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CLINICAL TRIALS AND OBSERVATIONS

Comment on Roussel et al, page 1531, Sanchorawala et al, page 1541, and Kimmich et al, page 1517

AL patients don't dare go without dara

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In this issue of *Blood*, 3 papers by the teams of Roussel et al, Sanchorawala et al, and Kimmich et al demonstrate high rates of efficacy and low rates of toxicity of single-agent daratumumab (dara) in patients with previously treated immunoglobulin light-chain (AL) amyloidosis.[1-3] These 3 reports include 2 small phase 2 prospective trials employing single-agent dara[1,2] and a compilation of 168 consecutive patients treated with either daratumumab and dexamethasone (DD) or bortezomib and DD (DVD).[3] Among previously treated AL patients, dara with low-intensity corticosteroid yielded partial hematologic response (PR) or better and very good partial response (VGPR) or better in 64% to 90% and in 56% to 86% of patients, respectively.[1-3] Progression-free survival (PFS) ranged from 12 to 28 months. Renal and cardiac responses were observed in 24% to 67% and 22% to 50% of patients, respectively. The vast majority of hematologic responses occurred after the first 4 doses of dara.[1,2]

There were fundamental differences among the 3 studies (see table). First, duration of therapy was restricted to only 6 months in the French study,[1] whereas treatment was for 24 months in the BU study.[2] Duration of therapy was not specified in the German series,[3] but median number of dara infusions was 14, suggesting ~5 months of therapy. Median levels of dFLC at enrollment were strikingly different, with the lowest values in the BU study and the highest values in the French study. Finally, the two phase 2 studies excluded patients with BMPC >30% and NT-proBNP >8500, but the German case series allowed for such patients; more than a third of patients in the German series had NT-proBNP >8500.

Predictors for outcomes were best gleaned from the German study.[3] Although it was only a case series, it was the largest collection of patients treated, and it was the closest to a real-world experience in that, unlike the 2 phase 2 trials, patients with higher levels of BMPCs and NT-proBNP were included. On multivariate analysis, VGPR was less likely to be reached among patients with high dFLC (>180 mg/L), and hematologic PFS and OS were adversely affected by high dFLC and NT-proBNP >8500. In addition, higher levels of albuminuria also adversely affected hematologic PFS. The results were similar for DVD. In contrast, in the French study, the only predictor for relapse was depth of hematologic response.[1] Their 18-month PFS was 100% and 70%, respectively, for CR and VGPR patients.

The most common nonhematological adverse events included infections. Rates of atrial fibrillation and congestive heart failure were manageable. Infusion reactions were lower than what has been reported in myeloma trials.[4] No patients stopped therapy because of toxicity in any of the studies.

On the face of it, it would appear that these outcomes are substantially better than what has been seen in relapsed/refractory multiple myeloma (RRMM) studies. Usmani et al reported a PR or better rate of 31% in myeloma patients treated with single-agent dara in the relapsed setting (see table).[4] Some of the apparent differences between AL and multiple myeloma (MM) outcomes, however, may be in part explained by differences among the RRMM trials (Sirius and GEN501)[4] and the relapsed/refractory AL (RRAL) trials.[1-3] First, the definition of refractory disease is different: in MM trials, refractory disease refers to absence of response; these AL studies included the absence of VGPR as refractory disease, which translated into a markedly lower tumor burden at enrollment (see table). In fact, in the BU trial, a "measurable" clone was not required; "presence" of a clone was sufficient. Second, the AL patients were less heavily pretreated with a median of 2 prior lines of therapy as compared with a median of 5 for the MM patients. Besides these study design differences, it is important to recall that AL and MM patients are intrinsically different in that adverse cytogenetics are rare in AL and that AL patients are sicker overall given their amyloid infiltration of major viscera.

It is unclear from these 3 studies as to whether 6 months, 24 months, or indefinite therapy is the best strategy in RRAL patients. The BU study, which treated patients for 24 months, had the highest hematologic response rates and organ response rates, but it is unclear if the apparent advantage is a function of lower plasma cell burden/dFLC at the time of instituting dara or the duration of therapy. It is interesting to note that the BU study had 3 patients who had received prior solid organ transplant, and dara did not appear to have an adverse effect on these allografts.

These data also provide us with little information about whether the role combinations of dara-based therapy will work in RRAL, but it is reassuring to discover

Summary of selected dara trials for RRAL and RRMM

	BU[2] (n = 22)	France[1] (n = 40)	Germany DD[3] (n = 106)	Germany DVD[3] (n = 62)	RRMM[4] (n = 148)
Study design	Phase 2	Phase 2	Consecutive patients		Phase 1/2
Eligibility	RRAL, NT-proBNP 8500, BMPC <30%		RRAL		RRMM
Months from last therapy	9	5	2	1	NA
Prior therapies, n	2	3	2	1	5
ASCT, %	Majority	0	23	8	78
Planned therapy	24 m	24 wk	Not specified, but median 14 infusions		Indefinite
Corticosteroid	MP 60 to 100 pre and20 to 80 post	MP 100 mg or Dex 20 mg with each dara dose	Dex 20 mg with each dara dose	Dex and weekly Bortez 4 of 5 wk	MP 60-100 pre and 40 post
dFLC, mg/L	81	164	136	117	NA
BMPC >30%, %	0	0	NA, >30% not excluded		32
NT-proBNP, ng/L (>8500 ng/L, %)	1264 (0)	917 (0)	4155 (34)	5475 (40)	NA
eGFR <60, %	NA	52	<50: 54%	<50: 53%	40
Follow-up, mo	20	26	21	17	21
Hematologic response, overall, %	90 (best)	70 (best)	64 (at 3 mo)	66 (at 3 mo)	31 (best)
CR/VGPR/PR, %	41/45/4.5	15/42/12	8/48/8	11/55/0	5/9/18
Organ response Renal, n (%) Cardiac, n (%)	Best 10 (67) 7 (50)	Best 8 (31) 7 (29)	At 6 mo 10 (24) 15 (22)	At 6 mo 7 (24) 11 (26)	NA
Hem PFS/OS, mo	28/NR	25/NR	12/26	19/NR	PFS 4/20

ASCT, autologous stem cell transplant; BMPC, bone marrow plasma cell; BU, Boston University; CR, complete response; Dex, dexamethasone; dFLC, absolute difference between κ and λ ALs; Hem,; MP, methylprednisolone; NA, not applicable or not available; NT-proBNP, N-terminal pro-brain natriuretic peptide; OS, overall survival.

that dara is well tolerated in patients with RRAL, making it probable that combinations will be feasible. Although the German study provides some information on the triplet DVD, prospective randomized controlled trials will provide answers. Time and commitment will reveal if dara performs in AL as well as it does in RRMM in combinations, most notably immune modulators,[5,6] proteasome inhibitors,[7,8] or venetoclax[9] (given the high rates of t(11;14)) in patients with AL. Regardless of what these future studies may show, the good news is that dara is highly effective in patients with AL.

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