Venetoclax salvage therapy in relapsed/refractory multiple myeloma

The BCL2 inhibitor venetoclax has emerged as an effective treatment option for multiple myeloma (MM), the second most common blood cancer. Despite the recent inclusion in European MM treatment guidelines, no approval for this use has yet been granted and the optimal dosage, combination partners and timing of treatment remain under investigation. We analyzed 38 MM patients treated with venetoclax at our institution. Sixty-four percent of them had a t(11;14) and all of them had been heavily pretreated. High-risk features were enriched in the cohort. Patients received either venetoclax alone or in combination with other MM drugs over a median of five cycles. Compared to patients not carrying the translocation, patients harboring t(11;14) had a better overall response rate (ORR), progression-free survival (PFS) and overall survival (OS). Toxicities were manageable, but three patients died under treatment.

Venetoclax is the first precision therapy in MM targeting a primary genetic event. Its clinically exploitable pro-apoptotic effects are particularly present in patients harboring the t(11;14) (q13;q32) (IGH::*CCND1* fusion), who account for 15-20% of all MM cases.[1] The ORR of MM patients with t(11;14) to venetoclax monotherapy was 86%[2] and consequently the phase III BELLINI trial tested venetoclax (800 mg/day)/bortezomib/dexamethasone *versus* placebo/bortezomib/dexamethasone in a pretreated population. It found an improved ORR (84 *vs*. 70%) and PFS (22.4 *vs*. 11.5 months) for the venetoclax combination.[3] Other combination partners tested in clinical trials are pomalidomide,[4] carfilzomib,[5] selinexor,[6] and daratumumab.[7]

We evaluated 38 MM patients who were treated with venetoclax-based therapy at our institution from November 2017 until June 2022. Patients with del(17p) or *TP53* mutation, t(4;14), t(14;16), t(14;20), and amp(1q) were considered high-risk. Revised International Staging System (R-ISS) stage was assessed at initiation of venetoclax treatment. Adverse events were determined according to the Common Terminology Criteria for Adverse Events version 5.0. ORR, OS and PFS were assessed according to the current criteria of the International Myeloma Working Group. t(11;14) status was defined via fluorescence *in situ* hybridization. The date of data censorship was January 2, 2023. The Ethics Committee of the Medical Faculty of Würzburg waived informed consent (waiver # 20220315 02).

For 36/38 patients (95%), fluorescence *in situ* hybridization analysis was available at therapy initiation. Seventeen patients (47.2%) had high-risk cytogenetics, comprising nine with t(11;14) (41% of all patients positive for this translocation) and eight without t(11;14) (57% of all those without this translocation). Nineteen patients (53%) were in R-ISS stage 3 and were well-balanced with 55% harboring t(11;14). Our cohort was heavily pretreated with a median of seven (range, 2-13) prior lines of therapy. Six patients suffered from extramedullary disease (EMD) and two from plasma cell leukemia (PCL) (Table 1). Thirty-five patients (92%) had received at least one autograft and three patients (8%) had undergone allogeneic stem cell transplantation before initiation of venetoclax. All patients were refractory to proteasome inhibitors and immunomodulatory drugs, 36/38 patients (95%) were triple-refractory, and 28/38 patients (74%) were penta-refractory prior to starting venetoclax. Three patients (8%) had been pretreated with T-cell redirecting therapies (*Online Supplementary Table S1*). The median follow-up was 16.7 (range, 3.1-56.4) months. Patients received nine different venetoclax combinations (*Online Supplementary Table S2*) and doses varied from 100 to 1,200 mg/day. The most prevalent dose in our cohort was 800 mg/day, which was given to 18 patients (47%). Two (5%) patients received 1,200 mg daily for five and two cycles without dose reductions or interruptions being necessary. We did not find any usage of strong CYP3A4 inhibitors in the co-medication history. Venetoclax dosing was higher for patients with t(11;14) at an average of 645.5 mg/day (median 800 mg/day) *vs*. 507.1 mg/day (600 mg/day) for those without t(11;14). The average duration of therapy was 7.1 months, with a median of 5.1 months.

All patients were evaluable for adverse events. Toxicity-relat-

Table 1. Patients' characteristics.

Demographics	
N of patients	38
Male/female, N	25/13
Age in years, mean (range)	62 (37-82)
ECOG score, years, mean (range)	1.2 (0-3)
Extramedullary disease, N	6
Plasma cell leukemia, N	2
Treatment line, median (range)	7.3 (2-13)
Cytogenetics	
N of patients	36
t(11;14), N (%)	22 (61.1)
High risk, N (%)	17 (47.2)
del17p/*TP53*-mutated, N (%)	10 (27.8)
amp(1q),N (%)	8 (22.2)
t(4;14), N (%)	3 (8.3)
t(14;16), N (%)	2 (5.6)
t(14;20), N	0

ECOG: Eastern Cooperative Oncology Group performance scale status.

ed discontinuation of therapy occurred in 5%. We observed three cases (8%) of tumor lysis syndrome during the first cycle of a venetoclax-containing regimen and in all three cases the treatment consisted of venetoclax in combination with daratumumab/carfilzomib/dexamethasone. There were no other predictors, pointing towards treatment intensity as an underlying cause. Of the four cases of transient kidney injury, three were associated with tumor lysis.

No difference in the treatment-associated fatality rate was observed between patients with or without t(11;14) (*P*=0.79). Importantly, none of the three patients (8%) who developed sepsis – which was fatal in two of them - had been on antibiotic prophylaxis at the time of infection and all of them had neutrophil counts above 1.0 x10^9/L. In addition, a third patient died unexpectedly and for unknown reasons outside of our institution, resulting in a total of three patients (8%) who died under a venetoclax-containing regimen. Last response assessment showed a very good partial response (VGPR) in all three patients. Generally, the rates of hematologic adverse events grade ≥3 and the treatment-associated mortality rate with 5.3% *versus* 4.0% infection-related deaths in our cohort are comparable to those of the BELLINI trial. However, while the BELLINI trial found an increased risk of death in patients without t(11;14) and raised significant safety concerns, all severe infectious complications in our study occurred in t(11;14)-positive patients independently of therapy duration. These results advocate for antibiotic prophylaxis and close monitoring of markers of infection in patients receiving venetoclax.

The ORR reached 53% in our cohort (n=20: ORR 59% *vs*. 50% in patients with and without t(11;14), respectively). Remissions were generally deep with nine patients (24%) achieving partial remission, seven patients (18%) experiencing VGPR and four patients (11%) reaching complete remission. Moreover, the disease remained stable for 3 months or longer in seven patients (18%), cumulating in a clinical benefit rate of 71% (Figure 1). Notably, EMD resolved fully in one patient and stabilized in another. Both patients suffering from PCL, one of them with and one without t(11;14), progressed under therapy.

The median PFS for all patients who received venetoclax in their treatment regimens was 5.1 months and was significantly longer in patients harboring the t(11;14) (11.2 *vs*. 4.4 months; *P*=0.095) (Figure 2). The median OS was 12.7 months for all patients and was not reached in the subgroup with t(11;14) *versus* 12.8 months in patients without this translocation (*P*=0.64). In three patients venetoclax therapy was consolidated with an autograft (after 15.1 months in partial remission), one patient received an allograft (after 5.1 months in stringent complete response), and one patient received BCMA-directed chimeric antigen receptor T-cell therapy 12.4 months after stopping venetoclax therapy and was in ongoing partial response at data censorship. At relapse 9 months later, this patient achieved partial response on re-starting venetoclax. Notably, 17 out of the 26 patients (65%) who eventually suffered from progression upon venetoclax-containing therapy were fit for subsequent therapy and eight of them (47%) responded to the salvage regimen.

Patients with high-risk cytogenetics had a lower ORR than patients with standard-risk disease (41 *vs*. 65%; *P*=0.38) and significantly shorter median PFS (3.9 *vs*. 18.1 months; *P*=0.025), while median OS did not differ significantly (not reached *vs*. 12.8 months; *P*=0.19). Of note, all non-responders had R-ISS stage 3 disease at the time of starting venetoclax treatment. Patients with more than six prior lines of therapy had a lower ORR (36.4%), shorter median OS (207 days *vs*. not reached; *P*=0.013) and shorter median PFS (2.8 *vs*. 17.7; *P*=0.015). VGPR or better was associated with better PFS (17.9 *vs*. 8.4 months; *P*=0.03) and OS (not reached *vs*. 11.9 months; *P*=0.1). Venetoclax doses ≥400 mg/day correlated with

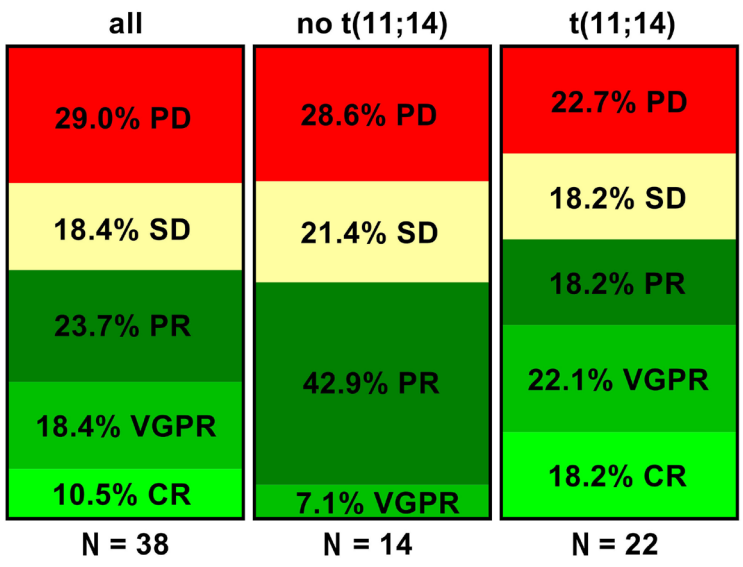

Figure 1. Responses and depth of response under treatment with a venetoclax-containing regimen. Stratification by International Myeloma Working Group criteria. PD: progressive disease; SD: stable disease; PR: partial remission; VGPR: very good partial remission; CR: complete remission.

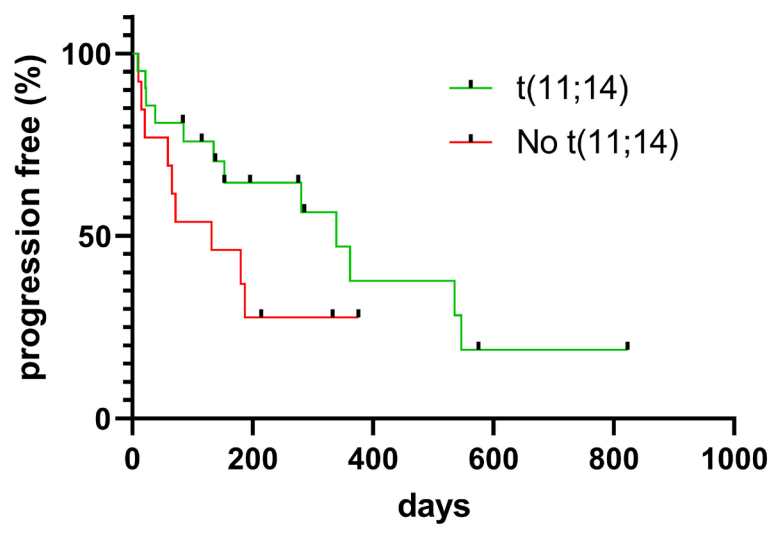

Figure 2. Progression-free survival of patients treated with a venetoclax-containing regimen, stratified by the presence or absence of t(11;14). Statistical significance: *P*=0.095. Number of patients at risk: 22 for patients with t(11;14) and 14 for those without t(11;14).

better median PFS (9.3 *vs*. 2.4 months; *P*=0.03) at comparable patient distribution (58% t(11;14)-positive patients and 61% t(11;14)-negative patients over 400 mg/day) but no such relationship could be determined for median OS (17.7 *vs*. 4.8 months; *P*=0.22) or ORR (57 *vs*. 50%; *P*=0.42). Notably, patients with EMD or PCL had an inferior median OS (1.9 *vs*. 9.3 months; *P*=0.01) and PFS (3.1 *vs*. 17.7 months; *P*=0.01), independently of t(11;14) status. Overall, venetoclax-containing regimens were not able to overcome the negative prognostic impact of high-risk cytogenetics, EMD and PCL, independently of t(11;14) status. With a median PFS of 4.4 and a median OS of 12.8 months, our data are in line with those from other real-world studies that demonstrated lower efficacy of venetoclax in t(11;14)-negative patients,[2,8] and increased PFS, OS and ORR in patients with t(11;14)-positive disease.[9,10] This highlights the importance of t(11;14) for predicting response to venetoclax-containing regimens. An overview of available trials and analyses of venetoclax-containing regimens can be found in *Online Supplementary Table S3*.

In summary, our real-world observational study confirms substantial clinical activity of venetoclax, particularly in t(11;14)-positive disease. Thus, this targeted therapy approach provides an additional and promising treatment option for heavily pretreated MM patients.

Authors

Maximilian J. Steinhardt,[1] Marietta Truger,[2] Max Bittrich,[1] Xiang Zhou,[1] Julia Noderer,[1] Christine Riedhammer,[1] Xianghui Xiao,[1] Sophia Gawlas,[1] Philipp Weis,[1] Florian Eisele,[1] Claudia Haferlach,[2] Julia Mersi,[1] Johannes Waldschmidt,[1] Hermann Einsele,[1] Leo Rasche[1,3] and K. Martin Kortüm[1]

[1]Medizinische Klinik und Poliklinik II, Universitätsklinikum Würzburg, Würzburg; [2]MLL Munich Leukemia Laboratory, Munich and [3]Mildred Scheel Early Career Center, Universitätsklinikum Würzburg, Würzburg, Germany

Correspondence:
M. KORTÜM - kortuem_m@ukw.de

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Disclosures

No conflicts of interest to disclose.

Contributions

MJS collected and contributed data, designed and performed the analysis and wrote the paper. MT contributed data and conceived the analysis. MB, XZ, JN, FE, and CH contributed data. JM and HE conceived the analysis. JW conceived the analysis and wrote the paper. LR conceived and designed the analysis. KMK conceived and designed the analysis and wrote the paper.

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Data-sharing statement

All data, if not given in this article, are openly available on request.

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