Higher cyclophosphamide dose grants optimal stem cell collection after daratumumab-based induction in multiple myeloma

Quadruplet induction with daratumumab, bortezomib, thalidomide and dexamethasone (Dara-VTd) followed by autologous stem cell transplantation (ASCT) and Dara-VTd consolidation has become the standard treatment for transplant-eligible newly diagnosed multiple myeloma patients (NDMM) in Europe.[1] Both improved response rates and progression-free survival (PFS) advantage were reported in the Dara-VTd arm of the CASSIOPEIA trial.[2] Nonetheless, concerns emerged with stem cell mobilization and collection after daratumumab.[3] Following cyclophosphamide 2 to 3 g/m^2 and granulocyte colony-stimulating factor (G-CSF) 10 μg/kg/day, patients treated with daratumumab experienced greater use of plerixafor, longer leukapheresis and lower total number of CD34$^+$ cells/kg collected per patient. Although the proportion of patients undergoing ASCT and obtaining hematopoietic reconstitution was similar between arms, longer intervals to platelet and neutrophil engraftment were observed in those receiving daratumumab.[3] Similar results after daratumumab exposure were reported in both GRIFFIN and MASTER study with chemotherapy-free mobilization approach based on G-CSF and plerixafor as well as in recent real-life reports with cyclophosphamide and G-CSF.[4–6]

We report a collaborative, retrospective analysis of NDMM that consecutively underwent stem cell mobilization and collection after Dara-VTd induction at two Italian centers (Ospedale Santo Spirito, Pescara, and IRCCS Ospedale San Raffaele, Milano). Inclusion criteria were NDMM and eligibility to ASCT. After Dara-VTd induction, patients received high-dose cyclophosphamide (HD-CTX) 4 g/m^2 as per institutional practice and were monitored in outpatient setting. G-CSF was administered at a dose of 5 μg/kg/day starting on day 3 to 5 after HD-CTX, with optional increase to 10 μg/kg/day at 48 hours before leukapheresis. Plerixafor 0.24 mg/kg was administered on demand on the day of planned leukapheresis either in patients with <20 CD34$^+$ cells/μL or in those predicted to be poor mobilizer according to subsequent criteria: i) white blood cells count >10x10^9/L together with CD34$^+$ count <15/μL; ii) ratio of patient body weight (kg) and CD34$^+$/μL >2; iii) yield <25% of total CD34$^+$ target dose on first day of leukapheresis. Preplanned total target dose was 10x10^6 CD34$^+$ cells/kg to allow for multiple ASCT. Aim of the study was to evaluate safety and efficacy of mobilization with HD-CTX 4 g/m^2 in terms of stem cell yield and transplantation outcomes. Patients were treated according to current institutional programs upon written informed consent for transplantation procedures and use of medical records for research.

From December 1, 2021 to February 28, 2023, 64 NDMM consecutively received Dara-VTd at our institutions. At data cut-off, 47 patients completed induction and were included in this analysis whereas 17 patients where still receiving induction (Figure 1). At diagnosis median age was 62 years (range, 38-71), 13 patients (28%) were International Staging System (ISS) III, five patients (11%) were Revised ISS (R-ISS III) and 26 patients (55%) were R2-ISS III-IV. Seventeen patients (36%) had high-risk cytogenetic abnormalities as del17p13, t(4;14) and t(14;16). Overall, a median of four Dara-VTd induction cycles (range, 4-6) was administered. Notably, 36 patients (76%) required thalidomide dose reduction, 12 patients (25%) needed bortezomib dose reduction and in two patients (4%) a single daratumumab administration was omitted due to adverse events and/or intolerance. Grade 3-4 adverse events occurred in ten patients (21%) (Figure 1). After Dara-VTd induction, overall response rate was 98%, with 22 patients (47%) in very good partial remission, three patients (6%) in complete remission and 11 patients (23%) in stringent complete remission. One patient progressed soon after the fourth Dara-VTd cycle. After a median of 133 days (range, 113-232) from start of induction and 32 days (range, 16-93) from last daratumumab administration, 46 patients received HD-CTX 4 g/m^2. Most frequent grade 3-4 adverse events were anemia (n=8; 17%), neutropenia (n=40; 87%), thrombocytopenia (n=21; 45%), and febrile neutropenia (n=4; 8%) (Figure 1). Notably, only two patients (4%) required platelets transfusion and two patients (4%) discontinued mobilization due to febrile neutropenia. Fourteen patients (30%) doubled G-CSF dose at 48 hours before leukapheresis. After a median of 11 days (range, 9-16) from HD-CTX, 43 of 46 patients (93%) underwent leukapheresis; 21 of them (49%) received plerixafor. All patients undergoing leukapheresis completed stem cell collection, harvesting a mean total amount of 10.68x10^6 CD34$^+$ cells/kg (standard deviation [SD] 2.54) (range, 4.92-18.8). Notably, at first day of leukapheresis the mean amount of CD34$^+$ cells/kg collected was 6.98x10^6 (SD 3.60; range, 1.4-17.6) and plerixafor was given in six patients (14%). Mean collection efficiency (CE) was high in our cohort and the majority of patients (n=28/43; 65%) required 2 days of apheresis to reach the collection target of 10x10^6 CD34$^+$ cells/kg. Details on stem cell mobilization and harvesting are shown in Table 1. Overall, three of 46 patients

(7%) who received HD-CTX 4 g/m^2 and G-CSF did not undergo stem cell collection. One patient discontinued mobilization due to concomitant severe acute respiratory syndrome coronavirus 2 infection. Unfortunately, both subsequent rescue attempts with chemotherapy-free G-CSF 10 μg/kg/day plus plerixafor and then CTX 2 g/m^2 plus G-CSF 10 μg/kg/day plus plerixafor failed. Two patients discontinued mobilization due to febrile neutropenia but were later able to collect enough CD34$^+$ cells/kg for single ASCT with a second procedure (a chemotherapy-free regimen and a bone marrow harvest, respectively). After a median of 195 days from start of induction (range, 164-283) and 49 days (range, 33-96) from stem cell collection, 35 of 43 (81%) patients who completed leukapheresis already underwent ASCT at time of data cut-off. Mean number of infused CD34$^+$ cells per patient was 4.84x10^6/kg (SD 1.20; range, 2.96-9.86). All patient obtained stable neutrophils and platelets engraftments after a median of 12 days (range, 9-14) and 16 days (range, 10-25), respectively. No unexpected toxicities of transplant procedure were reported. At last follow up, all patients are alive.

Recent years have seen the introduction of several novel agents for the treatment of NDMM, with improved response rates and prolonged survival. Nonetheless, ASCT still remains a standard of care for younger fit patients.[1,7] A long-standing debate exists about the value of double ASCT in MM: the phase III STaMINA trial showed a PFS benefit in high-risk patients receiving tandem ASCT, whereas in the EMN02/HO95 trial both PFS and overall survival advantage were reported.[8–10] To date both EHA-ESMO and NCCN guidelines still recommend double ASCT as an option for patients who do not achieve at least a very good partial reponse (VGPR) after the first ASCT and those with high-risk features (defined by cytogenetics or clinical characteristics as extramedullary disease).[1,7] Notably, ongoing randomized trials still incorporate a double ASCT arm for MRD-defined high-risk patients (MIDAS study; *clinicaltrials gov. Identifier: NCT04934475*). A second transplantation can be also considered at the time of disease relapse in carefully selected patients.[1,7] More recently, cryopreserved autologous CD34$^+$ cells have been used as rescue of prolonged cytopenias after CAR T, further in-

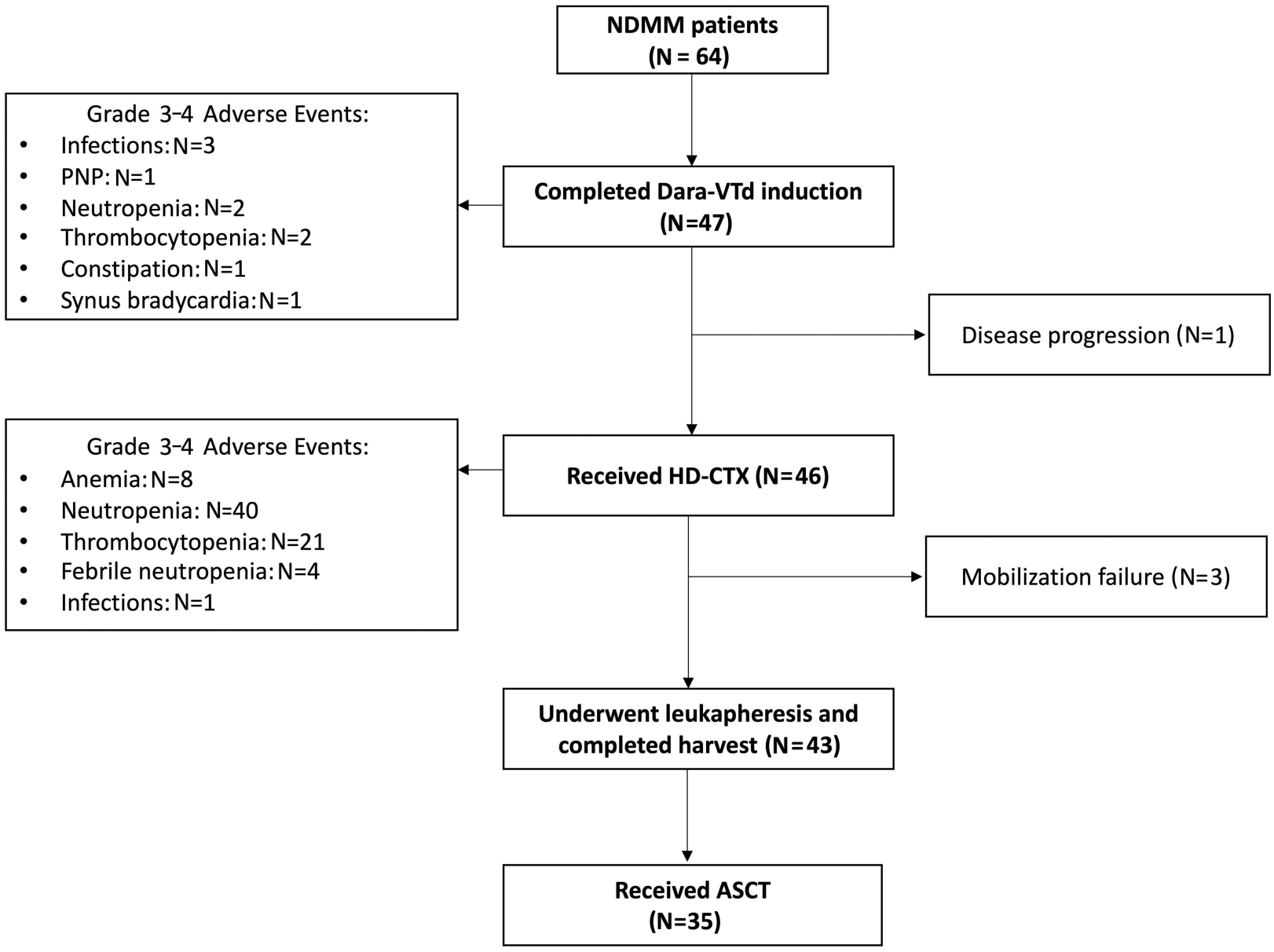

Figure 1. Profile of analyzed population. The diagram shows the distribution of analyzed patients. NDMM: newly-diagnosed multiple myeloma patients; Dara-VTd: daratumumab, bortezomib, thalidomide and dexamethasone; HD-CTX: high-dose cyclophosphamide; ASCT: autologous stem cell transplantation; PNP: peripheral neuropathy.

Table 1. Characteristics of stem cell mobilization and harvesting.

Characteristics of stem cell mobilization and harvesting	
Days from start of induction to HD-CTX, median (range)	133 (113-232)
Days from last daratumumab to HD-CTX, median (range)	32 (16-93)
Days from HD-CTX to first day of leukapheresis, mean [SD] (range)	11.6 [1.65] (9-16)
Total G-CSF μg/kg administered per patient, mean [SD] (range)	440 [128] (240-768)
Peripheral white blood cells/μL on first day of leukapheresis, median (range)	13,400 (1,600-67,000)
Peripheral CD34⁺ cells/μL on first day of leukapheresis, median (range)	57 (20-226)
Number of days of leukapheresis, N/N (%) 1 2	 15/43 (35) 28/43 (65)
Days of leukapheresis, mean [SD] (range)	1.7 [0.48] (1-2)
Plerixafor use, N/N (%) Indication <20 CD34⁺ cells/μL Other	21/43 (49) 14/21 (66) 7/21 (34)
Amount of CD34⁺ cells x10⁶/kg collected per patient, mean [SD] (range) - Day 1 - Day 2 - Total	 6.98 (1.4-17.6) 5.77 (3.2-12.6) 10.68 [2.54] (4.94-18.8)
Collection efficiency %, mean [SD] (range) - Day 1 - Day 2	 64 [17] (18-99) 71 [19] (26-100)
Total blood volume processed in liters, mean [SD] (range)	4.58 [2] (1.6-9.6)

HD-CTX: high-dose cyclophosphamide; SD: standard deviation; G-CSF: granulocyte colony-stimulating factor.

creasing the need for high collection numbers considering the expected increase in CAR T use in the next future.[11,12] Although a minimum dose of 2x10⁶ CD34⁺ cells/kg is sufficient for a single ASCT, the optimal dose for a timely and stable hematopoietic reconstitution usually ranges between 3x10⁶ and 5x10⁶ CD34⁺ cells/kg. Therefore, whenever feasible, the collection target should reach 8-10x10⁶ CD34⁺ cells/kg to allow for multiple ASCT.[13,14] Many centers are now implementing chemotherapy-free mobilization protocols, although these are associated with an increased risk of mobilization failure or low stem cell yield among patients exposed to daratumumab.[5,6] Cyclophosphamide is the most common chemotherapeutic agent used for mobilization in NDMM, with dosage ranging from 1.5 g/m² to 4 g/m². Despite greater toxicities, higher doses are associated with improved stem cell mobilization and harvesting, lower rate of collection failure and improved post-transplantation engraftment.[14,15] The present analysis represents, to the best of our knowledge, the first report of a mobilization strategy based on HD-CTX 4 g/m² after daratumumab-based quadruplet induction in NDMM. In our population, HD-CTX 4 g/m² was administered early after the end of induction and was well tolerated with limited toxicities in an outpatient setting. Notably, the majority of patients successfully underwent leukapheresis after a median of 11 days. In our cohort, we observed a high proportion of poor mobilizers after daratumumab exposure and frequent need for plerixafor to reach the preplanned target dose of 10x10⁶ CD34⁺ cells/kg. Nonetheless, HD-CTX 4 g/m² together with patient-tailored plerixafor allowed high CD34⁺ cells collection in the majority of patients, with a mean total amount of 10.68x10⁶ CD34⁺ cells/kg. Notably, high collection numbers with limited plerixafor administration were already achieved in the first day of leukapheresis. These results compare favorably to those reported in the Dara-VTd arm of CASSIOPEIA trial, where lower CTX doses (2-3 g/m²) led to collection of a mean of 6.7x10⁶ CD34⁺ cells/kg.[3] We also observed a low incidence of mobilization failure in our cohort. Patients could safely undergo ASCT, with timely hematological engraftment. While limitations of this study include retrospective non-randomized nature and patients number, multicentricity limits single-center effects and bias in patient management.

In conclusion, HD-CTX 4 g/m² and G-CSF after Dara-VTd induction in NDMM proved feasible in the outpatient setting and effective in terms of stem cell mobilization. Increased dose of CTX together with on-demand administration of plerixafor allowed high collection numbers of CD34⁺ cells per patient, thus limiting the potential detrimental effects of daratumumab on leukapheresis procedures and ensuring sufficient stem-cells for multiple ASCT and rescue of CAR T-related cytopenia.

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Data-sharing statement

Original data are available in anonymous form upon request by contacting corresponding author.

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