68Ga-Pentixafor PET/CT for Imaging of Chemokine Receptor 4 Expression in Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma: Comparison to 18F-FDG PET/CT

Yaping Luo1,2, Xinxin Cao3, Qingqing Pan1,2, Jian Li3, Jun Feng3, and Fang Li1,2

1Department of Nuclear Medicine, Chinese Academy of Medical Sciences and Peking Union Medical College Hospital, Beijing, People’s Republic of China; 2Beijing Key Laboratory of Molecular Targeted Diagnosis and Therapy in Nuclear Medicine, Beijing, People’s Republic of China; and 3Department of Hematology, Chinese Academy of Medical Sciences and Peking Union Medical College Hospital, Beijing, People’s Republic of China

18F-FDG PET/CT has some limitations in the evaluation of Waldenström macroglobulinemia/lymphoplasmacytic lymphoma (WM/LPL), an indolent B-cell lymphoma that primarily involves the bone marrow. Because there is a high level of chemokine receptor 4 expression in the B cells of WM/LPL patients, we performed a prospective cohort study to evaluate the performance of 68Ga-pentixafor, which targets chemokine receptor 4 in WM/LPL, and to compare it with the performance of 18F-FDG. Methods: Seventeen patients with WM/LPL were recruited. All patients underwent both 68Ga-pentixafor PET/CT and 18F-FDG PET/CT. A positive PET/CT result was defined as the presence of focal lesions with positive PET results or diffuse bone marrow patterns (uptake > liver). The rates of positive results for PET/CT scans of bone marrow, lymph nodes, and other extramedullary involvement were statistically compared. Results: 68Ga-pentixafor PET/CT had a higher rate of positive results than 18F-FDG PET/CT (100% vs. 58.8%; P = 0.023) in the recruited WM/LPL patients. The sensitivities of 68Ga-pentixafor PET/CT and 18F-FDG PET/CT for detecting bone marrow involvement were 94.1% and 58.8%, respectively (P = 0.077). In terms of detecting lymph node involvement, 68Ga-pentixafor/PET/CT had a significantly higher rate of positive results than 18F-FDG PET/CT (76.5% vs. 11.8%; P = 0.003). In addition, 68Ga-pentixafor detected more paramedullary and central nervous system involvement than 18F-FDG.

Conclusion: 68Ga-pentixafor might be a promising imaging agent for the assessment of WM/LPL.

Key Words: Waldenström macroglobulinemia; lymphoplasmacytic lymphoma; CXCR4; 68Ga-pentixafor; PET/CT

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Waldenström macroglobulinemia/lymphoplasmacytic lymphoma (WM/LPL) is an uncommon indolent non-Hodgkin lymphoma characterized by the accumulation of lymphoplasmacytic cells in the bone marrow and the excess production of monoclonal immunoglobulin. 18F-FDG PET/CT, a standard technique in the diagnosis and management of several types of tumors, has a limited role in diagnosing WM/LPL. According to the consensus recommendations of the International Conference on Malignant Lymphoma, 18F-FDG PET/CT is recommended for the routine staging of 18F-FDG–avid nodal lymphomas and is the gold standard for essentially all histologies; however, it is not indicated for WM/LPL, unless there is a suspicion of aggressive transformation (1). Data on the use of 18F-FDG PET/CT in WM/LPL are very limited. A study on the role of 18F-FDG PET/CT imaging in WM showed that only 43% of patients had abnormal bone marrow uptake (2), despite bone marrow being the primary site of involvement.

Chemokine receptor 4 (CXCR4) is a key factor for tumor growth and metastasis and is expressed at a high density in at least 20 different types of solid cancers and hematopoietic malignancies (3). 68Ga-pentixafor, a novel PET tracer with a high affinity for CXCR4, was recently introduced for the assessment of several lymphoproliferative diseases, such as multiple myeloma, diffuse large B-cell lymphoma, and acute myeloid leukemia (4–7). Studies have shown a higher level of CXCR4 expression in the B cells of patients with WM/LPL than in the B cells of healthy donors (8,9); this feature makes it possible for WM/LPL to be imaged with 68Ga-pentixafor. We previously reported data from a patient who had WM and in whom 68Ga-pentixafor PET/CT showed intense radioactivity in the bone marrow and lymph nodes that was superior to that shown by 18F-FDG PET/CT (10). In the present study, we aimed to further evaluate the performance of 68Ga-pentixafor PET/CT in WM/LPL and to compare it with the performance of 18F-FDG PET/CT, which served as a reference.

MATERIALS AND METHODS

Study Design and Patients

This is a preliminary report of an ongoing prospective study evaluating the role of 68Ga-pentixafor PET/CT in WM/LPL. The study was approved by the Institutional Review Board of Peking Union Medical College Hospital (protocol ZS-1113) and was registered at ClinicalTrials.gov (NCT 03436342). To compare differences between imaging techniques, we used the rates of positive results of 68Ga-pentixafor PET/CT and 18F-FDG PET/CT for WM/LPL as the endpoints.
in this preliminary study. A total of 17 patients diagnosed with WM/LPL at the Department of Hematology, Peking Union Medical College Hospital, were consecutively recruited from April 2017 to November 2018. Written informed consent was obtained from each patient. The clinical history and laboratory test results related to WM/LPL were recorded at enrollment in the study. Patients were then referred for 18F-FDG and 68Ga-pentixafor PET/CT for evaluation of the disease; the scans were performed within 1 wk after enrollment. The imaging characteristics were analyzed afterward.

PET/CT Imaging

The radiolabeling of 68Ga-pentixafor was performed manually immediately before injection. In brief, 45 µL of sodium acetate (1.25 M) was added to 1 mL of 68GaCl3 eluent (68Ga3+ in 0.5 M HCl) obtained from a 68Ge/68Ga generator (ITG) to adjust the pH to 3.5–4.0. After the addition of a 20-µL aliquot (1 µg/µL) of DOTA-CPCR4-2 (CSBio Co.), the mixture was heated to 105°C for 15 min. The reaction solution was diluted to 5 mL and passed through a preconditioned Sep-Pak C18 Plus Light cartridge (Waters), and the cartridge was eluted with 0.5 mL of 75% ethanol to obtain the final product. The radiochemical purity of the product was analyzed by thin-layer chromatography. The 68Ga-pentixafor injections were filtered through a 0.22-µm Millex-LG filter (EMD Millipore) before clinical use.

18F-FDG was synthesized in-house with an 11-MeV cyclotron (CTI RDS 111).

The PET scans were performed with dedicated PET/CT scanners (Biograph 64 TruePoint TrueV [Siemens]; Polestar m660 [SinoInon]). The PET/CT scans of 12 patients were performed with the same scanner, whereas 3 patients underwent PET/CT scans with different scanners. Two patients underwent 18F-FDG PET/CT at other hospitals. For 18F-FDG PET/CT, the patients fasted for at least 6 h, and the blood glucose levels were monitored (4.7–6.9 mmol/L) before an injection of 18F-FDG (5.55 MBq/kg). The PET/CT images (2 min/bed) were acquired with an uptake time of 68.5 ± 12.1 (mean ± SD) min (range, 47–89 min). For 68Ga-pentixafor PET/CT, imaging was performed (2–4 min/bed) with an uptake time of 47.8 ± 18.6 min (range, 30–90 min) after an injection of 84.6 ± 26.2 MBq of 68Ga-pentixafor (range, 37.0–136.9 MBq). The emission scan was obtained from the tip of the skull to the midthigh. All patients underwent unenhanced low-dose CT (120 kV; 30–50 mAs) for attenuation correction and anatomic reference. The acquired data were reconstructed using the ordered-subset expectation maximization method (Biograph 64: 2 iterations, 8 subsets, gaussian filter, image size of 168 × 168; Polestar m660: 2 iterations, 10 subsets, gaussian filter, image size of 192 × 192).

Image Interpretation and Statistical Analysis

Two experienced nuclear medicine physicians visually assessed the PET/CT images and were in consensus for the image interpretation. Because WM/LPL primarily involves the bone marrow, the distribution and intensity of bone marrow uptake were regarded as the main imaging characteristics. The presence and sites of positive lymph nodes and other extramedullary involvement were also recorded. For 18F-FDG, the intensity of bone marrow uptake and uptake in extramedullary lesions was based on the 5-point Deauville Scale, which is widely used for lymphoma. For 68Ga-pentixafor, the intensity of involvement was classified as mild, moderate, and intense, with the liver and spleen being used as the references (mild: uptake ≤ liver; moderate: liver < uptake ≤ spleen; intense: uptake > spleen). Positive bone marrow involvement was defined as the presence of focal lesions with positive PET results (circumscribed focus of ≥5 mm with increased radioactivity compared with the background uptake in bone marrow) or diffuse bone marrow patterns (homogeneous bone marrow uptake) with the following interpretation criteria: for 18F-FDG, a score of 4 for bone marrow uptake was set as a positive cutoff on the basis of the high interobserver concordance in a study of the visual descriptive criterion for multiple myeloma (11); and for 68Ga-pentixafor, moderate or intense uptake was considered positive. The presence of positive lymph nodes and other extramedullary involvement was defined as uptake with a score of greater than or equal to 4 in 18F-FDG PET and moderate or intense uptake in 68Ga-pentixafor PET. The McNe-

RESULTS

Clinical Characteristics

Seventeen patients with WM/LPL (11 men and 6 women; 62.6 ± 10.5 [range, 48–87] y old) were enrolled in the present study. Fifteen patients had newly diagnosed WM/LPL (1 patient with smoldering WM), and 2 patients had relapsed disease (patients 3 and 5). Anemia was found in 14 of 17 patients (82.4%), and 2 of 17 patients (11.8%) had thrombocytopenia. The median proportion of infiltrated lymphoplasmacytic cells found from bone marrow aspiration was 8.75% (range, 2.5%–31.0%). Peripheral neuropathy, a common disorder induced by paraprotein in WM/LPL, was found in 3 of 17 patients (17.6%) (patients 3, 4, and 9). One patient (patient 4) had Bing–Neel syndrome (WM involving the central nervous system). Two patients (patients 6 and 11) had secondary amyloidosis due to WM/LPL. According to the International Scoring System for Waldenström Macroglobulinemia (ISS-WM) proposed in 2009 (12), 7 patients were classified as being at high risk and 7 patients were classified as being at intermediate risk. Two patients were classified as being at low risk. One patient with IgD κ LPL (patient 13) had an unknown risk stratification because the serum M protein and β2-microglobulin levels were not measured; in addition, the ISS-WM may not be expanded enough to include risk stratification for IgD LPL.

Mutation of myeloid differentiation primary response 88, which has been identified in greater than 90% of WM/LPL patients by whole-genome sequencing (13), was documented in all patients in the present study. Three patients were found to have a CXCR4 mutation involving the C terminus that contains serine phosphorylation sites that regulate CXCR4 signaling by stromal cell–derived factor 1α (14). The clinical characteristics and biochemical investigations are summarized in Table 1.

Comparison of 68Ga-pentixafor and 18F-FDG PET/CT

With the formerly described visual assessment criteria, 68Ga-pentixafor PET/CT results were visually positive for 17 of 17 patients (100%), whereas 18F-FDG PET/CT results were positive for 10 of 17 patients (58.8%). The diagnostic performance of 68Ga-pentixafor PET/CT and 18F-FDG PET/CT in WM/LPL is shown in Table 2.

Bone Marrow Involvement. The fact that bone marrow is the predominant site of involvement in WM/LPL was confirmed by bone marrow aspiration and biopsy in all recruited patients. According to 68Ga-pentixafor and 18F-FDG PET/CT, bone marrow in the spine, pelvis, and appendicular skeleton was affected in all patients; rib involvement was found in 14 patients; and 10 patients had involvement in the skull. On 68Ga-pentixafor PET/CT, 10 patients had intense radioactivity in the bone marrow, with an SUVmax of 10.7 ± 4.1 (range, 6.0–21.3); 6 patients had moderate uptake in the bone marrow (SUVmax, 4.9 ± 0.8; range, 3.7–5.6). Only 1 patient had mild uptake in the bone marrow (SUVmax, 3.9) (classified as negative according to the visual assessment criteria in the present study); this patient had mildly elevated 68Ga-pentixafor
uptake in the skull, spine, pelvis, and both the proximal and the distal appendicular skeletons, including the carpals and metacarpals. With $^{18}\text{F}-\text{FDG PET/CT}$, 10 patients had bone marrow uptake with a score of 4, which was classified as positive; the remaining 7 patients had bone marrow intensity with a score of 3 (in 6 patients) and a score of 2 (in 1 patient). The individual $\text{SUV}_{\text{max}}$ of bone marrow for both $^{68}\text{Ga}$-pentixafor PET/CT and $^{18}\text{F}$-FDG PET/CT are shown in Supplemental Table 1 (supplemental materials are available at http://jnm.snmjournals.org).

In comparisons of $^{68}\text{Ga}$-pentixafor and $^{18}\text{F}$-FDG, 10 patients had visually higher uptake in the bone marrow on $^{68}\text{Ga}$-pentixafor PET than on $^{18}\text{F}$-FDG PET (example in Fig. 1A); in 6 patients, the intensities of the bone marrow uptake on $^{68}\text{Ga}$-pentixafor PET and $^{18}\text{F}$-FDG PET were comparable; and in only 1 patient was $^{18}\text{F}$-FDG

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (y)</th>
<th>Sex</th>
<th>ISS-WM*</th>
<th>Cytogenetics†</th>
<th>M protein type</th>
<th>M protein (g/L)</th>
<th>$\beta_2$-microglobulin (mg/L)</th>
<th>sFLC (mg/L)</th>
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<tr>
<td>1</td>
<td>69</td>
<td>M</td>
<td>High</td>
<td>MYD88L265P</td>
<td>IgM $\lambda$</td>
<td>66.99</td>
<td>47.7</td>
<td>9.54</td>
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<td>2</td>
<td>69</td>
<td>F</td>
<td>High</td>
<td>MYD88L265P</td>
<td>IgM $\kappa$</td>
<td>28.93</td>
<td>17.5</td>
<td>4.85</td>
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<td>3</td>
<td>56</td>
<td>M</td>
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<td>MYD88L265P</td>
<td>IgM $\kappa$</td>
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<td>13.1</td>
<td>9.28</td>
</tr>
<tr>
<td>4</td>
<td>61</td>
<td>M</td>
<td>IND</td>
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<td>IgM $\kappa$</td>
<td>30.49</td>
<td>18.5</td>
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<td>IgM $\kappa$</td>
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<td>1.1</td>
<td>3.68</td>
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<td>IgM $\kappa$</td>
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<td>10.8</td>
<td>12.8</td>
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<td>IgM $\kappa$</td>
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<td>2.1</td>
<td>8.93</td>
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<tr>
<td>8</td>
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<td>IgM $\kappa$</td>
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<td>34.3</td>
<td>3.06</td>
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<tr>
<td>9</td>
<td>72</td>
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<td>IND</td>
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<td>IgM $\kappa$</td>
<td>15.2</td>
<td>10.5</td>
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<td>2.34</td>
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<td>MYD88L265P</td>
<td>IgM $\kappa$</td>
<td>23.69</td>
<td>10.6</td>
<td>5.71</td>
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<td>64</td>
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<td>IND</td>
<td>MYD88L265P</td>
<td>IgM $\kappa$</td>
<td>53.3</td>
<td>32.5</td>
<td>5.27</td>
</tr>
<tr>
<td>13</td>
<td>48</td>
<td>F</td>
<td>N/A†</td>
<td>MYD88L265P</td>
<td>IgD $\kappa$</td>
<td>6.67 (IgD)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>14</td>
<td>55</td>
<td>F</td>
<td>Low</td>
<td>MYD88L265PCXCR4*$s_{338x}$</td>
<td>IgM $\kappa$</td>
<td>82.49</td>
<td>35.6</td>
<td>2.93</td>
</tr>
<tr>
<td>15</td>
<td>52</td>
<td>F</td>
<td>IND</td>
<td>MYD88L265P</td>
<td>IgM $\kappa$</td>
<td>38.13</td>
<td>21.6</td>
<td>3.34</td>
</tr>
<tr>
<td>16</td>
<td>53</td>
<td>M</td>
<td>IND</td>
<td>MYD88L265P</td>
<td>IgM $\kappa$</td>
<td>20.13</td>
<td>13.9</td>
<td>3.57</td>
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<td>17</td>
<td>48</td>
<td>M</td>
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<td>MYD88L265P</td>
<td>IgM $\kappa$</td>
<td>77.67</td>
<td>47.4</td>
<td>6.6</td>
</tr>
</tbody>
</table>

*International Staging System (ISS) for WM (ISS-WM) prognostic scoring includes age of >65 y, $\beta_2$-microglobulin level of >3 mg/L, hemoglobin level of ≤11.5 g/dL, platelet count of ≤100 $\times$ $10^9$/L, and IgM level of ≥7 g/dL. Low risk = ≤1 adverse characteristic and age of ≤65 y; high risk = ≥3 adverse characteristics; indeterminate (IND) risk = 2 adverse characteristics or age of >65 y.
†MYD88 and CXCR4 warts, hypogammaglobulinemia, infections, and myelokathexis syndrome-like somatic mutations were tested.
‡ISS-WM scoring system was not applicable (N/A) for IgD-type WM/LPL.
§Serum IgD level was measured as IgD-type M protein level.
sFLC = serum-free light chain; IND = indeterminate.

### Table 2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>$^{68}$Ga-pentixafor</th>
<th>$^{18}$F-FDG</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>% of patients</td>
<td>No. of patients</td>
</tr>
<tr>
<td>Patients with positive PET results*</td>
<td>17/17</td>
<td>100</td>
</tr>
<tr>
<td>Bone marrow involvement</td>
<td>16/17</td>
<td>94.1</td>
</tr>
<tr>
<td>Lymph node involvement</td>
<td>13/17</td>
<td>76.5</td>
</tr>
<tr>
<td>Paramedullary involvement</td>
<td>3/17</td>
<td>17.6</td>
</tr>
<tr>
<td>CNS involvement</td>
<td>1/17</td>
<td>5.9</td>
</tr>
</tbody>
</table>

*Difference in rates of positive results between $^{68}$Ga-pentixafor and $^{18}$F-FDG was significant.

CNS = central nervous system.

Positive results for $^{68}$Ga-pentixafor were defined by uptake > liver; positive results for $^{18}$F-FDG were defined by uptake with score of ≥4 (5-point scale).
Examples of WM/LPL \[18\] Luo et al.

PET/CT, the latter finding is partly \[18,19\] Fig. 3); another patient IN of 8.3 patients were found to have mildly\[18\] light chain levels and the proportion of lymphoplasmacytic cells in patients was 16.5 mm (range, 5–max\[15\]).

Regarding the extent of bone marrow involvement, patients had involvement in more than 5 lymph node regions. The maximum size of the positive node in each patient was 16.5 mm. The bone marrow involvement was more extensive with \[68\]Ga-pentixafor than with \[18\]F-FDG. Additional bone marrow disease was detected in craniofacial bones, ulna, radius, carpal bones, and metacarpal bones with \[68\]Ga-pentixafor. Submandibular, retroperitoneal, and inguinal lymph nodes had positive results on \[68\]Ga-pentixafor PET, but these lymph nodes were not \[18\]F-FDG–avid. uptake in the bone marrow higher than that of \[68\]Ga-pentixafor. Regarding the extent of bone, bone marrow involvement, \[68\]Ga-pentixafor PET demonstrated more extensive bone marrow disease in 3 patients than \[18\]F-FDG PET (example in Fig. 1B), specifically when the involvement of the craniofacial bones (in 7 patients) and distal upper extremity bones (in 2 patients) was visualized. The bone marrow involvement mainly appeared as diffuse bone marrow patterns with homogeneous radioactivity throughout the axial and appendicular skeletons; moreover, additional focal bone marrow lesions were detected by \[68\]Ga-pentixafor PET in 3 patients (example in Figure 2A). Among these 3 patients, only 1 was found to have focal lesions by \[18\]F-FDG PET. No bone destruction was found in the coregistered CT. Despite the superiority of \[68\]Ga-pentixafor over \[18\]F-FDG in detecting bone marrow involvement, we did not find significant correlations between the SUV of bone marrow in baseline \[68\]Ga-pentixafor PET and the laboratory results, including hemoglobin, serum IgM, M protein, B2-microglobulin, and serum free light chain levels and the proportion of lymphoplasmacytic cells in bone marrow biopsies.

**Lymph Node Involvement.** On \[68\]Ga-pentixafor PET/CT, 13 of 17 patients (76.5%) had positive lymph nodes (examples in Fig. 2), including neck (9 patients), axilla (7 patients), mediastinum (3 patients), internal mammary (1 patient), hepatoduodenal (11 patients), paraaortic (11 patients), iliac (7 patients), inguinal (7 patients), and epitrochlear (1 patient) nodes. Eight patients had involvement in more than 5 lymph node regions. The maximum size of the positive node in each patient was 16.5 mm (range, 5–26 mm), with an \(SUV_{\text{max}}\) of 8.3 (range, 4.0–18.8) (Supplemental Table 1). However, with \[18\]F-FDG PET/CT, only 2 patients were found to have mildly \[18\]F-FDG–avid lymph nodes (score, 3 or 4; \(SUV_{\text{max}}\), 2.9); moreover, \[68\]Ga-pentixafor PET/CT detected more positive lymph nodes with higher radioactivity in these 2 patients than \[18\]F-FDG PET/CT. No lymph node involvement was detected in 4 patients with either \[68\]Ga-pentixafor PET/CT or \[18\]F-FDG PET/CT.

**Follow-Up PET/CT After Chemotherapy**

Four patients underwent follow-up \[68\]Ga-pentixafor and \[18\]F-FDG PET/CT after 6 or 7 cycles of chemotherapy. The intervals between the last cycle of chemotherapy and the PET/CT study were 2 wk to 3 mo. According to the consensus response criteria adopted at the Sixth International Workshop on Waldenström Macroglobulinemia (15), 2 patients with a complete response or a very good partial response showed complete remission of the bone marrow and extramedullary involvement with both \[68\]Ga-pentixafor PET/CT and \[18\]F-FDG PET/CT (example in Fig. 3); another patient with a very good partial response had only several remnant CXCR4-positive axillary lymph nodes. The remaining patient who had a partial serological response showed a marked reduction of bone marrow uptake with \[68\]Ga-pentixafor and \[18\]F-FDG \([18\]F-FDG: score of 2; \[68\]Ga-pentixafor: mild uptake) and complete resolution of the involved lymph nodes.

**DISCUSSION**

The diagnosis of diffuse bone marrow involvement of lymphoma with \[18\]F-FDG PET/CT has always been a clinical dilemma for nuclear medicine physicians. Diffusely increased bone marrow \[18\]F-FDG uptake is commonly observed in patients with anemia or reactive hyperplasia or those treated with growth factors rather than patients with lymphomatous bone marrow involvement (16,17). Meanwhile, \[18\]F-FDG PET/CT can miss low-volume involvement (typically <20% of the marrow) and low-grade lymphoma in bone marrow (16). WM/LPL is an indolent lymphoma that primarily involves the bone marrow, and anemia is observed in more than 1 of 3 WM/LPL patients; the latter finding is partly related to B-cell infiltration in the bone marrow, blood loss, IgM-associated hemolysis, low erythropoietin levels, or concomitant iron deficiency (18,19). Therefore, bone marrow \[18\]F-FDG uptake in WM/LPL patients is complicated.
In the present study, 14 of 17 patients (82.4%) had anemia (median hemoglobin level of 89.5 g/L), which might have contributed to the bone marrow activity. In contrast, the percentage of lymphoplasmacytic cells that infiltrated the bone marrow was relatively low; more than 80% of the patients had less than 20% node involvement was significantly higher with 68Ga-pentixafor than with 18F-FDG (76.5% vs. 11.8%; P = 0.003) in the recruited WM/LPL patients. Most of the involved lymph nodes showed intense uptake of 68Ga-pentixafor (mean SUV\textsubscript{max} 8.3; range, 4.0–18.8). The most commonly involved lymph nodes were the hepatoduodenal (19%), paraaortic (19%), cervical (16%), axillary (12%), iliac (12%), and inguinal (12%) nodes. Because previous data on lymphadenopathy in WM/LPL were usually based on CT criteria, we believe that the true percentage of lymph node involvement in WM/LPL might be much higher than the current data suggest, on the basis of the findings of 68Ga-pentixafor PET/CT. Similarly, paramedullary involvement and central nervous system disease showed intense radioactivity on 68Ga-pentixafor PET, but the results were negative on 18F-FDG PET. These results imply that 68Ga-pentixafor might be a very promising imaging agent for the diagnosis and staging of WM/LPL.

There might be some limitations of 68Ga-pentixafor. First, apart from CXCR4-positive tumor cell infiltration, other activated inflammatory cells in the bone marrow with upregulated CXCR4 expression might also cause increased bone marrow uptake (21–23). Therefore, the specificity of diagnosing diffuse bone marrow involvement might be
hampered in the differentiation of different diseases in future studies. Second, because of the lack of histologic verification of lymph node involvement in the present study, false-positive results for lymph nodes might be caused by inflammation—especially for nodes with moderate $^{68}$Ga-pentixafor uptake and in patients with a limited number of positive nodes. Third, the incidence of splenic involvement caused by the infiltration of clonal cells was reported to be 20%–25% in WM/LPL (18,20). Consistent with the literature, splenomegaly with mildly increased $^{18}$F-FDG uptake (uptake > liver) was noted in 17.6% of patients in the present study. However, establishing an interpretation criterion to define the high spleen uptake of $^{68}$Ga-pentixafor might be difficult because there is considerable physiologic uptake in the normal spleen. Finally, in the 4 patients who underwent follow-up PET/CT after chemotherapy, we found an almost complete response on both $^{68}$Ga-pentixafor PET/CT and $^{18}$F-FDG PET/CT. However, the surface expression of CXCR4 in tumor cells is a dynamic process that is influenced by therapeutic interventions. Chemotherapy may induce CXCR4 downregulation in multiple myeloma, diffuse large B-cell lymphoma, and acute lymphoblastic leukemia (24,25). If this is also the case in WM/LPL, images must be interpreted with caution to avoid misinterpretation of the tumor response. Moreover, it is important to further investigate the time- and dose-dependent influence of each chemotherapeutic drug on CXCR4 expression in different tumors.

CONCLUSION

In the present study, we found that $^{68}$Ga-pentixafor PET/CT had a higher rate of positive results than $^{18}$F-FDG PET/CT for detecting tumor involvement of the bone marrow, lymph nodes, and other extramedullary organs in WM/LPL patients. Further studies are warranted to clarify the role of $^{68}$Ga-pentixafor in staging, assessing the response to therapy, and predicting the prognosis for WM/LPL patients.

DISCLOSURE

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KEY POINTS

QUESTION: Is $^{68}$Ga-pentixafor PET/CT superior to $^{18}$F-FDG PET/CT for detecting tumor involvement in Waldenstrom macroglobulinemia/lymphoplasmacytic lymphoma (WM/LPL)?

PERTINENT FINDINGS: In our prospective cohort study of 17 patients with WM/LPL, $^{68}$Ga-pentixafor PET/CT had a higher rate of positive results than $^{18}$F-FDG PET/CT for detecting bone marrow involvement, lymph node involvement, and other extramedullary involvement.

IMPLICATIONS FOR PATIENT CARE: $^{68}$Ga-pentixafor PET/CT might be a promising tool for the assessment of WM/LPL.

REFERENCES