Highlights in AL Amyloidosis from ASH 2021

DOI: 10.36000/HBT.OH.2022.11.0XX
Samii K. Highlights in AL Amyloidosis from ASH 2021: *healthbook TIMES Onco Hema*. 2022;(11):xx-xx.

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Quadruplet combination as the new SOC for patients with newly diagnosed AL amyloidosis

At ASH 2021, Dr Comenzo presented the 18-months landmark analysis of the phase III ANDROMEDA trial, which assessed the efficacy and safety of subcutaneous (SC) daratumumab plus bortezomib (V), cyclophosphamide (C) and dexamethasone (d) over the standard of care (SOC) in patients with newly diagnosed amyloid- light chain (AL) amyloidosis.[1] AL amyloidosis is a rare disease characterized by the deposition of insoluble fibrils in tissues, leading to organ dysfunction mainly in the heart and the kidney, liver, lung and intestine. At 6- and 12-months follow-up, the ANDROMEDA study showed a significant improvement in hematological complete response (CR) rates, prolonged major organ deterioration-progression-free survival (PFS), improved organ response and an acceptable safety profile upon addition of SC daratumumab to VCd.[2] Overall, 388 newly diagnosed AL amyloidosis patients with ≥1 organ impacted, a cardiac stage of I-IIIa and an estimated glomerular filtration rate (eGFR) ≥20 mL/min were randomized to receive daratumumab-VCd (SC daratumumab: 1800 mg) (n=195) (weekly, 6 cycles) or VCd alone (n=193).[1] The primary endpoint of the study was the overall hematological CR rate and the secondary endpoints were major organ deterioration-PFS, organ response rate, time to hematological response, overall survival (OS) and safety. Baseline characteristics were well balanced between both treatment arms with a time from diagnosis of approximately 45 days, ~35% of patients in cardiac stage IIIa and two thirds of patients with ≥2 involved organs.

At a median follow-up of 25.8 months, 77.2% of patients in the daratumumab plus VCd arm received daratumumab monotherapy after completing 6 cycles of daratumumab plus VCd.[1] Of these, 88.6% completed 18 cycles of daratumumab monotherapy, while the remaining 11.4% are still on treatment. A similar number of patients died on study treatment with daratumumab plus VCd (n=11) versus VCd alone (n=7). The higher rate of hematological CR with daratumumab plus VCd versus VCd alone was confirmed with longer follow-up (60% vs 19%; odds ratio: 6.0 [95% CI: 3.8–9.6]; p<0.0001). In addition, the CR rate and the rate of very good partial response or better (≥VGPR) increased from 53% to 60% and 77% to 79% with daratumumab plus VCd, respectively. The beneficial effect of the addition of daratumumab to VCd was consistent across all prespecified subgroups with an especially high benefit for patients with a baseline cardiac stage of III, cardiac involvement at baseline or translocation t(11;14).

Compared with the cardiac response analysis at 6 months (daratumumab-VCd vs VCd, 42% vs 22%), higher cardiac response rates were achieved with daratumumab-VCd compared with VCd at 18 months (53% vs 24%). Similarly, renal response rates remained superior with daratumumab-VCd vs VCd alone at 18 months (58% vs 26%) compared with 6 months (54% vs 27%). The addition of daratumumab to VCd did not show any additional safety signals. Fewer deaths occurred with daratumumab-VCd compared with VCd (17% vs 24%).

Serious treatment-emergent adverse events (TEAEs) occurred in 47% of daratumumab-VCd-treated patients versus 36% of VCd-treated patients. Pneumonia was the most common serious adverse event in both groups. The most common grade 3–4 treatment-related adverse event (TRAE) with daratumumab plus VCd versus VCd alone was lymphopenia (13% vs 10%).

In conclusion, with a longer follow-up, the ANDROMEDA study continued to show the superiority of daratumumab plus VCd over VCd alone with deepening response rates. These results support daratumumab in combination with VCd as a new SOC for patients with newly diagnosed AL amyloidosis.

Promising results with single-agent belantamab mafodotin in patients with RR AL amyloidosis

Currently, daratumumab plus VCd is the only approved therapy for newly diagnosed AL amyloidosis in Switzerland.[3] Belantamab mafodotin, a B-cell maturation antigen (BCMA)-targeting antibody-drug conjugate (ADC) has recently shown efficacy in heavily pretreated patients with relapsed/refractory multiple myeloma (RRMM).[4] At ASH 2021, the outcomes of patients with relapsed/refractory (RR) AL amyloidosis associated with myeloma who were treated with single-agent belantamab mafodotin were reported.[5] The retrospective analysis included 6 patients with RR AL amyloidosis who received ≥1 dose of belantamab mafodotin. Patients were 51–74 years old, 50% were male, the median infiltration of bone marrow was approximately 40% and the median involved free light chain (iFLC) level was 868 mg/L. In total, 4 patients had lambda-type amyloidosis, 2 had kappa-type amyloidosis and 5 patients had cardiac involvement. Additionally, patients had received 4–10 prior lines of therapy. At a median follow-up of 4.5 months, 5 patients showed a hematological response and 50% of patients showed hematological CR. Cardiac response was observed in 5 patients and one patient showed a renal response. The most common adverse event was keratopathy. The duration of treatment is rather short due to the short follow-up. Overall, 3 out of 6 patients achieved complete remission.

In conclusion, this retrospective analysis with all the attention to the small number could suggests real potential of belantamab mafodotin for the treatment of patients with RR AL amyloidosis that will be further investigated.[5]

Birtamimab is investigated for the treatment of Mayo Stage IV AL amyloidosis

Dr Morie A. Gertz presented the rationale for the confirmatory phase III AFFIRM-AL study, assessing birtamimab in patients with Mayo Stage IV AL amyloidosis.[6] The monoclonal antibody birtamimab was designed to neutralize circulating toxic aggregates of misfolded light chains and promote phagocytic clearance of organ deposited amyloid. Patients who meet Mayo Stage IV criteria have N-terminal pro-brain natriuretic peptide (NT-proBNP) ≥1800 pg/mL, Troponin-T >0.03 ng/mL and uninvolved free light chains (dFLC) ≥18 mg/dL. A post hoc analysis of the Mayo Stage IV subgroup (n=77) from the VITAL study previously showed a pronounced survival benefit upon addition of birtamimab to the SOC with a proportion of surviving patients of 74% versus 49% with SOC alone (HR: 0.413 [95% CI: 0.19–0.895]; p=0.025). Multiple infusions of birtamimab (24 mg/kg) were well tolerated and the most common TEAEs were similar in both treatment arms and included fatigue, nausea, peripheral edema, constipation and diarrhea. Baseline characteristics were generally well balanced between the treatment arms in the Mayo stage IV subgroup with a median NT-proBNP of 5254 pg/mL, a median troponin-T level of 0.06 ng/mL and a median 6-minute walk test (6MWT) distance of 342.6 meters.

The AFFIRM-AL study is planned to randomize patients with Mayo Stage IV AL amyloidosis (n=150) 2:1 to receive either birtamimab once every 28 days plus SOC (n=100) or placebo plus SOC (n=50).[6] The primary endpoint is all-cause mortality, while secondary endpoints include short-form health survey version-2.0 (SF-36v2), physical component scale (PCS) and 6MWT. In conclusion, the AFFIRM-AL study is designed to confirm the >50% reduction in all-cause mortality observed in the VITAL study for Mayo Stage IV AL amyloidosis patients.

CAEL-101 combined with anti-plasma cell therapy is safe in patients with AL amyloidosis

At ASH 2021, Dr Jason Valent presented the updated organ response results from an open-label study on the monoclonal antibody CAEL-101 in patients with AL amyloidosis who receive anti-plasma cell therapy.[7] By targeting a cryptic epitope on light chain protein in amyloid fibril, CAEL-101 aims to stimulate the immune-mediated clearance of amyloid fibrils. The reported phase II study investigated the safety of escalating doses of CAEL-101 and organ responses by institutional standard per consensus criteria. In the cohort, A patients were treated with escalating doses of CAEL-101 (from 500 mg/m^2 to 750 mg/m^2 to 1000 mg/m^2) in combination with VCd (n=13), with three of those continuing to receive daratumumab, while patients in cohort B received 1000 mg/m^2 plus daratumumab and VCd (n=5). Overall, 16 patients are still on treatment, 1 patient died from pneumonia and sepsis and 1 patient discontinued due to heart transplantation after 6 doses of CAEL-101. Toxicities of CAEL-101 were limited to grade 1–2 and included nausea, diarrhea and skin rash. Of note, eight out of nine patients with kidney involvement achieved organ response, showing many deep and durable responses. For patients with cardiac involvement, 2 out of 4 showed an improvement in global peak longitudinal strain (GLS) by ≥-5%. Finally, 1 of 2 patients with liver involvement showed organ response by alkaline phosphatase criteria. Conclusively, CAEL-101 has proven to be safe in patients with AL amyloidosis and the results suggest that CAEL-101 effectively stimulates immune-mediated clearance of amyloid fibrils which will be further investigated in the ongoing Caelum CARES phase III trials.

1. Comenzo R, Palladini G, Kastritis E, et al. Subcutaneous Daratumumab with Bortezomib, Cyclophosphamide, and Dexamethasone in Patients with Newly Diagnosed Light Chain (AL) Amyloidosis: 18-Months Analysis of the Phase 3 ANDROMEDA Study. Oral presentation presented at: 2021 ASH Annual Meeting & Exposition; 11–14 December 2021. Atlanta, GA, USA. Oral presentation 159.
2. Kastritis E, Palladini G, Minnema MC, et al. Daratumumab-Based Treatment for Immunoglobulin Light-Chain Amyloidosis. *N Engl J Med*. 2021;385(1):46-58. doi:10.1056/NEJMoa2028631
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4. Lonial S, Lee HC, Badros A, et al. Longer term outcomes with single-agent belantamab mafodotin in patients with relapsed or refractory multiple myeloma: 13-month follow-up from the pivotal DREAMM-2 study. *Cancer*. 2021;127(22):4198-4212. doi:10.1002/cncr.33809
5. Zhang Y, Godara A, Pan S, et al. Belantamab Mafadotin in Patients with Relapsed/Refractory AL Amyloidosis with Myeloma. Poster presented at: 2021 ASH Annual Meeting & Exposition; 11–14 December 2021. Atlanta, GA, USA. Poster 1670.
6. Gertz MA, Tripuraneni R, Kinney GG. Birtamimab in Patients with Mayo Stage IV AL Amyloidosis: Rationale for Confirmatory Affirm-AL Phase 3 Study Design. Poster presented at: 2021 ASH Annual Meeting & Exposition; 11–14 December 2021. Atlanta, GA, USA. Poster 2754.
7. Valent J, Silowsky J, Daniel E, et al. Updated Organ Response Results of an Open-Label Study to Evaluate the Safety and Tolerability of Cael-101 in Patients with AL Amyloidosis Receiving Anti-Plasma Cell Therapy. Poster presented at: 2021 ASH Annual Meeting & Exposition; 11–14 December 2021. Atlanta, GA, USA. Poster 2724.