Targeted venetoclax therapy of 11;14 translocated multiple myeloma

Ph.D. thesis

Virág Réka Szita

Károly Rácz Conservative Medicine Division
Semmelweis University

Supervisor: Gergely Varga, MD PhD

Official reviewers: Árpád Szomor, MD PhD
Bence Bátai, MD PhD

Head of the Complex Examination Committee:
Nóra Hosszúfalusi MD DSc

Members of the Final Examination Committee:

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1. Introduction

Multiple myeloma (MM) is one of the most common hematological malignancies, with more than 400 new cases estimated to occur in Hungary each year. In spite of recent advances and the plethora of drugs available, no definitively curative approach has yet been determined. More recent data have also shown that MM is a genetically heterogeneous disease, and it is becoming increasingly clear that t(11;14) myeloma is fundamentally different from other genetic subsets. Several groups of myeloma patients are difficult to treat: those who respond suboptimally to first line therapy; relapsed/refractory patients; as well as those with plasma cell leukemia (PCL), AL amyloidosis or kidney injury.

Venetoclax is a selective Bcl-2 inhibitor. It induces apoptosis by shifting the balance of antiapoptotic and proapoptotic proteins towards cell death. Studies showed an increased mortality due to infections if used indiscriminately in all myeloma populations; later studies, however, support the use of venetoclax in t(11;14) myeloma. In this genetic subset, genetic expression profiles are more similar to mature B-cells than plasma cells and they rely heavily on Bcl-2 for the evasion of apoptosis.

2. Objectives

The aim of our study was to evaluate venetoclax use in t(11;14) myeloma patients in the real life setting in Hungary.

We wanted

1. to describe the characteristics of the myeloma patients that have received venetoclax as well as the treatment regimens that were followed, including the dosing of venetoclax and concomitant use of CYP3A inhibitors.
2. to evaluate objective response rates to venetoclax therapy in the relapsed/refractory (R/R) setting.
3. to measure PFS and OS in the R/R setting and see whether it was comparable in length to other possible treatment options for this group.
4. to see whether we would find a survival difference in patients with or without high risk features such as del(17p) or kidney failure.
5. to assess whether early venetoclax salvage was effective in deepening hematological responses and to help eligible patients reach ASCT.
6. to estimate whether venetoclax salvage positively affected OS in t(11;14) patients responding unfavorably to standard therapy.

7. to evaluate PFS as compared to a similar cohort of patients.
8. to assess how venetoclax use impacted OS in t(11;14) patients in our praxis
9. to see how venetoclax performed in patient groups excluded from clinical trials, such as patients with kidney failure and whether renal failure affected the safety profile of venetoclax.
10. to overview how many PCL patients were treated with venetoclax in Hungary and the length of PFS that could be expected with venetoclax treatment.
11. to assess the range and severity of adverse effects associated with venetoclax use in our study population.

3. Methods

For detailed methodology, I refer to the publications and the thesis as per the doctoral school guidelines. As a brief overview:

We collected data evaluating venetoclax use in t(11;14) myeloma retrospectively, from our own praxis at the Department of Internal Medicine and Hematology, Semmelweis University, Budapest; in a countrywide project in 2021 in seven different hematology centers; as well as used a

comparative data set involving t(11;14) patients between 2012-16 at South Pest Central Hospital with the authors' permission.

Only t(11;14) myeloma patients with no other malignancy were included. We collected data about p53 loss, gain(1q21), ISS staging and hematological response and calculated PFS and OS from the initiation of venetoclax therapy either the date of last medical contact or the date of progression and death, respectively. We collected data about the number of prior therapy lines, including previous ASCT; the presence of AL amyloidosis, PCL or EMD; venetoclax and concurrent CYP3A inhibitor dosage; venetoclax treatment duration and adverse events associated with the venetoclax use. Venetoclax treatment was prescribed with individual OGYÉI 'off label' permissions and NEAK financial support in all cases. The research has been approved by Semmelweis University Regional, Institutional Science and Study Ethic Committee (ethic code: 12/2023) and conducted in accordance with the declaration of Helsinki.

4. Results

58 t(11;14) MM patients were reported. Patients were divided into a relapsed/refractory and a reinduction group (Table 1).

4.1 Patient characteristics

Table 1. Patient characteristics

Patient characteristic	**Relapsed/refractory group (n=37)**	**Reinduction group (n=21)**
male gender	17 (46%)	9 (43%)
age at the start of venetoclax therapy (years)	69 (45-89)	65 (50-91)
median time to venetoclax	4.7 years	2.6 months
ISS 1/2/3	14%/16%/57%	52%/5%/43%
loss of p53	12 (32%)	6 (29%)
gain(1q21)	21 (57%)	8 (38%)
GFR <45 ml/min	11 (30%)	5 (24%)
median lines of prior treatment	4 (1-12)	1 (1-2)
single/double/triple class refractory	0%/62%/38%	10%/24%/0%

37 patients were classed as relapsed/refractory: they were refractory to several classes of myeloma drugs and received venetoclax after numerous previous lines of therapy, often as a last resort. We classed 21 patients as the reinduction group, who showed suboptimal response to first line treatment and received venetoclax as a form of salvage in preparation for ASCT.

4.2 Characteristics of venetoclax therapy

Venetoclax doses had been appointed individually for each patient, based on gastrointestinal tolerance, concurrent CYP3A inhibitor use and the results from serum level measurements. To decrease the chance of TLS, treatment was started with a three-day ramp-up phase. The majority of patients (86%) received a concurrent CYP3A inhibitor to raise venetoclax levels two- to fivefold: 73% of all patients took clarithromycin, while 12% took fluconazole. Venetoclax was combined with other anti-myeloma agent(s), most commonly bortezomib.

4.3. Therapy outcomes

4.3.1. Relapsed/refractory group

The overall response rate was remarkable considering the heavily pretreated population: 92% of patients achieved at least a partial response (PR). 38% of patients reached even deeper

remission, either very good partial response (VGPR) or complete response (CR), see Figure 1.

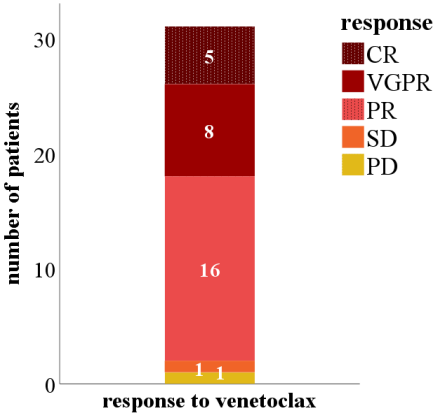

Figure 1. Treatment response rates in the relapsed/refractory group (CR - complete response, VGPR - very good partial response, PR - partial response, SD - stable disease, PD - progressive disease)

These response rates were associated with 10.0 months progression-free survival and 14.6 months overall survival from the start of venetoclax therapy (Figure 2.).

We compared the survival of those with adverse prognostic factors such as ISS stage, p53 loss or renal failure to those without them; no significant difference was found in any of these subgroups.

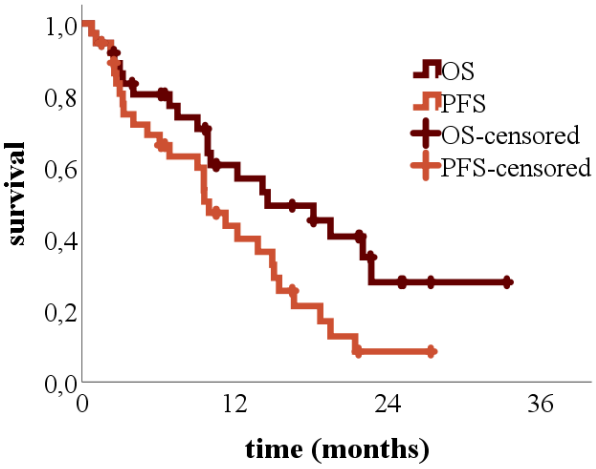

Figure 2. Progression-free survival (PFS) and overall survival (OS) in the relapsed/refractory group

4.3.2. Reinduction group

After venetoclax salvage, suboptimal frontline response (Figure 3) deepened to at least VGPR in all patients (100% ORR). Response rates further improved after ASCT in eligible patients. After a median 55.2 months observation, neither the median PFS nor the median OS were reached in this group (Figure 4).

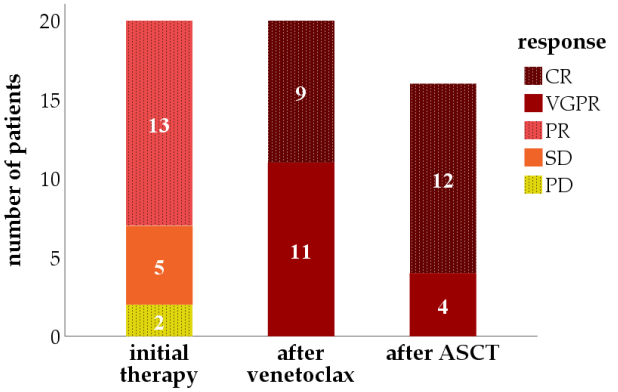

Figure 3. Treatment response rates in the reinduction group (CR - complete response, VGPR - very good partial response, PR - partial response, SD - stable disease, PD - progressive disease)

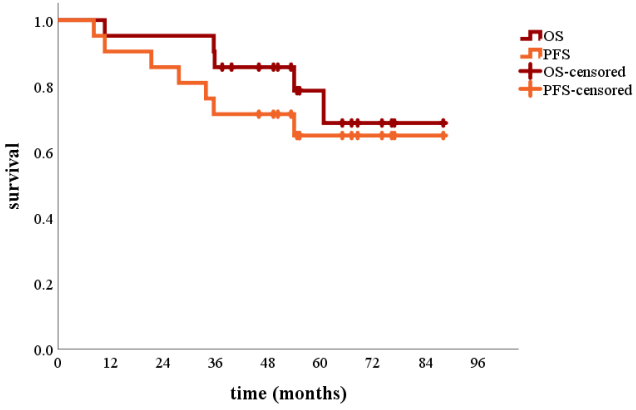

Figure 4. Progression-free survival and overall survival in the reinduction group

4.3.2.1. Comparison with a historical cohort

We compared our results to those from a large historical dataset, where we selected the 43 patients who only reached PR or less after receiving an IMID and/or PI containing induction regimen. 70% of these patients had reached PR, 19% SD and 11% PD after initial therapy, which was comparable to what we saw in our venetoclax study group . The 13 nonresponders here also received salvage. Of them, 54% responded vs 100% in our venetoclax cohort. 49% had been ASCT eligible, 52% of whom could proceed to ASCT, all of them in PR, vs all ASCT eligible patients in our venetoclax group, all in VGPR or CR.

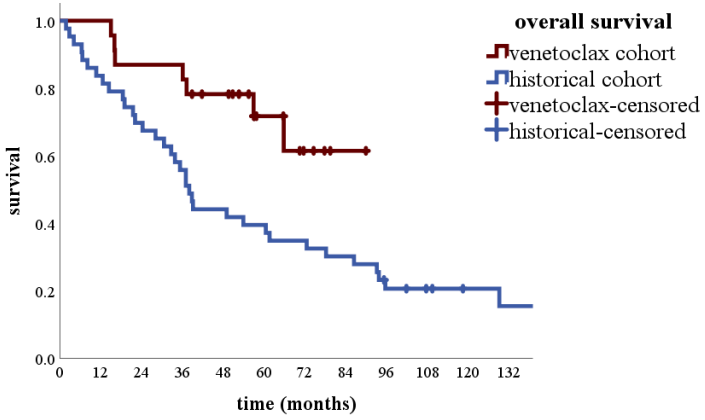

Figure 5. Overall survival (OS) in the venetoclax-treated reinduction group and the historical cohort

After a median 55.2 months follow-up in the venetoclax group, we found both significantly better PFS (median not reached vs 13.6 months p=0.000007) and OS (median not reached vs 39.1 months p=0.037), see Figure 5.

4.4. Patient subpopulations of special interest

4.4.1. Patients with impaired kidney function

More than a quarter of patients in our study group, 28% had impaired kidney function at the initiation of venetoclax treatment. During venetoclax therapy, we observed clinically relevant improvement in kidney function in five of these patients (45% of those with initial kidney failure). Three of the patients had required regular dialysis at the beginning, but during the course of therapy, all three of them had enough improvement in kidney function for dialysis to be stopped altogether. Twice as many patients in this subgroup reported adverse events, however, than patients with normal kidney function, 83% vs 37% of patients, respectively.

4.4.2. Plasma cell leukemia

Given the high prevalence of t(11;14) in plasma cell leukemia (50% on average), the limited available treatment options, and the typically dismal outcomes, we decided to analyze PCL patients in our study separately. Six patients were reported to have PCL, two with primary and four with secondary PCL.

Venetoclax treatment had been initiated shortly after the primary PCL diagnosis in one patient, with all others receiving venetoclax at a later relapse. Most patients had a high-risk cytogenetic abnormality present, p53 loss in three cases and gain(1q) in 2 cases. Each patient responded to venetoclax, with 1 reaching PR, 4 VGPR and 1 CR. Despite the remarkable hematological response rate, all relapsed/refractory patients eventually progressed after a median of 10.0 months PFS and passed away after a median of 12.2 months after the start of venetoclax therapy. The primary PCL patient that had been treated in an early line, did not progress and continues to be in CR 74 months after the diagnosis.

4.5. Safety

The safety profile of venetoclax treatment in our study was comparable to those prveiously published in trials.

Table 5. The incidence of adverse events in our study population

Adverse event	**Relapsed/refractory group (n=37)**	**Reinduction group (n=21)**
reported any adverse event	22 (59%)	8 (38%)
gastrointestinal complaints	6 (16%)	5 (24%)

(nausea/diarrhea)		
cytopenia	10 (27%)	1 (5%)
infections	11 (30%)	2 (10%)
tumor lysis syndrome	1 (3%)	0 (0%)
acute myocardial infarction	4 (11%)	0 (0%)

5. Conclusions

- We have collected real life data from a large number of hematological centers in Hungary and characterized venetoclax use in t(11;14) myeloma throughout the 2017-21 time period, including the use of CYP3A inhibitors and venetoclax dosing.
- In the relapsed/refractory setting, the t(11;14) patients in our study showed much better response rates to venetoclax than studies have reported for other agents possibly used in this population.
- In the relapsed/refractory setting, although venetoclax therapy was not effective indefinitely and progression could be expected after a median 10 months, the length of PFS and OS were nevertheless comparable or better to other treatment options for this group.

- We found no significant difference in the survival of patients with high risk features such as del(17p) or kidney failure compared to patients without them.
- We found that venetoclax salvage deepened the hematological response in t(11;14) patients to VGPR or CR reliably. After venetoclax therapy, all our eligible patients could proceed to ASCT, which could be carried out in either VGPR or CR.
- We could not prove that early venetoclax therapy would have a significant effect on long term overall survival in t(11;14) patients responding unfavorably to standard therapy.
- We found that the addition of venetoclax did lengthen progression-free survival and thus the time to further treatment in this group.
- We found that among the patients in our praxis, early venetoclax use in t(11;14) patients was associated with significantly better OS than the use of conventional therapy.
- We found that venetoclax was as effective in patients with renal failure (even if concurrently dialyzed) as in the normal kidney function population investigated in clinical trials, however, these patients were more prone to adverse events.

- Our study article reported the highest number of PCL patients successfully treated with venetoclax in the literature at the time. We found that PCL patients treated with venetoclax had 10 months PFS, significantly better than would be expected with other agents.
- Venetoclax treatment had an acceptable safety and toxicity profile in t(11;14) multiple myeloma patients, but attention should be paid to the possibility of coronary artery events.

6. Bibliography of the candidate's publications

Publications related to the thesis:

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    IF: -

∑IF: 17,87