Indian J Hematol Blood Transfus (July-Sept 2019) 35(3):584–586
https://doi.org/10.1007/s12288-019-01135-4

CORRESPONDENCE

Poor Mobilisation After Daratumumab Based Combination Chemotherapy in Patients of Newly Diagnosed Multiple Myeloma

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Received: 25 January 2019 / Accepted: 6 May 2019 / Published online: 10 May 2019

Dear Editor,

Multiple myeloma therapy has received a boost by introduction of multiple new drugs in the last couple of years [1, 2]. One of the most important additions to the growing list of anti-myeloma therapy is Daratumumab. A fully human, monoclonal antibody against CD38 has been approved by FDA since 2015. However, it was introduced in Indian market in 2017 [3]. Though initially approved for relapsed refractory multiple myeloma (RRMM), there is an increasing number of reports for its use upfront in newly diagnosed multiple myeloma (NDMM) [4, 5]. The daratumumab, bortezomib, melphalan, and prednisolone combination has been found effective in non-transplant eligible MM and now approved for transplant ineligible NDMM as first-line therapy [4]. There are ongoing trials to evaluate the use of daratumumab in NDMM irrespective of transplant eligibility [6]. Since 2017, we have been using daratumumab based combination chemotherapy in RRMM and NDMM (both transplant eligible and non-eligible). The overall response rate (ORR) of Daratumumab based combination chemotherapy in NDMM has been 85.71% (6/7). The hematological and non-hematological (infectious and immunological sequelae) at our center have been very much comparable to what has been reported by Rhee al. However, we would like to bring to the notice our observation of poor mobilization after daratumumab based chemotherapy in two patients.

Two of our NDMM patients received Dara-VRd (daratumumab, bortezomib, lenalidomide, and dexamethasone) for 05 cycles each (total 14 doses of daratumumab) and achieved stringent complete response (sCR), with minimum residual disease (MRD) negativity on bone marrow by multicolor flow cytometry. Each 28 day cycle of Daratumumab-VRd consisted of weekly daratumumab infusion (16 mg/kg IV) for eight doses followed by every 2 weeks for next 8 weeks; bortezomib (1.3 mg/m^2 s.c.) and dexamethasone (40 mg PO) were given weekly. Lenalidomide (25 mg PO) was given once a day for the first 21 days in each 28 days cycle. The dara-VRd was well tolerated by the patients with only notable toxicity was Grade 1 peripheral neuropathy in both the patients. They did not receive radiotherapy during induction. Their bone marrow cellularity during pre-transplant work-up were 20–30% and 30–40% respectively (Table 1). The last dose of lenalidomide and daratumumab were given 3 and 4 weeks prior to the G-CSF mobilisation respectively. Both the patients were mobilized with G-CSF and plerixafor and after two sessions of apheresis had inadequate stem cell harvest (Table 1). This leading to the cancellation of autologous stem cell transplantation (ASCT).

Daratumumab has been associated with a high rate of infusion-related reactions (IRR) and myelosuppression and rarely reported to have cardiac or GI adverse effects [2]. However, mobilization failure has not been reported with Daratumumab [5]. Transplant outcomes in 16 NDMM patients treated with similar antimyeloma regimen (Dara-VRd) albeit with a different schedule (21 days cycle) was presented as an abstract at the ASH 2018. All 16 patients underwent successful mobilization followed by autologous stem cell transplantation. However, our patients had lesser incidence of severe adverse events, probably due to 28 days cycle of Dara-VRd [6]. Our patients received an optimum dose of G-CSF and based on poor day + 4 peripheral blood CD34 count, and both received plerixafor,

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Table 1 Showing pre and post harvest details of pateints who had failed mobilisation after daratumumab based chemotherapy for NDMM

	Patient 1	Patient 2
Age (years)	61	52
Sex	Female	Female
Co-morbidity	Nil	Hypertension Grade1
Diagnosis	Multiple myeloma (IgGκ) C-R+A+B+	Multiple myeloma (IgAλ) C-R-A+B+
Bone marrow at diagnosis	Aspirate: 70% plasma cells	Aspirate: 68% plasma cells
	Biospy: hypocellular bone marrow with sheets of plasma cells	Biospy: hypocellular bone marrow with sheets of plasma cells
Stage	ISS III, RISS III	ISS III, RISS III
Cytogenetics	del 13	t(4;14)
Chemotherapy	5 cycles of Dara-VRd	5 cycles of Dara-VRd
Post-chemo repsonse	sCR	sCR
Diagnosis to harvest	5 months	5 months
Pre-harvest bone marrow	1% PC, MRD negative	2% PC, MRD negative
	Cellularity 20–30%	Cellularity 30–40%
Pre-harvest PET-CT	PET-negative	PET-negative
Day1 CBC	10.5/8300/2.86 L	11/4500/1.36 L
G-CSF dose	10 μg/kg/day	10 μg/kg/day
Day 4 WBC	15,100/μL	21,000/μL
Day 4 PB CD34	0.55	0.65/μL
Plerixafor	240 μg/kg	240 μg/kg
First harvest volume	14,000 mL	13,000 mL
Harvest bag volume	295 mL	262 mL
Harvest bag WBC	163,700/μL	104,100/μL
CD34/kg	0.4×10^6/kg	0.23×10^6/kg
Plerixafor	240 μg/kg	240 μg/kg
Second harvest volume	13,000 mL	12,000 mL
Harvest bag volume	262 mL	238 mL
Harvest bag WBC	81,100	87,800
CD34/kg	0.2×10^6/kg	0.23×10^6/kg

however, the yield after 2 days of apheresis was not adequate for even a single ASCT. G-CSF alone is associated with failure to mobilize in 10–30% of patients. However, when combined with plerixafor, the success rate is over 90% [7, 8]. The two cases here had excellent disease control, there was no cytopenia, and they had no co-morbidity, and the chemotherapy was stopped 04 weeks prior to the harvest, putting them at lesser risk of mobilization failure [9].

We conclude that, though the poor mobilization cannot be conclusively reported to be related to daratumumab, it certainly brings to the notice a possible hurdle for the use of daratumumab in transplant-eligible NDMM.

Compliance with Ethical Standards

Conflict of interest There is no conflict of interest between the authors.

Informed Consent Informed signed written consent was taken from the patient involved.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Human and Animals Rights No animals were involved in the study.

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