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LETTER TO THE EDITOR

# Preemptive therapy for cytomegalovirus reactivation after daratumumab-containing treatment in patients with relapsed and refractory multiple myeloma

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Dear Editor,

Daratumumab (Dara)-containing treatments have shown promising outcomes for relapsed and refractory multiple myeloma (RRMM) [1, 2]. Dara is an antibody against CD38, which is expressed not only on myeloma cells and B cells but also on natural killer cells and activated T cells [3]. Although the necessity of prophylaxis for herpes zoster was described in previous studies of daratumumab and recent guidelines from the European Society of Clinical Microbiology and Infectious Diseases Study Group for Infections in Compromised Hosts, cytomegalovirus (CMV) reactivation was not mentioned [4]. Recently, a few cases of CMV reactivation after Dara treatment have been reported in patients with RRMM [5, 6].

We report the cases of 5 patients with RRMM who experienced CMV reactivation after Dara-containing treatments (Table 1). We treated 13 patients with RRMM [median age, 62 (range, 47–75) years] using Dara/lenalidomide/dexamethasone ($n = 8$) and Dara/bortezomib/dexamethasone ($n = 5$) between November 2017 and October 2018. All patients received a median chemotherapy of 5 (range, 2–8) lines, and 7 patients underwent autologous stem cell transplantation. CMV antigenemia (pp65) was tested on clinical suspicion during Dara treatment in 11 of the 13 patients. Of these, 5 patients showed positive results at a median time of 21 (range, 16–70) days from the date of initiation of Dara, and the median CMV antigenemia level was 12 (range, 1–71)/slide. Clinical symptoms for these patients were fever ($n = 4$) and severe malaise ($n = 1$). All 5 patients were preemptively treated with valganciclovir ($n = 2$), ganciclovir ($n = 2$), or ganciclovir that was switched to valganciclovir ($n = 1$) for a median time of 13 (range, 10–33) days. All patients showed negative results for CMV antigenemia at a median time of 14 (range, 6–24) days from the date of initiation of antiviral therapy, and no CMV disease developed. No patients discontinued Dara treatment due to CMV reactivation, but one postponed treatment for 1 month. The rate of overall response was 60 and 50% in patients with and without CMV reactivation, respectively. Seven patients discontinued Dara-containing treatments due to disease progression ($n = 3$), adverse events ($n = 3$), and patient request ($n = 1$).

Once CMV disease develops in patients with RRMM, antimyeloma treatment might be interrupted. It is desirable to prevent CMV disease via monitoring and preemptive therapy in such patients at risk [7]. Median lymphocyte count just before the initiation of Dara-containing treatment was 750 (range, 180–1070)/μL and 1015 (range, 560–2230)/μL in patients with and without CMV reactivation ($P = 0.32$), respectively, and it was 200 (range, 140–470)/μL and 575 (range, 360–1760)/μL, respectively, at the time of the CMV antigenemia test ($P = 0.0135$). Hence, lymphocyte counts after Dara-containing treatment might affect the tendency of CMV reactivation. Other risk factors associated with CMV reactivation were not identified due to the small number of cases. Analysis of only 4 patients with non-IgG type myeloma showed the IgG levels just before Dara-containing treatment were 251 and 359 mg/dl in 2 patients with CMV reactivation, and that were 482 mg/dl and 793 mg/dl in 2 patients without CMV reactivation. By measuring intact immunoglobulin levels in a large cohort including IgG-type myeloma, it may be possible to clarify whether hypogammaglobulinemia is a risk factor for CMV reactivation.

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**Table 1** Clinical characteristics of patients with CMV reactivation during daratumumab-containing treatment

| Case | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| Age/sex | 69/male | 75/female | 50/female | 55/male | 70/male |
| Type of M protein | IgA-λ, BJP-λ | BJP-λ | IgG-κ | IgG-λ | IgG-κ |
| International scoring system | 3 | 1 | 1 | 3 | 1 |
| Extramedullary disease | No | No | Pancreas | No | Lung |
| Lines of prior treatment | 2 | 8 | 6 | 2 | 4 |
| Autologous stem cell transplant | No | No | Yes | No | No |
| Dara-containing treatment | DRd | DBd | DRd + RT | DBd | DRd |
| Infusion reaction | Fever, nausea | None | Fever | None | None |
| Response to Dara-containing treatment | PR | SD | PR | PR | SD |
| Time of positive CMV antigenemia after initiation of Dara-containing treatment (days) | 25 | 16 | 70 | 21 | 20 |
| Positive cells of CMV antigenemia (/slide) | 71 | 18 | 2 | 1 | 12 |
| Lymphocyte count before initiation of Dara-containing treatment (/μL) | 570 | 1070 | 180 | 970 | 750 |
| Lymphocyte count at CMV antigenemia (/μL) | 200 | 200 | 140 | 300 | 470 |
| Antiviral therapy | GCV, IVIG | VGCV | VGCV | VGCV | GCV, IVIG |
| Duration of CMV antigenemia (days) | 24 | 13 | 6 | 14 | 15 |

*BJP*, Bence–Jones protein; *CMV*, cytomegalovirus; *Dara*, daratumumab; *DRd*, Daratumumab/lenalidomide/dexamethasone; *DBd*, Daratumumab/bortezomib/dexamethasone; *RT*, radiation therapy; *PR*, partial response; *SD*, stable disease; *GCV*, ganciclovir; *IVIG*, intravenous immunoglobulin; *VGCV*, valganciclovir

The mechanism by which CMV reactivations occur after Dara-containing treatment has not been elucidated. It is also known that Dara reduces regulatory T cells and increases both helper and effecter T cell responses, so there is a possibility that the combination partners with Dara may be the cause of CMV reactivations [8]. Further investigation, including lymphocyte subsets and CMV serology, before the treatment of myeloma is necessary to clarify the risk factors for CMV reactivation during Dara-containing treatment and also treatment of other CD38 antibodies like Isatuximab, especially in demographic areas in which the seroprevalence of CMV is high [9].

## Compliance with ethical standards

This case study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

**Conflict of interest** The authors declare that they have no conflict of interest.

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## References


1. Palumbo A, Chanan-Khan A, Weisel K, Nooka AK, Masszi T, Beksac M, Spicka I, Hungria V, Munder M, Mateos MV, Mark TM, Qi M, Schecter J, Amin H, Qin X, Deraedt W, Ahmadi T, Spencer A, Sonneveld P, Investigators C (2016) Daratumumab, bortezomib, and dexamethasone for multiple myeloma. N Engl J Med 375(8):754–766. https://doi.org/10.1056/NEJMoa1606038
2. Dimopoulos MA, Oriol A, Nahi H, San-Miguel J, Bahlis NJ, Usmani SZ, Rabin N, Orlowski RZ, Komarnicki M, Suzuki K, Plesner T, Yoon SS, Ben Yehuda D, Richardson PG, Goldschmidt H, Reece D, Lisby S, Khokhar NZ, O'Rourke L, Chiu C, Qin X, Guckert M, Ahmadi T, Moreau P, Investigators P (2016) Daratumumab, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med 375(14):1319–1331. https://doi.org/10.1056/NEJMoa1607751
3. van de Donk N, Richardson PG, Malavasi F (2018) CD38 antibodies in multiple myeloma: back to the future. Blood 131(1):13–29. https://doi.org/10.1182/blood-2017-06-740944
4. Drgona L, Gudiol C, Lanini S, Salzberger B, Ippolito G, Mikulska M (2018) ESCMID study Group for Infections in compromised hosts (ESGICH) consensus document on the safety of targeted and biological therapies: an infectious diseases perspective (agents targeting lymphoid or myeloid cells surface antigens [II]: CD22, CD30, CD33, CD38, CD40, SLAMF-7 and CCR4). Clin Microbiol Infect 24(Suppl 2):S83–S94. https://doi.org/10.1016/j.cmi.2018.03.022
5. Lavi N, Okasha D, Sabo E, Oren I, Benyamini N, Bar-Yoseph H (2018) Severe cytomegalovirus enterocolitis developing following daratumumab exposure in three patients with multiple myeloma. Eur J Haematol 101:699–702. https://doi.org/10.1111/ejh.13164
6. Frerichs KA, Bosman PWC, Nijhof IS, Zweegman S, van de Donk N (2018) Cytomegalovirus reactivation in a patient with extensively pretreated multiple myeloma during daratumumab treatment. Clin Lymphoma Myeloma Leuk 19:e9–e11. https://doi.org/10.1016/j.clml.2018.10.002
7. Hasegawa T, Aisa Y, Shimazaki K, Ito C, Nakazato T (2016) Cytomegalovirus reactivation in patients with multiple myeloma. Eur J Haematol 96(1):78–82. https://doi.org/10.1111/ejh.12551

8. Krejcik J, Casneuf T, Nijhof IS, Verbist B, Bald J, Plesner T, Syed K, Liu K, van de Donk NW, Weiss BM, Ahmadi T, Lokhorst HM, Mutis T, Sasser AK (2016) Daratumumab depletes CD38+ immune regulatory cells, promotes T-cell expansion, and skews T-cell repertoire in multiple myeloma. Blood 128(3):384–394. https://doi.org/10.1182/blood-2015-12-687749

9. Cannon MJ, Schmid DS, Hyde TB (2010) Review of cytomegalovirus seroprevalence and demographic characteristics associated with infection. Rev Med Virol 20(4):202–213. https://doi.org/10.1002/rmv.655