COMMENTARY

blood advances

TO THE EDITOR:

Long-term remissions after stopping pembrolizumab for relapsed or refractory multiple myeloma

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We have previously shown that immunotherapy with an antibody targeting the programmed cell death-1 (PD-1)/PD-1 ligand (PD-L1) pathway, pembrolizumab, in combination with the immunomodulatory drug (IMiD) pomalidomide and dexamethasone, provided promising clinical activity in relapsed/refractory multiple myeloma (MM) patients (n = 48) in a phase I/II study (NCT02576977). The University of Maryland Institutional Review Board approved the study, which was conducted in accordance with the Declaration of Helsinki. Therapy was associated with frequent, but manageable, adverse events (AEs) in 35 of 49 (71%) patients, with grade 3 or higher AEs observed in 20 patients (41%). Immune-mediated events (irAEs) included interstitial pneumonitis (n = 6), hypothyroidism (n = 5), adrenal insufficiency (n = 2), hepatitis (n = 2), and vitiligo (n = 1). Overall response rate (ORR) was 60% (29 of 48 patients), including a stringent complete response (sCR) in 4 (8%) patients, a very good partial response (VGPR) in 9 (19%) patients, and a partial response (PR) in 16 (33%) patients; median progression-free survival (PFS) was 17.4 months.[1] In July of 2017, the US Food and Drug Administration placed our trial on hold, along with 30 others, and issued a safety alert after increased mortality was observed in 2 randomized trials (KEYNOTE-183 and KEYNOTE-185) using an IMiD (lenalidomide or pomalidomide) and dexamethasone, with or without pembrolizumab, in relapsed and newly diagnosed MM patients, respectively.[2] All active study subjects receiving therapy discontinued pembrolizumab (n = 12). In the following analysis, we provide long-term follow-up data on those 12 patients and 4 others who stopped therapy because of AEs.

Characteristics and outcomes of these patients are summarized in Table 1. Median age was 62 years (range, 35-83), with a median of 42 months from diagnosis to study entry. Patients had a median of 3 (range, 2-5) lines of prior therapy. All had received an IMiD and a proteasome inhibitor, and 12 of 16 (75%) were refractory to both; 9 (56%) had received an autologous transplant. Six (38%) had cytogenetic abnormalities [1q, t(4:14)]; none had deletion of 17p. Median duration on study was 17 months (range, 9-30), with a median follow-up of 39 months (range, 30-48) from pembrolizumab initiation and 18 months (range, 14-35) from discontinuation. At discontinuation, all 16 patients had objective responses, including sCR in 5 (31%), VGPR in 5 (31%), and PR in 6 (38%). After stopping pembrolizumab, 9 patients continued pomalidomide and dexamethasone, and 7 patients opted for observation only. Among the patients who opted for observation only, 4 of 7 (57%) have ongoing responses, including 3 in sCR at 18 (n = 2) and 27 months and 1 in PR at 17 months. Among the 9 who continued pomalidomide, 5 of 9 (56%) have ongoing responses, including 1 in sCR at 18 months, 3 in VGPR at 18 months, and 1 in PR at 22 months.

At last follow-up on 31 January 2019, all 16 patients were alive. Seven patients had relapsed, including 2 with del(17p), 2 with gain of (?) 1q, 2 with t(11:14), and 1 with high lactate dehydrogenase. Four patients relapsed while on pomalidomide at a median of 8 (range, 1-16) months, and 3 patients were on observation only at a median of 12 (range, 6-22) months. Six patients received daratumumab-based regimens; all responded (3 VGPR, 3 PR), with a median duration of response of 10 months (range, 6-17+); 1 patient relapsed on daratumumab at 8 months. One patient received single-agent venetoclax.

Analysis of pretreatment bone marrow samples revealed a trend for increased expression of PD-L1 on myeloma cells in deep responders who attained long-term remissions. PD-L1 staining was performed by immune-histochemistry; membranous staining was reported as proportion expression as follows: ≥50%, strong; ≥1% to 48%, intermediate; and <1%, weak. For patients in VGPR or better (n = 11), PD-L1 expression was available for 9 patients; 6 patients had strong expression, 1 patient had intermediate expression, and 2 patients had weak expression.

Table 1. Patient characteristics and outcomes stratified by response status at end of study

Pt. no.	Sex	Age, y	Race	Months from Dx	Lines of treatment, n	Months on study	Obs/ Pom	Remission from end of study, mo	Relapse	PD-L1*	Therapy for PD
sCR											
1	M	66	W	38	3 (+ASCT)	29	Obs	18+		Strong	
2	M	63	W	56	3 (+ASCT)	21	Obs	18+		N/A	
3	F	57	AA	47	3	14	Pom	18+		N/A	
4	F	57	AA	23	2	21	Pom	10	Yes	Weak	Dara/Carf/Dex (PR, 8 mo), 2nd relapse—BCMA antibody conjugate
VGPR											
1	M	66	AA	145	4	27	Pom	18+		Strong	
2	F	35	AA	60	3 (+ASCT)	17	Pom	18+		Weak	
3	M	50	H	80	3 (+ASCT)	15	Pom	18+		Intermed.	
4	F	83	W	307	4 (+ASCT)	17	Pom	12	Yes	Strong	Dara/Dex (VGPR 6, mo+)
5	F	56	AA	35	3	30	Pom	1	Yes	Strong	Dara/Pom/Dex (VGPR, 17 mo+)
PR											
1	M	67	AA	35	2	25	Obs	17+		Intermed.	
2	M	60	W	42	2 (+ASCT)	15	Pom	16	Yes	Weak	Venetoclax/Dex (PR, 2 mo+)
3	M	66	W	25	2 (+ASCT)	12	Obs	6	Yes	N/A	Dara/Len/Dex (PR,12 mo+)
Off study†											
1	F	65	AA	38	2	20 (sCR)	Obs	27+		Strong	Off study (breast cancer)
2	F	55	A	16	3	12 (PR)	Pom	22+		N/A	Off study (pneumonitis)
3	M	81	AA	41	3	9 (PR)	Obs	22	Yes	Intermed.	Off study (fatigue) Dara/Dex (PR, 8 mo+)
4	M	61	W	144	5 (+ASCT)	10 (VGPR)	Obs	12	Yes	Strong	Off-study (hepatitis) Dara/Pom/Dex (VGPR, 12 mo+)

AA, African American; A, Asian; BCMA, B-cell maturation antigen; Carf, carfilzomib; Dara, daratumumab, Dex, dexamethasone; Dx, diagnosis; H, Hispanic; Intermed., intermediate; N/A, not available; Obs, observation; PD, progressive disease; Pom, pomalidomide; Pt, patient; M, male; F, female; W, white; +ASCT, had autologous stem cell transplant.

*PD-L1 immune-histochemistry membranous staining.

†Because of toxicity.

These durable responses that were maintained even after discontinuation of therapy support a role for the immune effects of this regimen as seen in other malignancies treated with immunotherapy.[3,4] However, the small number of selected patients in this phase 1/2 study makes it difficult to fully evaluate the risk/benefit ratio of the regimen, which was further evaluated in 2 phase 3 randomized trials (KEYNOTE-183 and KEYNOTE-185), both of which failed to establish a clinical benefit. In KEYNOTE-183, relapsed MM patients in the pembrolizumab arm had more irAEs (18%) and more frequent deaths (16 from progressive disease and 13 from AEs vs 18 and 3 in the control arm, respectively), with a hazard ratio (HR) for death of 1.61 (95% confidence interval [CI], 0.91-2.85). Median PFS was 5.6 months for pembrolizumab vs 8.4 months for control; median OS was not reached in the pembrolizumab arm, and it was 15.2 months in the control arm. In a retrospective random forest analysis, age, performance status, disease stage, presence of plasmacytoma, and double-refractory status were more relevant contributors to death than treatment.[5] In the KEYNOTE-185 trial, newly diagnosed transplant-ineligible elderly patients were randomized to lenalidomide and dexamethasone with or without pembrolizumab; median age was 74 years (including 21% who were older than 80 years). More patients had renal insufficiency (14% vs 8%) and high-risk disease (16% vs 7%) in the pembrolizumab arm. Pembrolizumab treated patients had no difference in ORR (64% vs 62%) compared to lenalidomide and dexamethasone; moreover, they had a high treatment discontinuation rate (21% vs 8%), with an HR for death of 2.06 (95% CI, 0.93-4.55) (19, 13% vs 9%, 6%). Furthermore, pembrolizumab added no benefit in terms of PFS (82% vs 87%) or OS (87% vs 94%) compared to lenalidomide and dexamethasone.[6] Both trials were put on hold with a very short median follow-up in November of 2017 because of increased toxicity and mortality. This raised questions about the viability of the PD-1/PD-L1 axis as a therapeutic target in MM, because the risk/benefit ratio seemed unfavorable.

It is true that the combination of IMiDs and pembrolizumab, in our experience, resulted in higher rates of irAEs than expected with single-agent use. However, these events were manageable and transient, and most patients were able to continue therapy with dose modifications. We believe that rapid identification of irAEs and drug discontinuation and/or initiation of systemic immunosuppression were crucial in preventing irreversible injury and death in our study. The negative impact of irAEs will be mitigated as we gain more experience in the diagnosis and management of these events.

In solid tumors, immunotherapy benefit is clearly demonstrated by improvements in median ORR, PFS, and OS; however, these alone may fail to effectively describe the long-term impending benefits, because survival curves plateau in a minority of "cured" responding patients.[7-10] Our data highlight the need for extended follow-up to fully describe the full clinical benefits vs risk in the subsets of patients who enjoy long remissions even after stopping therapy.

The current data for combining IMiDs with PD-1 inhibition do not support the use of this combination outside of well-designed clinical trials. Future attempts to implement correlative studies, such as PD-L1 expression on myeloma cells, may help to select the patients who would benefit the most from rational combinations of other approaches to correcting T-cell dysfunction, such as targeted antibodies, bispecific T-cell engager antibodies, and chimeric antigen receptor T cells, to reach the full potential of immunotherapy in MM.

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