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Deep and sustained response after venetoclax therapy in a patient with very advanced refractory myeloma with translocation t(11;14)

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During the past decade, the survival of patients with multiple myeloma (MM) has dramatically improved. This remarkable change is largely due to an increase in the anti-myeloma armamentarium, including next-generation proteasome inhibitors (carfilzomib, ixazomib), next-generation immunomodulatory drugs (IMiDs) (pomalidomide) and monoclonal antibodies (elotuzumab, daratumumab). However, the disease still remains incurable in the majority of cases and innovative strategies are therefore needed. BH3 mimetics represent a new class of drug that induce tumor cell death by targeting the anti-apoptotic proteins. Venetoclax, the first-in-class oral Bcl-2-specific BH3 mimetic, demonstrated impressive results in Bcl-2 dependent malignancies, such as chronic lymphocytic leukemia (CLL) and mantle cell lymphoma. We previously demonstrated that a subgroup of myeloma cells is Bcl-2 dependent and therefore sensitive to venetoclax in vitro. Interestingly, sensitivity to venetoclax was found to be restricted to the myeloma cells harboring the translocation t(11;14). Here, we describe the case of a young patient with very advanced and refractory MM, who achieved a deep and durable response after venetoclax therapy.

The patient is a 25 year-old woman diagnosed with symptomatic IgG-λ MM in 2010 according to current IMWG criteria. At this time, she presented with symptomatic anemia. A bone marrow aspirate confirmed the presence of 27% plasma cells. The International Scoring System (ISS) score was intermediate (II). Fluorescence in situ hybridization (FISH) analysis revealed the presence of the translocation t(11;14) without other cytogenetic findings, such as t(4;14) or t(14;16), or 17p deletion. The therapies received by the patient are summarized in Figure 1. Disease response was assessed according to standard criteria. Frontline therapy consisted of 4 cycles of bortezomib – lenalidomide – dexamethasone (VRD) followed by high-dose melphalan and autologous stem cell transplantation (ASCT), and 2 consolidation cycles of VRD. After completion of therapy, the patient achieved a very good partial response (VGPR). She then received lenalidomide maintenance for one year from October 2011. The disease relapsed in January 2013 and the patient started lenalidomide – dexamethasone (Ld). The best response was only stable disease (SD) and the patient experienced a relapse in August 2015. At this time, FISH analysis revealed the presence of the 17p deletion in 76% of analyzed cells, in addition to the previously known translocation t(11;14). At that point, the triplet combination pomalidomide – bortezomib – dexamethasone (PVD) was started. After 2 cycles, the patient achieved a partial response (PR) but the disease progressed at the end of
the fifth cycle. Next, she received daratumumab plus dexamethasone (IFM 2014-04 clinical trial), but the disease progressed at the end of the first cycle. We then decided to start carfilzomib in combination with bendamustine and dexamethasone. Again, the patient achieved a PR, but experienced early progression during cycle 3, with the development of a symptomatic right humeral lytic lesion.

In this situation of end-stage refractory MM, with the disease progressing on bortezomib, carfilzomib, lenalidomide, pomalidomide, bendamustine, dexamethasone and daratumumab, and harboring both t(11;14) and the 17p deletion, we approached Abbvie laboratories for a compassionate use of venetoclax. Both Abbvie and the French drug agency ANSM (Agence Nationale de Sécurité du Médicament) gave their approval. In order to assess the plasma cells’ \textit{in vitro} sensitivity, a new bone marrow sample was obtained after informed consent and plasma cells were cultured with increasing doses of venetoclax over 24h. Cell death was assessed using flow cytometry by measuring the loss of CD138 expression, as previously described. The plasma cells were found to be sensitive to venetoclax, with a lethal dose (LD) 50 lower than 300 nM (Figure 2A). The patient started venetoclax (1200 mg/day) plus dexamethasone (40 mg/week) (Ven-Dex) in June 2016. At that time, she presented with anemia and symptomatic bone lesions. After one cycle of Ven-Dex, the M-spike decreased from 28 to 12 g/L (PR), bone pain disappeared and anemia was corrected without transfusion or use of any erythropoietin stimulating agent. (Figure 2B) After 3 cycles, the patient achieved a VGPR. No drug-related adverse event has been reported so far. At the present time (December 2016), the patient is still receiving Ven –Dex and is still in VGPR (positive immunofixation, but M-spike not measurable). She presents no disease-related symptoms and describes her quality of life as very good.

The survival of patients with relapsed MM refractory to bortezomib and lenalidomide is very poor. In the relapsed setting, several novel agents, including pomalidomide, carfilzomib and daratumumab, have improved the prognosis of myeloma patients and have therefore been recently approved by the American and European drug agencies. The present patient presented with end-stage myeloma refractory to bortezomib, lenalidomide, carfilzomib, pomalidomide and daratumumab. Moreover, she harbored a 17p deletion, a very high-risk cytogenetic feature. Despite these very poor characteristics, the patient achieved a deep (VGPR) and durable (at least 6 months) response after venetoclax therapy. For this patient,
the duration of response to Ven – Dex was longer than that obtained with pomalidomide, carfilzomib and daratumumab. We previously demonstrated that in vitro sensitivity to venetoclax was restricted to MM cells harboring the translocation t(11;14).\textsuperscript{5} Here, we were able to test the in vitro sensitivity of the patient’s plasma cells to venetoclax. The LD\textsubscript{50} was found to be in the nanomolar range, as previously observed for sensitive myeloma samples.\textsuperscript{5,6} Of interest, this result confirms the fact that the alteration of the p53 pathway does not impact the sensitivity to venetoclax. Recently, a phase 1 dose-escalation trial evaluated the safety and efficacy of venetoclax as a single agent in relapsed myeloma patients.\textsuperscript{13} In the final 1200 mg/day cohort, the maximal tolerated dose was not reached, justifying the dose used for the present patient. In this trial, patients had very advanced disease with a median of 5 prior therapies. For patients with translocation t(11;14), the overall response rate (ORR) (at least PR) was 40%, including 6% CR and 20% VGPR. For patients without translocation t(11;14), almost no responses were observed (ORR = 6%). These results are very promising and demonstrate for the first time the clinical activity of a single agent in a specific cytogenetic subgroup of patients. Dexamethasone has been shown to promote Bcl-2 dependence in myeloma cells in vitro.\textsuperscript{14} Therefore, we chose to add dexamethasone to venetoclax, even if the patient was refractory to dexamethasone. In conclusion, the present case demonstrates the ability of venetoclax to induce deep and sustained responses in MM patients with translocation t(11;14), even in a setting of end-stage disease with high-risk 17p deletion.
CONFLICT-OF-INTEREST DISCLOSURE
The authors have no conflict of interest to disclose.

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AUTHORSHIP CONTRIBUTIONS
CT, MA and PM wrote the manuscript. CD and MA performed the in vitro experiments. CT, SLG, BM, TG, NB, JSB treated the patient. HC analyzed response. All the authors critically reviewed the manuscript.
REFERENCES


FIGURE LEGENDS

Figure 1: Prior lines of therapy before the initiation of venetoclax
VRD: Bortezomib, lenalidomide, dexamethasone; ASCT: autologous stem cell transplantation, Len Dex: lenalidomide, dexamethasone; PVD: pomalidomide, bortezomib, dexamethasone; Dara: daratumumab; BKD: bendamustine, carfilzomib, dexamethasone; CR: complete response, PR: partial response; SD: stable disease

Figure 2: In vitro and clinical response to venetoclax
(A) Mononuclear cells were treated with 300nM of venetoclax for 24 hours. Cells were then stained with an anti-CD138-PE mAb. Plasma cell death was assessed by the loss of CD138 expression. Cell death percentage was calculated relative to control (ct) cells. (B) PR: partial response; VGPR: very good partial response
1. VRDx3 ASCT VRD x 2 - lenalidomide maintenance
   Best response: CR

2. Len Dex
   Best response: SD

3. PVD
   Best response: PR

4. Dara
   Progression after 1 month

5. BKD
   Best response: PR

6. Acquisition of 17p deletion