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Letter to Editor

Sudden Cardiac Arrest after Daratumumab Infusion

Sir,

Despite recent therapeutic advances, remission induction after myeloma relapse remains a major clinical challenge. Treatment of relapsed refractory multiple myeloma (RRMM) in the background of resistance to immunomodulators and bortezomib usually results in inferior outcomes.[1] The use of newer drugs such as pomalidomide, carfilzomib, and daratumumab in the management of RRMM has yielded unprecedented results and provided hope of achieving deeper and durable responses. Daratumumab, a humanized monoclonal antibody that targets CD38 receptors present on myeloma cells, has shown exceptional efficacy in RRMM as monotherapy and combination with conventional anti-myeloma regimens.[2] Combination of daratumumab with pomalidomide and dexamethasone has been recently approved by the US Food and Drug Administration in RRMM patients who have received at least two prior therapies.[3] Its recent availability in India has ushered a new optimism in the management of RRMM patients who otherwise had limited therapeutic options.[4]

A 72-year-old man, a known case of coronary artery disease for 25 years (postcoronary artery bypass graft in 2001 and postpercutaneous transluminal coronary angioplasty in 2010) was diagnosed as multiple myeloma in 2012. At baseline, he had anemia (Hb 7.4 g/dL), hypercalcemia (11.2 mg/dL), M spike (5.01 g/dL, IgA kappa), and 72% plasma cells on bone marrow examination; ISS Stage II disease and deletion 13q was positive on *in situ* hybridization; serum creatinine and skeletal survey were normal. After 3 cycles of Vd (Bortezomib 1.3 mg/m^2 subcutaneous plus dexamethasone 40 mg PO weekly; 28 days cycle), he achieved stringent complete response. Autologous hematopoietic stem cell transplantation was not considered in view of age, poor performance status, and comorbidities. Subsequently, in view of debilitating neuropathy (Grade 3), therapy was stopped, and he was put on observation alone. After a progression-free survival (PFS) of 15 months, he developed clinical relapse (anemia, Hb 7.6 g/dL) for which he was started on Rd. Subsequently, he received minimal residual disease and VCd for multiple relapses.

Currently, he presented with low backache and fatigue of 1-month duration; PFS of 4 months with the last therapy (VCd). Hb was 9.1 g/dL, and fludeoxyglucose-avid lytic lesions were present in dorsolumbar vertebrae on PET. Pomalidomide (4 mg PO once daily) and dexamethasone (40 mg PO once a week) were started, and the option of adding of daratumumab was given.

After receiving pomalidomide and dexamethasone for 1 week, he was admitted with gum bleeding. In addition to pallor, he had irregularly irregular pulse (116 bpm, pulse deficit = 14) at presentation. His blood pressure was 124/76 mmHg and LVS3 was audible on cardiac auscultation. He did not complain breathlessness, orthopnea, palpitations, or syncope. There was no peripheral edema; JVP was not raised. Investigations revealed pancytopenia (Hb 8.8 g/dL, TLC 3 × 10^9/L, absolute neutrophil count 2.04 × 10^9/L, and platelet count 9 × 10^9/L); serum creatinine 1.5 mg/dL (creatinine clearance 31.5 ml/min), atrial fibrillation with fast ventricular rate; corrected calcium and potassium were normal. Trop T and CK-MB levels were normal. It was decided to stop pomalidomide in view of gum bleeding and pancytopenia; bleeding gradually subsided after platelet transfusion. 2D Echo revealed severe left ventricular (LV) systolic dysfunction (EF 20%–25%). The case was discussed in detail with the cardiology team, and a possibility of underlying ischemic heart disease (with severe LV systolic dysfunction) giving rise to atrial fibrillation was considered. It was decided to adopt rate control strategy to manage atrial fibrillation with the fast ventricular rate. Rate control was gradually achieved after starting tablet metoprolol (extended release) 25 mg once daily. Antiplatelet drugs and Anticoagulation could not be started due to severe thrombocytopenia. After discussion with the patient, the option of daratumumab was considered. Due to cardiac dysfunction, it was decided to split daratumumab dose (16 mg/kg) into two and give it as slow infusion on consecutive days. The interval between pomalidomide cessation and daratumumab administration was 5 days. On day 1, daratumumab first half (8 mg/kg) was given intravenous (IV) under continuous cardiac monitoring over 8 h after premedication (injection dexamethasone 20 mg IV, injection pheniramine 25 mg IV, and tablet paracetamol 650 mg PO). He tolerated the infusion comfortably; heart rate remained stable between 90–105 bpm and no infusion-related reaction (IRR) was observed. Urine output was adequate in posttransfusion period; serum electrolytes were normal before infusion of the second half of daratumumab. Similarly, on day 2, daratumumab second half (8 mg/kg) was given under continuous cardiac monitoring. He tolerated the infusion well on day 2 also without any IRR. Five hours after the completion of daratumumab infusion on day 2, he developed sudden onset breathlessness and unconsciousness. Cardiac monitor showed asystole. He underwent cardiopulmonary resuscitation but could not be revived. Unfortunately, autopsy could not be done.

In Phase 1 and 2 trials, IRRs have been the most frequently reported adverse event with daratumumab (approximately 50%). Hematological adverse effects

(up to 80%) developing in daratumumab-based combination therapy (DCT) recipients have been primarily attributed to conventional antimyeloma drugs used in the combination.[2,5-7] In RRMM patients treated with DCTs outside clinical trials, the incidence of IRRs has been reported to be significantly low (22.7%).[8]

Although a direct causal relationship between sudden cardiac arrest in the index case (who also had underlying coronary artery disease and LV dysfunction) and the therapy he received (pomalidomide followed by daratumumab infusion) cannot be established, there are some noteworthy attributes that merit discussion. Although the patient had coronary artery disease with severe LV dysfunction along and atrial fibrillation, he was asymptomatic and hemodynamically stable; fast ventricular rate could be easily controlled with oral metoprolol. Although the patient received pomalidomide for 1 week duration; it seems less likely that it had major role in causing cardiac arrest in the index patient as the interval between pomalidomide cessation and cardiac arrest was 7 days. Neither any infusion reaction nor any hemodynamic instability was observed during daratumumab infusion and immediately after it but still, he developed cardiac arrest about 5 h after completion of infusion. These observations emphasize close clinical observation not only during daratumumab infusion but also in postinfusion period. Myeloma is conventionally a disease of elderly age group, and therefore, it shall not be uncommon to come across RRMM patients with underlying cardiac disorders who shall be candidates for receiving daratumumab. Daratumumab is a promising drug in RRMM therapeutic landscape, and its continued use is well anticipated in near future.[9] Detailed counseling and appropriate risk stratification of RRMM patients with cardiac comorbidities should be done before daratumumab administration. Sudden cardiac arrest in a clinically stable patient raises a genuine concern on the safety of daratumumab in patients with known cardiac comorbidities. This case also highlights the fact that at least lack of occurrence of daratumumab-related IRRs does not assure protection to the patient from develop life-threatening cardiac event after infusion completion which may or may not be directly related to daratumumab. Association of cardiotoxicity with monoclonal antibodies currently used in oncology practice (trastuzumab, bevacizumab, and rituximab) is not uncommon.[10] It shall be imperative to keep a close surveillance on adverse effects and tolerability of daratumumab in elderly RRMM patients with cardiac comorbidities as this subgroup of patients may need modification in dose and infusion intervals.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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References

1. Usmani S, Ahmadi T, Ng Y, Lam A, Desai A, Potluri R, *et al.* Analysis of real-world data on overall survival in multiple myeloma patients with ≥3 prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory drug (IMiD), or double refractory to a PI and an IMiD. Oncologist 2016. pii: theoncologist. 2016-0104.
2. Lonial S, Weiss BM, Usmani SZ, Singhal S, Chari A, Bahlis NJ, *et al.* Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): An open-label, randomised, phase 2 trial. Lancet 2016;387:1551-60.
3. McKeage K. Daratumumab: First global approval. Drugs 2016;76:275-81.
4. Yanamandra U, Khattry N, Kumar S, Raje N, Jain A, Jagannath S, *et al.* Consensus in the management of multiple myeloma in india at myeloma state of the art 2016 conference. Indian J Hematol Blood Transfus 2017;33:15-21.
5. Usmani SZ, Weiss BM, Plesner T, Bahlis NJ, Belch A, Lonial S, *et al.* Clinical efficacy of daratumumab monotherapy in patients with heavily pretreated relapsed or refractory multiple myeloma. Blood 2016;128:37-44.
6. Palumbo A, Chanan-Khan A, Weisel K, Nooka AK, Masszi T, Beksac M, *et al.* Daratumumab, bortezomib, and dexamethasone for multiple myeloma. N Engl J Med 2016;375:754-66.

7. Dimopoulos MA, Oriol A, Nahi H, San-Miguel J, Bahlis NJ, Usmani SZ, *et al.* Daratumumab, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med 2016;375:1319-31.
8. Lakshman A, Abeykoon JP, Kumar SK, Rajkumar SV, Dingli D, Buadi FK, *et al.* Efficacy of daratumumab-based therapies in patients with relapsed, refractory multiple myeloma treated outside of clinical trials. Am J Hematol 2017;92:1146-55.
9. Chari A, Suvannasankha A, Fay JW, Arnulf B, Kaufman JL, Ifthikharuddin JJ, *et al.* Daratumumab plus pomalidomide and dexamethasone in relapsed and/or refractory multiple myeloma. Blood 2017;130:974-81.
10. Rosa GM, Gigli L, Tagliasacchi MI, Di Iorio C, Carbone F, Nencioni A, *et al.* Update on cardiotoxicity of anti-cancer treatments. Eur J Clin Invest 2016;46:264-84.

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