Evaluation of Chemokine Receptor-4 Expression by 68Ga – Pentixafor PET/CT in Patients with Multiple Myeloma

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ABSTRACT

The aim of this study to demonstrate and compare the CXCR4 expression by means of 68Ga-Pentixafor PET/CT in patients with multiple myeloma with standard clinical parameters and 18F-FDG PET/CT findings. Twenty-four (17 women, 7 men; mean age: 58.9±12.7) multiple myeloma patients who had undergone 18F-FDG PET/CT imaging to evaluate the disease activity were included in the study. 68Ga-Pentixafor PET/CT imaging was performed within an average period of 12 days after initial 18F-FDG PET/CT imaging. 68Ga-Pentixafor PET and 18F-FDG PET/CT revealed focal pathological lesions in 13/24 (54%) and 16/24 (67%) patients, respectively. In 19/24 patients, both tracers showed concordant findings (CXCR4+ and FDG+ in 12 patients; CXCR4- and FDG- in 7patients). In the remaining 5 patients, findings were discordant. The number of focal lesions identified by means of 68Ga-Pentixafor and 18F-FDG were 89 (44%) and 113 (56%), respectively. 68Ga-Pentixafor PET/CT showed more lesions in 2/12 (17%) patients, whereas 18F-FDG PET/CT was proved to be superior in 7/12 (58%) patients. In the remaining 3/12 (25%) patients, both tracers detected an equal number of lesions. There was no significant difference in appendicular and axial skeletal and extramedullary distribution ratios for both PET/CT examinations (p> 0.05). There was no statistically significant correlations between the 68Ga-Pentixafor PET/CT and 18F-FDG PET/CT positivity and disease activity, MM subtype, ISS phase, light chain disease, beta2microglobulin, albumin, creatinine, LDH, FLC and M protein levels in during scans. 68Ga-Pentixafor PET/CT cannot replace 18F-FDG PET/CT for diagnostic imaging of patients with multiple myeloma, 68Ga-PET/CT seem to be a valuable probe for patient stratification in the context of CXCR4-targeted radioligand therapy.

Keywords: Multiple myeloma, Chemokine receptors, 68Ga-Pentixafor

ÖZET

Multipl Myelomalı Hastalarda Kemokin Reseptör-4 Ekspresyonunun Ga-68 Pentiksafor PET/BT ile Değerlendirilmesi

Bu çalışmanın amacı, multipl myelomalı hastalarda CXCR4 ekspresyonun Ga-68 PSMA Pentiksafor PET/BT ile gösterilmesi ve standart klinik parametreler ve 18F-FDG PET/BT bulguları ile karşılaştırılmasıdır. Çalışmaya multipl myelom tanısı ile hastalık aktivitesinin değerlendirilmesi amacıyla 18F-FDG PET/BT yapılan yirmi dört (17 kadın, 7 erkek; ort yaş: 58.9±12.7) hasta dahil edildi. Ga-68 Pentiksafor PET/BT, 18F-FDG PET/BT'yi takiben ortalama 12 günlük süre içinde uygulandı. Ga-68 Pentiksafor PET ve 18F-FDG PET/BT, sırası ile 13/24 (%54) ve 16/24 (%67) hastada fokal patolojik lezyonları gösterdi. 19/24 hastada her iki yöntem uyumlu bulgular 12 hastada CXCR4 ve FDG+; 7 hastada CXCR4 ve FDG- gösterdi. Geri kalan 5 hastada ise bulgular uyumsuzdu. Ga-68 pentiksafor ve 18F-FDG PET ile ortaya konulan fokal lezyon sayısı sırası ile 89 (%44) and 113 (%56) idi. 2/12 (%17) hastada Ga-68 Pentiksafor PET/BT daha fazla sayıda lezyon gösterirken, 7/12 (%58) hastada 18F-FDG PET/BT üstündü.

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Geri kalan 3/12 (%25) hastada ise her iki yöntem benzer sayıda lezyon gösterdi. Her iki yöntem ile saptanan apendiküler, aksiyel iskelet ve ekstramedüller lezyonların dağılımı arasındaki fark anlamlı değildi (p> 0.05). Ga-68 Pentiksafor ve 18F-FDG PET/BT pozitifliği ile hastalık aktivitesi, MM alt tipi, ISS fazı, hafif zincir hasalığı, beta2 mikroglobulin, albumin, kreatinin, LDH, FLC ve M protein düzeyleri arasında anlamlı ilişki saptanmadı. Ga-68 Pentiksafor PET/BT multipl myelomalı hastalarda tanısal görüntüleme yöntemi olarak 18F-FDG PET/BT nin yerini alamaz, Ga-68 Pentiksafor PET/BT, CXCR-4 hedefli radyoligand tedavi planlanan hastalarda hasta seçimi amacıyla faydalı olabilir.

Anahtar Kelimeler: Multipl myelom, Kemokin reseptörleri, Ga-68 Pentiksafor

INTRODUCTION

Chemokine receptor-4 (CXCR4) is a member of the G-protein coupled chemokine receptor family. Activation of CXCR4 by the endogenous ligand CXCL12/SDF-1 (stromal cell derived factor), coregulates cell adhesion and migration by activating SDF-1 MAP kinase and IP3 kinase pathways (1,2). CXCR4 is physiologically expressed on T- and B-lymphocytes, monocytes, macrophages, neutrophils, eosinophils, and hematopoietic stem cells and involved in stem cell migration and homing (3).

Multiple myeloma (MM) is the second most common B-cell malignancy. Despite advances in pharmacotherapy, most patients are not cured (4,5). A strong correlation between CXCR4/SDF-1 activation and MM-related bone disease has already been demonstrated (6,7). SDF-1 auto-secretion from MM cells causes autocrine stimulation of plasma cell proliferation. Thus, the CXCR4/SDF-1 pathway is an important molecular target for both physio-pathogenesis and development of drug resistance (8).

Despite its basic role in cancer and MM biology and upcoming CXCR4-targeted pharmacological therapies, routine tools for quantification and evaluation of the CXCR4 receptor status in vivo are still missing. First clinical data with the CXCR4-agonist 68Ga-Pentixafor (9,10) have recently been published (11-14) and were supplemented by first results on CXCR4-targeted radioligand therapy (15). An excellent overview on the current experience and potential of CXCR4 targeted PET imaging probes was recently published (16). However, 18F-FDG PET/CT is ineffective at identifying patients for CXCR4-targeted radionuclide treatment.

The purpose of this study was to a) demonstrate the suitability of CXCR4 targeted 68Ga-Pentixafor PET/CT as an imaging approach for myeloma-specific treatment, b) to compare the results with the standard clinical parameters and findings by 18F-FDG PET/CT, widely used to study disease activation in MM patients (17).

PATIENTS and METHODS

Patients

We enrolled 24 patients (17 F, 7 M; mean age: 58.9±12.7, range: 39-82) who underwent 18F-FDG PET/CT for evaluation of MM activation. The median interval between MM diagnosis and 18F-FDG PET/CT was 23 months (min-max: 1-78). 68Ga-Pentixafor PET/CT was performed on all patients within maximum 12 days after 18F-FDG PET/CT. All patients gave written informed consent for the 68Ga-Pentixafor PET/CT and standard 18F-FDG PET/CT. In addition to the PET/CT findings, serum free immunoglobulin light chains (FLC), M protein, lactate dehydrogenase (LDH), albumin, creatinine and beta-2 microglobulin levels were recorded. Nineteen patients have previously been treated with several chemotherapeutics including bortezomib and lenalidomide, and 13 of the 24 patients had undergone autologous stem cell transplantation. The patients' demographic features are detailed in Table 1.

Pentixafor is an unapproved, investigational drug. This study has been approved by the ethical committee of Ankara University and supported by the Scientific Research Project Office of Ankara University; numbers 15-962-17 and 17B0230006. The study has been performed in accordance with the Republic of Turkey Ministry of Health, Turkey Pharmaceuticals and Medical Devices Agency.

Table 1. Patient characteristics

Patients no	Sex	Age	Myeloma type	Disease duration (months)	ISS	M protein level	FLC level	EMD	ASCT
1	M	75	light chain κ	7	1	0	185	–	–
2	F	60	light chain λ	6	3	0	3.5	Yes	–
3	M	63	κ	78	1	0	16.3	–	Yes
4	F	53	light chain λ	114	2	0	80	–	Yes
5	F	72	κ	35	1	1.1	0	–	–
6	M	42	λ	1	2	0.4	8.6	–	–
7	F	57	κ	50	3	0.03	61.9	–	Yes
8	F	58	λ	46	2	0.9	31.8	–	Yes
9	F	65	κ	32	1	1.44	41	–	Yes
10	F	48	κ	77	2	0.07	60	–	Yes
11	F	72	light chain κ	1	3	1.8	1840	–	–
12	F	39	κ	43	1	0	6.4	Yes	Yes
13	M	55	κ	1	2	2	21	–	–
14	F	61	light chain κ	11	2	0	10.5	–	Yes
15	F	72	κ	22	1	0	8.7	–	Yes
16	F	55	κ	28	2	0.85	52	–	Yes
17	F	63	λ	1	3	9.2	158	–	–
18	F	73	κ	3	2	0.05	840	–	–
19	F	75	κ	1	3	0	1810	–	–
20	F	50	λ	30	1	0	18.2	Yes	Yes
21	M	65	light chain κ	7	3	0	1420	–	Yes
22	F	82	λ	52	3	2.6	1052	–	–
23	M	44	light chain λ	24	2	0	15.3	–	Yes
24	M	77	κ	19	3	0	183	–	–

18F-FDG and 68Ga-Pentixafor PET/CT Imaging

68Ga-Pentixafor was produced by means of a fully automated, GMP-compliant procedure on a GRP synthesis module SCINTOMICS GmbH, Germany), equipped with disposable cassettes (ABX, Germany) and connected to a 68Ge/68Ga generator (iThemba Labs). The eluate of the 68Ge/68Ga generator (68Ga3+ in 0.6 M HCl) was transferred to a cation-exchange cartridge eluted with 5 M NaCl and added to a solution of 25 μg Pentixafor (Scintomics, Fürstenfeldbruck, Germany) in HEPES-buffer and heated for 6 minutes at 125^{0}C. The product was immobilized on a SepPak C18 cartridge, washed with water, and eluted with ethanol/water (50/50, v/v). The eluate was passed through a sterile filter (0.22 μm) into a sterile vial and diluted with phosphate buffer solution to a total volume of 15 ml. The radiochemical purity (>97%) was determined by isocratic high performance liquid chromatography.

The PET/CT images were obtained with GE Discovery 710 PET/CT scanner. For 18F-FDG PET/CT, the patients were fasted for at least 6 h before imaging, and blood glucose levels were checked. Subjects with a blood glucose level above 150 mg/dL were not scanned. Whole body 18F-FDG PET/CT imaging was performed approximately 1 h after an intravenous injection of 296 - 370 MBq 18F-FDG.

No special precaution was needed for 68Ga-Pentixafor PET/CT. Imaging was initiated 30 min after injection of approximately 130-185 MBq 68Ga-Pentixafor. Oral or intravenous contrast agents were not used. Whole body images were

obtained while the patients were supine for both radiopharmaceuticals. During the waiting period, patients rested in a quiet room without muscle relaxants. The PET images were acquired 2 min per bed position. The PET images were reconstructed with non-contrast CT images. The CT images were also obtained via a standardized protocol at 140 kV, 70 mA, and tube rotation time of 0.5 s per rotation; the pitch was 6 and the slice thickness was 5 mm. Patients were allowed to breathe normally during the procedure.

Image Analysis

Attenuation-corrected PET/CT fusion images were reviewed in three planes (transaxial, coronal, and sagittal) on an Advance Workstation Volumeshare 5 (GE Medical Systems). The PET/CT images were evaluated and confirmed visually and semi-quantitatively with standardized uptake value (SUV) by consensus of two experienced nuclear medicine specialists. Image analysis were performed according to previous literatures (12,13,18). Focal increased tracer activity within the skeleton or in soft tissues are rated positive. If intra- and/or extra-medullary uptake is more intense compared to surrounding normal bone marrow uptake, with or without any underlying lesion identified by CT, it is accepted as positive.

Statistical Analysis

For statistical analysis SPSS (version 20) was used. Continuous variables were expressed as the mean±standard deviation or median (minimum-maximum). Compatibility of categorical variables was tested by using Chi-Square tests. The Mann-Whitney U test was used to analyze the medians of different groups. A P-value < 0.05 was considered to be significant.

Ethical Approval

This study was approved by the ethical committee of Ankara University (ethical number: 15-962-17). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

RESULTS

Clinical Findings

Based on clinical findings, the active disease status was found in 17 (71%) of the 24 patients. The medians (min-max) for serum FLC, beta-2 microglobulin, and M-protein were calculated as 46.5 (0-1840), 3.75 (1.5-18.7), and 0.025 (0-92). Serum albumin levels were < 3.5 g/dl in 3 (13%) of 24 patients. Serum creatinine level was > 1.2 mg/dl in 3 (13%) of 24 patients, and serum LDH level was > 250 IU/l in 2 (8%) of 24 patients. Bone, kidney involvement, and anemia were detected in 18 (75%), 9 (38%), and 17 (71%) patients, respectively.

PET/CT Findings

68Ga-Pentixafor PET/CT Findings

The disease was serologically active in 11 (85%) of 13 patients with positive 68Ga-Pentixafor PET/CT (54% of all patients), and it was inactive in the remaining 2 patients. In 6 (55%) of the 11 patients who were 68Ga-Pentixafor PET-negative, the disease was serologically active.

In the 68Ga-Pentixafor PET-positive patients, intramedullary involvement was detected in 7 (54%), intra- and extra-medullary involvement in 5 (38%) and disseminated extra-medullary involvement in 1 subject (8%). Extra-medullary involvement was detected in 46% (in 6 of 13 patients) of the 68Ga-Pentixafor PET-positive patients. While extra-medullary involvement was localized to the paramedullary soft tissue in 5 (83%) patients, it was seen in the muscle, pleura, and lung in the remaining single patient. Intramedullary involvement was localized in the same percentage of each 33% (4) to the appendicular, axial, and both axial and appendicular skeleton. Five patients had intramedullary involvement with extra-medullary involvement. Lesion numbers for appendicular and axial skeletons were 32 (36%) and 57 (64%), respectively.

Comparison of 68Ga-Pentixafor and 18F-FDG

Table 2. The summary characteristics of patients with CXCR4 (+) and FDG (+) findings

Patient No	Disease duration (monhs)	ISS	FLC level	M protein level	Disease activity during scan	EMD during scan	Other invove-ments	CXCR4 SUV	FDG SUV	CXCR4 positive FL	FDG positive FL
4	114	2	80	0	+	-	bone, kidney anemia	2.6	15.5	1	4
6	1	2	8.6	0.4	+	+	bone	5.1	20.2	1	12
8	46	2	31.8	0.9	+	+	bone, kidney anemia	12.9	7.8	41	28
9	32	1	41	1.44	+	-	bone	2.6	4.2	1	1
11	1	3	1840	1.8	+	-	bone, kidney anemia	8.3	5.2	2	5
12	43	1	6.4	0	negative	-	bone, anemia	2.6	10.2	1	5
16	28	2	52	0.85	+	+	bone, anemia	8.1	18.5	3	6
19	1	3	1810	0	+	-	bone, anemia	3.7	4.1	1	4
21	7	3	1420	0	+	+	bone, kidney anemia	31.4	8.1	30	21
22	52	3	1052	2.6	+	+	bone, kidney anemia	7.3	5.2	2	2
23	24	2	15.3	0	negative	-	bone, anemia	2.6	5.6	2	2
24	19	3	183	0	+	+	bone, anemia	4.3	15.1	2	6

PET/CT Findings

The 18F-FDG PET/CT was positive in 16 (67%) of 24 patients. In the combined evaluation, both 18F-FDG- and 68Ga-Pentixafor-PET/CT scans were positive in 12 (50%) of 24 patients and negative in 7 patients (29%). Details of the patients with concordant findings are presented in Tables 2 and 3. In 4 of 12 patients with both positive scans, the 68Ga-Pentixafor uptakes were higher than 18F-FDG. In particular, two patients had very intense and higher CXCR4 expression (Figure 1, #8). In the remaining 8 patients, the 18F-FDG uptakes were higher than 68Ga-Pentixafor uptakes. Five patients (#4, 6, 12, 16, and 24) had a much more FDG-avid lesion than 68Ga-pentixafor PET (Figure 2, #24). The correlation of positivity of both imaging methods (p= 0.004) and focal lesion numbers (p= 0.001) were statistically significant. In 2 of 12 patients with serologically inactive disease status, both imaging methods were positive.

The ISS (International Staging System) stages were 1-2 in all 7 patients with concordant negative findings. In 3 (43%) out of 7 patients both imaging methods were negative despite the disease being serologically positive.

The remaining 5 patients (21%) had discordant 68Ga-Pentixafor and 18F-FDG PET/CT scans (Table 4). The CXCR4 -/FDG + group had two patients (#2 and 10) with 18F-FDG uptake in a single focus in the axial skeleton. In another two patients

Table 3. The summary characteristic of patients with CXCR4 (-) and FDG (-) findings

Patient No	Disease duration (monhs)	ISS	FLC level	M protein level	Disease activity during scan	EMD during scan	Other invove-ments
1	7	1	160	0	positive	-	no
3	78	1	16.3	0	-	-	no
5	35	1	0	1.1	positive	-	no
14	11	2	10.5	0	-	-	anemia
15	22	1	8.7	0	-	-	bone
18	3	2	840	0.05	positive	-	no
20	30	1	18.2	0	-	-	anemia

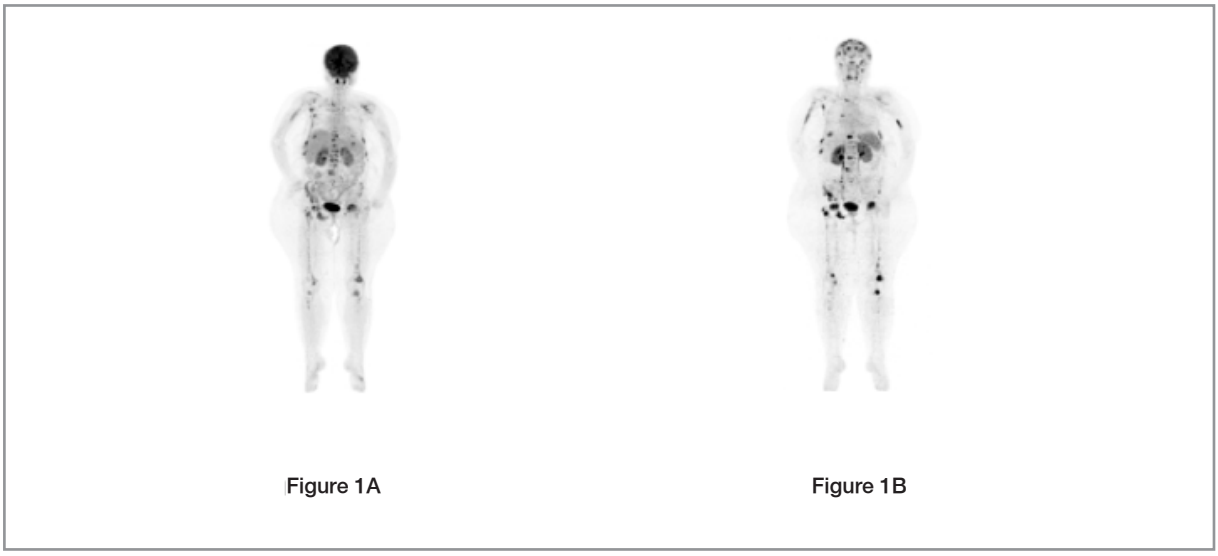

Figure 1A

Figure 1B

Figure 1. 58 years old patient (n= 8) with refractor multiple myeloma for 4 years had both 18F-FDG **(A)** and 68Ga-Pentixafor **(B)** PET/CT scan. 68Ga-Pentixafor uptakes were clearly higher than 18F-FDG uptakes, especially on cranium

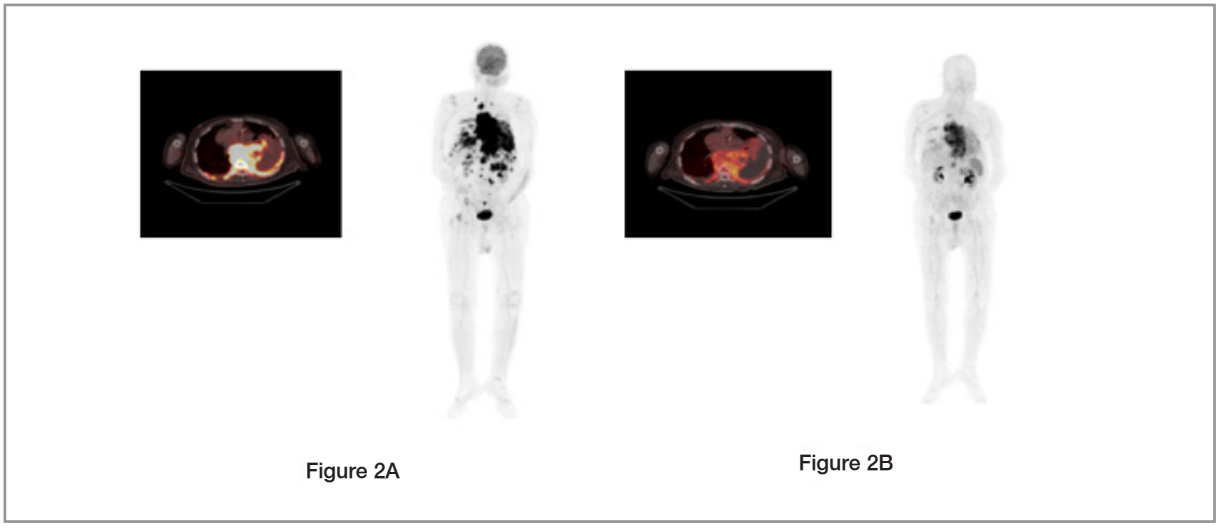

Figure 2A

Figure 2B

Figure 2. 77 years old patient (n= 24) with multiple myeloma had more intense FDG uptake **(A)** than 68Ga-pentixafor **(B)** in multiple intramedullary as well as extramedullary lesions

(#13 and 17) from this group, 18F-FDG uptakes were seen in multiple foci in the axial and appendicular skeleton. 68Ga-Pentixafor uptake was seen in the axial and appendicular skeleton in the only patient in the CXCR4 +/FDG – group.

The median SUVmax for 68Ga-Pentixafor and 18F-FDG PET was calculated as 5.8 (min-max: 2.6-31.4) and 6.85 (min-max: 3.4- 20.2), respectively. There was no significant difference in median SUVmax of both scans ($p > 0.05$). There was no significant correlation between 68Ga-Pentixafor or 18F-FDG PET positivity and disease activity, MM subtype, ISS stage, light chain disease, serum beta 2 microglobulin, albumin, creatinine, LDH, FLC, and M protein levels ($p > 0.05$).

DISCUSSION

Overexpression of CXCR4 receptor, determined by 68Ga-Pentixafor PET/CT, was previously seen in more than half of MM patients (12). Similarly,

Table 4. The summary characteristic of patients with discordant PET findings

Patient No	Disease duration (monhs)	ISS	FLC level	M protein level	Disease activity during scan	EMD during scan	Other invove-ments	CXCR4 SUV	FDG SUV	CXCR4 positive FL	FDG positive FL
2	6	3	3.5	0	-	-	-	-	3.4	-	1
7	50	3	61.9	0.03	+	-	bone, kidney, anemia		4.1	-	2 -
10	77	2	60	0.07	+	-	bone, anemia		-	4.9	- 1
13	1	2	21	2	+	-	bone, anemia		-	8.3	- 9
17	1	3	10.5	0	-	+	bone, anemia		-	6.0	- 6

we found CXCR4 positivity in 54% of patients. Lapa et al. compared 18F-FDG and 68Ga-Pentixafor PET/CT in 35 patients with a history of MM, and found positivity rates of 74% and 58% for 18F-FDG- and 68Ga-Pentixafor-PET/CT, respectively (13). In another study that included 14 advanced stage MM patients, 4/14 (64%) patients were 18F-FDG avid, 10/14 (71%) patients were 68Ga-Pentixafor avid (12). In our study, the 18F-FDG positivity rate was 67%, whereas the 68Ga-Pentixafor positivity rate reached only 54%. Since CXCR4 receptor overexpression is known to be a negative prognostic factor responsible to advanced disease stage, treatment resistance, and relapse in patients with several tumor types (19-21), the somewhat lower CXCR4-positvity of 54% might be related to the low number of advanced stage patients enrolled in our study cohort.

18F-FDG PET/CT has been widely utilized for evaluation of disease activity in MM patients. In former studies, 68Ga-Pentixafor and 18F-FDG PET/CT have been reported as complementary to each other (12). In our study, 68Ga-Pentixafor PET/CT was superior or equal to 18F-FDG PET in 42% of cases, whereas Lapa et al. reported superior or equal imaging performance of 68Ga-Pentixafor and 18F-FDG PET/CT in 63% of all patients investigated (13). The 68Ga-Pentixafor PET was superior to 18F-FDG PET in the detection of cranial lesions. In the patients with refractory treatment, CXCR4 positivity could identify candidates for CXCR4 targeted therapy. Lapa et al. recommended a combined evaluation of 68Ga-Pentixafor and 18F-FDG PET/CT in the pretreatment evaluation before CXCR4 targeted therapy. Thus, the detection of both viable MM cells and CXCR4-negative lesions that cannot benefit from endo-radiotherapy (ERT) might be possible (13). In our study, 5 patients (# 4, 6, 12, 16, and 24) had much more FDG avid lesions than 68Ga-Pentixafor PET. One patient showed disseminated 18F-FDG positivity, but some of these lesions had weak or absent CXCR4 expression.

Three of 7 patients with negative imaging findings in both scans had serologically active disease suggestive of hyperglycemia as well as a recent high dose of steroids, presence of sub-centimetric cranial lesions, or the presence of non-avid plasma cells-especially in 18F-FDG PET/CT (17, 22, 23). In this group, only one patient showed serology active disease.

Lapa et al. reported that 68Ga-Pentixafor PET positivity predicted short TTP and OS (13).

In agreement with the study of Lapa et al., we failed to demonstrate a statistically significant correlation between the 68Ga-Pentixafor PET and 18F-FDG PET positivity and disease activity, MM subtype, ISS phase, light chain disease, beta-2 microglobulin, albumin, creatinine, LDH, FLC, and M protein levels during scans.

Major limitations of this study are a lack of gold standard CXCR4 analysis of 18F-FDG and 68Ga-Pentixafor positive lesions, to not be consider of cytogenetic analysis results and the absence of long-term follow up data. Unfournately, no therapy was conducted as part of this work and the patients were not followed after standard of care treatment to assess imaging correlations with response.

Conclusion

68Ga-Pentixafor PET/CT cannot replace 18F-FDG PET/CT for diagnostic imaging of patients with multiple myeloma, 68Ga-PET/CT seem to be a valuable probe for patient stratification in the context of CXCR4-targeted radioligand therapy with the therapeutic compound Pentixather radiolabeled with - or even -emitters .

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Conflict of Interest:

Sashia Kropf is the CEO of Scintomics GmbH. Hans-J.Wester is the advisor of Scintomics GmbH. Other authors declares that they have no conflict of interest.

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