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TIMING AND OUTCOMES OF SECOND-LINE THERAPY IN THE ERA OF DARATUMUMAB-BASED FRONTLINE THERAPY IN AL AMYLOIDOSIS

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INTRODUCTION

Dara-VCd has become the standard of care for newly diagnosed AL amyloidosis since the ANDROMEDA trial. No current therapies are approved in the 2nd line setting, and the proportion of patients requiring subsequent therapies and their outcomes have not been investigated in the era of frontline Dara-VCd.

AIM

In this study, our aim was to report the real-world outcomes of patients who were treated with up-front daratumumab-based therapy and subsequently required a 2nd LoT.

METHOD

Study Design and Data Collection

- Single-center retrospective cohort study
- All consecutive patients with newly diagnosed AL amyloidosis treated with a frontline daratumumab-based regimen 01/2018-12/2023.

Definitions

- Biopsy-proven amyloidosis by immunohistochemistry, immunofluorescence microscopy, or mass spectrometry.
- Disease staging per modified 2004 & 2012 Mayo Clinic staging systems, and renal staging per proposed criteria by Palladini et al.[1]
- Cardiac, renal, and liver responses assessed using validated criteria.[1,2,3]
- Daratumumab-based combinations defined as any treatment regimen containing daratumumab but not venetoclax. When both drugs used, regimen labelled as venetoclax-based.

Endpoints

- TTNT defined as the time from diagnosis to initiation of 2nd LoT.
- EFS2 after 2nd LoT was defined as the time to either death or 3rd LoT initiation.

RESULTS

Response to 1st LoT (Median follow-up 22.3m)

Evaluable hematologic response: 84. CR (n=39, 46.4%), low-dFLC-PR (n=3, 3.6%), VGPR (n=18, 21.4%), PR (n=11, 13.1%), NR (n=13, 15.5%). Cardiac response (n=34/66, 51.5%), renal response (n=18/29, 62.1%), liver response (n=5/11, 45.5%).

Response to 2nd LoT (n=34) (Median follow-up 17.8m)

Ven-based (18, 52.9%), dara-based (11, 32.4%), ASCT (4, 11.8%), bendamustine-dex (1, 2.9%). CR (15, 45.5%), low-dFLC-PR (1, 3%), VGPR (6, 18.2%), PR (1, 3%), NR (10, 30.3%). Cardiac response (11/21, 52.4%). Retreatment with dara-based combination had low response rates (n=3/10, 30% ≥VGPR), vs ven-based (n=14/18, 77.8%) & others (n=5/5, 100%) (p=0.02).

Survival outcomes

1-year & 3-year TTNT 71% and 61%. 1-year & 3-year OS 87% and 72%. Factors affecting TTNT: dFLC ≥18 mg/dL, BMPC ≥15%. Factors affecting OS: dFLC ≥18, NYHA class IV, NT-proBNP ≥8500, no of organs involved, Mayo 2004 IIIB. EFS2 worse if no t(11;14) (p=0.0077).

Patient Characteristics	At 1st LoT (n=100) N (%); Median (Range) [IQR]	At 2nd LoT (n=34) N (%); Median (Range) [IQR]
Age at diagnosis	67.6 (39-91) [59.7-73.4]	68.9 (44-81) [61.2-72.2]
Sex Male	60 (60%)	24 (70.6%)
Race		
White	66 (67.3%)	23 (69.7%)
Black	19 (19.4%)	6 (18.2%)
NYHA Class		
I	17 (19.3%)	7 (23.3%)
II	32 (36.4%)	11 (36.7%)
III	31 (35.2%)	10 (33.3%)
IV	8 (9.1%)	2 (6.7%)
dFLC (mg/dL)	22.9 (0.23-907) [13-70.5]	9.15 (0.23-353) [3.1-18.68]
≥18	60 (60.6%)	9 (26.5%)
<18	39 (39.4%)	25 (73.5%)
NT-proBNP (pg/mL)	3317 (22-76000) [1230-8571]	2456 (264.3-30762) [535.8-7874]
≥ 8500	25 (26.9%)	7 (21.2%)
HS Troponin T (ng/L)	64 (0.00-231) [42-124]	57 (0.24-167) [27-85]
≥ 50	54 (63.5%)	16 (59.3%)
eGFR (mL/min)	59 (7-109) [45-68]	53 (13-99) [42-60]
< 50	33 (34%)	13 (39.4%)
Urine protein (g/24h)	0.75 (0.12-23) [0.19-3.0]	1.47 (0.16-15.53) [0.35-8.4]
≥ 3.5	19 (22.9%)	6 (40%)
BM Plasma Cells %	15 (2-90) [10-20]	20 (5-80) [10-20]
< 5%	5 (5.4%)	0 (0%)
5-15%	41 (44.1%)	11 (32.3%)
>15%	47 (50.6%)	23 (67.6%)
Cytogenetics		
t(11;14)	40 (46%)	14 (48.3%)
1q gain/amp	26 (40%)	9 (45%)
Hyperdiploid	20 (28.6%)	8 (33.3%)
Del(13q)	28 (39.4%)	7 (30.4%)
High Risk [del17p, t(4;14), t(14;20)]	9 (13.4%)	2 (8.3%)
Organ Involvement		
Heart	85 (85%)	27 (79.4%)
Kidney	55 (55%)	22 (64.7%)
Liver	12 (12%)	5 (14.7%)
2 Organs	39 (39.4%)	17 (50%)
3+ Orgnas	32 (32.3%)	8 (23.5%)
Mod Mayo 2004		
I	11 (11.3%)	5 (15.6%)
II	24 (24.7%)	11 (34.4%)
IIIA	38 (39.2%)	12 (37.5%)
IIIB	24 (24.7%)	4 (12.5%)

Table 1: Patient characteristics at diagnosis, and at initiation of 2nd LoT.

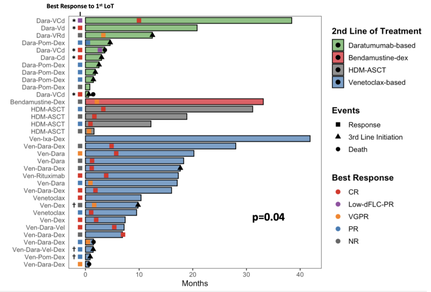


*Figure 1: Swimmer plot illustrating duration from initiation of 2nd LoT to either the start of third-line therapy or death stratified by treatment group. * Patients re- treated with Dara-VCd, Dara-Vd, or Dara-Cd had late disease progression/relapse after frontline therapy. † Patients treated with venetoclax-based therapy who did not have t(11;14) translocation.*

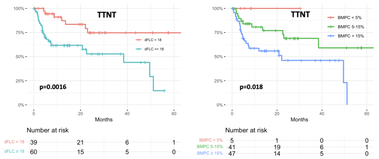


Figure 2: Time-to-next-treatment of newly diagnosed AL amyloidosis patients treated with frontline daratumumab-based therapy stratified by baseline free light chain difference and bone marrow plasma cell percentage at diagnosis.

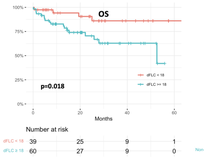


Figure 3: Overall Survival of newly diagnosed AL patients treated with frontline daratumumab-based therapy stratified by baseline free light chain difference.

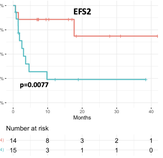


Figure 4: Event-free Survival of AL patients treated with frontline daratumumab-based therapy post second-line therapy stratified by t(11;14) status.

CONCLUSIONS

Around one-third of patients require 2nd LoT in the era of frontline Dara-VCd, mostly due to suboptimal hematologic response. Outcomes with subsequent LoT remains favorable, with two-thirds achieving a VGPR or better and ~90% alive at 2 years from initiation of 2nd LoT. Prospective studies on novel agents such as bispecific antibodies are urgently needed in this setting, particularly for patients who lack t(11;14) and for whom venetoclax is not an option.

REFERENCES

1. Palladini G, Hegenbart U, Milani P, Kimmich C, Foli A, Ho AD, et al. A staging system for renal outcome and early markers of renal response to chemotherapy in AL amyloidosis. Blood 2014;124:2325-32.

2. Palladini G, Dispenzieri A, Gertz MA, Kumar S, Wechalekar A, Hawkins PN, et al. New criteria for response to treatment in immunoglobulin light chain amyloidosis based on free light chain measurement and cardiac biomarkers: impact on survival outcomes. J Clin Oncol 2012;30:4541-9.

3. Zhao L, Ren G, Guo J, Chen W, Xu W, Huang X. The clinical features and outcomes of systemic light chain amyloidosis with hepatic involvement. Ann Med 2022;54:1226-32.

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