Mediterranean Journal of Hematology and Infectious Diseases

Letter to the Editor

Feasibility and Outcome of First-Line Autotransplant-Based Treatment in Newly Diagnosed Multiple Myeloma Patients Aged > 65 Years: Monocentric Retrospective Real-World Analysis

Keywords: Real world analysis; Multiple myeloma; Autologous stem cell transplantation (ASCT).

Published: Septemder 01, 2024 **Received: June 27, 2024** **Accepted: August 05, 2024**

Citation: Stefanoni P., Paris L., Pittalis N., Pavoni C., Cavallaro G., Rambaldi A., Galli M. Feasibility and outcome of first-line autotransplant-based treatment in newly diagnosed multiple myeloma patients aged > 65 years: monocentric retrospective real-world analysis. Mediterr J Hematol Infect Dis 2024, 16(1): e2024066, DOI: http://dx.doi.org/10.4084/MJHID.2024.066

To the editor.

Most randomised clinical studies (RCTs) place 65 years as the age limit for patients with newly diagnosed multiple myeloma (NDMM) to receive autologous stem cell transplantation (ASCT)-based treatments. There are, however, patients who, despite exceeding this age, have a degree of fitness adequate to receive these intensive treatments. Therefore, we performed a monocentric, retrospective real-world analysis (RWA) to evaluate the feasibility and the main results of an ASCT-based program in a cohort of 90 NDMM patients aged > 65 years who were deemed eligible for such a program on the basis of simplified frailty score. Seventy-six patients received at least one ASCT, and 14 patients received the second ASCT. No ASCT-related mortality was observed. During a median follow-up of 46 months, median progression-free survival (mPFS) was 42 months and overall survival (mOS) was estimated at 84 months. These results compare well with those of other RWAs and pave the way to further improvements upon incorporation of an anti-CD38+ monoclonal antibody in the ASCT programs.

Based on the results of several RCTs, ASCT still represents a cornerstone of NDMM patients' treatment, as stated also by the last EHA-ESMO guidelines.[1] These trials, in fact, have shown that the incorporation of ASCT into the first-line treatment improves the overall response rate (ORR), mPFS and, although not consistently, the mOS of the patients. However, most RCTs place 65 years as the age limit to receive ASCT-based treatments. There are, however, patients who, despite exceeding this age, have a degree of fitness adequate to receive these intensive treatments, which may be administered, in general, up to the age of 75 years. RWAs are the main source of information on the prevalence and the main clinical outcomes of the patients treated outside of RCTs.[2] When compared to RCTs, RWAs have advantages and disadvantages. Among the former, the inclusion of studies with heterogenous designs, the possibility to capture the patients' heterogeneity in terms of age, comorbidities and performance status (PS) and information about the different treatment patterns (i.e., duration, dosing, efficacy, tolerability and safety profile). Among the latter, there is the heterogeneity of datasets arising from heterogeneous clinical practice and documentation, the possibility of patients' selection biases and the potential lack of uniformly defined endpoints. Taking all these issues into account, we performed an RWA to evaluate the prevalence and clinical outcomes of symptomatic NDMM patients aged > 65-75 years treated from January 1, 2010, to December 31, 2021, in our Unit with an ASCT-based program, according to the experimental arm of the GIMEMA-MMY-3006 study.[3] Their degree of "fitness" was judged according to a simplified frailty score[3] that takes age ($\leq$75 years, score 0), Charlson Comorbidity Index (CCI) (CCI $\leq$1, score 0; CCI >1, score 1) and ECOG Performance Status (PS) (PS 0, score 0; PS 1, score 1; PS $\geq$2, score 2) as variables to discriminate between nonfrail (score 0-1) and frail (score $\geq$2) patients.[4] Data were collected using an ad hoc specifically developed database, which was implemented over time. Since we performed a monocentric, retrospective study on consecutive and uniformed selected patients who were treated with a uniform program, we could maximise the strengths and minimise the weaknesses of our RWA. PFS was calculated as the time from starting treatment to the time of first MM progression or death, whichever occurred first. OS was calculated as the time from starting treatment to the date of last contact or death for any cause. PFS and OS were estimated until the last contact or February 15, 2023, using the Kaplan-Meier method. All patients provided informed consent. Ninety patients (24%) were deemed eligible for ASCT-based treatments. They had a median age of 67.9 years (range

65.2-72.9 years); according to the simplified frailty score, 79 patients (88%) were non-frail, and 11 (12%) were frail before starting the treatment. Because their frailty status was a direct consequence of MM-related disabilities, also these 11 patients were enrolled in the ASCT-based program. During the induction phase, which consisted of 4 bortezomib-thalidomide-dexamethasone (VTD) cycles in 84 patients (93%) and 4 bortezomib-cyclophosphamide-dexamethasone cycles in the other 6 (7%), the dose of one or more of these drugs was reduced in 82 patients (91%): bortezomib (n=13), thalidomide (n=71), cyclophosphamide (n=2), dexamethasone (n=53). The patients' disposition through the treatment program is detailed in **Figure 1**.

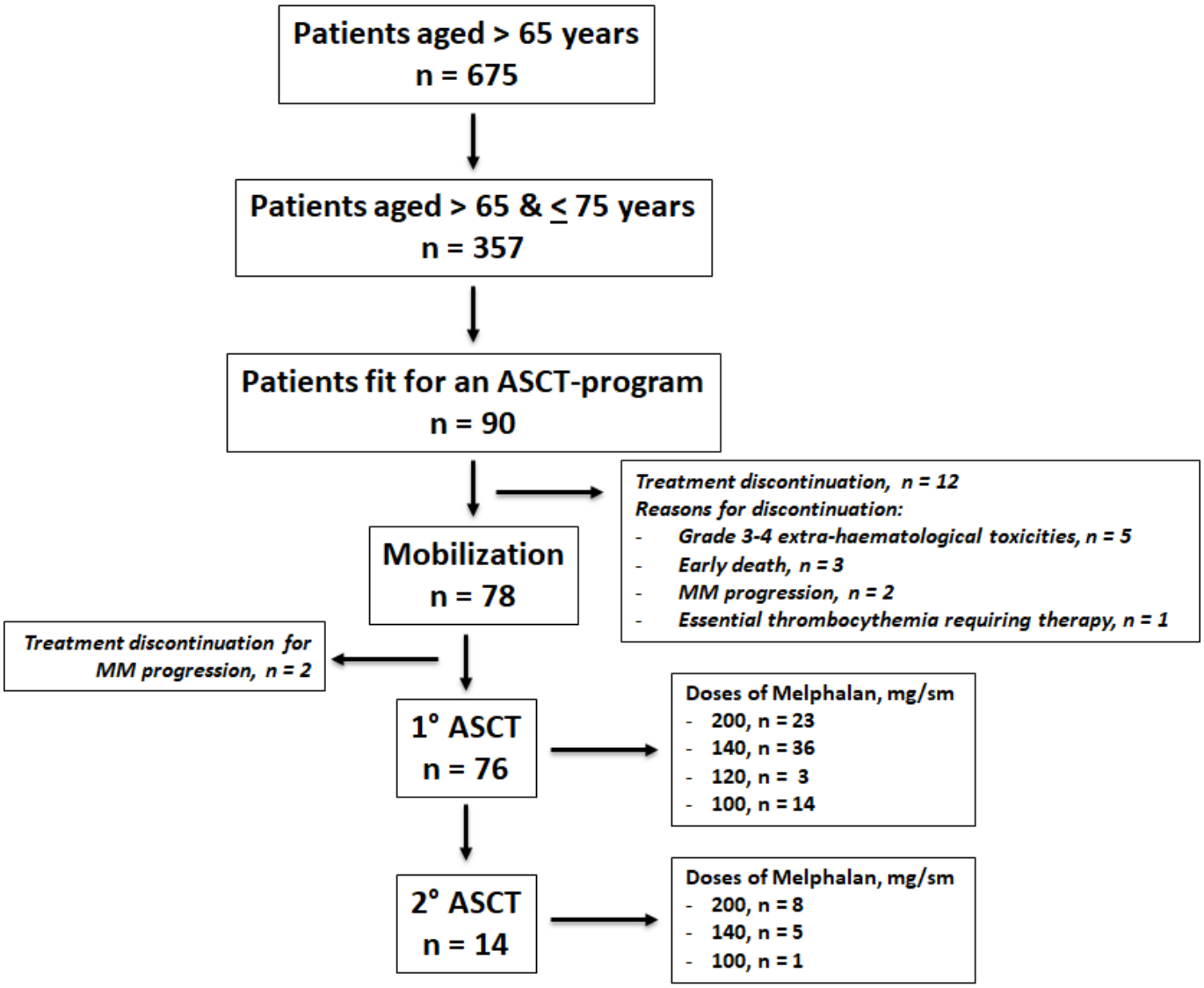

Figure 1. Patients' disposition.

Seventy-eight patients (87%) underwent the peripheral blood autologous stem cell mobilisation procedure: 40 of them mobilised with granulocyte-colony stimulating factor (G-CSF) alone, and the other 38 with cyclophosphamide 2gr/sm plus G-CSF. Seven patients also required Plerixafor. A median of $6.77x10^6$ CD34+ cells/kg body weight were harvested (range $2.56\text{-}44.85x10^6$). No harvesting failure was recorded. Seventy-six patients (84%) received at least one ASCT, following ev melphalan administration at doses ranging from 100 to 200 mg/sm. Eight of the 11 frail patients received one ASCT; none of them underwent the second procedure. Although 48 patients collected enough CD34+ for 2 ASCTs, only 14 of them were in less than very good partial response (VGPR) 3 months after the first ASCT: for this reason, they also received the second ASCT, following ev melphalan administration, again at different doses. All patients were hospitalised for the ASCT procedures, which were characterised by Grade 3-4 haematological toxicities in all cases, as expected. During the first ASCT procedure, 37 patients experienced Grade ≥ 2 extra-haematological toxicities: worsening of peripheral neuropathy (n=18), gastro-intestinal mucositis (n=11), fever (n=3), cardiac complications (n=2), upper respiratory infections (n=2), sepsis (n=1). During the second ASCT procedure, 3 patients experienced Grade ≥ 2 extra-haematological toxicities: peripheral neuropathy worsening (n=2) and

gastro-intestinal mucositis (n=1). No ASCT-related mortality was observed. The choice to omit cyclophosphamide during the mobilisation phase and/or to reduce the dose of pre-ASCT melphalan was driven by the patients' fitness, which was re-assessed before each phase of the treatment program. Forty-nine patients received post-ASCT maintenance with the following drugs: Lenalidomide (n=41) (approved in Italy since 2018), Dexamethasone (n=5), and Thalidomide (n=3). The prevalence of good-quality MM responses increased after each step of treatment (**Figure 2**).

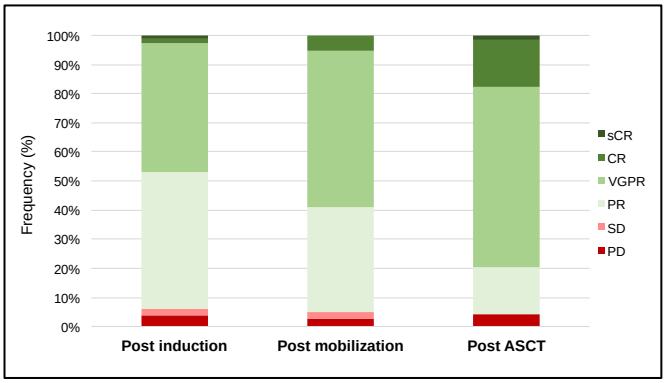

Figure 2. Multiple myeloma responses during the treatment program.[9] sCR = stringent complete response; CR = complete response; VGPR = very good partial response; PR = partial response; SD = stable disease; PD = progressive disease.

During a median follow-up of 46 months (range, 1-156 months), mPFS was 42 months (**Figure 3A**). MM relapsed or progressed in 44 out of the 76 patients who received at least one ASCT: 43 of them started the second line of treatment. As expected, the number of patients receiving $\geq$ 3 lines of therapy approximately halved with each further line. The patients'mOS was estimated at 84 months (**Figure 3B**). At the last follow-up, 55 patients are still alive. Our RWA on NDMM patients aged > 65 years confirmed that the application of a simple frailty score allowed us to correctly identify the elderly MM patients who can benefit from an ASCT-based treatment. In fact, most of our patients enrolled in such a program, indeed, completed it. Furthermore, the need to reduce and/or omit some drugs during each phase of treatment did not compromise the results, which are very close to the RWA reported by the Australian and New Zealand Myeloma and Related Diseases Registry in a cohort of 65-70 years-old MM patients treated with ASCT-based programs, which reported a mPFS of 46.7 months and a mOS of 76.9 months.[2] Our data must, however, be critically viewed in light of the results obtained by MM patients enrolled in non-ASCT-based first-line treatments containing the anti-CD38 monoclonal antibody daratumumab. In fact, the patients enrolled in the MAIA study,[5] who received daratumumab, lenalidomide and dexamethasone cycles until progression or unacceptable toxicity, showed an mPSF of 61.9 months and have not yet reached their mOS after a median follow-up of 64.5 months. Similarly, fit patients enrolled in the ALCYONE study,[6-7] who received 9 daratumumab, bortezomib, melphalan and dexamethasone cycles, followed by daratumumab and dexamethasone maintenance until progression or unacceptable toxicity, experienced an mPSF of 45.7 and a mOS of 82.7 months. Of note, both RCTs and our present study used the same criteria to define patients' frailty.[4] On the other side, we cannot exclude the possibility that the incorporation of daratumumab into ASCT-based treatments – which is possible in Italy from the beginning of 2022 - will further improve the results obtained in patients eligible for ASCT-based programs. In fact, the patients enrolled in the experimental arm of the CASSIOPEIA study,[8] who received 4 pre-ASCT induction and 2 post-ASCT consolidation cycles of daratumumab-VTD, reported a 29% rate of stringent complete response (sCR) and a 39% rate of CR or better at day 100 after ASCT. Their mPFS from the first randomisation has not been reached. Although this RCT also enrolled patients up to the age of 65 years, it showed that the addition of daratumumab did not increase toxicity when compared to the conventional VTD arm. Therefore, we do not expect a higher rate of adverse events in an elderly fit MM population.

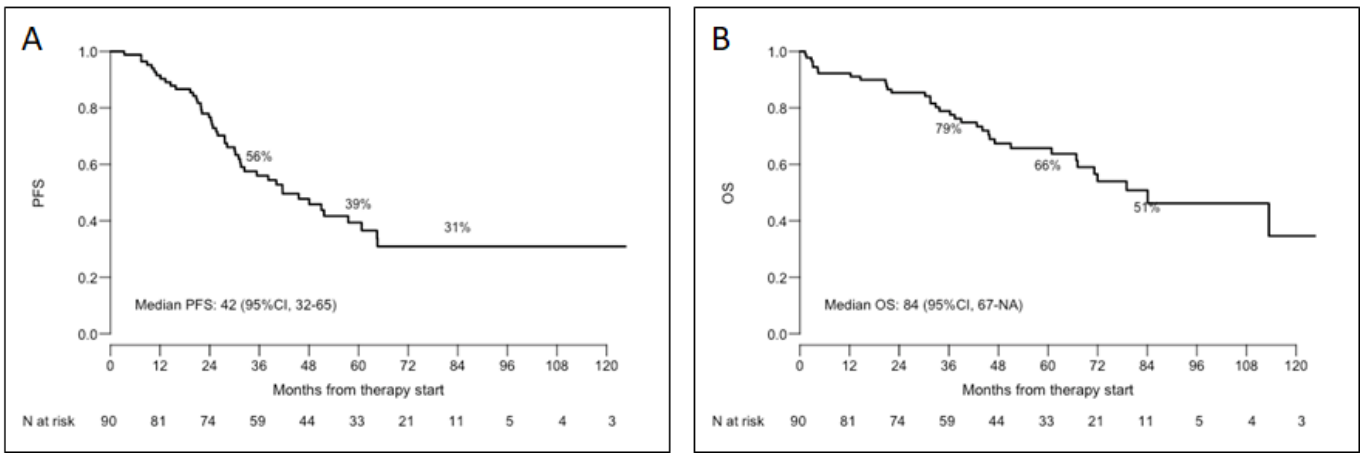

Figure 3. Outcomes of the 90 patients. A) Progression-Free Survival (PFS); B) Overall Survival (OS).

Conclusions. The dynamic evaluation of the degree of fitness helps to tailor the most appropriate treatment of elderly NDMM patients, paving the way for further improvements in their outcomes upon incorporation of an anti-CD38+ monoclonal antibody in the ASCT programs.

Paola Stefanoni[1], Laura Paris[1], Nicola Pittalis[1], Chiara Pavoni[1], Giancluca Cavallaro[1], Alessandro Rambaldi[1,2] and Monica Galli[1].

[1] Department of Oncology and Hematology, ASST Papa Giovanni XXIII, Bergamo, Italy.
[2] Department of Oncology and Hematology, Università degli Studi di Milano, Italy.

Competing interests: The authors declare no conflict of Interest.

Correspondence to: Monica Galli, MD, PhD. Dept. of Oncology and Hematology, ASST Papa Giovanni XXIII, p.zza OMS, 1, 24121 Bergamo, Italy. Tel: +39 035 267 4652. E-mail: monicagalli@asst-pg23.it

References:

1. Dimopoulos MA, Moreau P, Terpos E et al. Multiple myeloma: EHA-ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2021;32:309-322. https://doi.org/10.1016/j.annonc.2020.11.014 PMid:33549387
2. Bergin K, Wellard C, Augustson B et al. Real-world utilisation of ASCT in multiple myeloma (MM): a report from the Australian and New Zealand myeloma and related disease registry (MRDR). Bone Marrow Transplant 2021;56:2533-2543. https://doi.org/10.1038/s41409-021-01308-8 PMid:34011965
3. Cavo M, Tacchetti P, Patriarca F et al. Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study. Lancet 2010;376:2075-85. https://doi.org/10.1016/S0140-6736(10)61424-9 PMid:21146205
4. Facon T, Dimopoulos MA, Meulman N et al. A simplified frailty scale predicts outcomes in transplant-ineligible patients with newly diagnosed multiple myeloma treated in the FIRST (MM-20) trial. Leukemia 2020;34:224-233. https://doi.org/10.1038/s41375-019-0539-0 PMid:31427722 PMCid:PMC7214253
5. Kumar S, Moreau P, Bahlis BJ et al. Daratumumab plus lenalidomide and dexamethasone (D-Rd) vs lenalidomide and dexamethasone (Rd) alone in transplant-ineligible patients with newly diagnosed multiple myeloma (NDMM): updated analysis of the phase 3 MAIA study. Blood 2022;140 (suppl.1):10150-10153. https://doi.org/10.1182/blood-2022-163335
6. Mateos MV, Dimopoulos M, Cavo M et al. Daratumumab plus bortezomib, melphalan, and prednisone versus bortezomib, melphalan, and prednisone in transplant-ineligible newly diagnosed multiple myeloma: frailty subgroup analysis of ALCYONE. Clin Lymph Myel, Leuk 2021;21:785-791. https://doi.org/10.1016/j.clml.2021.06.005 PMid:34344638
7. Mateos MV, San-Miguel J, Cavo M et al. Daratumumab plus bortezomib, melphalan, and prednisone (D-VMP) versus bortezomib, melphalan, and prednisone (VMP) alone in transplant-ineligible patients with newly diagnosed multiple myeloma (NDMM): updated analysis of the phase 3 ALCYONE study. Blood 2022;140 (suppl.1):10157-10159. https://doi.org/10.1182/blood-2022-163347
8. Moreau P, Attal M, Hulin C et al. Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): a randomised, open-label, phase 3 study. Lancet 2019;394:29-38. https://doi.org/10.1016/S0140-6736(19)31240-1 PMid:31171419
9. Durie BG, Harousseau JL, Miguel JS et al. International uniform response criteria for multiple myeloma. Leukemia 2006;20:1467-73. https://doi.org/10.1038/sj.leu.2404284 PMid:16855634