Treatment of therapy-related acute myeloid leukemia and underlying multiple myeloma with decitabine/venetoclax and daratumumab

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Dear Editor,

With increased survival of patients with multiple myeloma (MM), therapy-related myelodysplastic syndrome (t-MDS) and t-acute myeloid leukemia (AML) may occur more frequently [1, 2]. We present here a patient with high-risk (HR) MM, who developed t-MDS and subsequent t-AML. AML treatment with decitabine/venetoclax resulted in complete remission (CR) of the t-AML, while progressive disease of MM was treated with daratumumab. We hypothesize that upregulation of CD38 in bone marrow plasma cells (BMPCs) after decitabine/venetoclax may have enhanced MM response. Additionally, we performed a review of the literature (Suppl. Table 1).

In June 2015, a 64-year-old female was diagnosed with IgG kappa (κ) MM. IgG levels were 46g/L, κ-serum-free light chains (SFLC) 75.4mg/L and β2-microglobulin 8.2mg/L (Fig. 1A). Anemia with a hemoglobin (Hb) of 8.4g/dL and osteolytic lesions were present. BMPC infiltration was 90%, and fluorescence in situ hybridization (FISH) revealed hyperdiploidy and del17p13 (Fig. 1B (a) and C). The MM was classified as International Staging System (ISS) III, R-ISS III, with 2/4 CRAB criteria. The patient’s revised myeloma comorbidity index was intermediate-fit [3].

Due to frailty at that time, she was ineligible for intensive AML induction therapy. Therefore, treatment with decitabine/venetoclax was started in February 2019. A BM biopsy in March 2019 confirmed CR of the t-AML (Fig. 1B (c)). However, PCs assessed by immunohistochemistry for CD38 had increased to 90%, and MFC confirmed aberrant PCs (aPCs) (Fig. 1D, right); therefore 2nd line daratumumab treatment was initiated (Fig. 1A). This induced VGPR and peripheral blood (PB) counts improved (Hb 10.2g/dL, leukocytes 3.2x10⁶/L, platelets 94x10⁶/L).

In June 2019, after worsening pancytopenia re-emerged and myeloid blasts were detectable in PB smears, decitabine/venetoclax was re-initiated. The BM biopsy in August 2019 showed persisting (30%) immature myeloid blasts (Fig. 1B (d)), upon which melphalan per os was started [5]. The patient died 2 months later of t-AML/MM progression, 50 months after the diagnosis of HR MM, and 9 months after t-AML.
A

1st LT MM: VCD

1st ASCT

R maintenance

1st LT t-AML: Deci-Ven

2nd LT MM: Dara

2nd LT t-AML: Mol

ID MM: BM, (CR)AB

Evolving MM: BM, (CR)AB

ID t-AML: BM

Relapse t-AML: BM

Time

B

BM 08/2015

ID MM

CD38

BM 01/2019

evolving MM + ID t-AML

CD38

BM 03/2019

PD MM + CRp t-AML

CD38

BM 08/2019

VGPR MM + PD t-AML

CD38

C

| Date   | 08/2015 | 01/2019 | 03/2019 | 08/2019 |
|--------|---------|---------|---------|---------|
| Disease Stage | ID MM | evolving MM | PD MM | VGPR MM |
| ID MM | - | - | - | - |
| evolving MM | - | - | - | - |
| PD MM | - | - | - | - |
| ID t-AML | - | - | - | - |
| CRp t-AML | - | - | - | - |
| FISH | Hyperdiploidy/del 17p13 (80%) | Hyperdiploidy/del 17p13 (30%) | Hyperdiploidy/del 17p13 (60%) | No Hyperdiploidy/del 17p13 |
| MA | not done | IDH1 (30%) | IDH1 (20%) | IDH1 (20%) |

D

BM 01/2019

evolving MM + ID t-AML

BM 03/2019

PD MM + CRp t-AML

0.01%

11.64%

CD38

23.63%

8.01%

6.61%

E

CD38 expression (Mean fluorescence intensity)

- MM
- t-AML

aPCs

MM t-AML

ID MM (01/2019)

ID t-AML (08/2019)

MGUS 1st CRp (03/2019)

MM 1st CRp (08/2019)
In summary, after decitabine/venetoclax induction and favorable T-ALL-response, MM progression required 2nd line daratumumab treatment, resulting in VGPR and improvement of PB counts. Notably, decitabine/venetoclax may have resulted in upregulation of CD38 (Fig. 1 D and E), possibly augmenting the response to daratumumab, although single-cell CD38 expression on aPCs before and after decitabine/venetoclax was not performed. In line with this hypothesis, Choudhry et al. showed that treatment of MM cell lines and primary patient samples with the demethylating agent 5-azacytidine resulted in CD38 upregulation [6]. Moreover, ATRA and the pan-deacetylase-inhibitor panobinostat may increase expression of CD38 in MM [7, 8]. Similarly, Zhao et al. demonstrated upregulation of CD38 on CD8-positive T-cells of AML patients receiving decitabine [9]. Furthermore, daratumumab has been shown to be effective in targeting adult CD38-positive AML and T-cell acute lymphoblastic leukemia (T-ALL) as well as pediatric T-ALL blasts in a preclinical patient-derived xenograft mouse model, and a phase II study (NCT03384654) investigating the efficacy of daratumumab in relapsed and refractory T-ALL is currently ongoing [10, 11]. Recently, Berthon et al. reported about a patient with simultaneous AML and MM who concomitantly received 5-azacytidine and daratumumab during MM relapse (Suppl. Table 1) [12]. Clinical trials are currently under way to investigate whether pretreatment with demethylating agents enhances the efficacy of daratumumab.

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Author contribution  K.S. designed the study, interpreted the data, and wrote the manuscript; J.J. and M.R. interpreted the data and wrote the manuscript; S.M.D. and V.R. performed FACS experiments and analyze and wrote the manuscript; M.P. performed cytogenetic analyses and provided information; G.H. provided patient data and wrote the manuscript; M.L., R.M. and R.W. helped with the conception and design of the study; M.E. designed the study, interpreted the data, and wrote the manuscript.

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Declarations

Ethics  Informed consent was obtained from the patient for being included in this study.

Conflict of interest  J.J, M.R, SMD, VR, MP, GH, RM, ML have no financial or other relationships that might lead to a conflict of interest. KS has received travel support from Abbvie and consultancy fees from Novartis. RW has received research and travel support from Sanofi, Gilead, Jazz, Celgene, and Amgen and has received consultancy fees from Sanofi, Pfizer, Gilead, Novartis, Amgen, and Takeda. ME has received educational and trial support from Amgen, Takeda, BMS, Janssen, and Novartis, in all unrelated to this case.

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Conflict of interest The authors declare no conflict of interest.
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