First-in-Human Experience of CXCR4-Directed Endoradiotherapy with ^{177}Lu- and ^{90}Y-Labeled Pentixather in Advanced-Stage Multiple Myeloma with Extensive Intra- and Extramedullary Disease

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Multiple myeloma is a cancer arising from clonally expanding plasma cells. Despite treatment advances such as proteasome inhibitors and immunomodulatory drugs alone or in combination with stem cell transplantation (SCT), multiple myeloma invariably relapses (*1–3*) and thus remains incurable. The low response rates to current therapy are in part explained by the emergence of multiple clones, leading to pronounced inter- and intratumor heterogeneity and rapid development of resistance (*4,5*). Therefore, novel strategies facilitating effective myeloma cell kill are urgently needed.

In cancer, overexpression of chemokine receptor 4 (CXCR4) and its activation by stromal cell–derived factor 1 binding are key triggers for tumor growth, progression, invasion, and metastasis (*6–8*). CXCR4 is overexpressed in multiple myeloma cells (*9,10*). Wester's group has successfully developed a radiolabeled CXCR4 ligand (^{68}Ga-pentixafor) for PET imaging (*11,12*). Proof of concept for visualization of CXCR4 expression has recently been demonstrated in patients with lymphoma (*13*) and multiple myeloma (*14*). To transfer this targeting vector to a therapeutic scenario, derivatives of the compound allowing labeling with various α- and β^--emitters have been developed. Here, we report our first experience with CXCR4-targeted endoradiotherapy in combination with high-dose chemotherapy and autologous SCT applied in 3 patients with advanced and heavily pretreated multiple myeloma.

MATERIALS AND METHODS

Subjects

Three patients (2 men and 1 woman aged 51, 62, and 66 y) with relapsed multiple myeloma were studied. Prior chemotherapies included lenalidomide, bortezomib, pomalidomide, and carfilzomib in various combinations. All patients had undergone autologous SCT and presented with clinically active disease and especially extensive extramedullary disease.

CXCR4 expression was confirmed by imaging in all 3 patients using ^{68}Ga-pentixafor PET/CT. ^{18}F-FDG PET/CT was additionally

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performed to measure glycolytic activity in active myeloma lesions. The patient characteristics are presented in Table 1. Given the lack of alternative treatments—and in view of the extensive extramedullary disease, documented CXCR4 expression, and availability of bone marrow for marrow rescue—an interdisciplinary board of specialists opted for CXCR4-targeted endoradiotherapy combined with high-dose chemotherapy and autologous SCT. The clinical ethics committee of our institution (Universitätsklinikum Würzburg) approved each individual treatment on a compassionate-use basis (German Drug Act, §13,2b). All subjects gave written informed consent before receiving the therapy.

Dosimetry

As part of this prospective protocol, a preendoradiotherapy dosimetric calculation using SPECT/CT and serial planar imaging was performed on all 3 patients after intravenous injection of approximately 200 MBq of ^{177}Lu-pentixather without nephroprotective medication. This was done to record sites of unexpected tracer accumulation that may denote potential toxicity, determine the organ radiation doses, and estimate the achievable tumor doses. The absorbed doses in tumors and organs were assessed by analyzing regions of interest in multiple planar total-body images to obtain pharmacokinetic data and a single SPECT/CT scan to scale the pharmacokinetic curve. All images were acquired using dual-head γ-cameras (Symbia E for planar imaging, Symbia T2 calibrated from phantom measurements with ^{177}Lu activity standards for SPECT/CT imaging; Siemens) equipped with medium-energy collimators. Pharmacokinetic data were fitted by biexponential functions. SPECT/CT data were reconstructed using 3-dimensional ordered-subsets expectation maximization (6 subsets, 6 iterations, 6-mm gaussian filter) with corrections for scatter and attenuation to obtain absolute activity quantification in voxels sized 0.11 cm^3. The 1-mL volume with the highest activity concentration was termed the maxV.

Therapy

Consistent with experience with peptide receptor radionuclide therapy in neuroendocrine tumor patients, preendoradiotherapy dosimetry identified the kidney as the dose-limiting organ. The administered endoradiotherapy activities were chosen to target at 23 Gy in the maxV. Accordingly, patients 1 and 2 were treated by intravenous infusion of 15.2 and 23.5 GBq of ^{177}Lu-pentixather, respectively. Additional posttherapy dosimetry scans were obtained in both patients. In neuroendocrine tumor patients, the high-energy emitter ^{90}Y has been shown to be more effective than ^{177}Lu for treating larger lesions (*15,16*). Therefore, a 6.3-GBq infusion of ^{90}Y-pentixather was administered in one patient (patient 3) with larger myeloma lesions. In an attempt to further reduce renal toxicity, 25 g of L-arginine and 25 g of L-lysine (pH 7.0, diluted in 2 L of normal saline), were intravenously administered over 4 h beginning 30 min to 1 h before endoradiotherapy as previously recommended for neuroendocrine tumor patients undergoing peptide receptor radionuclide therapy (*17*). Vital signs, complete blood count, and chemistry including kidney and liver function were documented as acute adverse events during the infusion and within 7 d after administration.

Response Assessment

Nonmetabolic myeloma response was assessed according to the criteria of the International Myeloma Working Group (*18*). Additionally, assessment by ^{18}F-FDG PET/CT early (within 21 d) after treatment was available in patients 1 and 3. Assessment for minimal residual disease as defined by Munshi and Anderson was not performed (*19*).

TABLE 1
Patient Characteristics

Characteristic	Patient 1	Patient 2	Patient 3
Sex	M	F	M
Age	62 y	66 y	51 y
Myeloma type	IgG κ	LC κ	LC λ
Disease duration*	18 mo	53 mo	59 mo
Sites of EMD	Soft tissue, testis	LN, leptomeninges	LN, pleura, soft tissue
Previous chemoTx†	PAD, pom, dex, carfilzomib	PAD, pom, dex, lenalidomide	VCD, PAD, revlimid, pom, dex
Previous autologous Tx	1 time	3 times	3 times
PreTx dosimetry	238 MBq ^{177}Lu	199 MBq ^{177}Lu	212 MBq ^{177}Lu
Mean kidney dose	1.02 Gy/GBq ^{177}Lu	0.93 Gy/GBq ^{177}Lu	0.48 Gy/GBq ^{177}Lu
Kidney dose maxV	1.39 Gy/GBq ^{177}Lu	1.08 Gy/GBq ^{177}Lu	2.9 Gy/GBq ^{90}Y est
Mean liver dose	0.38 Gy/GBq ^{177}Lu	0.79 Gy/GBq ^{177}Lu	0.62 Gy/GBq ^{177}Lu
Tumor dose maxV	3.3 Gy/GBq ^{177}Lu	9.5 Gy/GBq ^{177}Lu	4.9 Gy/GBq ^{177}Lu
Tx	15.2 GBq ^{177}Lu	23.5 GBq ^{177}Lu	6.3 GBq ^{90}Y
Mean kidney dose	0.57 Gy/GBq ^{177}Lu	0.50 Gy/GBq ^{177}Lu	2.2 Gy/GBq ^{90}Y est
Mean liver dose	0.37 Gy/GBq ^{177}Lu	0.56 Gy/GBq ^{177}Lu	1.7 Gy/GBq ^{90}Y est
Tumor dose maxV	3.5 Gy/GBq ^{177}Lu	3.0 Gy/GBq ^{177}Lu	11.3 Gy/GBq ^{90}Y est
Response	PR on ^{18}F-FDG	NA	CR^{18}F-FDG

*Time from primary diagnosis to endoradiotherapy.
†Including novel agents.
LC = (immunoglobulin) light chains; EMD = extramedullary disease; LN = lymph nodes; Tx = therapy; PAD = bortezomib, doxorubicin, dexamethasone; pom = pomalidomide; dex = dexamethasone; VCD = bortezomib, cyclophosphamide, dexamethasone; est = estimate based on pretherapy kinetics (nephron-protection unconsidered); PR = partial remission; NA = not applicable; CR = complete remission.

RESULTS

Pentixafor PET and Dosimetry

All patients showed intense CXCR4 expression in the intra- and extramedullary myeloma lesions on ^{68}Ga-pentixafor PET. All hypermetabolic lesions on ^{18}F-FDG PET/CT exhibited concordant ^{68}Ga-pentixafor uptake (Fig. 1A). Intra- and extramedullary manifestations showed no differences in ^{68}Ga-pentixafor positivity.

Since the bone marrow was one of the main therapeutic targets, a high radiation dose to this organ and myelosuppression were expected. The kidneys were the dose-limiting organs as determined by pretreatment dosimetry (Table 1). In relation to the respective tolerable organ doses, the kidney doses were higher than the liver doses in all 3 patients in pretreatment dosimetry and remained relatively higher in patients 1 and 2 during therapy, although nephroprotective treatment reduced the mean kidney dose by about 45% to 0.57 and 0.50 Gy/GBq, respectively. Therapeutic tumor doses of up to 60 Gy in patient 1 and 71 Gy in patient 2 were determined for the voxels with the highest activity concentration; corresponding maxVs were 53 and 70 Gy, respectively (Table 1). Up to an 84-Gy maximum voxel dose and 71 Gy in maxV were predicted for patient 3 on the basis of pretherapeutic measurements of the ^{177}Lu-pentixather kinetics decay corrected for ^{90}Y-pentixather.

Therapy and Posttherapy Images

No acute adverse effects were associated with ^{177}Lu- and ^{90}Y-pentixather therapy during the first 14 d after infusion. No changes in vital signs occurred. Posttherapeutic scintigraphic imaging after ^{177}Lu-pentixather therapy, including SPECT/CT and serial planar scans, demonstrated high pentixather uptake in all tumor lesions, consistent with diagnostic ^{68}Ga-pentixafor PET/CT and pretherapeutic ^{177}Lu-pentixather dosimetry scans. In one patient, additional imaging could be obtained as late as 14 d after injection of the radiopharmaceutical and demonstrated persistent pentixather retention (Fig. 1B).

Response Assessment with ^{18}F-FDG PET/CT and Serum Parameters

Two of the 3 patients underwent ^{18}F-FDG PET/CT for response assessment 14 and 21 d after treatment. Patient 1 (treated with ^{177}Lu-pentixather) showed a partial response with a reduction of SUV_{max} by greater than 35% in all lesions. Patient 3 had a complete metabolic response after ^{90}Y-pentixather treatment, showing visual resolution of all previous ^{18}F-FDG–positive lesions (Fig. 1). Consistently, a more than 50% decrease in the difference between involved and uninvolved serum free light chain levels was observed in patients 1 (90.0 mg/L before therapy, 23.0 mg/L after ^{177}Lu-pentixather, and 11.8 mg/L after SCT) and 3 (385.0 mg/L before therapy and 9.1 mg/L after ^{90}Y-pentixather and SCT). Patient 2 presented with sepsis shortly after autologous SCT and therefore did not undergo restaging with ^{18}F-FDG PET/CT. None of the 3 subjects underwent minimal residual disease evaluation with bone marrow examination and fluorescence-activated cell analysis for myeloma.

Outcome

After showing a partial response at the first posttherapeutic assessment by ^{18}F-FDG PET/CT, patient 1 underwent subsequent high-dose chemotherapy with autologous stem cell support. This patient, however, died 6 mo after pentixather therapy from myeloma relapse. Patient 2 died from sepsis 3 wk after pentixather therapy followed by high-dose chemotherapy (BEAM) and autologous SCT. The complete metabolic responder (patient 3) died 3 mo after ^{90}Y-pentixather therapy because of tumor progression with central nervous system disease. In none of the patients were any acute adverse events recorded immediately during or within 1 wk after pentixather therapy; in particular, no nausea or cardiac, renal, or hepatic toxicity occurred.

DISCUSSION

Here, we report the first-in-human administration of CXCR4-targeted radionuclide therapy using ^{177}Lu- and ^{90}Y-labeled pentixather in patients with advanced multiple myeloma. Application of ^{177}Lu- and ^{90}Y-pentixather was safe and well tolerated, without any acute nonhematologic adverse effects despite a prior history of multiple courses of chemotherapy, including novel agents and autologous SCT. However, pentixather treatment resulted in myeloablation in all 3 patients and might have contributed to the leukopenia and sepsis seen in patient 2. As all 3 patients had extensive extramedullary disease manifestations, pentixather was accordingly combined with preemptive autologous stem cell rescue. Even after a single application, pentixather was retained in all multiple myeloma lesions for up to 2 wk after initial treatment (Fig. 1B). Prolonged retention of pentixather will lead to a higher target radiation dose, which might be associated with a higher probability of treatment response.

In the 2 patients evaluable for response by ^{18}F-FDG PET/CT, one partial metabolic imaging response could be documented, as well as one complete response of all extramedullary lesions. All myeloma lesions had been refractory to all standard and novel regimens; thus, CXCR4-directed radiotherapy might prove a powerful new tool in addressing both intra- and extramedullary disease despite the limited progression-free survival documented in the patients (3–6 mo). Because advanced multiple myeloma represents multiclonal disease, the β-emitting

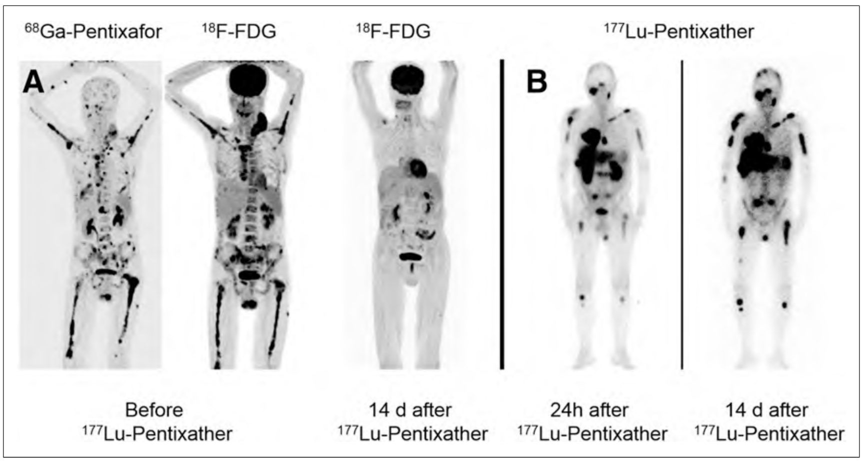

FIGURE 1. (A) In patient 3 before pentixather therapy, maximum-intensity projections of ^{68}Ga-pentixafor and ^{18}F-FDG PET/CT indicate high CXCR4 expression in multiple extra- and intramedullary ^{18}F-FDG–avid myeloma lesions. Corresponding ^{18}F-FDG PET/CT image 2 wk after ^{90}Y-pentixather shows complete metabolic response. (B) Scintigraphic images of patient 1 at 24 h and 15 d after 15.2 GBq of ^{177}Lu-pentixather confirm binding to CXCR4 target. Visual difference in tumor-to-background ratios is due to reduced background uptake at later time point and longer emission times due to lower count rates.

endoradiotherapy might also affect cell clones not directly targeted by pentixather because of the radiation-induced bystander effect. This may indeed be one of the key advantages of endoradiotherapy. However, because of the significant radiation dose administered to the bone marrow in these patients, a combination of CXCR4-directed radiotherapy with high-dose chemotherapy and consecutive stem cell support appears mandatory. All patients underwent CXCR4-targeted radiotherapy followed by high-dose conventional chemotherapy and consecutive SCT. In this setting, the therapeutic effects of each individual treatment component could not be dissected. However, because all patients had been heavily pretreated with multiple chemotherapeutic regimens and were presenting with refractory disease with lack of alternative treatments, the observed metabolic response was at least partially due to the CXCR4-directed endoradiotherapy. Nevertheless, this promising proof of principle in 3 patients requires further evaluation, including safety and toxicity studies, as well as prospectively designed clinical trials with well-defined primary and secondary endpoints, especially in view of the pivotal role CXCR4 seems to play in the pathogenesis of not only hematologic malignancies (*6,9,10*) but also solid tumors (*20*).

CONCLUSION

CXCR4-directed endoradiotherapy in addition to chemotherapy and autologous SCT is feasible and produced a promising response in our patients, warranting further investigation as a treatment option in heavily pretreated patients with advanced multiple myeloma, especially with extramedullary disease.

DISCLOSURE

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