CORRESPONDENCE

Peri-transplant Stem Cell Kinetics After Daratumumab-Based Induction in Patients with Multiple Myeloma: Response to Mishra et al

Ankur Jain¹

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Dear editor,

Daratumumab (DARA), an IgG-kappa monoclonal antibody against CD38, has changed the therapeutic paradigm of Multiple Myeloma (MM). Frontline DARA-based combinations result in rapid, deeper, and sustained responses, including minimal residual disease (MRD)-negativity. Since hematopoietic stem cells (HSC) express CD38, frontline use of DARA could theoretically affect peri-autologous stem cell transplant (ASCT) outcomes, including both HSC mobilization and post-ASCT hematopoietic reconstitution. We intend to review the existing data on effect of DARA on peri-ASCT outcomes, and comment on article by Mishra et al. recently published in Indian Journal of Hematology and Blood Transfusion [1].

Ma et al. studied the in-vitro effect of DARA including its binding, complement-dependent cytotoxicity (CDC), and colony-forming unit (CFU) capacity on mobilized CD34⁺ HSC. DARA neither resulted in cytotoxicity, nor affected the CFU-capacity of HSC, possibly because of low density of CD38 on HSC [2]. Clinically, DARA has been combined with frontline regimens in both non-randomized [cyclophosphamide-bortezomib-dexamethasone (CyBorD), bortezomib-lenalidomide-dexamethasone (VRD), carfilzomib-lenalidomide-dexamethasone (KRD)], and randomized [bortezomib-thalidomide-dexamethasone (VTD)] fashion in transplant-eligible MM patients [3–6]. Median HSC dose collected after frontline DARA-CyBorD, DARA-KRD, and DARA-VTD was $5.0 \times 10^6/\text{kg}$,

$10.6 \times 10^6/\text{kg}$, and $6.3 \times 10^6/\text{kg}$, respectively [3–6]. HSC data of DARA-VRD from Griffin trial is awaited [4]. Although DARA-treated patients required higher number of plerixafor and apheresis sessions, median HSC dose was almost comparable to the respective control arms (historical control for CyBorD and KRD; randomized control for VTD) [3–6]. Moreover, HSC dose has been correlated with time to platelet engraftment (PE) but not neutrophil engraftment (NE) after peripheral blood-ASCT [7]. Therefore, NE and PE are not expected to be affected by DARA-based induction regimens. In support for this, an updated analysis of CASSIOPEIA suggested that the time to NE and PE were similar for DARA-VTD and VTD arms (13 days vs. 13 days, and 14 days vs. 12 days). Authors concluded that DARA-based induction is safe, feasible, and did not affect the ASCT-outcomes, including hematopoietic reconstitution [8]. Definitive conclusions regarding effect of DARA on peri-ASCT outcomes could only be drawn by comparing DARA-chemotherapy with the same chemotherapy backbone without DARA in a prospective randomized control trial (RCT). CASSIOPEIA is the only RCT available till date, while results of Griffin and PERSEUS trials (DARA-VRD vs. VRD are awaited) [4, 9]. Given the potential synergism of DARA and lenalidomide [10], and a possible effect of lenalidomide on peri-ASCT outcomes [11], results of Griffin and PERSEUS would be interesting regarding the effect of DARA-lenalidomide based regimens on stem cell kinetics. Recently, Al Saleh et al. [12] found a negative effect of DARA-based induction on time to NE after ASCT. DARA arm (n = 12) was compared with non-DARA arm (n = 129) in a retrospective non-randomized fashion. The two arms were not balanced with respect to the sample size, number of prior chemotherapies received, and type of chemotherapies used in induction. This would make comparison of means less

✉ Ankur Jain
drankur589@yahoo.in

¹ Department of Hematology, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi 110029, India

reliable. While DARA arm consisted primarily of Ixazomib-lenalidomide-dexamethasone (IRD) combination, induction regimens in non-DARA arm were not available for comparison. A subgroup comparison of DARA-IRD versus IRD could possibly have dissected the individual role of DARA on NE and PE. Despite a similar median HSC dose, time to NE was different in both the arms, reflecting role of possible additional factors. Given these caveats, implicating only DARA in causing delayed NE would not be prudent at this stage [12].

In light of this background, we would like to comment on the findings by Mishra et al. [1]. Authors reported poor mobilization in 2 patients with Multiple myeloma after Dara-VRD induction. Considering a half-life of DARA (about 3-weeks) in circulation [13], and in-vitro data suggesting no significant effect of DARA on HSC [2], mobilization failure reported by Mishra et al. might not be due to DARA alone. Greater lenalidomide exposure pre-ASCT might have contributed to findings by Mishra et al. (21 days vs. conventional 14 days per VRD cycle, and 5 vs. conventional 4 pre-ASCT VRD induction cycles). This is possibly reflected in pre-ASCT hypocellular bone marrow (BM) biopsies of the reported cases [1]. Effect of different mobilization strategies on HSC collection could be also be argued (GCSF + plerixafor used by Mishra et al. [1], and cyclophosphamide + GCSF used in CAS-SIOPEIA [6]). Since both mobilization strategies have been shown to be at least equally efficacious, confounding effect of mobilization strategy seems less likely [14]. BM niche is well known to affect peri-ASCT outcomes, including post-ASCT recovery [15]. Therefore, the finding by Mishra et al. is interesting as it opens several research questions: (1) RCTs are essential to delineate the effect of adding DARA to chemotherapy combinations during induction; (2) given an inhibitory effect of DARA on CD31 (present on BM stromal cells) and CD38 interaction [16], potential effect of DARA on BM microenvironment cannot be excluded; and (3) animal BM models using stromal cells and HSC are needed to study the peri-ASCT stem cell kinetics after DARA-based induction. We conclude that validation from ex-vivo BM models and RCTs is needed before implicating a potential detrimental effect of DARA on peri-ASCT stem cell kinetics.

Compliance with Ethical Standards

Conflict of interest The author declares that he/she have no conflict of interest.

Ethical Statement Authors state that the manuscript has not been submitted to any other journal. The article follows guidelines according to declaration of Helsinki.

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