ChinaRxiv

AI translation · View original & related papers at
chinarxiv.org/items/chinaxiv-202212.00163

Postprint of a Real-World Study of Daratumumab-Based Chemotherapy Regimens in Multiple Myeloma

Authors: Wang Jun, Wu Jiafei, Yijing Wang, Zheng Boyue, Wang Yu, Jiang Chuanyan, Li Hui, Li Hui

Date: 2022-12-23T00:00:00+00:00

Abstract

Background Multiple myeloma is a common hematological malignancy. With the emergence of various novel agents, patient survival has improved; however, further investigation is needed to achieve deeper and faster remission and reduce relapse. Objective To investigate the efficacy and safety of daratumumab in the treatment of multiple myeloma. Methods Clinical data were retrospectively analyzed for 73 patients with multiple myeloma (70 cases of multiple myeloma and 3 cases of multiple myeloma with light-chain amyloidosis) who received daratumumab-based therapy at Sichuan Provincial People' s Hospital between January 2020 and July 2022. Results All patients received daratumumab-based regimens (including DVd, DKd, Dd, etc.), with 55 patients evaluable for efficacy. Among them, 41 patients (56.1%) were classified as high-risk by mSMART criteria. Regarding treatment regimens, 31 patients received DVd (daratumumab + bortezomib + dexamethasone), 13 received Dd (daratumumab + dexamethasone), 11 received DRd (daratumumab + lenalidomide + dexamethasone), 5 received DKd (daratumumab + carfilzomib + dexamethasone), 5 received DPd (daratumumab + pomalidomide + dexamethasone), and 8 received other regimens. After one course of daratumumab-based therapy, the overall response rate (ORR) was 72.7% [complete response (CR) rate 30.9%], with a median follow-up of 6.5 months (0.5–26.5 months), progression-free survival (PFS) of 6 (0.5–26.5) months, and median overall survival (OS) of 16 (3–103) months. For patients receiving daratumumab as first-line therapy, the ORR was 90.0% [CR rate 35.0%], while for relapsed/refractory patients, the ORR was 58.3% [CR rate 25%]. Renal impairment was present at initial diagnosis in 31 patients (42.5%); following daratumumab treatment, renal function improved in 20 patients (83.3%), with complete renal recovery in 7 patients (29.1%). The main adverse events following daratumumab administration were myelosuppression,

infusion-related reactions, and infections. Conclusion Daratumumab-based regimens demonstrate favorable efficacy and safety in the treatment of multiple myeloma.

Full Text

Daratumumab-Based Chemotherapy Regimens for Multiple Myeloma: A Real-World Study

Jun Wang[1], Jiafei Wu[2], Yijing Wang[3], Boyue Zheng[2], Yu Wang[3], Chuanyan Jiang[4], Hui Li[2],[3]*

[1]School of Clinical Medicine, Chengdu Medical College, Chengdu, 610500, China
[2]School of Clinical Medicine, University of Electronic Science and Technology of China, Chengdu, 610056, China
[3]Department of Hematology, Sichuan Academy of Medical Science and Sichuan Provincial People' s Hospital, Chengdu, 610000, China
[4]Department of Hematology, Chengdu Second People' s Hospital, Chengdu, 610000, China

Corresponding author: Hui Li, Deputy Director, Department of Hematology, Sichuan Provincial People' s Hospital, M.D.; E-mail: lihui606606@163.com

---

Abstract

Background: Multiple myeloma is a common hematologic malignancy. While the emergence of novel agents has improved patient survival, achieving deeper and faster remission while reducing relapse remains a critical challenge requiring further investigation.

Objective: To investigate the efficacy and safety of daratumumab-based regimens in the treatment of multiple myeloma.

Methods: We retrospectively analyzed clinical data from 73 patients with multiple myeloma (70 with multiple myeloma and 3 with multiple myeloma complicated by light-chain amyloidosis) who received daratumumab treatment at Sichuan Provincial People' s Hospital between January 2020 and July 2022.

Results: All patients received daratumumab-based regimens (including DVd, DKd, Dd, etc.), with 55 patients evaluable for efficacy. Among them, 41 patients (56.1%) were classified as high-risk by mSMART criteria. Chemotherapy regimens included: DVd (daratumumab + bortezomib + dexamethasone) in 31 patients, Dd (daratumumab + dexamethasone) in 13 patients, DRd (daratumumab + lenalidomide + dexamethasone) in 11 patients, DKd (daratumumab + carfilzomib + dexamethasone) in 5 patients, DPd (daratumumab + pomalidomide + dexamethasone) in 5 patients, and other regimens in 8 patients. After

one cycle of daratumumab-based therapy, the overall response rate (ORR) was 72.7% [complete response (CR) rate 30.9%]. The median follow-up duration was 6.5 months (range 0.5–26.5 months), median progression-free survival (PFS) was 6 months (range 0.5–26.5), and median overall survival (OS) was 16 months (range 3–103). For patients receiving daratumumab as first-line therapy, ORR was 90.0% [CR rate 35.0%], while for relapsed/refractory patients, ORR was 58.3% [CR rate 25%]. Renal impairment was present at diagnosis in 31 patients (42.5%), with 20 patients (83.3%) showing improved renal function after daratumumab treatment, including 7 patients (29.1%) with complete renal recovery. The main adverse events were myelosuppression, infusion-related reactions, and infections.

Conclusion: Daratumumab-based regimens demonstrate favorable efficacy and safety in the treatment of multiple myeloma.

Keywords: Multiple myeloma; Daratumumab; Renal insufficiency; Treatment

---

Introduction

Multiple myeloma (MM) is a common malignant clonal plasma cell disorder, accounting for approximately 10% of hematologic malignancies [1]. In China, the average age of MM patients is 57.9 years, with peak incidence occurring between 55–74 years in both sexes, and the national incidence rate is 1.15 per 100,000 [2]. While the advent of novel agents has substantially improved disease remission rates and long-term survival, MM remains incurable, with nearly all patients inevitably developing drug resistance or relapse, ultimately leading to death. The 2020 multiple myeloma guidelines first incorporated daratumumab into treatment recommendations. However, large-scale real-world data on daratumumab in MM patients remain limited. This study presents a retrospective analysis of daratumumab use in MM patients at our center to inform clinical practice.

1. Methods

1.1 Disease Definition Diagnosis was established according to the NCCN and IMWG guidelines [3] and the Chinese Multiple Myeloma Diagnosis and Treatment Guidelines (2022 revision) [4]. Disease staging was performed using the Revised International Staging System (R-ISS) based on the Durie-Salmon staging system [5,6] and the Mayo mSMART criteria.

1.2 Patient Inclusion We retrospectively analyzed clinical data from 73 patients with multiple myeloma (70 with MM and 3 with MM complicated by light-chain amyloidosis) who received daratumumab at Sichuan Provincial People' s Hospital between January 2020 and July 2022. All patients provided informed consent, and the study was approved by the hospital ethics committee. Baseline data collected included: complete blood count, blood biochem-

istry, immunoglobulin levels, immunofixation electrophoresis, serum protein electrophoresis, skeletal survey, bone marrow cytology, flow cytometry, bone marrow biopsy, molecular genetics (FISH on CD138-sorted cells, chromosome analysis), cardiac function (BNP, echocardiographic EF), hepatitis B/C screening, and T-cell subsets and cytokine monitoring in 60 patients.

1.3 Treatment Methods All patients received daratumumab-based regimens (including DVd, DKd, Dd, etc.). Specifically: 31 patients received DVd (daratumumab + bortezomib + dexamethasone), 13 received Dd (daratumumab + dexamethasone), 11 received DRd (daratumumab + lenalidomide + dexamethasone), 5 received DKd (daratumumab + carfilzomib + dexamethasone), 5 received DPd (daratumumab + pomalidomide + dexamethasone), 3 received DRBd (daratumumab + lenalidomide + bortezomib + dexamethasone), 1 received BDCVd (daratumumab + bortezomib + cyclophosphamide + vincristine + dexamethasone), 1 received DBCd (daratumumab + bortezomib + cyclophosphamide + dexamethasone), 1 received DKRd (daratumumab + carfilzomib + lenalidomide + dexamethasone), 1 received DRBd (daratumumab + lenalidomide + bortezomib + dexamethasone), and 1 received DTD (daratumumab + thalidomide + dexamethasone). Daratumumab was administered intravenously at 16 mg/m^2 every 28 days, weekly for the first 3 cycles, then every 2 weeks from cycle 4 to 8, and monthly thereafter starting from cycle 9. Premedication included intramuscular promethazine 25 mg and intravenous dexamethasone 10 mg prior to daratumumab infusion.

1.4 Efficacy Evaluation and Adverse Events Efficacy was assessed according to the Chinese Multiple Myeloma Diagnosis and Treatment Guidelines (2022 revision) [4], with response categories including complete response (CR), very good partial response (VGPR), partial response (PR), minimal response (MR), stable disease (SD), and progressive disease (PD). Overall response rate (ORR) was defined as the sum of CR, VGPR, and PR rates. Patients were followed through outpatient visits, hospitalizations, and telephone interviews until July 31, 2022. Median follow-up duration was 6.5 months (range 0.5-26.5). Progression-free survival (PFS) was defined as the interval from daratumumab initiation to disease progression or death. Overall survival (OS) was defined as the interval from diagnosis to last follow-up or death. Adverse events were graded according to NCI CTCAE version 5.0.

1.5 Statistical Analysis Data were analyzed using GraphPad Prism 9.3 software. Descriptive statistics were applied, and survival analysis was performed using the Kaplan-Meier method. $P < 0.05$ was considered statistically significant.

2. Results

2.1 Patient Baseline Characteristics A total of 73 patients (70 with MM and 3 with MM and light-chain amyloidosis) were included. Renal impairment

was present in 31 patients (42.4%) at diagnosis, with 7 already requiring dialysis. High-risk cytogenetics were identified in 30 patients (41.1%) at diagnosis, most commonly 1q21 amplification. Among the cohort, 28 patients (38.3%) received daratumumab as first-line therapy for newly diagnosed MM, 13 (17.8%) switched to daratumumab from other regimens, and 32 (43.8%) had relapsed/refractory MM (RRMM).

Table 1 Baseline Patient Characteristics

Characteristic	N (%)
Multiple myeloma	70 (95.9%)
With amyloidosis	3 (4.1%)
Age (years), median (range)	64 (30–86)
Anemia	38 (52.0%)
Renal dysfunction	35 (47.9%)
Hypercalcemia	61 (83.6%)
ISS-R Stage III	31 (42.4%)
High-risk cytogenetics	13 (17.8%)
Relapsed/refractory	32 (43.8%)
M protein type	
IgA	12 (16.4%)
IgG	16 (21.9%)
IgD	45 (61.6%)
Light chain	30 (41.1%)
Biclonal	12 (16.4%)
Non-secretory	33 (45.2%)

Note: Anemia: hemoglobin < 110 g/L; Renal dysfunction: creatinine > 104 mol/L; Hypercalcemia: serum calcium > 2.65 mmol/L. Definitions of relapsed/refractory disease, ISS-R staging, and high-risk cytogenetics follow the Chinese Multiple Myeloma Diagnosis and Treatment Guidelines (2022 revision) [4] and Interpretation of Relapsed/Refractory Multiple Myeloma Treatment [7].

2.2 Efficacy

2.2.1 Overall Efficacy Of 73 enrolled patients, 55 were evaluable for efficacy. After one cycle of daratumumab-based therapy, ORR was 72.7% [CR rate 30.9%], including 2 patients (3.6%) with stringent CR (sCR), 15 (27.3%) with CR, 6 (10.9%) with VGPR, 17 (30.9%) with PR, 5 (9.1%) with MR, 7 (12.7%) with SD, and 3 (5.5%) with PD. Median follow-up was 6.5 months (range 0.5–26.5), median PFS was 6 months (range 0.5–26.5), and median OS was 16 months (range 3–103).

2.2.2 Comparison Between First-Line and Relapsed/Refractory Patients Among 28 patients receiving first-line daratumumab, 10 were evaluable, with ORR of 90.0% [CR rate 35.0%], including 1 (5.0%) sCR, 6 (30.0%) CR, 2 (10.0%) VGPR, 9 (45.0%) PR, 1 (5.0%) MR, and 1 (5.0%) PD. Among 32 relapsed/refractory patients, 24 were evaluable, with ORR of 58.3% [CR rate 25%]. Survival curve analysis comparing first-line and relapsed/refractory groups showed $p = 0.055$, indicating no significant difference, suggesting daratumumab improves outcomes in relapsed/refractory patients [Figure 1: see original paper].

2.2.3 Renal Function Improvement Renal impairment was present at diagnosis in 31 patients (42.5%), including 7 (9.6%) on dialysis. After daratumumab treatment, 20 patients (83.3%) showed renal function improvement, with 7 (29.1%) achieving complete recovery, 7 (29.1%) showing >50% improvement, and 4 (16.7%) experiencing deterioration. Survival analysis comparing patients with and without baseline renal dysfunction showed $p = 0.0004$, indicating significantly worse prognosis in the renal impairment group [Figure 2: see original paper].

2.2.4 Comparison of Combination Regimens Given the diversity of combination therapies, we compared the three most commonly used regimens: DVd (n=31), Dd (n=13), and DRd (n=11). Survival analysis revealed $P < 0.05$ between DVd and Dd groups, indicating superior efficacy with DVd. Comparison between DRd and Dd ($P = 0.041$) and between DVd and DRd ($P = 0.5514$) showed no significant differences [Figure 3: see original paper].

2.2.5 High-Risk Cytogenetics Analysis Survival analysis based on mSMART high-risk stratification showed $p = 0.566$, indicating no significant difference, possibly due to insufficient follow-up duration in some patients [Figure 4: see original paper].

2.2.6 Analysis by M Protein Type Survival analysis by M protein type (IgA, IgG, IgD, light chain, biclonal, non-secretory) showed no significant differences between groups (all $P > 0.05$). However, biclonal and light-chain types demonstrated notably lower survival rates, suggesting a potential trend [Figure 5: see original paper].

2.3 Adverse Event Evaluation The main adverse events following daratumumab infusion were infusion reactions and myelosuppression. Most infusion reactions occurred during the first administration and were manageable by adjusting infusion rate and administering promethazine and dexamethasone. Myelosuppression was limited to grade $ $3 and resolved with granulocyte colony-stimulating factor and recombinant human interleukin-11.

3. Discussion

The widespread use of proteasome inhibitors, immunomodulatory drugs, and autologous stem cell transplantation has substantially improved survival in multiple myeloma [8,9]. However, nearly all patients eventually develop relapse and drug resistance, with each subsequent relapse yielding lower remission depth and shorter duration. Treatment efficacy diminishes with each relapse, posing greater challenges for heavily pretreated patients [10]. Therefore, achieving rapid and durable remission in newly diagnosed patients while safely and effectively re-inducing remission in RRMM patients represents an urgent clinical priority.

CD38 is expressed at relatively low levels on normal lymphoid and myeloid cells and some non-hematopoietic tissues but is highly expressed on MM cells. Daratumumab is a fully human anti-CD38 IgG monoclonal antibody that induces MM cell lysis through cytotoxic effects and immune microenvironment modulation by specifically binding CD38 epitopes on MM cells [11,12]. In modulating the immune microenvironment, daratumumab affects CD38 enzymatic activity, activates CD8+ and CD4+ T cells, alters T-cell ratios, and promotes MM cell death [13]. In our center, T-cell subsets and cytokines were monitored in 60 patients, with follow-up data available for 30 patients showing increased CD4+ cells in 12 (40%) and increased CD8+ cells in 18 (60%). Among 21 patients with NK cell follow-up, 12 (57.1%) showed decreased NK cell activity. Domenico Viola et al. [14] reported that daratumumab induces rapid degradation of CD38 protein associated with NK cell activation, leaving an activated CD38-negative NK cell population. Additionally, daratumumab targets CD38+ NK cells to promote monocyte activation, increase T-cell costimulatory molecules, and enhance anti-myeloma phagocytic activity in vitro and in vivo.

Compared with historical regimens, daratumumab-containing regimens have demonstrated superior response rates and longer survival in pivotal clinical trials for both newly diagnosed and relapsed/refractory MM [15-17]. In our study, daratumumab-based regimens achieved an ORR of 72.7% [CR rate 30.9%] after one cycle, confirming the efficacy of daratumumab alone or combined with proteasome inhibitors and immunomodulatory agents. However, our CR and ORR rates were lower than those reported in pivotal trials such as CASTOR [17] and POLLUX [18], likely reflecting real-world patient populations with poorer performance status, advanced age, multiple comorbidities, and inconsistent treatment adherence due to financial constraints.

Renal impairment occurs in 20-40% of MM patients, primarily due to monoclonal light-chain toxicity [19]. Approximately 25% of patients with normal renal function at diagnosis develop renal involvement during disease progression, and MM patients with renal dysfunction have inferior OS and higher early mortality risk [20]. Our analysis confirmed worse prognosis in patients with baseline renal dysfunction. However, 83.3% of renal impairment patients showed improved renal function after daratumumab, with 29.1% achieving complete recovery, con-

sistent with the MAIA study [16] and suggesting that daratumumab-containing regimens reduce disease progression and mortality risk in renally impaired patients.

Comparison of the three most common regimens (DVd, Dd, DRd) showed superior efficacy of DVd versus Dd ($P < 0.05$). This may be attributed to our Dd cohort comprising mostly elderly patients with multiple comorbidities and poorer baseline status. Nevertheless, most frail patients tolerated daratumumab plus dexamethasone, suggesting acceptable toxicity. No significant differences were observed between DRd versus Dd or DVd versus DRd, indicating that adding daratumumab improves outcomes across regimens, though larger cohorts and longer follow-up are needed for definitive comparisons. Studies have shown promising efficacy of daratumumab plus lenalidomide [21], and phase 3 data from Meletios Dimopoulos et al. [22] demonstrated favorable outcomes with carfilzomib plus daratumumab in RRMM. Six RRMM patients in our center received daratumumab plus carfilzomib, with ongoing follow-up.

Although our cohort was large, heterogeneous group sizes and insufficient follow-up may have impacted prognostic analyses. Extended follow-up is planned to determine optimal treatment strategies for newly diagnosed and RRMM patients.

In conclusion, real-world data from our center demonstrate that daratumumab is highly effective in MM patients, suitable as first-line therapy for newly diagnosed patients, and capable of improving outcomes in relapsed/refractory patients. Daratumumab achieves high response rates, prolongs survival, improves renal function, and enhances overall prognosis.

Author Contributions: Jun Wang: data collection, data analysis, manuscript writing; Jiafei Wu: data collection, data analysis; Yijing Wang, Boyue Zheng, Yu Wang, Chuanyan Jiang: data collection, patient follow-up; Hui Li: conceptualization, review and revision.

Conflict of Interest: The authors declare no conflicts of interest.

References

[1] FIRTH J. Haematology: multiple myeloma [J]. Clinical Medicine, 2019, 19(1): 58-60.

[2] WANG S, XU L, FENG J, et al. Prevalence and Incidence of Multiple Myeloma in Urban Area in China: A National Population-Based Analysis [J]. Frontiers Oncology, 2020, 9.

[3] RAJKUMAR S V, POWLES R, MERLINI G, et al. International Myeloma Working Group Recommendations for the Diagnosis and Management of Myeloma-Related Renal Impairment [J]. 2013.

[4] 中国医师协会血液科医师分会, 中华医学会血液学分会. 中国多发性骨髓瘤诊治指南（2022 年修订）[J]. 中华内科杂志, 2022, (05): 480-7.

[5] DURIE B G M, SALMON S E. A clinical staging system for multiple myeloma. Correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival [J]. Cancer, 1975, 36(3): 842-54.

[6] PALUMBO A. Revised International Staging System for Multiple Myeloma: A Report From International Myeloma Working Group [J]. Journal of Clinical Oncology, 2015, 33(26): 2863-9.

[7] 蔡真, 陈文明. 复发难治性多发性骨髓瘤治疗解读 [J]. 中华内科杂志, 2022, (05): 469-73.

[8] RAJKUMAR S V. Multiple myeloma: Every year a new standard? [J]. Hematological Oncology, 2019, 37(S1): 62-5.

[9] COWAN A J, GREEN D J, KWOK M, et al. Diagnosis and Management of Multiple Myeloma: A Review [J]. the American Medical Association, 2022, 327(5): 464-77.

[10] BAZARBACHI A H, AL HAMED R, MALARD F, et al. Relapsed refractory multiple myeloma: a comprehensive overview [J]. Leukemia, 2019, 33(10): 2343-57.

[11] HASHMI H, HUSNAIN M, KHAN A, et al. Cd38-directed therapies for management of multiple myeloma [J]. ImmunoTargets and Therapy, 2021, 10: 201-11.

[12] DE WEERS M, TAI Y T, VAN DER VEER M S, et al. Daratumumab, a novel therapeutic human CD38 monoclonal antibody, induces killing of multiple myeloma and other hematological tumors [J]. Journal Immunology, 2011, 186(3): 1840-8.

[13] KREJCIK J, CASNEUF T, NIJHOF I S, et al. Daratumumab depletes CD38+immune regulatory cells, promotes T-cell expansion, and skews T-cell repertoire in multiple myeloma [J]. Blood, 2016, 128(3): 384-.

[14] VIOLA D, DONA A, CASERTA E, et al. Daratumumab induces mechanisms of immune activation through CD38+ NK cell targeting [J]. Leukemia, 2021, 35(1): 189-200.

[15] MATEOS M V, CAVO M, BLADE J, et al. Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): a randomised, open-label, phase 3 trial [J]. The Lancet, 2020, 395(10218): 132-41.

[16] BAHLIS N, FACON T, USMANI S Z, et al. Daratumumab Plus Lenalidomide and Dexamethasone (D-Rd) Versus Lenalidomide and Dexamethasone (Rd) in Patients with Newly Diagnosed Multiple Myeloma (NDMM) Ineligible for Transplant: Updated Analysis of Maia [J]. Blood, 2019, 134: 1875.

[17] WEISEL K C, SONNEVELD P, MATEOS M V, et al. Efficacy and Safety of Daratumumab, Bortezomib, and Dexamethasone (D-Vd) Versus Bortezomib and Dexamethasone (Vd) in First Relapse Patients (pts) with Multiple Myeloma (MM): Four-Year Update of Castor [J]. Blood, 2019, 134: 3192.

[18] KAUFMAN J L, USMANI S Z, SAN-MIGUEL J, et al. Four-Year Follow-up of the Phase 3 Pollux Study of Daratumumab Plus Lenalidomide and Dexamethasone (D-Rd) Versus Lenalidomide and Dexamethasone (Rd) Alone in Relapsed or Refractory Multiple Myeloma (RRMM) [M]. John Wiley & Sons, Ltd.

[19] BOZIC B, RUTNER J, ZHENG C, et al. Advances in the treatment of relapsed and refractory multiple myeloma in patients with renal insufficiency: Novel agents, immunotherapies and beyond [J]. Cancers, 2021, 13(20).

[20] FOTIOU D, DIMOPOULOS M A, KASTRITIS E. Managing renal complications in multiple myeloma [J]. Expert Review of Hematology, 2016, 9(9): 839-50.

[21] FACON T, KUMAR S K, PLESNER T, et al. Daratumumab, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone alone in newly diagnosed multiple myeloma (MAIA): overall survival results from a randomised, open-label, phase 3 trial [J]. The Lancet Oncology, 2021, 22(11): 1582-96.

[22] DIMOPOULOS M, QUACH H, MATEOS M V, et al. Carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone for patients with relapsed or refractory multiple myeloma (CANDOR): results from a randomised, multicentre, open-label, phase 3 study [J]. The Lancet, 2020, 396(10245): 186-97.

Note: Figure translations are in progress. See original paper for figures.

Source: ChinaXiv —Machine translation. Verify with original.