

# Comparison of two strategies of peripheral blood progenitor cells induction with lenalidomide/dexamethasone in newly diagnosed multiple myeloma patients, followed by transplantation and lenalidomide maintenance treatment

Francisco Javier Capote Huelva<sup>1\*</sup>, Eduardo Ríos Herranz<sup>2</sup>, Miguel Ángel Álvarez Rivas<sup>3</sup>, José Joaquín Ruíz Arredondo<sup>4</sup>, Antonio Alcalá Muñoz<sup>5</sup>, Alicia Bailén García<sup>6</sup>, José Luís Guzmán Zamudio<sup>7</sup>, Gemma Ramírez Ramírez<sup>8</sup> and Antonio Fernández Jurado<sup>9</sup>

\*Correspondence: [fcapoteh@aejh.org](mailto:fcapoteh@aejh.org)



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<sup>1</sup>Puerta del Mar Hospital (Cádiz).

<sup>2</sup>Valme Hospital (Sevilla).

<sup>3</sup>Reina Sofía Hospital (Córdoba).

<sup>4</sup>Antequera Hospital (Málaga).

<sup>5</sup>Jaén Complejo Hospitalario (Jaén).

<sup>6</sup>Carlos Haya Hospital (Málaga).

<sup>7</sup>Jerez Hospital (Jerez de la Frontera, Cádiz).

<sup>8</sup>Virgen de la Victoria Hospital (Málaga).

<sup>9</sup>Juan Ramón Jiménez Hospital (Huelva).

## Abstract

**Background:** The most common therapy in young multiple myeloma patients include induction, mobilization, collection and graft of peripheral blood stem cells. The present phase 2, multi-center, randomized study was designed to compare the results after four (arm A) and two (arm B) cycles of induction with lenalidomide plus dexamethasone as first line of treatment. The main aim of the study was to compare the number of collected stem cells for transplant between both arms.

**Findings:** Of the 31 initially included patients, 23 patients were evaluable, 11 and 12 patients in arm A and B, respectively. After induction and mobilization a non-significantly different mean of  $4.30 \times 10^6$  CD34+ cells/kg in arm A and  $4.79 \times 10^6$  CD34+ cells/kg in arm B were obtained ( $p=0.460$ ), respectively. Although a lower number of CD34+ cells were obtained compared with previous studies, it was a sufficient yield for transplantation. The overall response rate was 94.8% and 93.9% at induction and at autologous stem cell transplantation (ASCT), respectively. No differences were observed between arms in the response rate, which was similar to that reported in previous studies. On the other hand, to sufficiently contrast differences in the overall survival and the progression-free survival endpoints, this study suffered from the limitation of the low number of patients followed.

**Conclusion:** Our study confirmed the existing results about grafts quality obtained with lenalidomide and the effectiveness of mobilization with cyclophosphamide and granulocyte colony stimulating factor (G-CSF), although wider randomized studies should confirm the extension and implication of the observations related to response rate, overall survival and progression-free survival.

**Keywords:** Multiple myeloma, lenalidomide, dexamethasone, peripheral blood stem cells, autologous transplantation, stem cell mobilization

## Introduction

Multiple myeloma (MM) is a malignant neoplasm of plasma cells that accumulate in bone marrow, leading to bone mar-

row failure, bone destruction, hypercalcemia, and renal failure.

MM accounts for 1% of all malignant diseases and 15% of the haematological malignancies [1]. The outcome for patients with

MM has improved over the last years and various therapies, now, are available and the therapy is tailored to each patient; in young MM patients consists of the induction treatment with different drugs for 3-6 months, followed by high-dose chemotherapy and autologous stem cell transplantation (ASCT) [2,3]. Lenalidomide plus dexamethasone is an option for pretransplant induction therapy [4].

The number of CD34<sup>+</sup> cells collected for ASCT depends on numerous factors: number of expected transplants (traditionally, the target for CD34<sup>+</sup> cell collection for a single ASCT has been 4 to 6 x10<sup>6</sup> CD34<sup>+</sup>/kg); age (it is expected a decreasing yield with advancing age); patient performance status (patients with good performance status may undergo transplantation up into their mid-70s); comorbidities (i.e. marrow disease is associated with lower number of CD34<sup>+</sup> cells collected), etc. [5].

The main objective of this study was to compare the total number of peripheral blood stem cell (PBSC) collected after 2 or 4 induction cycles with lenalidomide plus dexamethasone.

## Patients and methods

### Study design and treatment

This was a phase 2, multi-center, controlled against alternative experimental treatment, randomized (1:1) and stratified (according to age and *International Staging System* [ISS] stage [6]) clinical trial.

Eligible patients were candidates for ASCT with symptomatic MM who were not previously treated and with *Eastern Cooperative Oncology Group* (ECOG) score ≤2 [7]. The main exclusion criteria were peripheral neuropathy grade above 2, severe renal failure, history of active malignancy during the past 3 years (with exception of skin, cervical or breast carcinoma), hypersensitivity to thalidomide or to dexamethasone, and primary amyloidosis.

The population was randomized in two different treatment arms. Arm A patients received four treatment cycles (lenalidomide 25 mg/day on days 1 to 21 of each 28-day cycle and dexamethasone 40 mg/day on days 1, 8, 15 and 22 each 28-day cycle) and the mobilization and apheresis of hematopoietic cells from bone marrow was performed after the four cycles. Arm B patients received two treatment cycles with the same treatment schedule as arm A and the mobilization and apheresis was realized after this two cycles, afterwards two more cycles were administered.

The PBSC mobilization was performed with cyclophosphamide 1.5 g/m<sup>2</sup> on day 1 and granulocyte colony stimulating factor (G-CSF) 10 µg/kg/day on day 3 until completion of PBSC collection between days 10 and 13, approximately. The apheresis was performed from day 10 to about day 13. In both arms, high dose chemotherapy treatment with melphalan 200 mg/m<sup>2</sup> was carried out. ASCT was performed 48 hours after chemotherapy.

Patients who achieved at least one partial response received maintenance therapy with lenalidomide 10 mg/day for 21 days in each 28-day cycle and acetylsalicylic acid 10 mg/day at 3

months of autotransplantation. Maintenance treatment was maintained until disease progression, unacceptable toxicity or until the patient decided not to participate in the study.

### Statistical analysis

Qualitative variables were described by frequency and percentages based on the size of the non-missing sample. The quantitative variables were obtained through the non-missing sample size (n), mean, standard deviation (SD), confidence interval (CI), median, quartile 1 (Q1), quartile 3 (Q3), maximum and minimum. Missing data were not imputed.

## Results

### Disposition, baseline demographics and disease characteristics

The study enrolled a total of 31 patients and, finally, 23 patients were included in the per protocol population (arm A: 11 patients; arm B: 12 patients). The reasons to be withdrawn were: 1 selection fail, 6 interrupted interventions and 1 principal response assessment not available. **Table 1** shows the

**Table 1. Demographics, baseline and clinical characteristics of patients.**

|                                       | Arm A<br>(n=11) | Arm B<br>(n=12)       | Total<br>population<br>(n=23) |
|---------------------------------------|-----------------|-----------------------|-------------------------------|
| Sex, Male, n (%)                      | 5 (45.5)        | 8 (66.7)              | 13 (56.5)                     |
| Age, years, mean (SD)                 | 55.1 (6.8)      | 55.7 (11.3)           | 55.4 (9.2)                    |
| Weight, Kg, mean (SD)                 | 81.4 (13.1)     | 77.5 (13.2)           | 79.3 (13.0)                   |
| <b>ISS prognostic index, n (%)</b>    |                 |                       |                               |
| I                                     | 4 (36.4)        | 8 (66.7)              | 12 (52.2)                     |
| II                                    | 3 (27.3)        | 4 (33.3)              | 7 (30.4)                      |
| III                                   | 4 (36.4)        | 0 (0.0)               | 4 (17.4)                      |
| <b>ISS classification, n (%)</b>      |                 |                       |                               |
| I                                     | 0 (0.0)         | 2 (16.6)              | 2 (8.7)                       |
| II                                    | 4 (36.4)        | 5 (41.7)              | 9 (39.2)                      |
| III                                   | 6 (54.5)        | 5 (41.7)              | 11 (47.8)                     |
| Unknown                               | 1 (9.1)         | 0 (0.0)               | 1 (4.3)                       |
| <b>ECOG Performance Status, n (%)</b> |                 |                       |                               |
| 0                                     | 6 (54.5)        | 4 (33.3)              | 10 (43.5)                     |
| 1                                     | 3 (27.3)        | 5 (41.7)              | 8 (34.8)                      |
| 2                                     | 2 (18.2)        | 2 (16.7)              | 4 (17.4)                      |
| Unknown                               | 0 (0.0)         | 1 (8.3)               | 1 (4.3)                       |
| Abnormal ECG, n (%)                   | 1 (11.1)*       | 2 (22.2) <sup>†</sup> | 3 (16.7)                      |
| Cytogenetic test available, n (%)     | 7 (83.3)        | 8 (66.6)              | 15 (65.2)                     |
| chromosome 13 deletion, n (%)         | 1 (14.3)        | 2 (25.0)              | 3 (20.0)                      |
| chromosome 17 deletion, n (%)         | 0 (0.0)         | 2 (25.0)              | 2 (13.3)                      |
| Translocation (4:14), n (%)           | 0 (0.0)         | 0 (0.0)               | 0 (0.0)                       |
| Translocation (4:16), n (%)           | 1 (14.3)        | 1 (14.3)              | 2 (13.3)                      |

SD=standard deviation; ISS= International Staging System; ECOG= Eastern Cooperative Oncology Group; ECG= Electrocardiogram

\*Mitral insufficiency

<sup>†</sup>1 right bundle branch block (RBBB) and 1 incomplete RBBB

main demographics and disease characteristics.

### Obtaining CD34<sup>+</sup> cells

A mean number ( $\pm$ SD) of 2.3 ( $\pm$ 0.9) and 1.5 ( $\pm$ 0.8) apheresis was performed in arm A and arm B, respectively. The median (Min-Max) PBSC collected was 4.30 x10<sup>6</sup> CD34<sup>+</sup> cells/kg (2.3-8.2) and 4.79 x10<sup>6</sup> CD34<sup>+</sup> cells/kg (2.27-13.6) in arm A and arm B, respectively (**Figure 1**). There was no statistically significant difference between both arms ( $p=0.460$ ).

### Response rate

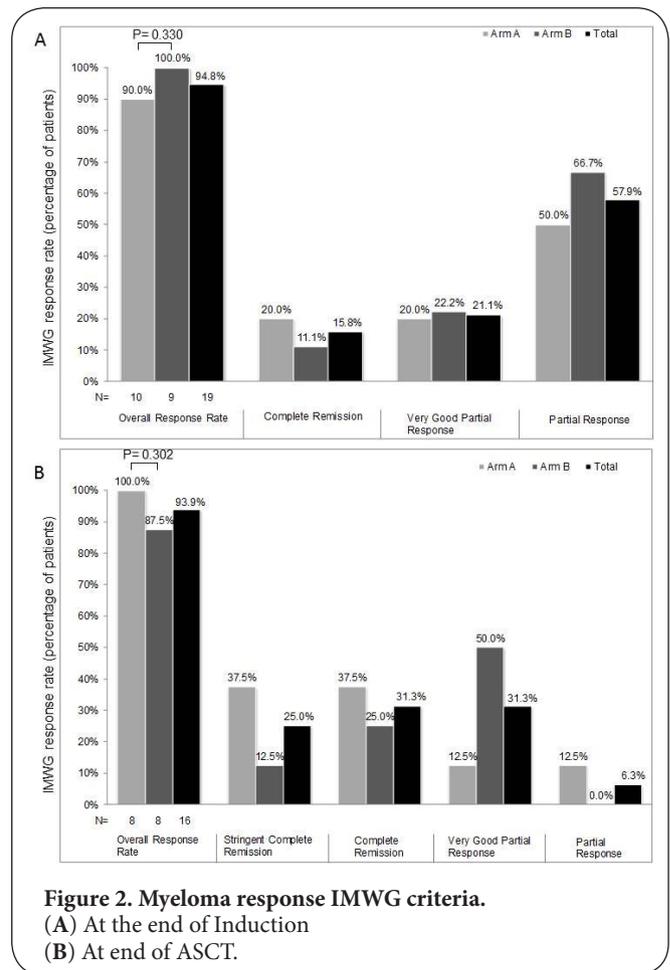
The response rate (RR) was assessed with *International Myeloma Working Group* (IMWG) criteria at the end of induction and ASCT phases (**Figure 2**). At induction, the overall RR was 94.8%; with stringent complete remission (sCR), complete remission (CR), very good partial response (VGPR) and partial response (PR) of 0.0%, 15.8%, 21.1% and 57.9%, respectively. At ASCT, the overall RR was 93.9%; with sCR, CR, VGPR and PR of 25.0%, 31.3%, 31.3% and 6.3%, respectively. No significant differences in RR were observed between both arms at any time.

### Overall Survival and Progression-Free Survival

For arm A, the median (95% CI) overall survival (OS) was 17.3 months (14.7-19.8) and the median (95% CI) progression-free survival (PFS) was 19.1 months (14.9-23.4). The median OS and PFS were not reached for arm B due to the low number of events and limited follow-up in this cohort ( $p$  long Rank test=0.005 and 0.013, respectively).

### Safety

There were a total of 11 severe adverse events reported, including 5 treatment-related events (1 back pain, 1 neutropenia, 1



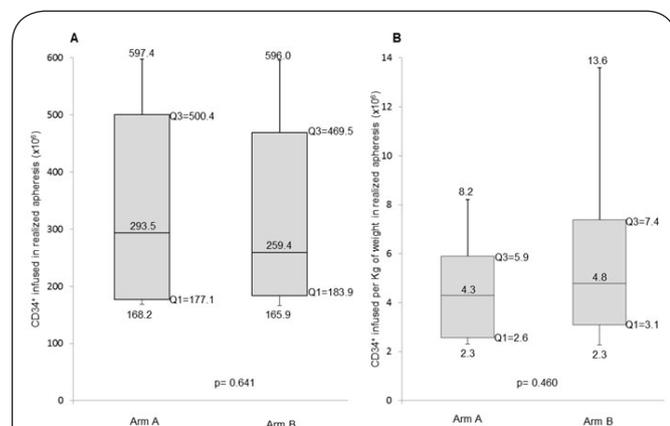
*E.coli* infection, 1 hypotension and 1 exanthema). No exitus occurred during the study.

### Discussion

The main conclusion of the study was that limited lenalidomide exposure before cyclophosphamide based mobilization resulted in adequate grafts to perform a single ASCT could be collected in all patients.

Previous studies, which assessed the impact of lenalidomide treatment upon the mobilization in newly diagnosed MM patients, showed a decrease in the CD34<sup>+</sup> cells collected in patients treated with lenalidomide compared to those who received dexamethasone, thalidomide-dexamethasone or vincristine-doxorubicin-dexamethasone (VAD), either with G-CSF or with cyclophosphamide plus G-CSF. Nevertheless, there was no effect on quality of PBSC collected based on similar engraftment across all groups [8]. In our study, we observed similar results. Moreover, the lower blood CD34<sup>+</sup> cell counts after lenalidomide exposure can usually be offset by the use of plerixafor [9].

When we focus on the mobilization treatment, results published in different studies [10-13] show that the stem cells



collection (among  $5.6 \times 10^6$  and  $8.7 \times 10^6$  CD34<sup>+</sup>/kg depending on the study) is enough when the mobilization is carried out with cyclophosphamide and G-CSF. Our study confirms the effectiveness of this mobilization procedure and although our number of collected progenitors was lower, it was sufficient for the successful transplant. This decrease in the total number of collected stem cells may be motivated by the use of a lower dose of cyclophosphamide ( $1.5 \text{ g/m}^2$  in our study versus doses of 2 to  $4 \text{ g/m}^2$  in the cited studies); as well as the cellular separators yield used in the different sites.

In the present study and despite the limitation of the small number of patients in our series, the RR was comparable with those in other published studies [12-15] with not previously treated MM patients. Due to the limited number of patients who continued maintenance treatment, unfortunately, conclusions cannot be drawn about its usefulness under maintenance in our specific cohort of patients, which is still a controversial issue today [16]. However, the results of the most recent meta-analysis showing a significant OS benefit

in patients treated with lenalidomide maintenance argue in favor of establishing lenalidomide maintenance as the standard of care in the post-ASCT setting [17].

Interpretation and comparison of OS and PFS with other studies is hampered by the limited number of patients and current restricted follow-up. It has to be mentioned also, the possibility that the earlier cyclophosphamide administration in arm B, could influence the differential results between arms A and B.

As other studies using dexamethasone-lenalidomide in untreated MM patients have previously reported, the regimen was generally well tolerated, with predictable and manageable toxicity. No exitus occurred during the treatment in this study. Our study confirms the results about grafts quality obtained with lenalidomide despite obtaining lower overall yields. Moreover, this study also confirms the effectiveness of mobilization with cyclophosphamide and G-CSF. However, wider randomized studies should confirm the extension and implication of the observations on RR, OS and PFS in the future.

### Competing interests

The authors declare that they have no competing interests.

### Authors' contributions

| Authors' contributions             | FC | ER | MA | JR | AA | AB | JG | GR | AF |
|------------------------------------|----|----|----|----|----|----|----|----|----|
| Research concept and design        | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  |
| Collection and/or assembly of data | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  |
| Data analysis and interpretation   | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  |
| Writing the article                | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  |
| Critical revision of the article   | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  |
| Final approval of article          | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  |
| Statistical analysis               | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  | ✓  |

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