International Journal of Research in Medical Sciences
Ray V et al. Int J Res Med Sci. 2025 Feb;13(2):714-721
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20250242

Original Research Article

Comparing diagnostic PET versus response PET at the 16th week induction and it's correlation with MFC MRD: a deeper look into myeloma genomics

Vedanta Ray[1]*, Uddiptya Goswami[2], Mages Sarvanen[3], Ramya Ananthakrishnan[1], Kumanan Jayaraman[1], Raja Thirumalairaj[1]

[1]Department of Medical Oncology, Apollo Cancer Centre, Chennai, India
[2]Department of Nuclear Medicine, Apollo Cancer Centre, Chennai, India

Received: 25 November 2024
Revised: 12 December 2024
Accepted: 28 December 2024

***Correspondence:**
Dr. Vedanta Ray,
E-mail: vedanta.roy@gmail.com

ABSTRACT

Background: Multiple Myeloma is a heterogenous disease. A homogenous approach to a heterogeneous disease is discouraged as more and more data evolves. Diagnostic PET is recorded for measuring the disease burden along with metabolic uptake of the burden. Minimal residual disease (MRD) measurement at the end of induction, consolidation and pre-maintenance have been looked into by multiple authors. Also, follow-up PET is done at multiple time points by multiple authors and has been correlated with molecular response. In this study, we shall correlate PET response post 16 weeks of induction and MRD assay.
Methods: We have a retrospective analysis of the newly diagnosed multiple Myeloma (NDMM) with all the baseline data available at our centre and received the standard induction regimen for 16 weeks and the follow-up data was analyzed.
Results: At the end of the 16th week of induction, 41 patients were in complete resolution in PET. Of them, 26 had MRD detected and 15 had no MRD detected. Ten patients had stable disease, with all of them positive for MRD. One patient with positive MRD was having a partial response. Four patients with detectable MRD had progressive disease on PET, with (p=0.058).
Conclusions: MRD should be correlated with follow-up FDG PET/CT for a comprehensive evaluation of treatment response. We firmly believe that the genome of the disease drives the disease and definitely, MRD-PET correlation should be attributed to genomics.

Keywords: Induction, Minimal residual disease, Newly diagnosed multiple myeloma, PET/CT

INTRODUCTION

Multiple myeloma (MM) is a slow-growing, systemic crippling disease, making it a debilitating pathology as far as quality of life is concerned. The key to solving the treatment-molecular response puzzle for plasma cell disorders is to develop a sensitive instrument to periodically measure the residual clonal burden at the deepest level of the tumor microenvironment (TME).[1] The process of defining and selecting this prediction approach, as well as the correlation between MRD and success or failure, has seen a benchmark evolution. MRD negativity is defined as the absence of a tumor cell detection per 10^-5 to 10^-7 events, provided the limit of quantification (LOQ) and limit of detection (LOD) has been standardized. It is known that clinico-pathological kinetics prior to standard triplet or quadruplet induction shows a promising result, especially in terms of resolution in the patient's physiological metabolic values, but the in-depth deepest response in TME is the subject of importance in

today's myeloma puzzle. Pre-induction high-risk cytogenetics has been established to show a poor molecular outcome, as far as MRD is taken into account.[2] Now, the methodology of doing this sensitive assay has evolved over time, from 3 color-single-tube colorimetry to today's 13 color-single-tube-colorimetry to PCR-based assay and finally NGS based assay.[3]

Apart from obeying IMWG response criteria in the treatment paradigm, attention to the genomic build of the disease remains the cornerstone. Also, there has been a significant evolution in radiological impressions of the disease over the past two decades. Numerous studies, notably by Zamagni and colleagues', have demonstrated that FDG PET/CT has great sensitivity and specificity ranges from 80% to 100% for identifying osteolytic myeloma lesions. Also, there are studies where both MR and FDG PET/CT imaging modalities demonstrated equivalent success in detecting localized lesions in the spine of myeloma patients.[4] With more and more emerging data, IMWG has suggested the utilization of both sensitive bone marrow-based tests and functional imaging methods with the ability to identify MRD beyond the confines of the bone marrow. The recent FORTE trial's discrepancy between bone marrow MFC MRD and PET MRD has also opened a lot of discussion between the induction intensification versus marrow response versus radiological residue and the impact of cytogenetic profile. FORTE did this observation at the end of ASCT before starting the maintenance.[5] Our study shall look into the at-the-end-induction PET's residual disease with MFC MRD and the diseases' genomic-built as a novel approach to guide the disease/treatment interface-paradigm.

The main Objective of the study is to compare diagnostic FDG-PET/CT with at-the-end-of-16th-week-induction PET/CT, establish a correlation with MFC MRD assessment and correlate myeloma genome and radiological response.

Primary objective

PET response at the end of the 16th week of induction therapy

Secondary objective

MFC MRD assay at the end of the 16th week and cytogenetic assay at the end of the 16th week.

METHODS

Our study is retrospective, from August 2022 to April 2024. Patients who have been newly diagnosed with Multiple Myeloma, with all the diagnostic evaluation data available, have received 4 cycles of first-line induction therapy at Apollo Cancer Centre, Teynampet, Chennai. All the NDMM patients were treated with standard triplet/quadruplet induction therapy and at the end of the 16th week, post-induction MRD was measured in the institution with all the follow-up metabolic-serologic-radiological data available as well. Any other malignancies associated (synchronous or metachronous) with multiple myeloma, smouldering myeloma and relapse/refractory subjects were excluded from the study. All the patients' diagnostic metabolic, radiological and serological data were maintained in MS Excel sheets. At the end of the third or fourth month from the beginning of the therapy, patients who had completed 4 cycles of induction were followed up in the OPD with relevant investigations, including response-PET/CT. Diagnostic FISH was done to capture the chromosomal rearrangements at the baseline using the FISH panel as shown in Table 2.

Patients who had an added aberration along with high risk cytogenetic(s) signature, were labelled complex cytogenetic(s), as per mSMART 4.02. In the diagnostic PET, we recorded the median standardized uptake value (SUV) of the mediastinal pool and hepatic pool, as well as the baseline SUV of all the focal lesions, bone marrow and liver, including the morphological dimensions in the CT component at the baseline. Type of therapy, clinical, biochemical and radiological response were correlated with the MRD response (with MFC). Also, the PET/CT was correlated with the genomic build of the patient at the baseline and compared with the response PET/CT and its correlation with MFC MRD. MFC assay has been done as per the panel shown in table 3. The data was maintained in an Excel sheet and will be updated in the SPSS worksheet and statistical analysis was done using the same SPSS version 29.0.

Myeloma MRD processing SOP followed in our study

Procedure for preparation

Label a clean test tube with the patient's name, add 4 ml of Optilyse C to 0.5 ml of BMA / PB sample and leave it for 15 minutes. Centrifuge for 5 minutes at 2000 rpm and discard the supernatant. Add 4 ml of PBS, mix well, centrifuge at 2500 rpm and discard the supernatant. Repeat the washing process 3 times until the RBC debris is removed completely. To the cell pellet, add 1 ml of PBS and mix well to resuspend cells. If any clot is present, the sample is filtered.

Label a clean tube with the patient's name and add the antibodies: CD56, CD10, CD38, CD138, CD19, CD27, CD81, CD117, CD319 and CD45. Add 100 µl of the patient cell suspension to the antibody cocktail in the tube. Incubate for 20 minutes at room temperature. Add 3 ml of PBS & mix well centrifuge at 2500 rpm and discard the supernatant.To the cell pellet, add 1 ml of PBS and mix well to resuspend the cells. 5.0 million events are acquired for analysis of phenotyping

Procedure for cytoplasmic staining used in our study

After the routine surface markers staining, add 20 µl of Reagent 1 from the prefix NC kit, mix well and incubate

for 15 minutes. Add 200 µl of reagent 2, mix well and wait for 5 minutes, then add 10 µl of the required cytoplasmic marker, cyto Kappa, cyto Lambda, etc. and incubate for 20 minutes. Add 4 ml of PBS and wash one time. Resuspend the pellet with 2 ml of PBS and acquire the events in the flow cytometer. We have standardized MRD at our institute using 13 color-one tube-3 laser MFC to detect myeloma cells per 10^5 events as LoQ, with 10^6 event(s) as LoD.[6]

Methodology for imaging study

Newly diagnosed multiple Myeloma (NDMM) patients underwent FDG PET/CT at multiple time points, including diagnostic/pre-induction and at the end of the 16th-week induction. Patient preparation and Procedure were performed according to EANM 2015 guidelines for FDG-PET/CT as follows-Patients were asked to visit the Department of PET/CT and Theranostics, Apollo Cancer Centre, Teynampet, Chennai, with 6 hours of fasting and adequate hydration - at least 1 litre of water 2 2 hours prior to the scan. After a thorough history, clinical evaluation and biochemical correlation, patients were administered 0.1 mCi/kg of F18-FDG intravenously through an IV cannula. Patients were isolated and made to rest in a quite dim-lit room for 45 minutes.

Patients were asked to void immediately prior to the scan to empty the bladder and improve background clearance.[7] F-18 FDG-PET/CT was acquired from head to toe without administration of intravenous contrast in Siemens Biograph 450 digital PET/CT and image analysis was done using Syngovia image analysis software by experienced nuclear medicine physicians with exclusive exposure in multiple Myeloma PET/CT.

Qualitative visual analysis of the study was done using Deauville criteria with a score assigned to the most avid lesion of the patient. Deauville scoring is as follows: no significant uptake, uptake less than mediastinal blood pool, uptake more than mediastinal blood pool but less than or equal to liver uptake, uptake moderately higher than liver, uptake markedly higher than liver or appearance of new lesions in a follow-up study. A

Deauville score of less than 2 indicates a negative study or CMR. Deauville score 3 – equivocal response; a score of 4 or more indicates the high metabolic activity of disease or disease progression in a follow-up study.[8]

Statistical analysis

Statistical analysis was performed using IBM statistical software, SPSS Statistics version 29 (IBM Inc.). The assumption of normality was evaluated using the Shapiro-Wilk test. Outliers were identified on visual inspection of the box plots. Statistically significant differences between the means of two or more independent groups were evaluated using one-way analysis of variance (ANOVA). The chi-square test of correlation shall be used to assess the associations between categorical variables. Univariate analysis has been conducted to assess the impact on MFC MRD of various prognostic factors, including age, myeloma subtype, baseline PET as well as response PET, Revised International Staging System (R-ISS) stage, interphase fluorescent in situ hybridization (FISH) cytogenetics at baseline and type of induction therapy, response metabolic parameters, at-the-response-FISH assay. The paired-sample t-test was used to determine whether the mean difference between paired observations was statistically significantly different from zero. The independent-sample t-test was used to determine if a difference exists between the means of two independent groups on a continuous dependent variable. To lower the risk of type I errors, the statistical significance level was set at p less than 0.05.

RESULTS

Of the 56 patients, 33 of the total patients were male, 23 were female. 27 of the total patients were fully active with ECOG 0, 27 had restricted movement with ECOG 2, whereas 2 had ECOG 1 score, as shown in Table 4. 28 patients were grouped as age above 65 years and 28 patients were below 65 years. Of the 56 patients, 24 patients were ISS-I, 15 patients were ISS-II and 17 patients were ISS-III. Also 14 patients were R-ISS I, 32 patients were R-ISS II and 9 patients were R-ISS III and 1 patient could not be staged. 14 patients were staged as per R2-ISS, where 11 patients were R2-ISS intermediate stage, 3 patients were R2-ISS were high risk and the rest 75% of patients were not under the purview of R2-ISS staging, as shown in Table 4.

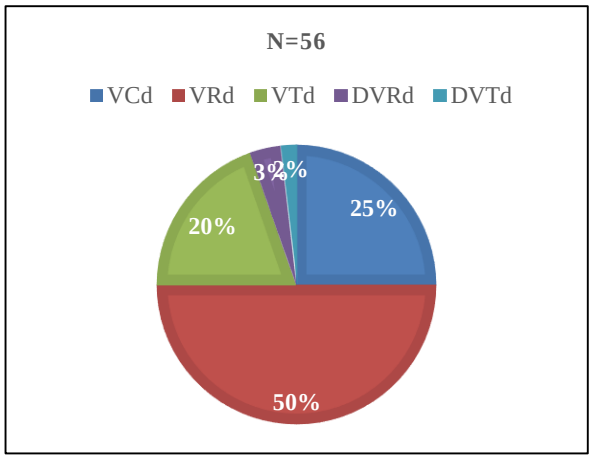

Figure 1: Patient distribution as per induction regimen.

39 patients had normal karyotypes, 13 patients had complex karyotypes and 4 patients' karyotype details were not available at baseline. As per the diagnostic FISH done at the baseline, 14 patients (25%) had no cytogenetic rearrangement, 40 patients (71.4%) had high risk cytogenetic aberration(s)(HRCA)/complex aberration(s),

1 patient (1.8%) had standard risk mutation and one patient (1.8%) had no data available, depicted in Table 4.

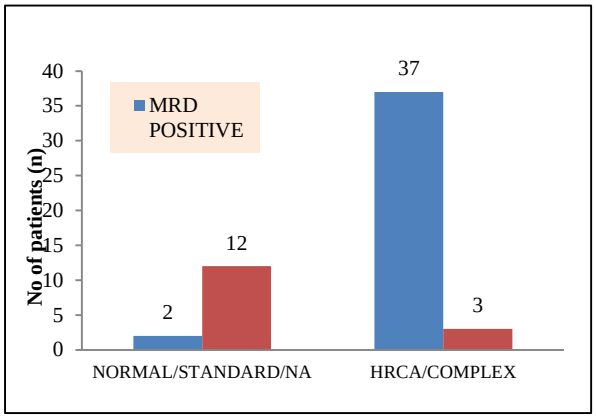

Figure 2: Diagnostic FISH and MRD (p<0.001).

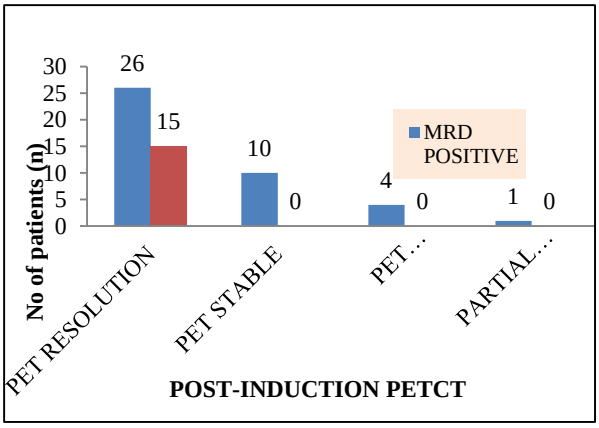

Figure 3: Post-induction PET and MRD (p<0.05).

Also, we have compared the disease burden as shown in the diagnostic PET and has been compared with the post-16th-week induction follow-up PET and has been correlated with minimal residual disease (MRD) detection, as shown in Table 5 and Figure 3. Also, diagnostic FISH and MRD correlation has been shown, in Figure 2. Fourteen patients received induction using VCd (Bortezomib-Cyclophosphamide-Dexamethasone) regimen; twenty-eight patients received VRd (Bortezomib-Lenalidomide-Dexamethasone), eleven patients had VTd (bortezomib-thalidomide-dexamethasone) induction, two patients Dara-VRd (daratumumab-bortezomib-lenalidomide-dexamethasone), one patient received Dara-VTd (Daratumumab-Bortezomib-Thalidomide-Dexamethasone), shown in Figure 1. Of the 28 patients who were treated with VRd, 19 patients achieved PET complete metabolic resolution at the end of the 16th week of induction, with 2 patients having standard risk mutations, with one patient (1.8%) achieving MRD negativity, but the other patient (1.8%) had MRD detected. Eight patients (28.5%) with HRCA/Complex cytogenetic(s) were in PET-CMR at the end-of-16th weeks induction, with MRD detection, as shown in Table 5.

Nine patients (32.4%) who were not in PET-CMR also had MRD detection, as explained per disease biology. Also, nine patients (32.1%) were in PET-CMR, with no MRD detection, as shown in table 5. Fourteen patients (25%) who were treated with VCd, had 9 patients in metabolic resolution on PET(PET-CMR), of which 6 patients had MRD detection (42.8%) explained by it's cytogenetic aberration(s), two patients (14.2%) had no cytogenetic aberration(s) and one patient (7%) had no baseline cytogenetic data available.

Five patients who were not in PET-CMR had MRD detection, owing to it's high risk cytogenetic(s), as depicted in Table 5 (p=0.001). Eleven patients (19.6%) were treated with VTd, of whom 5 patients (45%) with HRCA/complex cytogenetic(s) were in PET-CMR with MRD detected at the end of 16 weeks induction, as could be explained by it's disease cytogenetic(s) and also 2 more patients (18%) with no baseline cytogenetic(s) rearrangement, were in PET-CMR but one patient each had MRD detection and no detection, respectively.

Also, 4 patients (37%) who had HRCA/complex cytogenetic(s) were not in PET-CMR and had MRD detected. Two patients (3.5%) who were treated with Dara-VRD, both had achieved PET-CMR with no MRD detection; one patient each had HRCA/complex cytogenetic(s) and no rearrangement, respectively. Also, we had one patient (1.9%) who was treated with 16 weeks induction protocol, had HRCA/complex cytogenetic(s) had MRD detection despite being in PET-CMR. Among the triplet therapy exposed patients, the rate of MRD not detected is highest among VRd (48%), followed by VCd (20%) and lowest among VTd-exposed patients (14%)(p=0.001).

Table 1: Deauville criteria and interpretation.

Score	Visual assessment	Interpretation
1	No significant uptake	Negative study (complete metabolic response/resolution)
2	Uptake<MBP	
3	MBP<Uptake< Liver	Equivocal
4	Uptake>Liver	Positive study (progression / stable disease)
5	Uptake>>Liver or appearance of new lesions	

Table 2: FISH panel used for multiple myeloma.

Aberration	Probe	Cells scored
IGH rearrangement	Vysis LSI IGH Dual color, break apart rearrangement probe	400
t (4;14) (p16;q32) FGFR3-IGH	Vysis IGH/FGFR3 Dual Fusion FISH probe	400
t (11;14) (q13;q32) CCND1-IGH	MetaSystem IGH/CCND1 Dual Fusion FISH probe	400
t (14;16) (q32; q23) IGH-MAF	Vysis IGH/MAF Dual Fusion FISH probe	400
t (14;20) (q32;q12) IGH-MAFB	MetaSystems XL IGH/MAFB Dual fusion probe	400
Hyperdiploidy 5, 9 & 15	MetaSystem XL 5p15/9q22/15q22 (Spectrum orange/green/blue) probe	400
17p (TP53) deletion	Vysis LSI TP53/CEP 17 FISH probe	400
13q deletion	CytoTest D13S319/13q34 FISH probe	400
Del1p32/dup1q21	MetaSystem 1p32/1q21 Deletion/Amplification probe	400
t(8;14)(q24;q32) IGH-Cmyc	Vysis LSI IGH/MYC/CEP 8 Tri-color dual fusion probe	400

Table 3: Antibody panels used in detecting MRD assay treated with conventional therapy and also with daratumumab (In cases treated with daratumumab, initial gating of plasms cells is done with CD 319 and not CD 38).

Tube No.	MM tube
FITC	Cyto kappa
PE	Cyto lambda
ECD	CD56
PC5.5	CD138
PC7	CD38
APC	BCMA
APC700	CD19
APC750	CD27
PB	CD81
KO	CD45
BV605	CD117
BV711	CD319
BV786	CD200

Table 4: Descriptive table of patient, ECOG, stage and induction regimen.

Characteristics	N (%)		P value
Gender	Male	33 (59)	0.053
	Female	23 (41)	
Age	Less than 65 years	28 (50)	0.365
	More than 65 years	28 (50)	
ECOG	0	27 (48)	0.210
	1	02 (04)	
	2	27 (48)	
ISS stage	I	24 (43)	0.001
	II	15 (27)	
	III	17 (30)	
RISS stage	I	14 (25)	0.001
	II	32 (57)	
	III	09 (16)	
	NA	01 (02)	
R2ISS stage	intermediate	11 (20)	0.152
	HIGH	03 (05)	
	not applicable	42 (75)	
Induction	VRd	28 (50)	0.043

Continued.

Characteristics	N (%)		P value
	VCd	14 (25)	
	VTd	11 (20)	
	Dara-VRd	02 (03)	
	Dara-VTd	01 (02)	
Diagnostic FISH	No rearrangement	14 (25)	0.001
	Standard risk	01 (1.8)	
	HRCA/Complex	40 (71.4)	
	NA	01 (1.8)	
Post-induction PET	Complete Metabolic Response (CMR)	41 (73.2)	0.05
	Not CMR	15 (26.8)	
IMWG conventional response	sCR	05	0.001
	CR	15	
	VGPR	28	
	PR	06	
	PD	02	

Table 5: Comparison and correlation of diagnostic FISH cytogenetic aberration(s) with post-induction PET at 16th week end-of-induction and MRD assessment.

Regimen N (%)	Cytogenetic aberration(s)	N (%)	Post 16th week induction PET	MRD at 10^-5
VRD 28 (50)	Standard risk	1 (3.5)	Complete Metabolic response (CMR)	Not detected
		1 (3.5)	Complete Metabolic response	Detected
	HRCA/Complex	8 (28.5)	Complete Metabolic response	Detected
		9 (32.4)	Not CMR	
	Negative for rearrangement	9 (32.1)	Complete Metabolic response	Not detected
VCD 14 (25)	HRCA/Complex	6 (42.8)	Complete Metabolic response	Detected
		5 (36)	Not CMR	
	Negative for rearrangement	2 (14.2)	Complete Metabolic response	Not detected
	Not available	1 (7)	Complete Metabolic response	Detected
VTD 11 (19.6)	HRCA/Complex	5 (45)	Complete Metabolic response	Detected
		4 (37)	Not CMR	
	Negative for rearrangement	1 (9)	Complete Metabolic response	Not detected
		1 (9)	Complete Metabolic response	Detected
DVRD 2 (3.5)	HRCA/Complex	1 (50)	Complete Metabolic response (CMR)	Not detected
	Negative for rearrangement	1 (50)	Complete Metabolic response	Not detected
DVTD 1 (1.9)	HRCA/Complex	1 (100)	Complete Metabolic response (CMR)	Detected

(p=0.001)

DISCUSSION

In 2011, Zamagni et al, reported that diagnostic PET and post-transplant PET correlation could decide the PFS and, subsequently, the OS4. In the study, close to 50% of the study population was in ISS II and III, whereas in our study, with 56 patients, 24 patients were ISS-I, 15 patients were ISS-II and 17 patients were ISS-III.

Of the 192 patients who underwent PET study, around 81 patients had del 13q, del 17p, t(4;14), combined, whereas all our study subjects have undergone diagnostic PET; and majorly, we had 40 patients (71.4%) with high-risk cytogenetic aberration(HRCA)/complex cytogenetics, as depicted in Table 4. The study treated its patients with thalidomide-dexamethasone (TD) followed by autologous stem cell transplant (AuSCT)4. In contrast, our study had a majority, 28 patients (50%) were treated with VRd and 11 patients (20%) were treated with VTd. We shall discuss how our VTd patients did post-exposure with respect to PET-MFC MRD correlation. In the above-mentioned study, post-AuSCT, the CR and above rate (%), VGPR and above rate (%) were 58% and 80%, respectively. In our study, as shown in table 4. 4 patients (36%) achieved CR, 4 (36%) patients achieved VGPR, 2 patients (18%) achieved PR and 1 patient (10%) had disease progression, at the end of 16th-week induction.

Also, we have showcased PET-MRD response evaluation in all eleven patients in table 5. Of the 4 patients who were in CR at the end of the 16th week of VTd induction, all four patients achieved PET resolution. In four patients who were in VGPR at the end of induction post-VTd exposure, 3 patients (75%) achieved PET resolution and 1 patient had PET-stable disease, as shown in Table 5. One patient who had achieved IMWG partial response (PR) had PET progression, whereas another patient in PR had PET stable at the end of the 16th week of induction. One patient who had progressive disease had radiological progression as well, as shown in Table 5. One patient who was treated with VTd and was in CR had no MRD detectable, but the rest all the three patients who were in CR had MRD detected at the end of the 16th week of induction. Rest all the patients who were in VGPR, PR and progressive disease had MRD detection. This variation has imminent genomic implications, as charted in Table 5, which has recorded diagnostic FISH and follow-up FISH at the end of the 16th-week induction.

In the FORTE study by Zamagni et al, it has been demonstrated that KRd plus AuSCT had comparable PFS and OS as KRd12, but both the regimens showed superior outcomes as compared to KCd plus AuSCT. Both cytogenetic high-risk and ISS II/III had more PET negativity with MFC negativity, as well in the former two regimens than in the latter.[5] In our study, all five patients who had sCR after 16 weeks of VRd had no MRD detection and had achieved PET resolution, upholding the PET CMR-MFC MRD correlation.[5,9]

Of those 5 sCR patients, all had no chromosomal rearrangements, except one patient, who had standard risk mutation along with 11q gain, as shown in Table 5. We have discussed VTd-exposed patients in depth in the previous section. Among the VRd-exposed subjects, six patients were in CR after 16 weeks of VRd; of them, 2 patients had MRD detection, rest had no MRD detected. Also, two patients who had PET-stable disease(not PET-CMR) had MRD detected, whereas the rest of the VRd exposed had complete metabolic response in PET (PET-CMR). Fourteen patients who were in VGPR, only two patients, had achieved PET resolution and MRD remained undetectable.

Both had no chromosomal rearrangement at the baseline, showing a strong PET-MFC correlation, as shown in Table 5. Of the twelve patients who had MRD detected, nine were in PET-CMR and rest had PET stable disease. One of the patient, despite having standard risk mutation, has MRD detection, but PET resolution was achieved, as discussed. The MFC behaviour is explained by the complexity of the chromosomal aberrations, as mentioned in Table 5, but the PET behaviour may be attributed to metabolic clonal load, which considers both the intramedullary and extramedullary site(s).

Two patients, who had achieved IMWG PR post 16 weeks of VRd, of whom one had PET resolution and the other had PET stable disease, despite both having MRD detected, at the end of induction. As per Table 5, it's evident that HRCA/complex cytogenetic(s) was the reason for MRD detection and also the reason for not achieving PET remission (p=0.001). The patient, who had PD, with PET progression (not CMR) and MRD detected, were explained by HRCA/complex cytogenetic(s). In the VCd treated 14 patients, none achieved sCR after 16 weeks of VCd, however 6 patients were in CR with PET resolution (PET-CMR). Two patients, who had no MRD detected, were negative for any chromosomal aberration. As per table 4 and table 5, seven patients had achieved VGPR, with MRD detection in all, after 16 weeks of VCd. Interestingly, PET response was not coherent with MFC MRD, as also depicted in Figure 3 (p=0.001). The high risk cytogenetic aberration(s), clearly explains the aberrant behaviour of discordance, between PET and MFC, as shown in Table 5. Only one patient had partial response, with PET progression and MRD detection, explained by the HRCA/Complex cytogenetic(s). We had 3 patients treated with Daratumumab based quadruplet, with all three of them achieving VGPR and PET resolution. One patient had MRD detected at the end of 16 weeks of Dara-VTd induction, but the other 2 patients treated with Dara-VRd had no MRD detection, as show in Table 5.

It's quite evident from our document, that, deeper molecular response is strongly governed by cytogenetic aberration(s).

The incoherent pattern of MFC and PET discordance, strongly upholds, the paper by Paiva et al, where it was demonstrated that immunophenotypic load is determined by genomic(s), as the author extensively correlated immunophenotype markers at the baseline and post AuSCT and strongly upheld the contribution of genomics, as was shown in genomic expression profiling (GEP), then. Though, our document has not performed GEP, but, extensive cytogenetic aberration data, as per our available data, clearly states that cytogenetic aberration(s) governs both MFC MRD and also the PET response, as depicted in table 5.[10]

CONCLUSION

Multiple Myeloma is a heterogenous disease, as determined by it's genomic built. The molecular heterogeneity replicates in it's pattern of PET response and definitely in the MFC MRD response. GEP may be beyond the scope of majority of the centres, but FISH remains the cornerstone to record the cytogenetic alterations. This document has strongly upheld the concept, that cytogenetic-aberration(s), PET imaging and MFC MRD are correlating and upholds the literature available till date.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Heider M, Nickel K, Högner M, Bassermann F. Multiple myeloma: molecular pathogenesis and disease evolution. Oncol Res Treat. 2021;44(12):672–81.
2. Kumar S, Fonseca R, Ketterling RP, Dispenzieri A, Lacy MQ, Gertz MA, et al. Trisomies in multiple Myeloma: impact on survival in patients with high-risk cytogenetics. Blood. 2012;119(9):2100–5.
3. Kostopoulos IV, Ntanasis-Stathopoulos I, Gavriatopoulou M, Tsitsilonis OE, Terpos E. Minimal residual disease in multiple myeloma: current landscape and future applications with immunotherapeutic approaches. Front Oncol. 2020;10:860.
4. Zamagni E, Patriarca F, Nanni C, Zannetti B, Englaro E, Pezzi A, et al. Prognostic relevance of 18-F FDG PET/CT in newly diagnosed multiple myeloma patients treated with up-front autologous transplantation. Blood. 2011;118(23):5989–95.
5. Zamagni E, Oliva S, Gay F, Capra A, Rota-Scalabrini D, D'Agostino M, et al. Impact of minimal residual disease standardised assessment by FDG-PET/CT in transplant-eligible patients with newly diagnosed multiple Myeloma enrolled in the imaging sub-study of the FORTE trial. E Clinical Medicine. 2023;60:102017.
6. Costa LJ, Derman BA, Bal S, Sidana S, Chhabra S, Silbermann R, et al. International harmonization in performing and reporting minimal residual disease assessment in multiple myeloma trials. Leukemia. 2021;35(1):18–30.
7. Boellaard R, Delgado-Bolton R, Oyen WJ, Giammarile F, Tatsch K, Eschner W, Verzijlbergen FJ, Barrington SF, Pike LC, Weber WA, Stroobants S. FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. European J Nucl Med and Molec Imag. 2015;42:328-54.
8. Zamagni E, Nanni C, Dozza L, Carlier T, Bailly C, Tacchetti P, et al. Standardization of 18F-FDG-PET/CT According to deauville criteria for metabolic complete response definition in newly diagnosed multiple myeloma. J Clin Oncol Off J Am Soc Clin Oncol. 2021;10;39(2):116–25.
9. Zamagni E, Nanni C, Gay F, Dozza L, Rota Scalabrini D, Omedé P, et al. MRD Evaluation By PET/CT according to deauville criteria combined with multiparameter flow cytometry in newly diagnosed transplant eligible multiple myeloma (MM). Blood. 2019;134(1):4321.
10. Paiva B, Corchete LA, Vidriales MB, Puig N, Maiso P, Rodriguez I, et al. Phenotypic and genomic analysis of multiple myeloma minimal patients enrolled in the phase ii randomized forte trial residual disease tumor cells: a new model to understand chemoresistance. Blood. 2016;127(15):1896–906.

Cite this article as: Ray V, Goswami U, Sarvanen M, Ananthakrishnan R, Jayaraman K, Thirumalairaj R. Comparing diagnostic PET versus response PET at the 16th week induction and it's correlation with MFC MRD: a deeper look into myeloma genomics. Int J Res Med Sci 2025;13:714-21.