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Blood 142 (2023) 4972–4974

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

731.AUTOLOGOUS TRANSPLANTATION: CLINICAL AND EPIDEMIOLOGICAL

Phase 1/2 Trial to Jointly Optimize Dose and Administration Schedule of Evomela in Newly Diagnosed Multiple Myeloma Patients Undergoing Autologous Hematopoietic Cell Transplantation

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Background: Eligible patients with multiple myeloma (MM) are offered autologous hematopoietic cell transplantation (auto-HCT) in their first remission. The usual conditioning regimen consists of melphalan (Alkeran) 200 mg/m ^{2} infused over ~ 30 minutes due to its limited stability. Evomela is a newer formulation of melphalan, which is stable at room temperature for ~ 24 hours. The current trial studied the dose escalation and compared the short versus extended infusion time of evomela used as a conditioning regimen before auto-HCT.
Methods: Patients with newly diagnosed MM, age $\leq$ 70, were eligible. Two dose levels, 200 and 225 mg/m ^{2} were studied. Patients were randomized between two infusion schedules: 30-60 minutes (short) and an extended infusion of 8-9 hours. Disease response was measured using IMWG criteria. Minimal residual disease (MRD) was measured by flow cytometry at 10^{-5}.
Results: Sixty patients were enrolled. The first 3 patients in each arm were treated at evomela 200 mg/m ^{2}. Since no dose-limiting toxicity (DLT) was observed, all subsequent patients (n=54; 27 in each arm) were treated at evomela 225 mg/m ^{2}. The results are presented for patients treated at evomela 225 mg/m ^{2}. Patient characteristics were evenly distributed (Table 1). The median age was 58.6 years (range: 42.6 -70.3). Twelve (22%) patients had high-risk cytogenetics (4 [15%] in the short infusion; 8 [30%] in the extended infusion arm), p-value 0.19.
There were no deaths, and no patient experienced grade > 3 adverse events (AE). Grade 2-3 AEs were seen in 53 (98%) patients (26 [96%] in the short infusion; 27 [100%] in the extended infusion). Twenty-four (44%) patients experience grade 2-3 diarrhea (16 [60%] in the short infusion; 8 [30%] in the extended infusion). Grade 2-3 esophagitis was seen in 3 (6%) patients overall (0 in the short infusion; 3 [11%] in the extended infusion). Atrial fibrillation was seen in one patient (grade 2, extended infusion).
Before transplant, six (22%) patients were in stringent complete remission (sCR) or CR in the short infusion arm vs. 4 (15%) patients in the extended infusion arm. At day-90 post-transplant, 13 (48%) patients in each arm were in sCR/CR, and 17 (63%) patients in each arm achieved MRD-negative status. Overall, 23 (43%) patients achieved MRD-negative plus sCR/CR status at day-90 (11 [41%] in short and 12 [50%] in the extended infusion arm).

The median follow-up was 14.5 (range: 6-40) months (13.8 months in the short infusion and 14.8 months in the extended infusion arm). The median progression-free survival (PFS) was not reached in the overall trial population (Figure). The median PFS in the short infusion arm was not reached vs. 28.2 months in the extended infusion arm. The 2-year progression-free survival (PFS) was 91% in the short infusion arm vs. 77% in the extended infusion arm (hazard ratio (HR)=9.5 with 95% CI: 1-91.2), p-value=0.022. On multivariate analysis, controlling for age and cytogenetic risk category, the extended infusion arm was associated with a shorter PFS (HR 10.96; 95% CI 1.18 - 102.02), p-value 0.0355, although the range for HR was notably wide, which could be attributed to a small number of events in each arm.

Conclusions: Dose escalation of evomela to 225 mg/m ^{2} is safe and associated with an acceptable toxicity profile and a high response rate. Short and extended infusions of evomela are well-tolerated and associated with high response rates. The PFS is longer with the short infusion schedule, however, to affirm these preliminary observations, additional follow-up is needed.

Disclosures Bashir: *Stemline:* Research Funding; *Acrotech:* Research Funding; *GSK:* Research Funding; *Pfizer:* Research Funding. **Kebriaei:** *Pfizer:* Consultancy, Honoraria; *Jazz:* Consultancy, Honoraria. **Khouri:** *Pfizer:* Research Funding. **Nieto:** *Astra Zeneca:* Research Funding; *Secura Bio:* Research Funding; *Affimed:* Research Funding. **Srour:** *Orca Bio:* Research Funding. **Saini:** *GSK:* Research Funding; *Panbela Theraputics:* Research Funding. **Lee:** *Amgen:* Research Funding; *GlaxoSmithKline:* Consultancy, Research Funding; *Regeneron:* Consultancy, Research Funding; *Sanofi:* Consultancy; *Pfizer:* Consultancy; *Takeda:* Consultancy, Research Funding; *Allogene Therapeutics:* Consultancy; *Janssen:* Consultancy, Research Funding; *Genentech:* Consultancy; *Bristol Myers Squibb:* Consultancy, Research Funding. **Thomas:** *Cellectar Biosciences:* Consultancy; *Ascentage Pharma:* Research Funding; *Janssen Pharma:* Research Funding; *Cellectar Biosciences:* Research Funding; *X4 pharma:* Research Funding; *Genentech:* Research Funding; *Abbvie, Cellectar Biosciences:* Consultancy; *Bristol Myers Squibb, Janssen Pharma Genentech, X4 pharma, Cellectar Biosciences, Ascentage Pharma:* Research Funding. **Manasanch:** *A:* Consultancy; *G:* Consultancy. **Patel:** *AbbVie; Arcellx, AstraZeneca; Bristol Myers Squibb/Celgene Corporation; Caribou Science; Cellectis; Curio Bioscience; Genentech; Janssen Pharmaceuticals, Inc.; Karyopharm; Legend Biotech; Merck & Co., Inc.; Oncopeptides; Pfizer; Precision BioSciences:* Consultancy; *AbbVie; Allogene Therapeutics, Inc.; Arcellx; Bristol Myers Squibb/Celgene Corporation; Cellectis; Janssen Pharmaceuticals, Inc.; Nektar Therapeutic; Poseida Therapeutics; Precision BioSciences, Inc.; and Takeda Pharmaceuticals U.S.A., Inc.:* Research Funding; *Takeda:* Consultancy. **Orlowski:** *AbbVie, Adaptive Biotech, Asylia Therapeutics, Inc., BioTheryX, Bristol-Myers Squibb Pharmaceuticals, Karyopharm Therapeutics, Meridian Therapeutics, Monte Rosa Therapeutics, Nanjing IASO Biotherapeutics, Neoleukin Corporation, Oncopeptides AB, Pfizer, In:* Consultancy, Honoraria; *Asylia Therapeutics, BioTheryX Inc., Heidelberg Pharma:* Other: Laboratory Research Funding, Research Funding; *Asylia Therapeutics:* Current equity holder in private company, Patents & Royalties; *BMS/Celgene Corporation, CARsgen Therapeutics, Exelixis Inc., Heidelberg Pharma, Janssen Biotech Inc., Sanofi/Genzyme, Takeda Pharmaceuticals USA Inc.:* Other: Clinical Research Funding, Research Funding. **Champlin:** *Cell Source:* Research Funding; *Omeros:* Consultancy; *Actinium Pharmaceuticals:* Consultancy; *Johnson & Johnson/Janssen:* Consultancy; *Kadmon:* Consultancy; *Takeda Corporation:* Patents & Royalties; *Arog:* Consultancy; *Orca Bio:* Consultancy. **Shpall:** *Syena:* Other: License agreement; *Affimed:* Other: License agreement; *Takeda:* Other: License agreement; *Adaptimmune:* Membership on an entity's Board of Directors or advisory committees; *Navan:* Membership on an entity's Board of Directors or advisory committees; *Celaid Therapeutics:* Membership on an entity's Board of Directors or advisory committees; *Fibrobiologics:* Membership on an entity's Board of Directors or advisory committees; *Axio:* Membership on an entity's Board of Directors or advisory committees; *NY Blood Center:* Membership on an entity's Board of Directors or advisory committees. **Qazilbash:** *Bioline:* Other: Advisory board; *Angiocrine:* Research Funding; *Amgen:* Research Funding; *NexImmune:* Research Funding; *Janssen:* Research Funding.

Table 1. Patient characteristics and disease response.

Variable		Overall	30 - 60 mins	8 - 9 hours	P-value
Overall	N	54 (100%)	27 (50.00%)	27 (50.00%)	
Median Age (range)	54	58.6 (42.6-70.2)	60.3 (42.6 – 70.2)	58.3 (45 – 68.2)	0.492
Gender	Female	17 (31.48%)	12 (44.44%)	5 (18.52%)	0.040
	Male	37 (68.52%)	15 (55.56%)	22 (81.48%)	
R_ISS Stage	I	11 (20.37%)	6 (22.22%)	5 (18.52%)	0.416
	II	31 (57.41%)	13 (48.15%)	18 (66.67%)	
	III	4 (7.41%)	2 (7.41%)	2 (7.41%)	
	Unknown	8 (14.81%)	6 (22.22%)	2 (7.41%)	
Cytogenetics Risk Category, n (%)	Standard-risk	42 (77.78%)	23 (85.19%)	19 (70.37%)	0.190
	High-risk	12 (22.22%)	4 (14.81%)	8 (29.63%)	
Induction regimens	Carfilzomib/ Cyclophosphamide/ Dexamethasone	1 (1.85%)		1 (3.70%)	0.682
	Carfilzomib/ Lenalidomide/ Dexamethasone (KRd)	11 (20.37%)	5 (18.52%)	6 (22.22%)	
	KRd + Daratumumab	1 (1.85%)		1 (3.70%)	
	Cyclophosphamide/ Dexamethasone/ Daratumumab	1 (1.85%)	1 (3.70%)		
	Ixazomib/ Lenalidomide/ Dexamethasone	1 (1.85%)		1 (3.70%)	
	Bortezomib/ Cyclophosphamide/ Dexamethasone (CyBorD)	1 (1.85%)		1 (3.70%)	
	CyBorD + Daratumumab	2 (3.70%)	1 (3.70%)	1 (3.70%)	
	Bortezomib/ Lenalidomide/ Dexamethasone (VRd)	24 (44.44%)	15 (55.56%)	9 (33.33%)	
	Bortezomib/ Dexamethasone + Daratumumab	1 (1.85%)		1 (3.70%)	
	VRd + Daratumumab	11 (20.37%)	5 (18.52%)	6 (22.22%)	
Maintenance therapy	Carfilzomib/ Lenalidomide	1 (1.96%)		1 (4.17%)	0.067
	Daratumumab/ Lenalidomide	5 (9.8%)	1 (3.7%)	4 (16.67%)	
	Daratumumab/ Lenalidomide/ Dexamethasone	1 (1.9%)		1 (4.17%)	
	Pomalidomide	1 (1.9%)		1 (4.17%)	
	Lenalidomide	39 (72.22%)	24 (88.89%)	15 (62.5%)	
	Ixazomib/ Lenalidomide	1 (1.96%)	1 (3.7%)		
	Bortezomib/ Lenalidomide/ Dexamethasone	2 (3.92%)		2 (8.33%)	
	Bortezomib/ Lenalidomide	1 (1.96%)	1 (3.7%)		
Response Status					
Pre-transplant response	CR	2 (3.70%)	2 (7.41%)		0.697
	sCR	8 (14.81%)	4 (14.81%)	4 (14.81%)	
	VGPR	27 (50.00%)	12 (44.44%)	15 (55.56%)	
	PR	17 (31.48%)	9 (33.33%)	8 (29.63%)	
Response at Day-90 post-transplant	CR	5 (9.26%)	3 (11.11%)	2 (7.41%)	0.881
	sCR	21 (38.89%)	10 (37.04%)	11 (40.74%)	
	CR+sCR	26 (48.15%)	13 (48.15%)	13 (48.15%)	
	VGPR	21 (38.89%)	10 (37.04%)	11 (40.74%)	
	PR	6 (11.11%)	4 (14.81%)	2 (7.41%)	
	PD	1 (1.85%)		1 (3.70%)	
	Overall response rate ≥ PR	53 (98.15%)	27 (100.00%)	26 (96.30%)	
Best response	CR	6 (11.11%)	3 (11.11%)	3 (11.11%)	0.523
	sCR	31 (57.41%)	14 (51.85%)	17 (62.96%)	
	CR+sCR	37 (68.52%)	17 (62.96%)	20 (74.07%)	
	VGPR	16 (29.63%)	10 (37.04%)	6 (22.22%)	
	PR	1 (1.85%)		1 (3.70%)	
Minimal Residual Disease (MRD)					
Pre-transplant MRD	Negative	25 (46.30%)	11 (40.74%)	14 (51.85%)	0.413
	Positive	29 (53.70%)	16 (59.26%)	13 (48.15%)	
MRD at Day-90 post-transplant	Negative	34 (62.96%)	17 (62.96%)	17 (62.96%)	0.238
	Positive	17 (31.48%)	10 (37.04%)	7 (25.93%)	
	Not Done	3 (5.56%)		3 (11.11%)	
MRD-negative + sCR/CR at Day-90 post-transplant	No	28 (54.90%)	16 (59.26%)	12 (50.00%)	0.507
	Yes	23 (45.10%)	11 (40.74%)	12 (50.00%)	

R-ISS, revised international staging system; CR, complete response; sCR, stringent CR; VGPR, very good partial response; PR, partial response; PD, progressive disease

Figure: Kaplan-Meier estimates for PFS

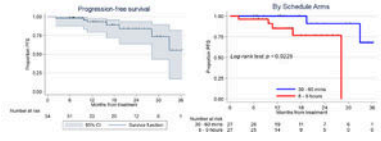

Figure 1

https://doi.org/10.1182/blood-2023-189844