



Daratumumab is Highly Effective Therapeutic Intervention in AL Amyloidosis

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Background

Light chain AA is a clonal plasma cell (PC) disorder that usually presents with multiorgan involvement mainly the heart and kidney. Treatment of AL amyloidosis has evolved over the years, nevertheless the outcome in advanced AA remains poor.

Objectives

To report the therapeutic effect of CD38 monoclonal antibody (DARA) in a patient with refractory AA and conduct a literature review to assess the DARA safety/efficacy in AA

Case:

A 60-year-old male with a history of diabetes mellitus, hypertension, chronic kidney disease and ischemic heart disease was evaluated for chronic anemia. Investigations showed hemoglobin 110 g/L, mild hypercalcemia and Creatinine 155 µmol/L. Serum protein electrophoresis and immunofixation showed M band 15.6 g/L (IgG-λ) free light chain-λ 491mg/L and ratio of 0.01. Bone marrow revealed 45% clonal PC. Upper GI endoscopy for dyspepsia revealed amyloid (LC-λ) deposition. ECHO demonstrated evidence of AA.

He was refractory to velcade, cyclophosphamide and dexamethasone (VCD). Subsequently, he received Daratumumab monotherapy and achieved complete remission post cycle 2. The treatment was well tolerated apart from grade I infusion related reactions. (IRR) He remains on therapy till date (Cycle 12 maintenance).

Discussion:

Light chain amyloidosis is a clonal plasma cell disorder that produce misfolded immunoglobulin light chain that infiltrates tissue of different organs causing organ dysfunction with heart (76%) and kidney (65%) being the most affected organs. Therefore, majority of pts are not transplant (ASCT) ineligible at the time of diagnosis. Use of novel agents based therapy have increased the overall response rate (ORR), but relapse and treatment related mortality remained high during the first year. DARA is a first in class human monoclonal antibody against a highly expressed epitope CD38 on the surface of clonal plasma cells, inducing cell death through different mechanism including antibody dependent cell mediated cytotoxicity, complement-dependent cytotoxicity, antibody-dependent cellular phagocytosis and direct cellular apoptosis.

It showed excellent activity and tolerability in heavily pretreated relapsed multiple myeloma. Treatment for advanced AA with organ dysfunction remains a medical unmet need. Early clinical experience of DARA in AA shown that therapy is well tolerated with no serious adverse events and excellent activity (shown in table). Our pt is currently 1 yr onto his DARA maintenance. Of note, pt was complaining of hoarseness that was believed to be due to vocal cords involvement and was affecting his quality of life as he is a college professor. This has improved completely with therapy.

No. of cases	Protocol (Mono or Combo)	ORR%	GR3-4 IRR%	Reference
2	Mono	100%	0%	Sher et al blood 2016
25	Mono	76%	0%	Kaufman et al blood 2017
2 *	Mono	100%	0%	Gran et al EJM 2017
8	Mono	NR	0%	Blood 2017 (NCT028401330)
45	Mono (n=22), Combo (n=23)	84%**	21% all Grades	Abeykoon et al ASCO 2018
15	Combo (SC DARA+CyBorD)	NR	0%	ASCO 2018 (NCT03201965)

* Two pts, one on hemodialysis and the other post heart transplant

** Mono ORR 77% while Combo 88%

Conclusions

DARA results in rapid and deep responses in heavily pretreated pts, therefore incorporating it in frontline setting as monotherapy or in combination should be explored especially in advanced AA.

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