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VTD-melphalan is well tolerated and results in very high rates of stringent CR and MRD-negative status in multiple myeloma

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Abstract: The addition of cytotoxic drugs to high-dose melphalan as a preparative regimen for autologous stem cell transplantation in multiple myeloma has not resulted in superior activity. Although novel agents have significantly improved outcome in multiple myeloma, their role in preparative regimens remains largely unknown. We have evaluated the toxicity and efficacy of combining bortezomib, thalidomide, and dexamethasone with high-dose melphalan. An institutional review board-approved retrospective analysis was performed on 100 consecutive patients receiving 153 transplants; 53 had tandem transplants; 64 patients received early transplants; and 36 had salvage transplantation. Endpoints were treatment-related toxicity and mortality, and quality of response post-transplantation with assessment of stringent complete remission (sCR) and minimal residual disease (MRD) status. Median age was 61 years, and median follow-up was 16.2 months. At 6 months, sCR was attained in 56% of patients and CR in 20%. An MRD status, assessed by sensitive (10^{-4}) multiparameter flow cytometry, was achieved in 85%. The 100-day mortality rate was 2.6% (4/153); 1.8% for early transplants and 4.5% for salvage transplants. Grade 3–5 non-hematologic toxicities were mainly related to metabolism/nutrition; gastrointestinal and infectious problems. Median time to absolute neutrophil count of >500/μL was 12 days for both early and salvage transplantations. No significant differences in quality of response were observed between early and salvage transplantation or between single and tandem autologous stem cell transplantation. Since both sCR and MRD are excellent early surrogate markers for progression-free and overall survival, this regimen will likely be superior to melphalan alone, but it needs to be formally assessed in a randomized study.

Keywords: multiple myeloma, autologous transplantation, response, toxicity, mortality, minimal residual disease

Introduction

The combination of autologous stem cell transplantation (ASCT) with novel agents in the induction, especially in the maintenance/consolidation phase, has resulted in the best outcomes in multiple myeloma (MM).[1–11] Currently, ASCT in the upfront setting remains the standard of care for transplant-eligible patients.[11–14] High-dose melphalan (HDM) at 200 mg/m^2 is the standard preparative regimen for transplantation as established by Barlogie et al.[15] The superiority of HDM compared to conventional chemotherapy was demonstrated in an Intergroupe Francophone du Myélome study.[16] Several trials have compared various combination therapies either in a randomized study against HDM or in a non-comparative setting, but these trials were not superior and often highly toxic.[17–25] Combination therapies frequently resulted in a reduction

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in the dose of melphalan, which may explain the lack of their superiority.

With laboratory evidence suggesting synergistic effect of HDM with novel agents,[26,27] we decided to incorporate these into the preparative transplant regimen. In newly diagnosed and relapsed patients, the combination of a proteasome inhibitor with an immunomodulatory drug (IMiD) and dexamethasone is superior to treatment with dexamethasone with either an IMiD or a proteasome inhibitor only.[28–32] Thalidomide is the least myelosuppressive of the IMiDs and thus, has the lowest probability of endangering engraftment. Bortezomib prevents DNA repair after HDM by interfering with the Fanconi anemia/BRCA DNA damage repair pathway through blockade of the nuclear factor kappa B pathway.[33,34] In addition, both proteasome inhibitors and IMiDs decrease cell adhesion-mediated drug resistance,[35–39] while high-dose dexamethasone dampens the release of anti-apoptotic cytokines after HDM.[40–42]

With the availability of more effective antimyeloma therapy, the need has arisen for more sensitive assays to assess the quality of responses. The International Myeloma Working Group has introduced the concept of stringent complete remission (sCR),[43] while others have focused on minimal residual disease (MRD) status. Different ways to assess MRD in myeloma are available, including sensitive multiparameter flow cytometry (MFC) (≥8-color), allele-specific oligonucleotide polymerase chain reaction and next-generation or high-throughput sequencing. MFC has a sensitivity of $\leq 10^{-4}$.[44–47]

We report that in 100 consecutive patients treated with bortezomib–thalidomide–dexamethasone–melphalan (VTD-MEL), a very high percentage attained an sCR (56%) and an even higher percentage achieved an MRD status (83%). Such results were observed in early and salvage transplantation, and after single or tandem autologous transplants. This regimen was well tolerated and did not interfere with engraftment.

Patients, methods, and materials

Patients

The University of Iowa School of Medicine institutional review board-approved retrospective analysis was performed on all MM patients receiving either single or tandem transplants in an upfront or salvage setting at our institution between February 2012 and February 2015. Patients aged ≥65 years received a single transplant based on the Medicare guidelines. Early transplant patients aged <65 years received tandem transplants if they had insurance coverage. Salvage transplant patients aged <65 years received a single transplant if the tumor load at relapse was low.

Definitions

Patients with ≤12 months of induction chemotherapy without progression on treatment were defined as early transplants. Patients who had progressed prior to transplant and/or who had received >12 months of prior chemotherapy were classified as salvage transplants. The presence of high-risk cytogenetics was defined as 17 p deletion, *t*(14;16) or *t*(4;14). Patients were classified according to International Staging System and the revised International Staging System classification.[45]

Stem cell mobilization

Stem cell mobilization was achieved either with D-PACE (dexamethasone, cisplatin, adriamycin, cyclophosphamide, etoposide) plus granulocyte-colony stimulating factor ± mozobil in 86 patients or granulocyte-colony stimulating factor ± mozobil alone in 14 patients.

Preparative regimen

The preparative chemotherapy regimen consisted of melphalan 100 mg/m^2 on days −4 and −1, bortezomib 1 mg/m^2 intravenously on days −4, −1, +2, +5, thalidomide 100 mg orally from day −4 to day +5 and dexamethasone 20 mg/day orally from day −4 to days −1 and day +2 to day +5. Adjusted and ideal body weights [ABW =0.4 (ABW–IBW) + IBW] was calculated to dose melphalan and bortezomib in patients weighing >60 kg, and at least 5 feet tall. The total dose of melphalan and bortezomib was capped at 2 m^2. In patients with a creatinine >2 mg/dl and/or in patients aged >70 years, a reduced dose of melphalan 70 mg/m^2 was administered on days −4 and −1. All patients started consolidation therapy with VTD when counts had adequately recovered post-transplantation and transplant-related complications were largely resolved, usually around day +50.

This preparative regimen had first been tested in patients who had relapsed after transplantation and required a salvage transplant. It was subsequently tested in a formal institutional review board-approved study in myeloma patients with up to 12 months of prior therapy and was listed at https://clinicaltrials.gov/ct2/show/NCT00670631.

Supportive care

All patients had cryotherapy with HDM. Patients were started on infection prophylaxis on day −4. Meropenem was routinely initiated on day +5, irrespective of fever status. Routine meropenem administration was implemented after observing the initial cohort of patients treated with VTD-MEL in the study referred above. Several cases of

severe septicemias with hypotension on oral Ciprofloxacin prophylaxis required admission to the intensive care unit. Almost all these severe infections were due to *Escherichia coli* resistant to Ciprofloxacin. Antibiotics were continued until recovery of ANC to >500/μL or until completion of required treatment for a documented infection. Neupogen 300 μg per day was initiated on day +6 and was discontinued after ANC increased to ≥500/μL.

Toxicities, 100-day mortality, and response

The endpoints were grade 3–5 toxicities during the first 100 days after transplantation, 100-day mortality, and the quality of response at day +180 for patients reaching this time point. Frequencies of toxicities were tabulated on a per transplant basis.

We applied the Common Terminology Criteria for Adverse Events, version 4.0 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf). For patients receiving tandem transplants, each transplant was considered independently. All patients, who were planned to receive tandem transplants, proceeded to a second transplant. None died prior to receiving the second transplant.

All responses were recorded according to the updated International Myeloma Working Group uniform response criteria.[45] The quality of response was available prior to transplant and at 3 and 6 months post-transplant.

MRD was assessed by 10-color flow cytometry with a sensitivity of $\geq 10^{-4}$.[46,47] Whenever possible, 2 million events were analyzed. Fluorescence in situ hybridization analysis was performed on highly selected $CD138^{+}$ bone marrow cells, using probes previously found to be abnormal, as well as the 17p13 probe to detect existing or acquired p53 loss. The sensitivity of this test is estimated at 10^{-4} when sCR patients had ≤1% plasma cells in the bone marrow. An average of 200 selected plasma cells were analyzed per probe.

Statistical analysis

Chi-square tests were used for comparison of response rates. Wilcoxon rank-sum tests were applied for comparisons of time to neutrophil recovery and length of stay. Univariate logistic regression models were applied to determine whether demographic or clinical variables were significantly associated with either quality of response (not sCR+CR vs sCR+CR) or MRD status (negative vs positive). All statistical testing was two-sided and assessed for significance at the 5% level using SAS v9.4 (SAS Institute, Cary, NC, USA).

Results

Patients and treatment characteristics

We identified 100 eligible patients; 36 patients received a salvage transplant, 20 of whom had received prior autologous transplantation. Baseline characteristics are listed in Table 1.

Table 1 Patient characteristics

Variable	Level	n	%
Tandem or single	Single	47	47.0
	Tandem	53	53.0
Early salvage	Salvage	36	36.0
	Early	64	64.0
Previous transplant	No	80	80.0
	Yes	20	20.0
Cytogenetics	Chromosome 1 abnormalities	18	18.0
	High risk	24	24.0
	Standard risk	76	76.0
Durie-Salmon staging and subclassification at diagnosis	I	16	16.3
	II	12	12.2
	III	70	71.4
	Missing	2	–
ISS	I	30	33.3
	II	34	37.8
	III	26	28.9
	Missing	10	–
R-ISS	I	18	25.7
	II	41	58.6
	III	11	15.7
	Missing	30	–
Pre-transplant MRD status	Negative	11	11.6
	Positive	84	88.4
	Missing	5	–
Pre-transplant response	1: sCR	1	1.0
	2: CR	11	11.0
	3: VGPR/nCR	11	11.0
	4: PR	56	56.0
	5: SD	19	19.0
	6: PD	1	1.0
	8: Never treated	1	1.0
Post-transplant MRD status	Negative	82	85.4
	Positive	14	14.6
	Missing	4	–
Post-transplant response	1: sCR	55	56.1
	2: CR	20	20.4
	3: VGPR/nCR	10	10.2
	4: PR	12	12.2
	5: SD	1	1.0
	Missing	2	–
		Median	**Range**
Age at first transplant		60.5	37.0–80.0
Creatinine at diagnosis (mg/dL)		1.0	0.5–19.0
Albumin at diagnosis (g/dL)		3.9	0.3–5.1
LDH at diagnosis (U/L)		1.7	0.8–4.2
Length of follow-up (months)		16.2	1.5–35.0

Abbreviations: CI, confidence interval; ISS, International Staging System; LDH, lactate dehydrogenase; MRD, minimal residual disease; nCR, near complete response; R-ISS, revised International Staging System; sCR, stringent complete remission; SD, stable disease; VGPR, very good partial response; CR, complete remission; PR, partial remission; PD, progressive disease.

Median age was 61 years (range 37 to 80) with 37 patients aged >65 years; 16 patients had a creatinine >2 mg/dL. Two patients failed to reach the day +180 time point; the median follow-up was 16.2 months. The average $CD34^+$ cell dose infused per transplant was 8.08 million/kg. These 100 patients received a total of 153 transplants; 24 patients had high-risk cytogenetics.

Recovery/engraftment

The median time to neutrophil recovery >500/μL was 12 days (range: 8–41 days); 90% had a neutrophil recovery >500/μL by day +15. There was no statistical difference in time to neutrophil recovery for patients receiving a salvage versus an early transplantation (P=0.98). The median time to platelet recovery >20,000/μL untransfused was 20 days (range: 10–161); 90% had platelets >20,000/μL untransfused by day 41. There was no statistical difference in time to platelet recovery for patients receiving salvage versus an early transplant (P=0.21).

Toxicities and safety

Grade 3 and higher toxicities are listed in Table 2.

Most notable grade 3 and higher toxicities seen in at least 10% of transplants were related to metabolism/nutrition (60%), gastrointestinal (38%), and infectious problems (35%). The metabolism/nutrition grade 3 toxicities and higher were hypophosphatemia, 40%; hypocalcemia, 29%; hypokalemia, 16%; anorexia requiring total parenteral nutrition, 12%; hyperglycemia, 10%; hyponatremia, 6%; hypoalbuminemia, 2.5%; hypomagnesemia, 2%; hyperkalemia, 2%; and hypernatremia, 0.7%. Since multiple patients had experienced multiple grade 3 or higher metabolism/nutrition toxicities, the total percentage of those different complications was more than the overall total of 60%. The infectious problems (35%) were pneumonia in 8.5%, of which the large majority (6%, nine cases) were viral and caused by human meta-pneumovirus (four cases), para-influenza type 3 (two cases), RSV (one case), influenza A (one case) and cytomegalovirus (CMV) (one case); catheter-related

Table 2 Rate of maximum grade 3–5 and overall toxicity per transplant

	Grade			Overall	
		n	%	n	%
Blood and lymphatic system disorders	3	4	2.6	152	99.3
	4	148	96.7		
Metabolism and nutrition disorders	3	79	51.6	93	60.8
	4	14	9.2		
Other hepatobiliary disorders	3	6	3.9	7	4.6
	4	1	0.7		
Gastrointestinal disorders	3	53	34.6	58	37.9
	4	5	3.3		
Infections and infestations	3	48	31.4	56	36.6
	4	7	4.6		
	5	1	0.7		
Respiratory, thoracic and mediastinal disorders	3	12	7.8	13	8.5
	4	1	0.7		
Cardiac disorders	3	10	6.5	12	7.8
	4	2	1.3		
General disorders and administration site conditions	3	22	14.4	24	15.7
	4	2	1.3		
Vascular disorders	3	17	11.1	18	11.8
	4	1	0.7		
Other bleeding complication	3	2	1.3	3	2
	4	1	0.7		
Nervous system disorders	3	13	8.5	15	9.8
	4	2	1.3		
Other musculoskeletal and connective tissue disorders	3	6	3.9	6	3.9
Psychiatric disorders	3	8	5.2	8	5.2
Other skin and subcutaneous tissue disorders	3	2	1.3	3	2
	4	1	0.7		
Immune system disorders – engraftment syndrome	3	10	6.5	11	7.2
	4	1	0.7		
Renal and urinary disorders	3	10	6.5	11	7.2
	4	1	0.7		
Eye disorders	3	1	0.7	1	0.7

infections in 7%, the majority was related to vancomycin-resistant enterococcus at 4.5%; *Clostridium difficile* colitis in 6%; bacteremia in 6%; CMV reactivation in 2.5%; soft tissue infection in 2%; urinary tract infection in 2%; and esophagitis in 0.7%. No grade 3 peripheral neuropathy was observed. The median time of hospitalization for VTD-MEL patients starting on day −4 was 19 days (range: 8–57 days); the median time for historical controls receiving HDM only (N=112) and starting on day −2 was 18 days (range: 5–53 days) ($P<0.01$). However, when hospitalization was calculated from the day of transplant, the median duration was 15 days (range: 4–53 days) for the study patients compared to 16 days (range: 3–51 days for HDM) ($P=0.61$). The 100-day mortality rate was 2.6% (4/153) for all transplants; 1.8% (2/109) for early transplants, and 4.5% (2/44) for the salvage transplants. None of the four deaths had received a previous transplant. The cause of death was infection related in three patients and respiratory failure in one.

Response rates

Of the 98 patients who were alive at 180 days post-transplant, 56% achieved sCR, 20% CR, 10% very good partial response, 12% partial response, and 1% stable disease; 49% of patients receiving a single transplant achieved sCR compared to 63% for tandem transplants ($P=0.17$). The combined sCR and CR rate was 76%; 70% for the single transplant group and 82% for the tandem transplants ($P=0.16$).

Since 12 patients were already in sCR (n=1) or CR (n=11) prior to transplantation, the effective change in response from non-sCR/CR to sCR/CR after transplantation was 73%.

We observed very high rates of MRD-negative status (85%) at day +180. The MRD-negative group included 55 sCR, 13 CR, 7 very good partial response/near CR (nCR), and 7 partial response patients. Eleven patients were already MRD negative prior to transplant. Among the remaining patients, 83% became MRD following transplant.

Prognostic factors

None of the typical prognostic factors was significantly associated with quality of response (Table 3) or MRD status (Table 4).

The presence of high-risk cytogenetics had no impact on the quality of response at 180 days post-transplant; 12.5% in the high-risk versus 15.3% in the standard risk group remained MRD positive post-transplantation ($P=0.74$). A history of previous transplantation and salvage transplants showed a trend toward a negative impact on quality of response and MRD status.

Table 3 Univariate association between prognostic factors and best response within 180 days post-transplant

Covariate	Level	n	Odds of having sCR or CR				
			OR	95% CI		OR *P*-value	Overall *P*-value
Age (years)	65+	36	0.55	0.21	1.41	0.21	0.21
	<65	62	Ref	–	–	–	
Cytogenetics	High risk	24	1.73	0.52	5.70	0.37	0.37
	Standard Risk	74	Ref	–	–	–	
Previous transplant	No	78	2.80	0.97	8.06	0.06	0.06
	Yes	20	Ref	–	–	–	
Early or salvage	Early	63	2.47	0.95	6.40	0.06	0.06
	Salvage	35	Ref	–	–	–	
Durie-Salmon staging and subclassification at diagnosis	II	12	0.51	0.10	2.57	0.41	0.22
	III	69	1.57	0.43	5.71	0.50	
	I	15	Ref	–	–	–	
ISS	II	32	0.71	0.20	2.56	0.61	0.65
	III	26	0.54	0.15	1.98	0.35	
	I	30	Ref	–	–	–	
R-ISS	II	40	0.18	0.02	1.50	0.11	0.19
	III	11	0.59	0.03	10.48	0.72	
	I	18	Ref	–	–	–	
Tandem or single	Tandem	51	1.98	0.76	5.14	0.16	0.16
	Single	47	Ref	–	–	–	
Creatinine at diagnosis	Units =1	90	0.94	0.82	1.09	0.40	0.40
Albumin at diagnosis	Units =1	90	1.21	0.66	2.22	0.54	0.54
LDH at diagnosis	Units =1	64	2.48	0.57	10.89	0.23	0.23

Abbreviations: CI, confidence interval; LDH, lactate dehydrogenase; OR, odds ratio; ISS, International Staging System; CR, complete response; R-ISS, revised International Staging System; sCR, stringent complete response; Ref, reference.

Table 4 Univariate association between prognostic factors and MRD status within 180-days post-transplant

Covariate	Level	n	Odds of MRD positivity				
			OR	95% CI		OR *P*-value	Overall *P*-value
Age (years)	65+	36	1.83	0.58	5.72	0.30	0.30
	<65	60	Ref	–	–	–	
Cytogenetics	High risk	24	0.79	0.20	3.12	0.74	0.74
	Standard risk	72	Ref	–	–	–	
Previous transplant	No	77	0.56	0.15	2.03	0.38	0.38
	Yes	19	Ref	–	–	–	
Early or salvage	Early	62	0.35	0.11	1.11	0.07	0.07
	Salvage	34	Ref	–	–	–	
Durie-Salmon staging and subclassification at diagnosis	II	11	0.61	0.09	4.14	0.61	0.25
	III	68	0.32	0.08	1.26	0.10	
	I	15	Ref	–	–	–	
ISS	II	31	0.13	0.01	1.14	0.07	0.17
	III	26	0.91	0.24	3.44	0.89	
	I	29	Ref	–	–	–	
R-ISS	II	39	2.91	0.32	26.24	0.34	0.59
	III	11	1.60	0.09	28.56	0.75	
	I	17	Ref	–	–	–	
Tandem or single	Tandem	51	0.86	0.28	2.68	0.80	0.80
	Single	45	Ref	–	–	–	
Creatinine at diagnosis	Units =1	88	0.94	0.72	1.23	0.67	0.67
Albumin at diagnosis	Units =1	88	0.75	0.36	1.53	0.42	0.42
LDH at diagnosis	Units =1	62	0.41	0.05	3.14	0.39	0.39

Abbreviations: CI, confidence interval; LDH, lactate dehydrogenase; MRD, minimal residual disease; OR, odds ratio; ISS, International Staging System; R-ISS, revised International Staging System; Ref, reference.

Discussion

ASCT, especially tandem transplants with HDM, had contributed robustly to the long-term disease control and survival in the pre-novel agent era.[1,9,10,48,49] However, no further improvement in response rate or outcome was observed by the addition of other chemotherapeutic agents to HDM. We have demonstrated that VTD can be added safely to HDM without the need to decrease the dose of melphalan. The Milan group has reported on the combination of VTD with melphalan 100 mg/m^2 in relapsed refractory myeloma patients,[50] but to our knowledge, no reports are available on the combination of VTD with melphalan 200 mg/m^2. VTD-MEL was well tolerated. The high-grade toxicities we observed were predominantly metabolic/nutritional (electrolyte abnormalities, hyperglycemia and need for total parenteral nutrition) and gastrointestinal problems (mucositis, nausea/vomiting and diarrhea), which were controlled relatively easily with available supportive measures, and did not result in an increased mortality or duration of hospitalization when calculated from the date of transplant. Infection-related toxicities were the major cause of early mortality. Infectious complications in general were common. However, the overall incidence of infectious problems was certainly not higher than what has been reported for autologous transplants in myeloma and lymphoma.[51,52] It should also be noted that we included CMV reactivation, which is not routinely checked in most centers after autologous transplantation, and diarrhea related to *C. difficile*. The overall mortality of 2.6% was comparable to historical mortality data with HDM.[53–55] However, it must be noted that all deaths, except one, occurred in the first year after the introduction of this trial regimen in our institution. The higher mortality in the first year of the study could also have been at least partially attributable to the unexpectedly high incidence of fatal human meta-pneumovirus infections, involving the lower respiratory tract, as substantiated by bronchoalveolar lavage; a high mortality rate in such patients had been reported previously.[56] We did not observe increased toxicity in patients with extensive prior treatment, including the 20 patients who had a prior transplant. There was no mortality in this subgroup. There was no grade 3 peripheral neuropathy during the first 100 days after transplantation, probably due to the limited administration of bortezomib and thalidomide in the peri-transplant period. Thirty-seven percent of our patients were aged >65 years and showed no significant increase in toxicity or mortality. Studies evaluating transplantation in patients aged ≥65 years have found that ASCT continues to have a positive impact on survival, not too dissimilar from the younger population.[57,58] Additionally,

a recent SEER database analysis reported that ASCT in patients aged >65 years is cost-effective compared to conventional chemotherapy only.[59]

VTD-MEL was an effective regimen, resulting in 56% sCR and 20% CR rates and 85% MRD negative rate at day +180 in a heterogeneous group of patients receiving early or salvage transplantation. The reason why the MRD rate is higher in our study than the sCR rate is related to the fact that patients with sCR had to be MRD-negative by definition to fulfill the criterion of absence of clonal plasma cells in the bone marrow, since no immunohistochemistry for cytoplasmic kappa/lambda was performed on our bone marrow samples. Some of these MRD-negative patients still had a positive serum immunofixation or a marginally abnormal serum-free light chain ratio. It could be argued that some of these excellent responses might have been partly related to the consolidation therapy with VTD, which was started around day +50. However, it is well known that the maximal response to transplantation without consolidation/maintenance is not seen until 3 to 6 months after the transplant. The ultimate proof of better efficacy of a new anti-myeloma approach is an improved overall survival (OS) with good quality of life, limited toxicity, and a long time off all therapy. However, this requires a long follow-up of at least 7 to 10 years. Therefore, early surrogate markers for better OS are necessary. The best surrogate markers available are attainment of an sCR and/or an MRD-negative status after transplantation. A Mayo Clinic retrospective study by Kapoor et al on 445 consecutive ASCT patients, receiving a transplant within 12 months after diagnosis, reported a significantly increased 5-year OS in patients achieving an sCR compared to other outcomes.[60] sCR was attained at any time post-transplantation in 25% of such patients; the median follow-up after ASCT in this study was 77 months. The median time to progression (TTP) from ASCT for patients achieving sCR was significantly longer (50 months) than that of patients achieving only a CR or nCR (20 and 19 months, respectively). On multivariate analysis, post-ASCT sCR was an independent prognostic factor for survival (hazard ratio, 0.44; 95% confidence interval, 0.25 to 0.80; vs CR; P=0.008). However, the importance of achieving an sCR was challenged in a recent report from the GEM/Pethema group.[61] In their retrospective analysis of 94 patients achieving either CR or sCR, no significant benefit was derived from attaining an sCR versus CR, while patients who were MRD negative, as assessed by MFC with a sensitivity of 10^{-4}, had a significantly superior outcome with a median TTP of 68 versus 45 months, respectively (P=0.03); the median follow-up was >65 months. The key point of the paper was that achieving an MRD-negative A status was more important than the normalization of the serum free light chain ratio. Unfortunately, the paper does not provide any information about the frequency of sCR in their patients. Also, this paper combined results of two different trials, one in transplant-eligible patients and another in transplant-ineligible patients. In these two trials combined, only 69 achieved an sCR, and approximately one-half of those had received an ASCT.

Achieving an MRD-negative status is a powerful predictor of progression-free survival (PFS) and OS in hematologic malignancies such as acute lymphoblastic leukemia, and it is considered an early surrogate endpoint of efficacy of a new treatment modality in those diseases.[62–64] Paiva et al were the first to show in a prospective study including 295 newly diagnosed myeloma patients uniformly treated with ASCT, that MFC with a sensitivity of 10^{-4} was the most relevant prognostic factor.[65] With a median follow-up of 57 months, median PFS was 71 months and median OS was not reached for patients attaining a MRD-negative status (42% of all patients) at day 100 post-transplantation, versus 37 and 89 months, respectively, for the MRD-positive patients (P<0.001 and P=0.002). Similarly, Rawstron et al, also using MFC with a sensitivity of 10^{-4}, reported on results of the Medical Research Council myeloma IX study,[66] which included 397 newly diagnosed myeloma patients who were treated with ASCT. At day 100 after transplantation, 62% were MRD negative. A MRD-positive status was associated with a significantly inferior PFS (15.5 versus 28.6 months; P<0.001) and OS (59 versus 80.6 months; P=0.018) and was found to be an independent prognostic factor for survival. These data strongly support the role of MRD assessment as a surrogate endpoint for OS in clinical trials. In an MRD study using deep sequencing in patients who had achieved at least a very good partial response after front-line therapy, a significant difference in outcome was observed according to different levels of MRD; median TTP for MRD $\geq 10^{-3}$ was 27 months; for MRD 10^{-3} to 10^{-5} 48 months and for MRD $<10^{-5}$, it was 80 months (P=0.003–0.0001).[67] Thus, a further increase in sensitivity of MFC is likely to increase its prognostic significance. Interestingly and encouragingly, a similar outcome advantage was observed in patients with favorable and adverse cytogenetics.[66,68] In the latter study on 31 newly diagnosed MM patients treated in a Phase II study with RVD induction and consolidation plus transplantation, 58% achieved a CR and 68% achieved an MRD-negative status.[68] In our study, the presence of poor prognosis markers such as high-risk cytogenetics had no impact on the quality of response.

A recent study by Jiminez-Zepeda et al appears to support the superiority of adding novel agents to HDM.[69] They compared quality of response with bortezomib and HDM to HDM only in a non-randomized fashion. At 100 days, the CR rate was 22% in the bortezomib–HDM arm versus 9% in the HDM only; the CR/nCR rates were 41% versus 15% (P=0.025). A higher response rate was also noted in high-risk patients treated with bortezomib–HDM (P=0.059). MRD-negative CRs were observed in 19.6% in the bortezomib–HDM arm versus 4.5% in the HDM only (P=0.008). Paiva et al recently published an interesting study on 40 newly-diagnosed elderly patients with MM who were transplant ineligible, and analyzed the phenotypic and genomic characteristics of the MM cells still present after nine cycles of induction therapy.[70] They showed that these MRD cells overexpressed integrins, chemokine receptors, and adhesion molecules by flow cytometry. Since IMiDs and proteasome inhibitors target adhesion of myeloma cells to the stroma, it may explain, at least partially, why the addition of VTD to HDM resulted in deeper responses.

The limitations of our study are the retrospective design and lack of a standard HDM control arm. However, the very high sCR and MRD-negative rate obtained with VTD-MEL without a significant increase in toxicity are sufficiently encouraging to make this the new standard induction regimen for myeloma transplants if our data can be confirmed in a randomized trial versus HDM alone.

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Author contributions

KN, KKSA, FZ and GT provided concept and design. SLM performed all statistical analyses. LD, AT and AS collected and assembled the data. SB coordinated all patient care. All authors assisted with manuscript preparation and meet the authorship criteria. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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