

Case series: MRD negativity assessment using ^{11}C -Acetate PET with 3-weekly daratumumab-based quadruplet induction in newly diagnosed multiple myeloma

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Abstract: Complete response (CR) is an important favorable factor for survival in multiple myeloma (MM). However, CR patients continue to relapse, especially in the presence of minimal residual disease (MRD). Bone marrow (BM) MRD is predictive of progression-free survival (PFS) in MM. However, myeloma outside the BM aspiration site may result in subsequent relapse despite MRD-negativity. Therefore, positron emission tomography-computed tomography (PET-CT) based on F-fluorodeoxyglucose (FDG) is a complementary tool to monitor residual disease in MM. However, FDG may miss myeloma lesions that are not FDG-avid. On the other hand, ^{11}C -Acetate (ACT) has been found to be a more sensitive and specific tracer than FDG in MM. Recently, the addition of daratumumab to bortezomib, thalidomide, dexamethasone (VTd) or bortezomib, lenalidomide, dexamethasone (VRd) backbone has been proven to improve outcomes. Herein, we report three newly-diagnosed MM patients achieving deep responses with imaging CR using ACT PET in addition to conventional immunofixation CR and MRD-negative CR after a 3-weekly daratumumab-based quadruplet induction regimen.

Keywords: 3-weekly daratumumab, ^{11}C -Acetate PET, MRD negativity, newly diagnosed multiple myeloma, quadruplet induction

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Introduction

Multiple myeloma (MM) is a clonal hematopoietic neoplasm of the plasma cells in the bone marrow. With remarkable advances in the advent of novel agents, there is an increase in the rate of complete response (CR), which, according to the International Myeloma Working Group, is defined as negative immunofixation in the serum and urine and disappearance of any soft tissue plasmacytomas, and $<5\%$ plasma cells in the bone marrow. Nevertheless, MM continues to relapse, especially in the presence of minimal residual disease (MRD).¹ Therefore, MRD-negative CR, which signified a deeper response, was defined.²

Current methods to detect MRD include next-generation flow cytometry (NGF) and next generation sequencing (NGS) that possess a sensitivity of up to 10^{-6} .² Apart from the proprietary NGS method by ClonoSeq, the usage of the LymphoTrack system, with a sensitivity of 10^{-5} has been recently validated.^{3,4} On the other hand, previous studies have demonstrated the prognostic effect of ^{18}F -fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT).^{5,6} However, given the limitation of FDG-PET in MM, other tracers have been investigated, including, but not limited to, ^{18}F -choline and ^{11}C -choline, ^{11}C -acetate (ACT), ^{11}C -methionine, ^{68}Ga -pentixafor, and

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^{89}Zr -Daratumumab.⁷ As myeloma plasma cells have been shown to utilize lipid metabolism,⁸ ACT is a potentially useful tracer in MM. Indeed, in our previous pilot study using dual-tracer PET-CT with both ACT and FDG, ACT was shown to be a much more sensitive and specific tracer than FDG for MM.⁹

The addition of daratumumab (Dara) to a bortezomib, thalidomide, dexamethasone (VTd) or a bortezomib, lenalidomide, dexamethasone (VRd) triplet induction regimen has been shown to result in a higher CR rate and MRD-negativity in newly diagnosed MM, translating into superior progression-free survival (PFS).^{10,11} However, daratumumab is expensive; therefore, it is unaffordable for many patients, especially in resource-constrained regions, including Hong Kong. In view of the long plasma half-life of daratumumab,¹² as well as the success of 3-weekly rituximab in the rituximab, cyclophosphamide, hydroxydaunomycin, vincristine (R-CHOP) regimen for lymphoma,¹³ a 3-weekly daratumumab-based induction regimen has been proposed and adopted in our center.^{14,15} Herein, we report three newly diagnosed MM patients achieving imaging CR with ACT PET, in addition to conventional immunofixation CR and MRD-negative CR after a 3-weekly daratumumab-based induction regimen.²

Case presentation

We present three cases of newly diagnosed MM. Two were transplant candidates, whereas one was transplant ineligible. The characteristics and investigation results of the three patients at diagnosis were summarized in Table 1. Patients were staged using the International staging system (ISS), a prognostic scoring system comprising beta-2-microglobulin and albumin, enabling stratification of MM patients into stage I, II, or III with inferior survival in patients with higher ISS stage. All received a four-drug Dara-based regimen with the addition of Dara to a triplet regimen comprising a bortezomib (V), an immunomodulatory agent (IMiD) with either thalidomide (T) or lenalidomide (R), and dexamethasone (d), followed by autologous stem cell transplant (ASCT) if the patient is transplant eligible, and then maintenance with single agent IMiD. The choice of IMiD depended on the affordability of the patient, as thalidomide is provided by the Hospital Authority, but lenalidomide is a self-financed item.

The Dara-based regimen used was a 3-weekly regimen.^{14,15} Daratumumab was given as an infusion at a dose of 16 mg/kg once every three weeks. Bortezomib was given at a dose of 1.3 mg/m² once a week. Lenalidomide was given at a dose of 25 mg daily five times per week, and thalidomide was given at a dose of 100–200 mg daily. Dexamethasone was kept at 20 mg daily two times per week. After achieving \geq VGPR, patients received single agent IMiD maintenance, thalidomide 50 mg daily, or lenalidomide 15 mg daily, till disease progression.

MRD assessment in our patients was performed in the bone marrow samples, either 30 days and 90 days after ASCT for transplant candidates, or within 3 months after CR for non-transplant candidates, by NGS using the LymphoTrack system with a sensitivity of 10⁻⁵.^{3,4} Our patients had dual-tracer PET-CT at diagnosis and after the achievement of MRD-negative CR using both ACT and FDG as tracer as previously described.⁹ The exact time of reassessment PET-CT was generally within 6 months after MRD-negative CR but would be adjusted according to the next follow-up date or patient preference.

Patient 1

A 63-year-old man was diagnosed with International Staging System stage 3 (ISS3), cytogenetic high-risk immunoglobulin G (IgG) MM. He presented with weight loss of eight kilograms over six months and was found to have anemia with hemoglobin (Hb) 10 g/dl and reverse albumin/globulin ratio. Serum creatinine, calcium, and LDH levels were normal. Serum protein electrophoresis (SPE) showed monoclonal IgG lambda of 26.54 g/l. Bone marrow yielded 20% plasma cells with lambda light chain restriction. Fluorescence *in situ* hybridization (FISH) showed both t(4;14) and del(17p). Serum albumin measured 33 g/l and beta-2-microglobulin (B2M) 8.21 μ g/ml; hence, the ISS3 IgGL MM with two high-risk cytogenetic alterations. Dual ACT/FDG PET-CT showed diffusely accentuated marrow activities on ACT-PET with maximum standard unit value (SUVmax) 5.4 (normal ACT SUVmax < 3.8) while marrow FDG activity was only marginally increased (FDG SUVmax 3.3, normal SUVmax < 3.1). No focal hypermetabolic lesion was seen with either tracer. This patient achieved immunofixation-negative CR after eight cycles of Dara-VRd prior to autologous stem cell transplant (ASCT) in March 2020,

Table 1. Characteristics and investigation results of the three patients at diagnosis.

	Patient 1	Patient 2	Patient 3
Age	62	59	71
Sex	M	F	M
ISS stage	3	2	1
R-ISS stage	3	2	2
Hb, g/dl (13.3–17.1)	10	7.3	10.6
Cr, $\mu\text{mol/l}$ (67–109)	72	62	86
Ca, mmol/l (2.24–2.63)	2.41	2.57	2.22
LDH, U/l (118–221)	181	143	127
B2M, $\mu\text{g/ml}$ (<1.42)	8.51	4.04	2.55
Albumin, g/l (39–50)	33	37	43
IgG/IgA/IgM, mg/dl (819–1725/70–386/55–307)	5070/326/100	377/2393/38	538/4250/12
SPE, g/l	IgG lambda : 28.84	IgA kappa : 26.15	IgA kappa : 27.45
UPE, g/l	NMD	NMD	WQ
BME	20% BMPC	96% BMPC	58% BMPC
FISH	Positive for t(4;14) & TP53 del	Negative	Positive for t(4;14) & gain(1q21)
Dual-tracer PET-CT	Diffusely accentuated marrow activities by ACT (SUVmax 5.4) and FDG (SUVmax 3.3)	Diffuse BM uptake by ACT (SUVmax 5.4) with multiple ACT-avid focal bone lesions	Diffusely ACT-avid (SUVmax 4.1) BM activity in axial skeleton

ACT, ^{11}C -acetate; B2M, beta-2-microglobulin; BM, bone marrow; BME, bone marrow examination; BMPC, bone marrow plasma cells; Ca, calcium; Cr, creatinine; FDG, ^{18}F -fluorodeoxyglucose; FISH, fluorescence *in situ* hybridization; Hb, hemoglobin; IgG/A/M, immunoglobulin G/A/M; ISS, international staging system; LDH, lactate dehydrogenase; NMD, no monoclonal band detected; PET-CT, positron emission tomography-computed tomography; R-ISS, revised international staging system; SPE, serum protein electrophoresis; SUVmax, maximum standard unit value; UPE, urine protein electrophoresis; WQ, weak monoclonal band detected.

followed by lenalidomide maintenance thereafter. BM on Day 30 and Day 90 after ASCT confirmed MRD-negative CR (Figure 1) and dual-tracer PET-CT five months after MRD-negative CR showed metabolic CR with complete resolution of the previous diffusely increased ACT uptake in bone marrow (ACT SUVmax 2.9, FDG SUVmax 1.9). Currently, he remained in CR 17 months since diagnosis.

Patient 2

A 60-year-old woman was diagnosed with ISS2, cytogenetic standard-risk immunoglobulin A

(IgA) MM. She presented with symptomatic anemia with Hb 7.3 g/dl. Serum creatinine, calcium, and LDH levels were normal. SPE showed monoclonal IgA Kappa of 33.53 g/l. BM showed 96% plasma cells with kappa light chain restriction. FISH was negative for high-risk cytogenetics including del(17p), t(4;14) and t(14;16). Serum albumin was 37 g/l and B2M was 4.04 $\mu\text{g/ml}$; hence, ISS stage 2 IgAK MM. Dual-tracer PET-CT showed diffuse BM uptake by ACT (SUVmax 5.4) with multiple ACT-avid focal bone lesions consistent with a combined focal and diffuse MM disease pattern. FDG-PET was negative in both. She achieved CR after five cycles of

Clonal sequence in CDR3 :			
GTGGACACAGCCACATATTACTGTGCACGCATTAGGGGCCATACCAGCCCTTTGAGTACTGGGGCCAGGGAACCT			
V _H 2.5(3)-4-(8)D1.26(0)-1-2-(4) _H 4			
Replicate	Reads of 10 ⁻⁵ control	Reads of 10 ⁻⁴ control	Reads of myeloma sequence
1	1684	24092	0
2	0	12062	0
3	0	10854	0

Figure 1. MRD study of BM by NGS of patient 1. Upper panel showed clonality detection of BM at diagnosis by NGS. Bases in red showed the CDR3 sequence of the myeloma clonal sequence with the utilization of V_H2, D_H1, and J_H4 gene segments. Lower panel showed MRD detection by NGS in triplicates of BM DNA at clinical CR that showed detection of sensitivity control at the concentration of 1×10⁻⁵, and the absence of MRD as evidenced by the absence of MRD reads in all three BM triplicates.

Dara-VTd induction, followed by ASCT, and then thalidomide maintenance. Both Day 30 and Day 90 post-ASCT BM yielded MRD negativity, hence MRD-negative CR. Reassessment dual-tracer PET-CT one month after MRD-negative CR showed complete ACT-PET metabolic response. (Figure 2) She is currently in CR 12 months since diagnosis.

Patient 3

A 73-year-old man was diagnosed with ISS1, cytogenetic high-risk IgA MM. He presented with a protracted viral illness in June 2018. Blood tests showed Hb 10.3 g/dl, with normal creatinine and calcium level. SPE showed monoclonal IgA Kappa with a level of 28.31 g/l. BM yielded 58% plasma cells. FISH showed both t(4;14) and gain(1q21). Serum LDH was normal, and albumin was 43 g/l with B2M level of 2.55 µg/ml; hence, ISS stage I IgAK MM. Dual-tracer PET-CT showed ACT-avid (SUVmax 4.1) diffusely increased bone marrow activity in the axial skeleton without focal lesions. FDG-PET marrow activity was normal (SUVmax 2.1). He achieved MRD-negative CR with seven cycles of Dara-VRd induction. Subsequent dual-tracer PET-CT two months after MRD-negative CR showed an interval partial response with normalization of previous diffuse ACT-avid BM activity (SUVmax 1.7) in the axial skeleton except a solitary lesion on the left side of T3 vertebra showing decreased ACT clearance (SUVmax 2.6) compared with the rest of normalized BM activity. As he was not a transplant candidate, he was put on single agent lenalidomide maintenance. Reassessment dual-tracer PET-CT

nine months after last PET-CT showed complete metabolic CR, including the T3 lesion. A repeated MRD study 27 months after diagnosis showed persistent MRD-negative CR in August 2020. Currently, he is in CR 30 months after diagnosis.

Discussion

Daratumumab is an anti-CD38 monoclonal antibody leading to myeloma cell killing *via* direct induction of apoptosis, Fc-related mechanism of myeloma cytotoxicity, and eradication of CD38+ve immunosuppressive cells in the BM microenvironment.¹⁶ The addition of daratumumab to VTd and VRd has been shown to confer superior CR rate as demonstrated in two large randomized controlled trials. In the Cassiopeia study, the rate of ≥CR post-ASCT was higher with the addition of Dara to VTd (Dara-VTd: 39% *versus* VTd: 26%), resulting in a superior PFS (18-month PFS of Dara-VTd: 93% *versus* VTd: 85%).¹⁰ Similarly, in the Griffin study, the rate of ≥CR post-consolidation was superior in Dara-VRd than VRd arm (51.5% *versus* 42.3%), together with better PFS (24-month PFS of Dara-VRd: 95.8% *versus* VRd: 89.8%).¹¹ On the other hand, in non-transplant candidates, Dara-Rd has been shown to confer a superior rate of ≥CR and PFS than Rd in the MAIA study.¹⁷ In these clinical trials, the daratumumab used was mainly on a weekly basis during induction. However, despite the less frequent use of daratumumab, our patients achieved not only immunofixation-negative CR but also NGS MRD-negative and ACT PET-negative CR, including two patients (patients 1 and 3) harboring ultra-high-risk cytogenetics

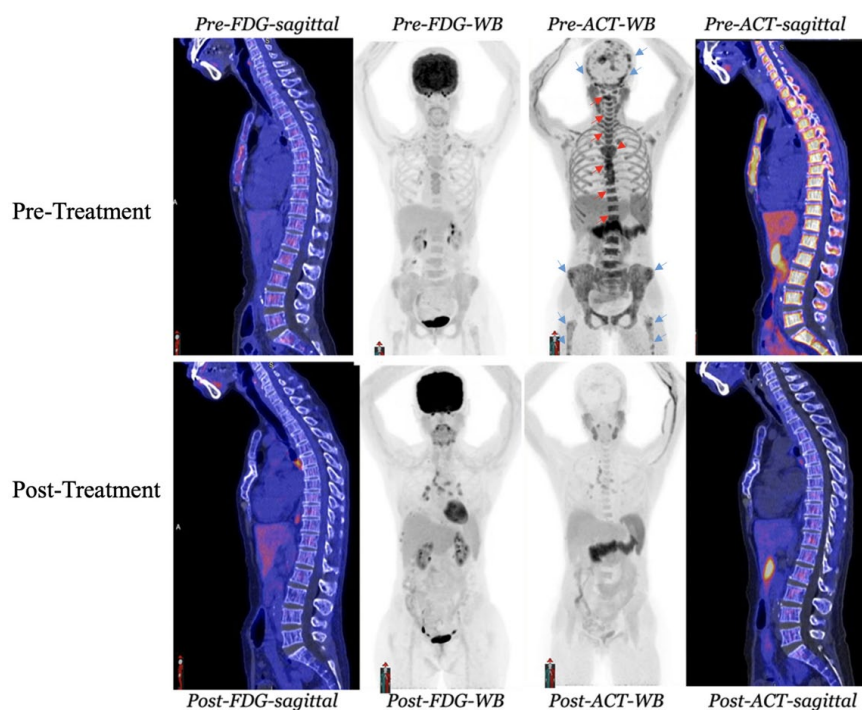


Figure 2. Pre- and post-treatment dual-tracer PET-CT of patient 2. Pre-treatment FDG-PET (Left upper) showed absence of hypermetabolic BM lesions while pre-treatment ACT-PET (Right upper) showed diffusely hypermetabolic BM uptakes in the axial skeleton (red arrows), including sternum (red arrowhead) with focally hypermetabolic lesions in calvarium and femora (blue arrows). Repeat post-treatment ACT-PET (Right lower) at clinical CR showed complete resolution of ACT-avid BM lesions, hence ACT PET-CR. Post-treatment FDG-PET (Left lower) remained unremarkable except for non-specific inflammatory thoracic lymph nodes and tiny right lower rib fractures, which are FDG-avid.

[t(4;14) plus TP53 del or gain (1q21)]¹⁸ which was associated with inferior outcomes than those with the single high-risk cytogenetic alteration.¹⁹

Depth of response in MM is highly prognostic of survival. Patients achieving immunofixation-negative CR had superior survival than those achieving very good partial response (VGPR) with negative SPE but positive immunofixation.²⁰ Moreover, MRD-negativity has been shown to confer superior PFS in MM. In a recent IFM-DFCI (Intergroupe Francophone du Myelome/Dana-Farber Cancer Institute) study that interrogated if ASCT was necessary in the era of VRD triplet induction, MRD-negativity was shown to confer a superior PFS using NGS with ClonoSeq.²¹ ClonoSeq is a proprietary NGS platform, for which a sensitivity of 10^{-6} has been demonstrated in myeloma patients.^{22,23} On the other hand, we have validated a standardized protocol using the LymphoTrack platform and verified experimentally that a sensitivity of 10^{-5} was consistently achieved in each and every MRD BM sample by

including a spike-in sensitivity control at a concentration of 10^{-5} in each MRD BM sample.^{3,4}

As BM infiltration by MM plasma cells is often focal and patchy, MRD-negativity at a single BM site cannot rule out myeloma infiltration outside the BM aspiration site. Therefore, PET-CT, empowered to detect hypermetabolic intramedullary or extramedullary bone lesions, is complementary to BM MRD to document remission status in MM. Indeed, the number of hypermetabolic bone lesions was shown to be prognostic of survival,⁶ and complete resolution of hypermetabolic BM lesions prognostic in MM in CR.⁵ FDG PET has been widely used for this purpose. However, we have reported that FDG is not a PET tracer sensitive or specific enough for MM. In our dual-tracer (using both ACT and FDG) PET-CT study in MM,⁹ a significant proportion of patients in whom no diffuse or focal FDG-avid BM lesions were found, hypermetabolic ACT-avid lesions were detected. This is also illustrated in patients 2 and 3, in whom diffusely accentuated

marrow activities were only detected by ACT-PET. Of note, in diagnostic dual-tracer PET-CT of patient 2, multiple focal bone lesions were only found to be ACT-avid without FDG-avidity. Moreover, even in patients who had both FDG and ACT-avid bone marrow lesions, higher SUVmax was noted by ACT than FDG, which can be illustrated by patient 1 with diagnostic dual-tracer PET-CT showing diffuse BM uptake by both tracers yet higher ACT uptake than FDG (SUVmax of ACT: 5.4 versus FDG: 3.3). An *in vitro* study⁸ on the biochemical derangement of mouse MM cells showed that ACT utilization was elevated because an enzyme fatty acid synthase (FASN) activity was upregulated for energy production and lipid synthesis, unlike many tumors that commonly prefer Warburg's glycolysis for tumor growth. Therefore, the underlying molecular basis explains why ACT is a much more sensitive and specific tracer for MM than FDG. Patient 3 had residual hypermetabolic ACT-avid T3 lesion upon MRD-negative CR after induction that turned eumetabolic in a subsequent PET-CT. Without a biopsy, the nature of the residual T3 lesion could not be ascertained. However, as the ACT-avid T3 lesion resolved completely in the follow-up PET-CT later, the lesion was likely due to residual disease.

In conclusion, 3-weekly daratumumab-based quadruplet induction regimen appeared effective in achieving deep responses with ACT PET-CR in addition to the widely-used conventional immunofixation CR and MRD-negative CR in newly diagnosed multiple myeloma. However, future validation with additional studies of the long-term efficacy, cost, and quality-of-life assessment would be required.

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Author contributions

CN drafted the manuscript. CSC treated the patients and drafted the manuscript. GCH and SC provided PET-CT images. SK reviewed the manuscript and provided critical advice. All authors read and approved the final manuscript.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Ethics approval and consent to participate

This study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (Reference number: UW 19-108). Written informed consents were obtained from the patients.

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