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– ORIGINAL PAPERS –

DRD vs. D-VCD in Newly Diagnosed AL Amyloidosis: A Retrospective Single-Center Study

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Abstract

Aim: *This study evaluates hematologic responses in AL amyloidosis patients receiving first-line Daratumumab therapy with two regimens: D-VCD and DRD. DRD was preferred for patients with severe neurological involvement and those diagnosed before January 2023, when D-VCD was reimbursed in Romania.*

Methods: *Between January 2021 and December 2023, 38 patients were treated with Daratumumab at Fundeni Clinical Institute, Romania: 23 with D-VCD and 15 with DRD.*

Results: *The median age at diagnosis was 61.5 years. 65% of patients had ≥3 organ involvement. At 2 months, 88.2% of D-VCD patients reached ≥VGPR vs. 33.3% of DRD patients (p=0.010). In the DRD group, 55.5% and 75% reached ≥VGPR at 6 and 12 months, respectively. Six patients underwent ASCT, all in the D-VCD group, and have maintained ≥VGPR. No significant survival differences were noted between groups.*

Conclusions: *DRD achieves significant hematologic responses at 6 and 12 months and may be a suitable first-line option for patients with severe neurological involvement.*

Keywords: *DRD, D-VCD, AL Amyloidosis, ≥VGPR, ASCT*

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Introduction

Light chain amyloidosis (AL) is an incurable clonal plasma cell disorder with an incidence of 5 to 12 persons per million per year characterized by the deposition of immunoglobulin light chains in tissues, leading to organ dysfunction. [1]

The choice of treatment regimen is crucial in achieving hematologic responses and improving patient outcomes. Early diagnosis is crucial to prevent irreversible damage.

Treatment is tailored based on risk assessment, especially cardiac biomarkers, with therapies such as proteasome inhibitors, immunomodulatory drugs, high-dose chemotherapy, and stem cell transplantation showing effective suppression of amyloid production.[2], [3]
Daratumumab, a monoclonal antibody targeting CD38 on plasma cells, has recently been introduced as part of first-line therapy for systemic light chain amyloidosis. Its use in combination with other agents, such as cyclophosphamide, bortezomib, and dexamethasone (CyBorD), has shown promising results, improving hematologic and organ responses in patients with AL amyloidosis.[4], [5] The addition of daratumumab has been shown to accelerate the reduction of amyloidogenic light chains, which is critical for preventing organ damage, particularly in patients with cardiac or renal involvement. Its efficacy, as demonstrated in the phase-3 ANDROMEDA trial, positions daratumumab as a key component in the treatment of newly diagnosed AL amyloidosis, offering significant clinical benefits and improving survival outcomes.[4]

Objective:

This retrospective, single-center study aims to evaluate hematologic responses in patients receiving first-line Daratumumab-based therapy, comparing two regimens: Daratumumab-Bortezomib-Cyclophosphamide-Dexamethasone (D-VCD) and Daratumumab-Lenalidomide-Dexamethasone (DRD). The DRD regimen was preferentially administered to patients with severe neurological involvement and those diagnosed before January 2023 when D-VCD was introduced in Romania.

Methods

Between January 2021 and December 2023, 53 patients were diagnosed with AL amyloidosis at the Fundeni Clinical Institute, Romania. Among them, 38 patients underwent Daratumumab therapy and were divided into two subgroups: 23 patients received the D-VCD protocol, while 15 patients received the DRD protocol (Figure 1). The hematologic response was assessed at 2, 6 and 12 months using very good partial response (VGPR) or better as the endpoint.
The Mayo Cardiac Staging System was used for stratification. Furthermore, stage III patients were divided into 2 groups based on whether amino-terminal pronatriuretic peptide type-B (NT-proBNP) was below (stage IIIa) or above (stage IIIb) 8500 ng/L, which indicates very poor prognosis.
Hematologic responses were assessed according to the International Society of Amyloidosis criteria.
Clinical data included age at the time of AL diagnosis and disease characteristics, including median onset to diagnostic and median follow-up period. The data also covered organ involvement and hematologic response at 2,6 and 12 months.

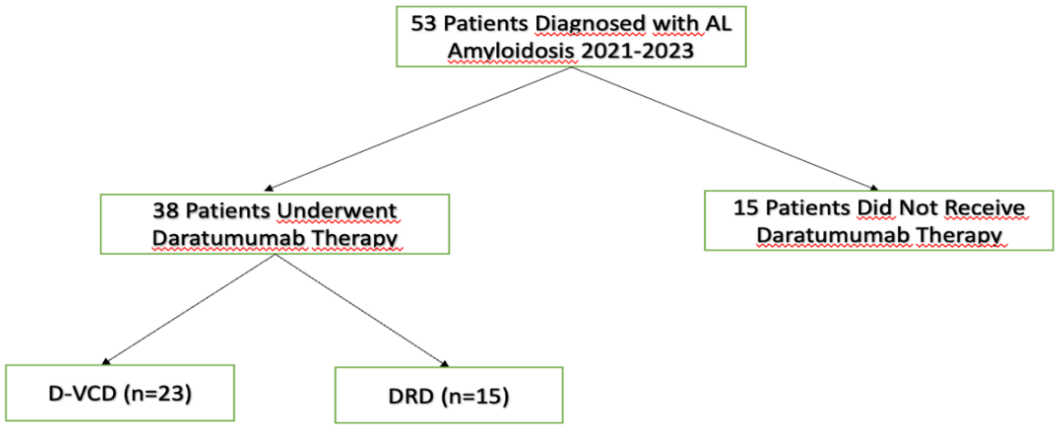

Figure 1. *Patient treatment history of the study group*

Results

Cohort characteristics

The median age at diagnosis was 61.5 years (range, 44–77), with 25 patients (65%) presenting with ≥3 organ involvement. Cardiac involvement was noted in 21 patients (55%). All patients with severe neurological involvement (n=5, 33.3%) were treated with the DRD regimen (Table 1).

Analysis of patient characteristics in Table 1 reveals notable differences between the two treatment groups. The DRD cohort had a higher median age (63.7 vs. 59.6 years) and a longer follow-up period (18.8 vs. 8.9 months).

The percentage of patients with cardiac involvement was higher in the DRD group (73.3% vs. 43.5%), as was the incidence of peripheral nervous system involvement (60% vs. 26.1%) and severe neuropathy (33.3% vs. 0%), reinforcing the rationale for selecting DRD for those with significant neurological manifestations. Moreover, while renal involvement was more frequent in the D-VCD group (73.9% vs. 60%), the DRD group had a higher percentage of patients with multi-organ involvement (73.3% vs. 60.9%).

Patient characteristics	**D-VCD (n=23)**	**DRD (n=15)**
Median age at diagnosis (years)	59.6	63.7
Gender, M:F	0.53	2
Median onset-to-diagnosis duration (months)	11.8	13.2
Median follow-up period (months)	8.9	18.8
Light chain isotype lambda	73.9%	86.7 %
Cardiac involvement	10 (43.5%)	11 (73.3%)
MAYO 2004		
• I	5 (45.5%)	1 (12.5%)
• II	0 (0%)	2 (25%)
• IIIA	1 (9%)	2 (25%)
• IIIB	5 (45.5%)	3 (37.5%)
Renal involvement	17 (73.9%)	9 (60%)
Peripheral nervous system involvement	6 (26.1%)	9 (60%)
Severe neuropathy (grade II / III)	0 (0%)	5 (33.3%)
≥3 organ involvement	14 (60.9%)	11 (73.3%)
Hematologic response ≥VGPR		
• ≥VGPR at 2 months	88.2%	33.3%
• ≥VGPR at 6 months	90.9%	55.5%
• ≥VGPR at 12 months	-	75%

***Table 1**. Patient characteristics in the study group*

Treatment details

At 2 months, 88.2% of patients in the D-VCD group achieved ≥VGPR, whereas only 33.3% of patients in the DRD group reached this threshold (p=0.010, Chi2 test). However, the hematologic response in the DRD group improved over time, with 55.5% and 75% achieving ≥VGPR at 6 and 12 months, respectively. Six patients (15.7%) underwent autologous stem cell transplantation (ASCT), all from the D-VCD cohort, maintaining ≥VGPR status post-transplant. Median survival was not reached in either group, and no statistically significant differences in survival outcomes were observed.

Outcomes

The median survival for both groups has not been reached in either treatment arm (Figure 2). Figure 3 compares survival between the D-VCD and DRD groups, showing a trend toward better early survival in the DRD cohort, but this result is not significant due to the longer follow-up period in the DRD group.

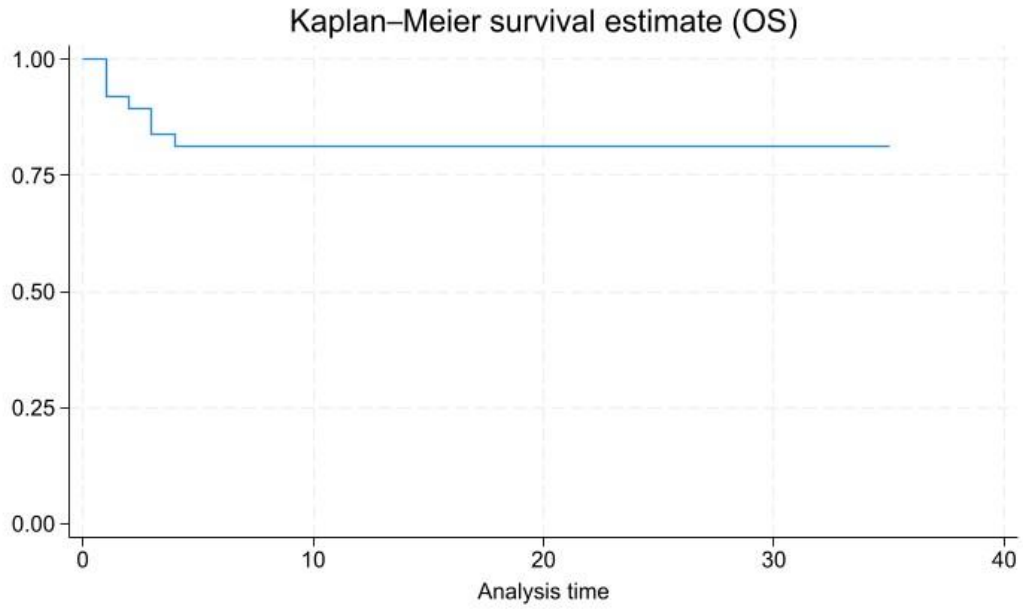

Figure 2. *Median survival of the study group*

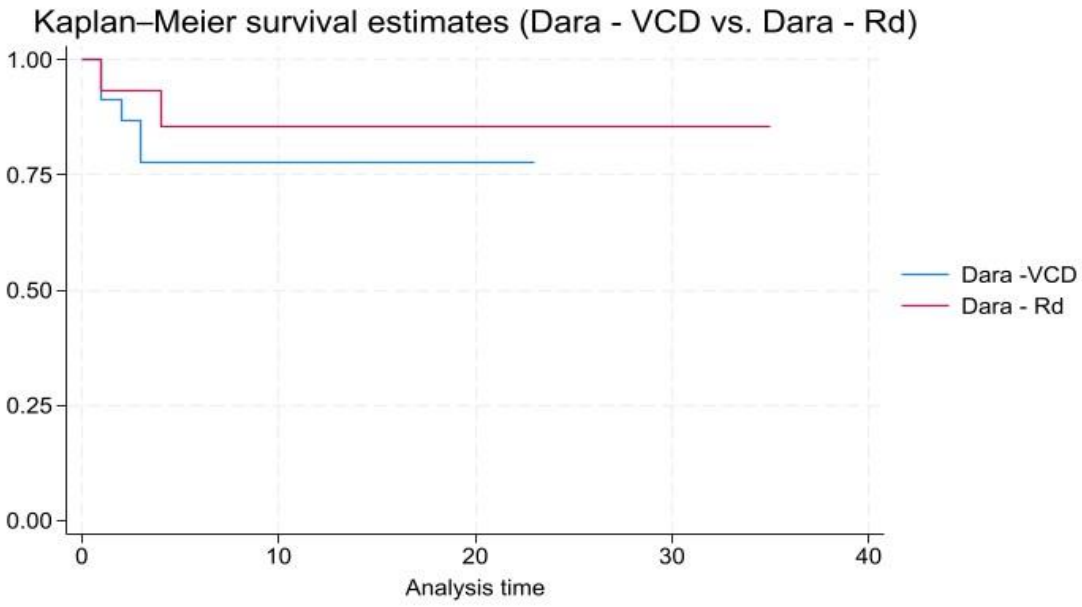

Figure 2. *Estimated median survival of the study group based on treatment*

Discussions

The results of this study indicate that while the D-CyBorD regimen demonstrates efficacy in achieving a deep hematologic response, the DRD regimen proved particularly effective in patients with severe neurological involvement, showing substantial improvements in hematologic response over time, especially at 6 and 12 months. Despite a lower initial response rate at 2 months (33.3%), 55.5% of patients on DRD achieved ≥VGPR at 6 months, and 75% reached this response at 12 months.

These findings are consistent with the phase III ANDROMEDA trial (NCT03201965), which evaluated

daratumumab as part of the first-line treatment regimen for AL amyloidosis. In this trial, adding subcutaneous daratumumab to CyBorD resulted in a 96% hematologic response rate, with 82% of patients achieving VGPR or better, and a median time to response of only 9 days for hematologic and 19 days for deep responses.[4] The ANDROMEDA trial also showed that D-CyBorD led to superior outcomes compared to CyBorD alone, with significantly higher response rates (92% vs. 77%) and better cardiac (42% vs. 22%) and renal (54% vs. 27%) responses.[4] Additionally, the trial demonstrated that the inclusion of daratumumab in the regimen improved major organ deterioration progression-free survival (MOD PFS), which is crucial in preventing irreversible organ damage in AL amyloidosis patients.[4]

In our study, D-VCD demonstrated higher initial hematologic response rates at 2 months (88.2% vs. 33.3%). However, the DRD group showed substantial improvements in hematologic responses over time, with 55.5% and 75% achieving ≥VGPR at 6 and 12 months, respectively. This long-term progression suggests that DRD may still be an effective regimen for patients with severe neurological involvement, who were preferentially selected for DRD in this study.

Furthermore, a retrospective cohort study on the use of DRD in newly diagnosed multiple myeloma patients with systemic AL amyloidosis also supports the efficacy of DRD. This study reported a high hematologic response (90%) and 50% achieving VGPR or better after a median follow-up of 11.5 months. The overall survival rate at 24 months was estimated to be 80%. DRD was well-tolerated, with limited toxicity, making it a viable treatment option, especially for patients who are ineligible for ASCT due to age or organ dysfunction.[6]

Another retrospective study evaluating DRD starting from the second-line treatment in 44 AL amyloidosis patients showed an ORR of 84% at 3 months and 82% at 6 months, with DRD used as second-line in 27 patients, third-line in 11, and fourth-line in 6.[7] The median hematologic event-free survival was 17.4 months, and overall survival was 29.1 months, though patients with gain 1q21 had significantly worse outcomes.[7]

Conclusion

In our study, while D-VCD demonstrated higher initial hematologic response rates at 2 months (88.2% vs. 33.3%), the long-term improvement seen in the DRD group, particularly for patients with significant neurological involvement, suggests that DRD may be a viable alternative for such cases. Importantly, the lack of significant differences in survival outcomes between the two groups, despite the longer follow-up in the DRD cohort, underscores the need for further studies with longer follow-up periods to better evaluate the long-term survival benefit and potential complications.

Conflicts of interest

"This research did not receive any grant from agencies in the public, commercial, or not-for-profit sectors.

None of the authors has any conflict of interest.

The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national laws. Informed consent was obtained from all the patients included in the study."

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