjh short report

Real-world data on safety and efficacy of venetoclax-based regimens in relapsed/refractory t(11;14) multiple myeloma

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Summary

The treatment for relapsed/refractory multiple myeloma (RRMM) continues to be challenging despite recent therapeutic advancements. Venetoclax, an inhibitor of the anti-apoptotic protein BCL-2, is a promising agent, especially in patients harbouring t(11;14). Our objective was to review our experience with venetoclax-based regimens at our institution. All ten RRMM patients treated with venetoclax were included and had a median of six prior lines of therapy. The overall response rate was 78% and one patient with cardiac amyloidosis and MM achieved a cardiac organ response. Haematologic toxicities requiring red blood cell and platelet transfusion and non-haematologic toxicities, most commonly gastrointestinal upset, were observed.

Keywords: venetoclax, relapsed/refractory multiple myeloma, amyloidosis, translocation, amyloid.

Overall survival in multiple myeloma (MM) has improved in the last decade. Numerous developments in MM treatment including the second-generation proteasome inhibitors (carfilzomib and ixazomib), new immunomodulatory drugs (pomalidomide), and monoclonal antibodies (daratumumab and elotuzumab) have improved patient outcomes (Chim *et al.*, 2018). Despite these advances, patients that remain refractory to these medications continue to have a poor prognosis, necessitating development of drugs with distinct mechanisms of action (Kumar *et al.*, 2017b).

A hallmark of tumour cell survival in MM is overexpression of anti-apoptotic proteins including BCL-2, BCL-XL, BCL-W, or myeloid cell leukaemia sequence (MCL)-1 (Touzeau *et al.*, 2018; Punnoose *et al.*, 2016). Venetoclax, an inhibitor of the anti-apoptotic protein, BCL-2, has recently been approved by the US Food and Drug Administration (FDA) for the treatment of chronic lymphocytic leukaemia, small lymphocytic lymphoma, and acute myeloid leukaemia (Mihalyova *et al.*, 2018). Importantly, venetoclax has shown promise as a potential therapeutic agent in other haematologic malignancies, including MM, light chain amyloidosis, and primary plasma cell leukaemia. Primary plasma cell leukaemia is a highly aggressive plasma cell dyscrasia with about 50% of these patients harbouring the t(11;14) mutation (Jelinek *et al.*, 2019). Venetoclax, therefore, seems to be a promising option in these patients as seen in a few case reports (Jelinek *et al.*, 2019; Nalghranyan *et al.*, 2019). About 15–20% of patients with MM have t(11;14) which results in overexpression of BCL-2, with venetoclax having a robust single-agent activity in these patients (Kumar *et al.*, 2017a).

There have been a few studies assessing venetoclax regimens in the relapsed/refractory MM (RRMM) patient populations as both monotherapy and combination therapy (Kumar *et al.*, 2017a; Moreau *et al.*, 2017; Costa *et al.*, 2018). An open-label, phase 1 trial using venetoclax as monotherapy in this patient group showed promising therapeutic potential with an overall response rate (ORR) of 21% and with ≥very good partial response (VGPR) 15% in the entire cohort and ORR 40% with ≥VGPR 27% in the t(11;14) cohort (Kumar *et al.*, 2017a). Venetoclax has also been studied in combination with dexamethasone and either bortezomib or carfilzomib which showed ORRs of 67% and 78% in a phase 1b and phase 2 study respectively (Moreau *et al.*, 2017; Costa *et al.*, 2018). The BELLINI trial is the first randomized, controlled clinical trial to study venetoclax in RRMM and compared venetoclax *versus* placebo in combination with bortezomib and dexamethasone (Kumar *et al.*, 2019). The addition of venetoclax to bortezomib and dexamethasone in this trial showed statistically significant improvement in progression-free survival (PFS), ORR, and percentage of patients achieving ≥VGPR compared to bortezomib and dexamethasone alone, but increased death was seen in patients in the venetoclax arm (Kumar *et al.*, 2019). These results led to a temporary hold by the FDA for further randomized

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controlled trials involving venetoclax use in RRMM, necessitating more clinical data. Given that increased death was not seen in the t(11;14) patient population in the BELLINI trial, the FDA released the hold on further studies with venetoclax use in these patients (Loewe, 2019).

Here, we report additional real-world experience with venetoclax-based regimens in patients with t(11:14) RRMM at our institution. Our objective was to review outcomes and safety of venetoclax-based regimens in this patient group.

Patients and methods

The Cleveland Clinic Institutional Review Board approved this study. The Cleveland Clinic MM database was queried to identify patients meeting the following inclusion criteria: (i) relapsed or refractory MM, and (ii) treated with one or more cycles of venetoclax-based therapy outside of a clinical trial. Venetoclax was initiated at 400 mg for one week and then titrated to 800 mg depending on tolerability and insurance approval. All patients meeting the above criteria through April 2019 were included and followed until September 30, 2019. Two investigators, DB and RC, independently reviewed clinical data and conflicts were resolved by consensus. International Myeloma Working Group (IMWG) criteria were used to assess disease response in all patients (Kumar *et al.*, 2016). The primary endpoint was ORR.

Results

Patient characteristics at initiation of venetoclax therapy

A total of ten patients were included in our analysis. Among them, five were males, all were Caucasian, and five had an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or 3 at treatment initiation. Four patients had International Staging System (ISS) stage III at diagnosis (Table I). All had t(11:14) translocation, five had deletion (13q), three had deletion (17p), and three had abnormal metaphase cytogenetics with a complex karyotype. Patients received a median of six lines of treatment prior to venetoclax (range, 2–19) (Table I). Notably, 10/10 were refractory to bortezomib, 4/10 to carfilzomib, 4/10 to ixazomib, 9/10 to lenalidomide, 7/10 to pomalidomide, 3/10 to elotuzumab, and 8/10 to daratumumab (Table I). Five patients had received a prior autologous stem cell transplantation, among whom two had relapsed within a year post-transplant. A total of five patients had clinical relapse without extramedullary disease, three had clinical relapse with extramedullary disease, and two had biochemical-only relapse at initiation of venetoclax. The median time from diagnosis to initiation of venetoclax was 51·6 months (range, 3·1–179.5). Furthermore, median haemoglobin was 9·6 (range, 6·8–13.7), median serum creatinine was 1·05 (range, 0·50–4·87), and median albumin was 3·0 (range, 2·1–4.5) at venetoclax initiation.

Response to venetoclax-based therapies

The most common regimen used was venetoclax in combination with bortezomib and dexamethasone. Venetoclax was initiated at 400 mg for one week and then titrated to 800 mg depending on tolerability and insurance approval.

Table I. Patient characteristics prior to venetoclax therapy.

Variable	*n* (%)
Gender	
Male	5 (50)
Female	5 (50)
Myeloma subtype	
IgG	5 (50)
Light chain only	3 (30)
IgM	1 (10)
Non-secretory	1 (10)
ISS stage (n = 9)	
I	2 (22)
II	3 (33)
III	4 (44)
Genetic mutations (# and % yes; >1 possible)	
Deletion (13q)	5/9 (56)
Deletion (17q)	3 (30)
t(11;14)	10 (100)
t(14;16)	0 (0)
t(14;20)	0 (0)
14q32 translocation	4 (40)
High-risk FISH cytogenetics	4 (40)
Abnormal metaphase cytogenetics	3 (30)
Refractory to bortezomib	
Yes	10 (100)
Refractory to carfilzomib	
Yes	4 (40)
No	3 (30)
Naïve	3 (30)
Refractory to ixazomib	
Yes	4 (40)
Naïve	6 (60)
Refractory to thalidomide	
Yes	2 (20)
No	1 (10)
Naïve	7 (70)
Refractory to lenalidomide	
Yes	9 (90)
Naïve	1 (10)
Refractory to pomalidomide	
Yes	7 (70)
Naïve	3 (30)
Refractory to elotuzumab	
Yes	3 (30)
Naïve	7 (70)
Refractory to daratumumab	
Yes	8 (80)
No	1 (10)
Naïve	1 (10)

FISH, fluorescence in situ hybridization; Ig, immunoglobulin; ISS, International Staging System.

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Among nine patients who were evaluable for response, the ORR was 78% (seven out of nine patients). Among these seven responding patients, one achieved a complete response, one achieved a very good partial response, four achieved a partial response, and one achieved a minimal response to therapy (Table II). Notably, the best responses were seen in those patients who received carfilzomib and dexamethasone in addition to venetoclax (Table II). One patient (Patient #10

Table II. Treatment response and adverse events with venetoclax-based combination regimens in relapsed/refractory t(11;14) multiple myeloma.

	Regimen	Lines of therapy for venetoclax	Best response	Status	Adverse events
Patient 1	Venetoclax–bortezomib–dexamethasone	3	PR	Alive	Haematologic toxicities: anaemia (requiring transfusions), thrombocytopenia (no platelet transfusions required) Non-haematologic toxicities: diarrhoea, nausea, fever requiring hospitalization (not neutropenic)
Patient 2	Venetoclax–bortezomib–dexamethasone	20	PR	Alive	Haematologic toxicities: anaemia, neutropenia, thrombocytopenia (not requiring transfusion) Non-haematologic toxicities: fatigue, nausea, vomiting, abdominal pain requiring one episode of hospitalization, weight loss (approximately 7 kg over the duration of venetoclax treatment)
Patient 3	Venetoclax–bortezomib–dexamethasone	3	PD	Dead)cause of death: progressive disease)	Haematologic toxicities: thrombocytopenia (not requiring transfusion)
Patient 4	venetoclax–carfilzomib–dexamethasone	7	VGPR	Alive	Haematologic toxicities: anaemia, thrombocytopenia, leukopenia (no transfusions required) Non-haematologic toxicities: fatigue (led to dose reduction of venetoclax from 800 to 400 mg), nausea, loss of appetite, weight loss (4.5 kg, leading to holding dose for one week)
Patient 5	venetoclax–bortezomib–dexamethasone	7	PR	Dead (cause of death: septic shock, acute hypoxic respiratory failure)	Haematologic toxicities: anaemia, leukopenia, thrombocytopenia (requiring transfusions) Non-haematologic toxicities: septic shock due to invasive aspergillosis in the setting of disease progression, acute hypoxic respiratory failure due to above, fatigue
Patient 6	Venetoclax–carfilzomib–dexamethasone	3	CR	Alive	Haematologic toxicities: leukopenia Non-haematologic toxicities: mild diarrhoea (one or two episodes a day)
Patient 7	Venetoclax–bortezomib–dexamethasone	12	NA	Dead (cause of death: patient transitioned to hospice due to declining overall health status)	Haematologic toxicities: thrombocytopenia (leading to haematemesis, haematochezia, and epistaxis, with EGD showed bleeding angioectasia that was clipped), anaemia (requiring transfusions) Non-haematologic toxicities: fatigue
Patient 8	Venetoclax–bortezomib–dexamethasone	11	MR	Dead (cause of death: likely relapsed MM, transitioned to hospice)	Haematologic toxicities: anaemia, thrombocytopenia, and neutropenia (not attributed to venetoclax; present prior to treatment initiation). Non-haematologic toxicities: headache (leading to dose reduction of venetoclax from 800 to 600 mg), acute cholecystitis (requiring cholecystectomy) in the setting of disease progression
Patient 9	Venetoclax, dexamethasone	11	PD	Alive	Haematologic toxicities: thrombocytopenia and anaemia (both requiring transfusions) Non-haematologic toxicities: diarrhoea nausea, and fatigue
Patient 10	Venetoclax–bortezomib–daratumumab–dexamethasone	3	PR	Alive	Non-haematologic toxicities: productive cough, fatigue

CR, complete response; EGD, esophagogastroduodenoscopy; MM, multiple myeloma; MR, minimal response; NA, not available; PD, progressive disease; PR, partial response; VGPR, very good partial response.

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in Table I) who had cardiac amyloidosis achieved an organ response, with around 45% reduction in NT-pro-BNP. Six patients were alive at most recent follow-up with a median follow-up of 5·2 months from venetoclax initiation (range, 3·1–13.5) (Table II). The six6-month overall survival (OS) was 77% (95% CI) and six-month PFS was 28% (95% CI) as calculated by the Kaplan–Meier method.

Safety data

The cause of death was relapsed MM in three and septic shock/acute hypoxemic respiratory failure due to invasive aspergillosis (in the setting of disease progression) in one patient. The toxicity profile in individual patients has been summarized in Table II. Non-haematologic toxicities seen in more than one patient included fatigue, weight loss, appetite loss, and gastrointestinal toxicity (nausea, diarrhoea, and abdominal cramps). Four out of ten patients required red blood cell or platelet transfusions for haematologic toxicity.

Discussion

Given promising efficacy data in t(11;14) MM, we have been using venetoclax-based combination regimens in patients harbouring this translocation at our institution once they are refractory to other approved anti-myeloma agents. Our results corroborate the reported efficacy of venetoclax-based combination regimens in a heavily pretreated real-world cohort of RRMM patients. Furthermore, the safety profile observed in our study is similar to that reported in clinical trials. Based on our results, venetoclax is effective in patients with heavily pretreated relapsed/refractory t(11;14) MM, with seven out of nine response evaluable patients achieving at least a partial response leading to an ORR of 78%. Furthermore, one bortezomib and daratumumab refractory patient with concomitant systemic amyloidosis and MM achieved a cardiac organ response after addition of venetoclax. Interestingly, the best responses were seen in patients treated with the combination of venetoclax, carfilzomib, and dexamethasone with one patient achieving VGPR and the other a CR with this regimen.

It is also important to identify and consider potential side effects and toxicity associated with venetoclax therapy. The addition of venetoclax to bortezomib and dexamethasone in the BELLINI trial suggested increased mortality in the venetoclax arm, with most causes of death being due to infection (Kumar *et al.*, 2019). This same study, however, showed a positive trend in OS in patients with t(11;14) treated with venetoclax (Kumar *et al.*, 2019). In our cohort, one patient had an infectious cause of death and it was not clear whether the infection was related to venetoclax therapy. Our data also suggest the possibility of haematologic toxicities including anaemia and thrombocytopenia, which may require transfusion therapy. Additionally, some major symptomatic side effects that were identified in our cohort included fatigue, nausea, abdominal pain, and weight loss. Since symptomatic adverse events are underreported by clinicians and can have a potentially major impact on quality of life, future clinical trials of venetoclax should incorporate patient-reported outcome measurements to assess tolerability. Overall, the results seen in our study highlight potential toxicities and side effects of venetoclax, but are encouraging and warrant further investigation in a larger cohort of patients with RRMM and amyloidosis.

Author contributions

DB, RC and JV collected and analyzed the data, wrote the first draft of the report, and revised the paper critically. JV designed the research project. LR analyzed the data and revised the paper critically. NR, JR, MK, KS, HD, MK and JV performed patient management, revised the paper critically, and participated in final data analysis.

Conflicts of interest

DB, RC, LR, NR, JR, MK, KS, HD, MK and JV report no competing financial interests.

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