Feasibility of six cycles of lenalidomide-based triplet induction before stem cell collection for newly diagnosed transplant-eligible multiple myeloma

Satoshi Yoshihara a,b, Kyoko Yoshihara a, Yoshifumi Shimizu c, Takehito Imado d, Hiroyuki Takatsuka d, Hiroyuki Kawamoto e, Mahito Misawa f, Hideki Ifuku d, Yokiko Ohe e, Masaya Okada a and Yoshihiro Fujimori a,b,e

aDepartment of Hematology, Hyogo College of Medicine Hospital, Hyogo, Japan; bDepartment of Transfusion Medicine and Cellular Therapy, Hyogo College of Medicine Hospital, Hyogo, Japan; cDepartment of Hematology, Takarazuka City Hospital, Hyogo, Japan; dDepartment of Hematology, Amagasaki Chuo Hospital, Hyogo, Japan; eDepartment of Hematology, Uegahara Hospital, Hyogo, Japan; fDepartment of Hematology, Ako Central Hospital, Hyogo, Japan

ABSTRACT

Objectives: Achieving a deep response with induction therapy has a major impact on outcomes following autologous stem cell transplantation. Although longer and intensified induction therapy may provide better disease control, longer exposure to lenalidomide negatively affects stem cell yield. We examined the feasibility of 6 cycles of lenalidomide-based triplet induction therapy before stem cell collection in transplant-eligible multiple myeloma patients.

Methods: In this prospective study, patients received a combination of bortezomib, lenalidomide, and dexamethasone for 6 cycles. For patients who did not achieve a deep response after 3 cycles, bortezomib was substituted with carfilzomib for the last 2 cycles (5th and 6th courses).

Results: Although only half of the patients achieved a deep response after 3 cycles, all but 1 patient achieved a very good partial response (n = 4) or complete response (n = 5) after completing 6 cycles. Among 9 patients who received cyclophosphamide-based stem cell mobilization, 1 patient required a second mobilization that was successfully performed using plerixafor. After autologous transplantation, 7 patients showed complete response, including 5 with minimal residual disease-negative status.

Conclusion: This study demonstrates that 6 cycles of lenalidomide-based induction therapy before stem cell collection are a feasible and promising approach for transplant-eligible newly diagnosed multiple myeloma patients.

Trial registration: UMIN Clinical Trials Registry as UMIN000026936.

KEYWORDS

Multiple myeloma; induction therapy; lenalidomide; bortezomib; carfilzomib; stem cell collection; autologous hematopoietic stem cell transplantation; minimal residual disease

Introduction

The prognosis of multiple myeloma (MM) has significantly improved with the use of combinations of multiple novel drugs. High-dose melphalan-based autologous hematopoietic stem cell transplantation (ASCT) following induction therapy is a part of the standard frontline treatment for eligible patients. While MM remains an incurable disease, studies have shown that patients who achieved a deep response, a very good partial response (VGPR), or better, prior to or after ASCT, can enjoy a long-term progression-free survival (PFS) and overall survival (OS) [1,2]. While the VAD (vincristine, doxorubicin, and dexamethasone) regimen used to be the standard regimen for induction therapy [2], various drug combinations have been examined after the emergence of proteasome inhibitors and immunomodulatory drugs. One of the most frequently used induction regimens in current practice is a combination of bortezomib, lenalidomide, and dexamethasone (VRD). Despite changes in the drug combination, the number of cycles of VRD administered prior to ASCT remains the same (i.e. 3–4 cycles) [3,4] as that in the VAD era, when the number of the cycles was limited due to concerns about cardiac toxicity. In theory, the prolongation of the induction regimen deepens the pre-transplant response levels, which translates into the depth of the response after ASCT.

We examined the feasibility of performing 6 cycles of lenalidomide-based triplet induction therapy in transplant-eligible MM patients. During the 6 cycles of prolonged induction, we also examined the feasibility of a response-based approach, in which VRD was switched to KRD (the combination of carfilzomib, lenalidomide, and dexamethasone) in patients who did not achieve VGPR after 3 cycles.
Methods

Study design and patients

The study included newly diagnosed patients with active MM, as defined by the International Myeloma Working Group criteria [5], who were aged 20–70 years and eligible for ASCT. Additional eligibility criteria included an Eastern Cooperative Oncology Group performance status of 0–2 (or 3 if the status was due to MM); an absolute neutrophil count of $\geq 1.0 \times 10^9/L$; a platelet count of $\geq 75 \times 10^9/L$; aspartate transaminase and alanine transaminase levels of $\leq 3$ times the upper limit of normal; a total bilirubin level of $\leq 1.5$-times the upper limit of normal; creatinine clearance of $\geq 30$ mL/min; and a left ventricular ejection fraction of $\geq 50$%. Patients who did not meet the eligibility criteria were excluded.

Each study site’s independent ethics committee approved the study protocol. The study was designed and conducted in accordance with the ethical principles of the Declaration of Helsinki and the International Council for Harmonization Guidelines. Patients provided informed consent authorizing the use of their personal information for research purposes. The study is registered at UMIN Clinical Trials Registry as UMIN000026936.

Treatment

We used a 28-day cycle modified VRD regimen, in which bortezomib 1.3 mg/m$^2$ was administered weekly (day 1, 8, and 15), lenalidomide 25 mg was administered from day 1 to day 21, and dexamethasone 20 mg was administered twice per week. The dose of lenalidomide was reduced to 15 mg for those who were aged 65 years or older. The dose of lenalidomide was also reduced in patients with insufficient renal function (i.e. creatinine clearance of $\leq 60$ mL/min). Prephase treatments were allowed with lenalidomide and dexamethasone ($\leq 2$ weeks) and/or bortezomib and dexamethasone ($\leq 2$ weeks) prior to the start of the VRD induction regimen.

For the patients who did not achieve VGPR after 3 courses of modified VRD, KRD was used in the 5th and 6th courses (i.e. VRD for 4 courses and KRD for 2 courses). For those who achieved VGPR or better after 3 courses of modified VRD, VRD was continued for the full 6 courses.

After the completion of the induction treatment, the patients underwent peripheral blood stem cell collection following stem cell mobilization using low-dose cyclophosphamide (CY, 2 g/m$^2$) and granulocyte-colony stimulating factor (G-CSF). The use of plerixafor (G-CSF + plerixafor protocol) was reserved for a second attempt at stem cell collection, but it was allowed for use as a first attempt at the doctor’s discretion. As a conditioning regimen before ASCT, patients received melphalan 200 mg/m$^2$ (< 65 years old) or melphalan 160 mg/m$^2$ (≥ 65 years old). Treatment after ASCT (i.e. consolidation and maintenance therapy) was not defined by the protocol.

Response was assessed after each course of induction therapy and on day 100, 1, and 2 years after ASCT, in accordance with the International Myeloma Working Group criteria [6]. Minimal residual disease (MRD) assessment was performed by next-generation flow cytometry using the EuroFlow standard operational procedure or a validated equivalent method [7]. Grading of adverse events was performed according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03).

Results

Patient characteristics

Between May 2017 and March 2019, 11 transplant-eligible patients at two institutions were enrolled in the study. One patient dropped out from the study in the prephase, due to fatigue associated with lenalidomide treatment, and was excluded from further analysis. Patient characteristics are summarized in Table 1. The median age was 63 years (range: 45–70), and the M-protein type was IgG in 6 patients and Bence-Jones in 4 patients. Three patients had International Staging System stage III disease, and 1 patient had high-risk cytogenetics, defined as t(4;14), t(14;16), and/or del(17p).

Induction therapy

None of the patients had progressive disease during the induction therapy. All patients completed the 6 cycles of induction regimen, including 1 patient who received the 2 last cycles without lenalidomide (i.e. carfilzomib and dexamethasone) after developing deep vein thrombosis (grade 2). Among the 5 patients in whom KRD was used, 3 patients were switched from VRD because of the failure to achieve VGPR after 3 courses, and 2 patients were switched due to adverse events (1 with grade 2 peripheral neuropathy and 1 with grade 2 urinary retention) after the initial dose of bortezomib. One patient received VRD for 6 cycles despite a
failure to achieve VGPR after 3 courses, since the patient developed grade 3 liver toxicity with carfilzomib. Except for the above-described adverse events, grade 2 liver toxicity in 1 patient and grade 2 peripheral neuropathy in 1 patient were observed. No patients had grade \( \geq 2 \) neutropenia and no patients were admitted to the hospital due to infection.

**Response with induction therapy and ASCT**

Although only half of the patients achieved a deep response after 3 cycles of induction therapy, all but 1 patient achieved VGPR \( (n = 4) \) or complete response \( (CR, n = 5) \) after completing the 6 cycles of induction therapy (Table 2).

Subsequently, all the patients proceeded to stem cell collections: 9 with CY + G-CSF and 1 with G-CSF + plerixafor (Table 3). Only 1 patient who was mobilized with CY + G-CSF required a second mobilization attempt with G-CSF + plerixafor. All patients achieved a sufficient number of CD34+ cells for autologous transplantation, with a median of \( 4.1 \times 10^6 \) cells/kg.

All patients underwent stem cell transplantation following high-dose melphalan treatment and achieved hematopoietic engraftment (Table 3). The median times to neutrophil recovery \( (\geq 0.5 \times 10^9/L) \) and platelet recovery \( (\geq 50 \times 10^9/L) \) were 10 and 13.5 days, respectively. Two patients with VGPR before ASCT showed CR after ASCT (Table 2). Moreover, among the 7 CR patients, 5 were confirmed to be MRD-negative at a threshold of 1 tumor cell/10^5 white cells.

We demonstrated that 6 cycles of lenalidomide-based induction therapy are feasible and provides a remarkably high rate (9 out of 10 patients) of deep response prior to ASCT. Noticeably, among the 5 patients who were in partial response after 3 cycles of VRD, which is the current standard of induction therapy, 4 patients showed improvement to VGPR or better after the completion of induction therapy, in which KRD or KD was administered in the last 2 cycles. These results clearly demonstrated the usefulness of the prolongation and response-oriented intensification of induction therapy. As expected, ASCT further deepened the response: 7 CR, including 5 MRD-negative at a threshold of 1 tumor cell/10^5 white cells, and 2 VGPR among 10 patients.

Although the longer and intensified induction therapy is assumed to provide a better disease control before ASCT, it has not been utilized since several retrospective studies showed that a longer exposure to lenalidomide has a negative impact on a stem cell yield \[8,9\]. Thus, an expert panel of the International Myeloma Working Group recommended the stem cell mobilization after a maximum of 4 cycles of a lenalidomide-based regimen \[10\].

One approach to circumvent this issue is to perform stem cell collection at the midst of the induction therapy. Indeed, in the PETHEMA/GEM2012 study, stem cell collection was performed after the 3rd cycle of the induction therapy, in which 6 cycles of VRD were administered in total \[11,12\]. In contrast, we chose to perform stem cell collection after the completion of induction therapy. Stem cell collection in the midst of the induction therapy results in a significant period of interruption of the anti-myeloma treatment, which does not occur with our strategy.

Another aim of our approach was to collect an autograft with the fewest number of contaminating myeloma cells as possible. The failure to demonstrate a benefit for purging myeloma cells from autografts using CD34-positive selection in an old study from before the era of novel agent-based induction therapies \[13\] may be attributable to the residual myeloma cells in the bone marrow after high-dose therapy. Interestingly, Takamatsu et al. reported that

### Table 2. Responses with induction therapy and ASCT.

| Induction therapy (cycles) | Response after 3 cycles | Response after 6 cycles | Toxicities that lead changes in the treatment | Response at day 100 after ASCT |
|----------------------------|-------------------------|-------------------------|---------------------------------------------|------------------------------|
| 1 VRD × 6                  | VGPR                    | VGPR                    | Liver toxicity                              | VGPR                         |
| 2 VRD × 6                  | PR                      | PR                      | Peripheral neuropathy                       | PR                           |
| 3 VRD × 2, KRD × 4         | CR                      | CR                      | Urinary retention                           | CR, MRD-negative             |
| 4 KRD × 6                  | CR                      | CR                      | Deep vein thrombosis                        | CR                           |
| 5 VRD × 4, KD × 2          | PR                      | CR                      | MRD-negative                                | CR, MRD-negative             |
| 6 VRD × 4, KRD × 2         | PR                      | VGPR                    | MRD-negative                                | CR, MRD-negative             |
| 7 VRD × 4, KRD × 2         | PR                      | VGPR                    | MRD-negative                                | CR, MRD-negative             |
| 8 VRD × 6                  | VGPR                    | VGPR                    | MRD-negative                                | CR, MRD-negative             |
| 9 VRD × 4, KRD × 2         | PR                      | CR                      | MRD-negative                                | CR, MRD-negative             |
| 10 VRD × 6                 | VGPR                    | VGPR                    | MRD-negative                                | VGPR                         |

### Table 3. Peripheral blood stem cell collections and ASCT.

| Induction therapy (cycles) | CD34+ cells yield \((10^6 \text{ cells/kg})\) | Neutrophil recovery (day) | Platelet recovery (day) |
|----------------------------|-----------------------------------------------|---------------------------|-------------------------|
| 1 CY + G-CSF               | 6.7                                           | 9                         | 13                      |
| 2 CY + G-CSF, G-CSF + plerixafor | 0.75, 4.3                               | 10                        | 11                      |
| 3 CY + G-CSF               | 4.4                                           | 12                        | 17                      |
| 4 CY + G-CSF               | 3.7                                           | 11                        | 11                      |
| 5 CY + G-CSF               | 8.2                                           | 10                        | 15                      |
| 6 CY + G-CSF               | 2.0                                           | 10                        | 14                      |
| 7 CY + G-CSF               | 3.2                                           | 11                        | 13                      |
| 8 CY + G-CSF               | 2.9                                           | 49                        | 20                      |
| 9 CY + G-CSF               | 3.7                                           | 10                        | 14                      |
| 10 G-CSF + plerixafor      | 26.9                                          | 9                         | 11                      |
patients whose autografts tested negative on next-generation sequencing-based MRD assessment had a PFS rate of 92% and an OS rate of 100% at 4 years post-ASCT [14]. Achieving MRD negativity in the autograft should be a goal for novel agent-based induction therapies to improve outcomes after ASCT.

In our study, 8 of 9 patients mobilized with CY + G-CSF achieved the minimally required number of CD34+ cells (2 × 10^5/kg). Nonetheless, the median number of CD34+ cells was relatively low, which might be associated with the prolonged lenalidomide exposure. Previous studies have shown that lenalidomide is not toxic to hematopoietic stem cells [15], but it induces the localization of CXCR4 to the cell surface and blockade of receptor internalization [16]. Increased binding of CXCR4 to the SDF-1α secreted by the bone marrow niche might subsequently block the mobilization of hematopoietic stem cells. Blocking the CXCR4 receptor by plerixafor disrupts this cycle and permits mobilization. Indeed, the use of plerixafor overcomes the negative effect of lenalidomide in stem cell mobilization [16–18]. In our study, 2 patients, including 1 patient who had poor mobilization with CY + G-CSF, achieved >4 × 10^6 CD34+ cells/kg with G-CSF + plerixafor. Taken together, mobilization after 6 cycles of lenalidomide-based treatment seems to be practicable, particularly when G-CSF + plerixafor is used in the mobilization protocol.

This study has several inherent limitations, particularly the small number of the patients. In addition, while a major objective of stem cell collection after the prolonged induction therapy is to obtain an autograft with fewer contaminating myeloma cells, we did not examine MRD status in the autografts in this study. Recently, Tageja et al. reported that after induction therapy with 4–8 cycles of KRD, at stem cell collection, 11/30 patients (36.6%) showed MRD-negativity in the bone marrow and 29/30 patients, including 18 patients who showed MRD-positivity in the bone marrow, had MRD-negative autografts [19]. Consistent with our study, stem cell mobilization was successfully conducted in 13 patients who received 6 or 7 cycles of KRD with or without the use of plerixafor.

In conclusion, this study demonstrates that 6 cycles of response-oriented lenalidomide-based induction therapy before stem cell collection are a feasible and promising approach for transplant-eligible newly diagnosed multiple myeloma patients. These findings may serve as a rationale for conducting future trials on prolonged and intensified induction therapies.

**Author contributions**
SY and KY designed the study, analyzed the data, and wrote the manuscript. YS designed the study and analyzed the data. TI analyzed the data. HT, HK, MM, HI, YO, and MO designed the study. YF designed the study and wrote the manuscript.

**Disclosure statement**
SY received honoraria from Janssen Pharmaceutical KK and Celgene (Bristol-Myers Squibb).

**Funding**
This work was supported by MEXT KAKENHI, Ministry of Education, Culture, Sports, Science and Technology: [Grant Number 17K07142].

**ORCID**
Satoshi Yoshihara http://orcid.org/0000-0002-8537-2422

**References**
[1] van de Velde HJ, Liu X, Chen G, et al. Complete response correlates with long-term survival and progression-free survival in high-dose therapy in multiple myeloma. Haematologica. 2007;92(10):1399–1406.
[2] Harousseau JL, Aver-Loiseau H, Attal M, et al. Achievement of at least very good partial response is a simple and robust prognostic factor in patients with multiple myeloma treated with high-dose therapy: long-term analysis of the IFM 99–02 and 99–04 trials. J Clin Oncol. 2009;27(34):5720–5726.
[3] Roussel M, Lauwers-Cances V, Robillard N, et al. Frontline transplantation program with lenalidomide, bortezomib, and dexamethasone combination as induction and consolidation followed by lenalidomide maintenance in patients with multiple myeloma: a phase II study by the Intergroupe Francophone du Myelome. J Clin Oncol. 2014;32(25):2712–2717.
[4] Attal M, Lauwers-Cances V, Hulin C, et al. Lenalidomide, bortezomib, and dexamethasone with transplantation for myeloma. N Engl J Med. 2017;376(14):1311–1320.
[5] Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol. 2014;15(12):e538–e548.
[6] Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol. 2016;17(8):e328–e346.
[7] Takamatsu H, Yoroidaka T, Fujisawa M, et al. Comparison of minimal residual disease detection in multiple myeloma by SRL 8-color single-tube and EuroFlow 8-color 2-tube multiparameter flow cytometry. Int J Hematol. 2019;109(4):377–381.
[8] Kumar S, Dispensieri A, Lacy MQ, et al. Impact of lenalidomide therapy on stem cell mobilization and engraftment post-peripheral blood stem cell transplantation in patients with newly diagnosed myeloma. Leukemia. 2007;21(9):2035–2042.
[9] Popat U, Saliba R, Thandi R, et al. Impairment of filgrastim-induced stem cell mobilization after prior lenalidomide in patients with multiple myeloma. Biol Blood Marrow Transplant. 2009;15(6):718–723.
[10] Kumar S, Giralt S, Stadtmauer EA, et al. Mobilization in myeloma revisited: IMWG consensus perspectives on stem cell collection following initial therapy with thalidomide-, lenalidomide-, or bortezomib-containing regimens. Blood. 2009;114(9):1729–1735.

[11] Rosiñol L, Oriol A, Rios R, et al. Bortezomib, lenalidomide, and dexamethasone as induction therapy prior to autologous transplant in multiple myeloma. Blood. 2019;134(16):1337–1345.

[12] Paiva B, Puig N, Cedena MT, et al. Measurable residual disease by next-generation flow cytometry in multiple myeloma. J Clin Oncol. 2020;38(8):784–792.

[13] Stewart AK, Vescio R, Schiller G, et al. Purging of autologous peripheral-blood stem cells using CD34 selection does not improve overall or progression-free survival after high-dose chemotherapy for multiple myeloma: results of a multicenter randomized controlled trial. J Clin Oncol. 2001;19(17):3771–3779.

[14] Takamatsu H, Takezako N, Zheng J, et al. Prognostic value of sequencing-based minimal residual disease detection in patients with multiple myeloma who underwent autologous stem-cell transplantation. Ann Oncol. 2017;28(10):2503–2510.

[15] Pal R, Monaghan SA, Hassett AC, et al. Immunomodulatory derivatives induce PU.1 down-regulation, myeloid maturation arrest, and neutropenia. Blood. 2010;115(3):605–614.

[16] Li S, Fu J, Ma H, et al. Lenalidomide-induced upregulation of CXCR4 in CD34+ hematopoietic cells, a potential mechanism of decreased hematopoietic progenitor mobilization. Leukemia. 2013;27(6):1407–1411.

[17] Dosani T, Covut F, Pinto R, et al. Impact of lenalidomide on collected hematopoietic myeloid and erythroid progenitors: peripheral stem cell collection may not be affected. Leuk Lymphoma. 2019;60(9):2199–2206.

[18] Partanen A, Valtola J, Silvennoinen R, et al. Impact of lenalidomide-based induction therapy on the mobilization of CD34(+) cells, blood graft cellular composition, and post-transplant recovery in myeloma patients: a prospective multicenter study. Transfusion. 2017;57(10):2366–2372.

[19] Tageja N, Korde N, Kazandjian D, et al. Combination therapy with carfilzomib, lenalidomide and dexamethasone (KRd) results in an unprecedented purity of the stem cell graft in newly diagnosed patients with myeloma. Bone Marrow Transplant. 2018;53(11):1445–1449.