Journal of Cancer Research and Practice

journal homepage: www.ejcrp.org

Original Article

Real-world Evidence of Daratumumab-Lenalidomide-Dexamethasone in Relapsed/Refractory Multiple Myeloma Patients: A Single-center Experience in Taiwan Focusing on Efficacy

Ling-Jung Chiu, Chin-Yuan Kuo, Ming-Chun Ma, Chun-Kai Liao, Hung-Lin Liu, Ming-Chung Wang*

Division of Hematology and Oncology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan

Abstract

Background: Daratumumab (DARA) introduced in the multiple myeloma (MM) treatment strategy, producing a direct antitumor activity and immunomodulatory effects in phase I-II trial GEN501. In the POLLUX trial, the combination of DARA with lenalidomide and dexamethasone (DRd) reported impressive response rates. In Taiwan, the Dara-based regimen was supported by National Health Insurance recently, but there were no real-world data in Taiwan. **Materials and Methods:** We described a heavily pretreated group of 31 patients with MM who had received one or more lines of therapy to receive DRd therapy after Taiwan Food and Drug Administration approval. The primary end point was progression-free survival (PFS). **Results:** After a median follow-up of 22.87 (95% confidence interval [CI]: 16–29.73) months, the median time to first response was 59 days (95% CI: 24.8–81.6). Median PFS was 24.082 months (95% CI: 14–33) in patients who received DRd therapy. Twelve-month PFS showed 80.7% in the DRd group. Patients who achieved at least very good partial response (VGPR) had longer median PFS (39.8 months) than those who achieved partial response (7.35 months). The complete response rate and VGPR were 35.5% and 29%, respectively. About 22.6% of patients had a partial response. The average treatment duration was 11.48 ± 7 months. Patient experienced biological relapse at 5.88 months after discontinuing DRd treatment. **Conclusion:** After DRd treatment for 11.48 months, most of the patients showed biological relapse at 5.88 months, suggesting the good efficacy; however, the need of a longer maintenance treatment of DARA. The median PFS in real-world setting was consistent with the POLLUX trial regardless of more patients with high cytogenetic risks. Patient who could achieve deep response above VGPR had better PFS than those who did not.

Keywords: Daratumumab, dexamethasone, lenalidomide, relapse and refractory multiple myeloma

Address for correspondence: Dr. Ming-Chung Wang, Division of Hematology and Oncology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, 123, Ta Pei Rd., Niao Sung District, Kaohsiung 833, Taiwan.
E-mail: wang9595@ms32.hinet.net

Submitted: 10-Nov-2022 **Revised:** 30-Dec-2022
Accepted: 03-Jan-2023 **Published:** 10-Mar-2023

Access this article online

Quick Response Code:

Website: www.ejcrp.org

DOI: 10.4103/ejcrp.eJCRP-D-22-00032

How to cite this article: Chiu LJ, Kuo CY, Ma MC, Liao CK, Liu HL, Wang MC. Real-world evidence of daratumumab-lenalidomide-dexamethasone in relapsed/refractory multiple myeloma patients: A single-center experience in Taiwan focusing on efficacy. J Cancer Res Pract 2023;10:19-23.

Introduction

Most patients with multiple myeloma (MM) have a relapse under the incorporation of proteasome inhibitors and immunomodulatory drugs in the past 10 years.[1-3]

Daratumumab (DARA) provides a substantial single-agent efficacy in relapsed/refractory multiple myeloma (RRMM).[4,5] A phase 3 trial combined with DARA, lenalidomide, and dexamethasone (DRd) in a patient with RRMM provided therapeutic benefits.[6] In current studies, DRd treatment cycles of 28 days continued until disease progression, an unacceptable level of toxic events. Here, we report the results of a real-world data, of which we assessed the efficacy and safety of DRd under limited resources in patients with RRMM in Taiwan.

Materials and Methods

Study design

Patients in Kaohsiung Chang-Gung hospital who were treated with DARA plus lenalidomide and DRd from January 2018 to March 2022 were retrospectively analyzed. Adult patients (≥18 years) with RRMM who have been previously treated with PI and IMiD and who have progressed after the last line of therapy were included in the study. Patients who received DARA in combination with other drugs were all excluded from the study. During each 28-day cycle, all the patients received oral lenalidomide (25 mg on days 1 to 21) and oral DRd (40 mg on days 1, 8, 15, and 22) until disease progression or unacceptable toxic effects. For patients who had a creatinine clearance between 30 and 50 ml per minute, a reduced dose of lenalidomide (10 mg) was recommended. Adjustment of the dose of lenalidomide was recommended in the case of neutropenia and thrombocytopenia. Patients who were older than 75 years of age or who had a body mass index (the weight in kilograms divided by the square of the height in meters) of <18.5 received DRd at a dose of 20 mg once weekly. Patients in the DARA group received intravenous DARA at a dose of 16 mg/kg of body weight once weekly during cycles 1 and 2, every 2 weeks during cycles 3 through 6, and every 4 weeks thereafter; preinfusion medications were administered approximately 1 h before each DARA dose.

Data were collected, including clinical and laboratory characteristics (age, sex, kidney function, heavy and light chain isotype, staging, paraskeletal, and extramedullary plasmacytomas) before initiating DARA. Kidney dysfunction was defined as a persistent creatinine ≥2 mg/dL.

The primary end point was progression-free survival (PFS) according to the International Myeloma Working Group criteria.[7] Secondary end points were clinical benefit rate (overall response rate, time to partial response, and time to relapsed time). Response to treatment and disease progression were evaluated according to the IMWG response criteria at the end of each treatment cycle.[8,9] Safety assessments included the evaluation of adverse events. The institutional review board of this hospital (KCGMH) approved this study (Number: 202201653B0). Informed consent was obtained from all patients enrolled in this study.

Statistical analyses

Categorical data were evaluated using the Chi-square test or Fisher's exact test. Time-to-event end points were follow-up time and PFS. Analyses and graphical representations were made by the Kaplan–Meier method. Major efficacy secondary end points of time to disease progression, rate of very good partial response (VGPR), and overall response rate were sequentially tested, each with an overall two-sided alpha of 0.05. Statistical significance was evaluated by the log-rank test. Time 0 was considered the day of the first DARA infusion. Progressive disease included those patients whose response was not evaluable. Analyses were performed using IBM SPSS statistics version 26.

Results

Between January 01, 2018, and March 30, 2022, 46 patients were enrolled, of which 31 patients were DRd group and 15 in the DARA-based group. The median age was 60.5 years (range: 32–88) and 48.4% were male. Seven patients (19.4%) had renal impairment with a serum creatinine ≥2 mg/dL [Table 1]. Seven patients had TP53 mutation (58.1%), whereas 18 patients (22.6%) had no TP53 mutation. Only one patient had triple mutation, including TP 53, IGH/FGFR3, and 1q21 [Table 2]. DRd as second-line therapy was 77.4%. Seven patients received more than two lines of therapy (22.6%). 51.6% had undergone an autologous stem cell transplant (auto-SCT). The median follow-up time since initiate DARA was 18.95 months (12.3–25.6). All patients had received bortezomib and 19.4% of them had received lenalidomide. Four (12.9%) patients were refractory to the last line of therapy. Refractoriness to bortezomib, lenalidomide, and combinations of PI + IMiD was 2 (6.5%), 1 (3.2%), and 0%, respectively [Table 3].

Overall, 31 were evaluable for response. The objective response rate (ORR) was 96.8% (41.9% ≥CR, 19.4% VGPR, and 35.5% PR), and progressive disease was 3.2%. Response rates are summarized in Table 4. The time to partial response was 52.93 days (range: 21.8–81.06). After a median follow-up of 17.37 months, the median PFS for the DRd was 24.08 months [Figure 1]. Regarding response, median PFS for patients with above VGPR and PR was 39.8 months (95% CI: 28–41) and 7.3 months (95% CI: 0.8–10), respectively ($P < 0.01$) [Figure 2].

Median PFS was unreached and 24.1 months (95% CI: 14–34) for patients with serum creatinine <2 mg/dL and ≥2 mg/dL, respectively ($P = 0.95$). Compare the patients between TP 53 mutation and TP 53 wild type, the median PFS revealed 24.08 months (95% CI: 2.3–45.8) and nonreached, respectively ($P = 0.72$). Median relapse time after stopped DARA revealed to be 5.88 months. Fifteen patients who previously received an ASCT achieved 93.3% of ORR,

Table 1: Demographic and clinical characteristics in the daratumumab with lenalidomide and dexamethasone group

	DRd (*n*=31), *n* (%)
Age	60.5±12 (32-88)
Gender	
Male	15 (48.4)
Female	16 (51.6)
Creatinine	
<2	25 (80.6)
>2	6 (19.4)
ISS*	
1	6 (19.4)
2	12 (38.7)
3	13 (41.9)
Type	
IgG	16 (51.6)
IgA	10 (32.3)
Light chain	4 (12.9)
Others (nonsecretory type)	1 (3.2)
Light chain	
Kappa	19 (61.3)
Lambda	12 (38.7)
Lab	
White blood count	5264.96
Hemoglobin (g/dL)	9.729
Lactate dehydrogenase	175.48
Creatinine	1.37

*ISS disease stage is derived based on the combination of β2 - macroglobulin and albumin levels. Higher stages indicate more advanced disease. IgG: Immunoglobulin G, IgG: Immunoglobulin A, DRd: Daratumumab with lenalidomide and dexamethasone, ISS: International Staging System

Table 2: Cytogenetics analysis in the daratumumab with lenalidomide and dexamethasone group

	DRd (*n*=31), *n* (%)
Chromosome	
Normal	24 (77.4)
Complex	7 (22.6)
TP 53	
Negative	18 (58.1)
Positive	7 (22.6)
Not available	6 (19.3)
Cytogenetics*	
Standard	13/31 (41.9)
High risk	11/31 (35.5)
Median time since diagnosis (y)	2.335
Cytogenetic analysis	
IGH/FGFR3	3 (9.6)
1q21.3(CKS1B)	2 (6.4)
TP53	5 (16)
TP 53, IGH/FGFR3, 1q21	1 (3.2)

*Complete cytogenetic data were not available at the clinical cutoff data, and a prospective. DRd: Daratumumab with lenalidomide and dexamethasone

including 13 above VGPR (86%) and 1 PR (7.3%). Median PFS was 39.8 compared to 22 months (95% CI: 11.1–61) for those with versus without a previous history of autologous transplantation ($P = 0.13$).

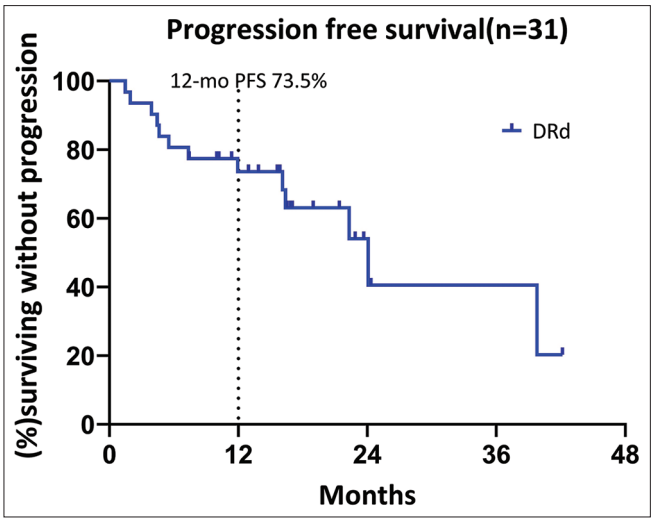

Figure 1: Progression-free survival. Shown are the results of the Kaplan–Meier analysis of progression-free survival. The DRd group received daratumumab, lenalidomide, and dexamethasone. NE denotes could not be estimated

The most prevalent adverse events of any grade were hematological. One thrombocytopenia and one neutropenia developed as Grade 1–2. One (5%) had Grade 5 neutropenic fever. Infusion-related reaction was mild (only one patient developed Grade 2 IRR). No patient discontinued treatment because of an infusion-related reaction. No safety concerns were found in patients with renal failure or previous autologous hematopoietic stem cell transplantation.

Discussion

Despite the small number of our sample and the relatively short follow-up time, our results seem to confirm the registration studies and other real-life experiences. In the POLLUX trial, DARA in combination with lenalidomide led to a deep quality of response and high overall response rate in the RRMM subset. In our study, ORR (96.8%) and CR rate (35.5%) were similar in the POLLUX study (i.e., 92.9 and 43%, respectively), as well as 1-year PFS placing at 73.5% in our study versus 83.2% in the POLLUX trial, respectively. These differences may be largely attributed to baseline patient characteristics, with several comorbidities in our cohort, which included renal impairment at 19% and injury severity score (ISS) score 3, 41.9%. In the POLLUX trial, most of the patient's ISS scores demonstrated at ISS I 47.9%. Moreover, our patients had more high cytogenetic risks than the POLLUX trial, 35.5% versus to 15.4%. We observed, in our cohort, a higher percentage of adverse cytogenetic abnormalities than in the POLLUX study with an expected impact on PFS. Further, we recruited patients who were treated with lenalidomide (19.4%), a category excluded from the POLLUX study by default. Patients who had better disease

Table 3: Baseline disease in the DRd group

	DRd (*n*=31), *n* (%)
Previous therapy	
Proteasome inhibitor	31 (100)
Thalidomide	28 (90.3)
Lenalidomide	6 (19.4)
Alkylating agent	24 (77.4)
ASCT*	16 (51.6)
Refractory disease	
To last line therapy	4 (12.9)
To proteasome inhibitor only	2 (6.5)
To lenalidomide only	1 (3.2)
To Valcade and lenalidomide	0
Line of Daratumumab	
First line	0
Second line	24 (77.4)
More than 2 line	7 (22.6)
Median follow-up time	17.37

*High-dose chemotherapy with melphalan followed by ASCT.
ASCT: Autologous stem cell transplantation, DRd: Daratumumab with lenalidomide and dexamethasone

Table 4: Summary of responses among patients with a response that could be evaluated*

	DRd (*n*=31), *n* (%)
Overall response	
Rate (%)	96.8
Best overall response	
Complete response	11 (35.5)
Very good partial response	9 (29)
Very good partial response or better	20 (64.5)
Partial response	7 (22.6)
Stable disease	0
Progressive disease	1 (3.2)
Response could not evaluate	3 (9.7)
Relapse after stopping daratumumab	5 (27.7)
No relapse after stopping daratumumab	13 (72.2)
Median relapse time after stopping daratumumab (months)	5.88 months

*Response was assessed according to the Uniform Criteria Consensus recommendations of the International Myeloma Working Group.[10,11] The analysis included patients who had a confirmed diagnosis of multiple myeloma and measurable disease at baseline or screening. In addition, patients had to have received at least one administration of trial treatment and must have had at least one disease assessment after the baseline visit.
DRd: Daratumumab with lenalidomide and dexamethasone

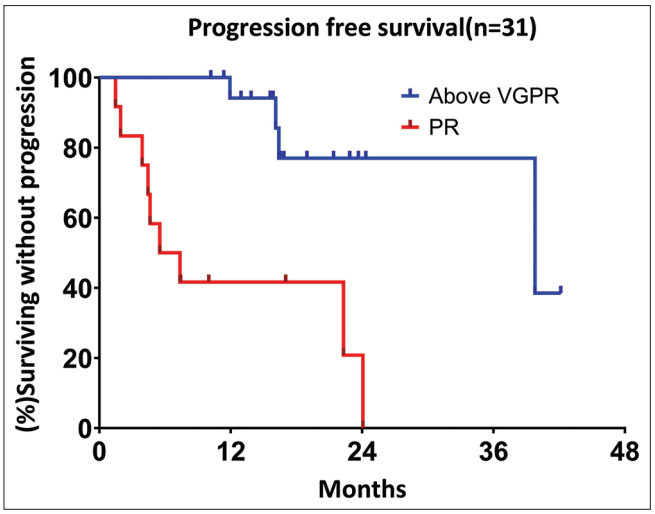

Figure 2: Progression-free survival. Shown are the results of the Kaplan–Meier analysis of progression-free survival. The *P* value is based on a stratified log-rank test. Achievement of above VGPR after daratumumab therapy versus partial response. VGPR: Very good partial response

control that achieving above VGPR had previously received autologous transplants (63.2%). Achievement of a VGPR or better after IT was associated with a superior PFS in patients receiving upfront ASCT in the Intergroup Francophone du Myeloma 2005-01 trial.[12] Transplant trials that use novel agents clearly showed that responses are deepened so that the fraction of patients with CRs and VGPRs increase between the induction phase and the post-ASCT consolidation phase. This sequential increase in deep response rates has been a consistent finding after ASCT.[13] Our time to partial response was around 52.93 days. The median time to achieve at least a PR was 45 days (range: 28–120 days) from the start of therapy in other retrospective studies.[14] We also noted one patient died of neutropenia and infectious complications such as pneumonia. Two of the patients had Grade 2 hematologic adverse effects. Sixteen patients stopped DRd due to run out of the quota from the benefits package from second-generation NHI. Whereas eight patients (25.8%) discontinued the Dara-Rd combination mainly because of disease progression compared to other retrospective studies, 81% of patients stopped DRd due to disease progression and that 10 patients (22%) had died.[14] Only one patient underwent progressive disease at 5 months. Only five patients revealed complete response, two patients VGPR, and one patient showed partial response. Only five patients relapsed after stopping DARA. Median relapse time showed 5.88 months after stopping DARA. According to the previous study, CD38 expression was reduced in both bone marrow-localized and circulating MM cells following the first DARA infusion. CD38 expression levels on MM cells increased again following DARA discontinuation.[15] It is possible that microvesicles loaded with ectoenzymes leading to the production of ADO may trigger long-term responses, even after cessation of antibody treatment. A hypothesis already confirmed in animal models implies that tumors targeted by antibody therapy can induce the patient's immune system to generate an antitumor T-cell memory response.[10] DARA concentrations in serum were not determined after administration of the last infusion. However, interference of DARA in the indirect antiglobulin test, as a result of binding to CD38-positive donor erythrocytes, persisted 2–6 months after the last DARA infusion,[11] indicating that DARA remains present in serum for up to 6 months. In the above theories may explain the relapsed time reveals around ½ year. It seems patients who had received ASCT in the frontline revealed better

survival or gained more benefit from DRd in our study. Based on the CASSIOPEIA study, which showed D-VTd before and after autologous stem cell transplantation improved depth of response and PFS with acceptable safety.[16] In selected heavily pretreated DARA -refractory patients, salvage ASCT indicates that it can lead to long-term MM control.[17] Early studies suggested that lenalidomide therapy impaired stemcell collection and, therefore, and that induction is usually capped at six cycles to prevent prolonged lenalidomide exposure.[18] However, in both MASTER study and GRIFFIN study revealed among those who underwent mobilization and collection, four cycles of DARA and lenalidomide-based quadruplet induction therapy had minimal impact on stem cell mobilization and allowed predictable stem cell harvesting and engraftment in all patients who underwent ASCT.[19] Deep responses, including stringent complete responses, translate into improved overall survival in patients undergoing early autologous stem cell transplantation,[20] supporting its predictive value as a surrogate end point and that DRd followed by autologous transplantation matters. The limitation of this retrospective study is that it did not compare with the Rd regimen, which is the regular standard regimen in second-line treatment in the context of PFS and overall survival and major adverse events. Despite these pitfalls, this is the first study in Taiwan so far addressing the Dara-RD combination outside of the clinical trial setting. Our data state this therapeutic modality to be effective and relatively safe even in a relapsed disease subset.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Kumar SK, Rajkumar SV, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, *et al.* Improved survival in multiple myeloma and the impact of novel therapies. Blood 2008;111:2516-20.
2. Kumar SK, Dispenzieri A, Lacy MQ, Gertz MA, Buadi FK, Pandey S, *et al.* Continued improvement in survival in multiple myeloma: Changes in early mortality and outcomes in older patients. Leukemia 2014;28:1122-8.
3. Moreau P, Touzeau C. Multiple myeloma: From front-line to relapsed therapies. Am Soc Clin Oncol Educ Book 2015:e504-11.
4. Lonial S, Weiss BM, Usmani SZ, Singhal S, Chari A, Bahlis NJ, *et al.* Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): An open-label, randomised, phase 2 trial. Lancet 2016;387:1551-60.
5. Lokhorst HM, Plesner T, Laubach JP, Nahi H, Gimsing P, Hansson M, *et al.* Targeting CD38 with daratumumab monotherapy in multiple myeloma. N Engl J Med 2015;373:1207-19.
6. Palumbo A, Chanan-Khan A, Weisel K, Nooka AK, Masszi T, Beksac M, *et al.* Daratumumab, bortezomib, and dexamethasone for multiple myeloma. N Engl J Med 2016;375:754-66.
7. Rajkumar SV. Updated diagnostic criteria and staging system for multiple myeloma. Am Soc Clin Oncol Educ Book 2016;35:e418-23.
8. Durie BG, Harousseau JL, Miguel JS, Bladé J, Barlogie B, Anderson K, *et al.* International uniform response criteria for multiple myeloma. Leukemia 2006;20:1467-73.
9. Rajkumar SV, Harousseau JL, Durie B, Anderson KC, Dimopoulos M, Kyle R, *et al.* Consensus recommendations for the uniform reporting of clinical trials: Report of the international myeloma workshop consensus panel 1. Blood 2011;117:4691-5.
10. DiLillo DJ, Ravetch JV. Differential Fc-receptor engagement drives an anti-tumor vaccinal effect. Cell 2015;161:1035-45.
11. Oostendorp M, Lammerts van Bueren JJ, Doshi P, Khan I, Ahmadi T, Parren PW, *et al.* When blood transfusion medicine becomes complicated due to interference by monoclonal antibody therapy. Transfusion 2015;55:1555-62.
12. Moreau P, Attal M, Pégourié B, Planche L, Hulin C, Facon T, *et al.* Achievement of VGPR to induction therapy is an important prognostic factor for longer PFS in the IFM 2005-01 trial. Blood 2011;117:3041-4.
13. Siddiqui M, Gertz M. The role of high-dose chemotherapy followed by peripheral blood stem cell transplantation for the treatment of multiple myeloma. Leuk Lymphoma 2008;49:1436-51.
14. Antonioli E, Staderini M, Pilerci S, Perfetto F, Cappelli F, Allinovi M, *et al.* Daratumumab, lenalidomide, and dexamethasone combination in relapsed/refractory myeloma patients: A real-life single-center experience. Leuk Lymphoma 2020;61:3255-8.
15. Nijhof IS, Casneuf T, van Velzen J, van Kessel B, Axel AE, Syed K, *et al.* CD38 expression and complement inhibitors affect response and resistance to daratumumab therapy in myeloma. Blood 2016;128:959-70.
16. Moreau P, Attal M, Hulin C, Arnulf B, Belhadj K, Benboubker L, *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.
17. Yarlagadda L, Gundarlapalli S, Parikh R, Landes RD, Kottarathara M, Ogunsesan Y, *et al.* Salvage autologous stem cell transplantation in daratumumab-refractory multiple myeloma. Cancers (Basel) 2021;13:4019.
18. Bhutani D, Zonder J, Valent J, Tageja N, Ayash L, Deol A, *et al.* Evaluating the effects of lenalidomide induction therapy on peripheral stem cells collection in patients undergoing autologous stem cell transplant for multiple myeloma. Support Care Cancer 2013;21:2437-42.
19. Chhabra S, Callander N, Watts NL, Costa LJ, Thapa B, Kaufman JL, *et al.* Stem cell mobilization yields with daratumumab-and lenalidomide-containing quadruplet induction therapy in newly diagnosed multiple myeloma: Findings from the MASTER and GRIFFIN trials. Transplant Cell Ther 2022;S2666-6367(22)01802-4.
20. Kapoor P, Kumar SK, Dispenzieri A, Lacy MQ, Buadi F, Dingli D, *et al.* Importance of achieving stringent complete response after autologous stem-cell transplantation in multiple myeloma. J Clin Oncol 2013;31:4529-35.