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Feasibility of CXCR4-Directed Radioligand Therapy in Advanced Diffuse Large B-Cell Lymphoma

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refractory or relapsed disease have a worse prognosis, and second-line chemotherapy is administered to achieve a second response before high-dose chemotherapy and subsequent stem cell transplantation (SCT).

C-X-C-motif chemokine receptor 4 (CXCR4) is overexpressed on lymphoma cells (3–6) and has been identified as a potential drug target. Wester et al. successfully developed a radiolabeled CXCR4 ligand (⁶⁸Ga-pentixafor) for PET imaging (5,7,8) that visualizes CXCR4 expression in patients with hematologic and solid malignancies (5,9–17). Recently, we and others also reported on experience with ¹⁷⁷Lu- and ⁹⁰Y-labeled pentixather (18), the therapeutic counterpart of ⁶⁸Ga-pentixafor for CXCR4-targeted radioligand therapy (RLT) in acute leukemia (19) and in patients with advanced multiple myeloma (20,21). In this article, we evaluate the feasibility of CXCR4-directed RLT as part of the conditioning regimen before allogeneic SCT in patients with relapsed DLBCL of very advanced stage.

MATERIALS AND METHODS

Subjects

Six patients (3 men, 3 women; aged, 54 ± 8 y) with relapsed, refractory DLBCL were included in the study. All patients had undergone multiple lines of previous treatment (2–6 lines of treatment; median, 3 lines) and presented with refractory, progressive disease.

Given the lack of alternative treatments in this advanced disease stage, experimental CXCR4-directed treatment was offered to the patients on a compassionate-use basis (German Drug Act, §13,2b) in compliance with §37 of the Declaration of Helsinki as part of the conditioning regimen before repeated allogeneic SCT. Treatment was approved by the clinical ethics committee of our institution. All subjects gave written informed consent before therapy. Patient characteristics are depicted in Table 1.

⁶⁸Ga-Pentixafor Imaging

CXCR4 expression was confirmed in all patients using ⁶⁸Ga-pentixafor PET/CT on a dedicated scanner (Biograph mCT 64; Siemens Medical Solutions). CXCR4-directed PET/CT imaging was performed 60 min after injection of 62–165 MBq (median, 95 MBq) of ⁶⁸Ga-pentixafor as previously described (21). ⁶⁸Ga-pentixafor-positive lesions were visually determined as focally increased tracer retention as compared with surrounding normal tissue or contralateral structures.

Pretherapeutic Dosimetry and CXCR4-Directed RLT

RLT was preceded in every patient by a pretherapeutic dosimetry study with 200 MBq of ¹⁷⁷Lu-pentixather intended to identify critical

Diffuse large B-cell lymphoma (DLBCL) is the most common histologic subtype of non-Hodgkin lymphoma, accounting for approximately 25% of all cases (1). Systemic chemotherapy, immunotherapy with the recombinant anti-CD20 antibody rituximab, and external radiotherapy are the mainstay of therapy and achieve 10-y survival rates of 40%–50% (2). However, patients with

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TABLE 1
Patients' Characteristics

Patient no.	Sex	Age (y)	Disease	Previous lines of therapy	Conditioning regimen	Additional radioimmuno-therapy	RLT to neutropenia	SCT to neutrophil reconstitution	Best response	Progression-free survival	Overall survival
1	M	62	DLBCL	2	Fludarabine, busulfan, thiotepa, ATG	No	8	9	NA	29	29
2	F	46	DLBCL	3	Fludarabine, busulfan, thiotepa	No	15	10	Mixed	110	334
3	F	64	DLBCL	5	Fludarabine, busulfan, thiotepa, ATG	No	7	NA	NA	34	34
4	M	47	DLBCL	3	Fludarabine, busulfan, thiotepa, ATG	No	7	13	Mixed	34	62
5	F	52	DLBCL	3	Busulfan, thiotepa, ATG	Yes (^{188}Re -anti-CD66)	5	13	PR	89	89
6	M	55	DLBCL	6	Fludarabine, treosulfan, thiotepa, ATG	Yes (^{90}Y -Zevalin)	20	11	PR	109	115

ATG = antithymocyte globulin; NA = not applicable.
All time intervals are given in days.

organs and the safely administrable activities and to estimate the achievable tumor doses as outlined previously (21).

On the basis of their individual dosimetry, patients were treated by intravenous injection of ^{90}Y -labeled pentixather (Table 2). ^{90}Y -pentixather was used for treatment to enhance cross irradiation of potential areas of reduced uptake in extramedullary lesions and, more importantly, to shorten the time to SCT. With its 64-h physical half-life, ^{90}Y activity and thus the residual absorbed dose are reduced to 2.6% of the total absorbed dose after 2 wk by physical decay only. The effective half-life of ^{90}Y -pentixather in the red marrow is even shorter, typically not exceeding 2.5 d. The residual dose to the red marrow is therefore less than 0.75 Gy 14 d after ^{90}Y -pentixather treatment with 30 Gy of red marrow dose, and SCT can be safely administered.

RLT was performed at a median of 4 d (range, 2–23 d) after pretherapy dosimetry. To reduce renal toxicity, 2 L of an amino acid solution containing arginine and lysine (25 g/L each) were coinfused in accord with the joint International Atomic Energy Agency, European Association of Nuclear Medicine, and Society of Nuclear Medicine and Molecular Imaging practical guidance on receptor radionuclide therapy in neuroendocrine tumors (22). Kidney protection by amino acids has been reported to reduce kidney uptake of ^{177}Lu -pentixather by about 45% (20). Vital signs, complete blood count, and blood chemistry were documented during the infusion and within 7 d after administration.

Concomitant Radioimmunotherapy

In 2 patients, radioimmunotherapy aiming at CD20 for direct targeting of CD20-positive lymphoma cells or CD66 for indirect targeting of bone marrow infiltration was added to enhance anti-lymphoma activity. For targeting CD20 on DLBCL cells, a 15 MBq/kg dose of ^{90}Y -ibritumomab tiuxetan (Zevalin; Spectrum Pharmaceuticals)

was infused 7 d after administration of CXCR4-directed RLT, preceded by rituximab at a dose of 250 mg/m² of body surface area 1 wk before and on the day of radioimmunotherapy.

In the patient receiving additional radioimmunotherapy targeting CD66 because of high-risk lymphoma with initial bone marrow infiltration (and loss of CD20), the murine anti-CD66 monoclonal antibody BW 250/183 (anti-Granulocyte; Scintec Diagnostics) was labeled with ^{188}Re as previously described (23) and delivered from the Department of Nuclear Medicine (radiopharmaceutical division) of Dresden University Hospital. Two days after ^{90}Y -pentixather treatment, anti-CD66–targeted radioimmunotherapy with 5.6 GBq (maximum amount available) of ^{188}Re -anti-CD66-BW250/183 was performed. Favorable antibody distribution was verified using whole-body planar scintigraphy 44 h after radioimmunotherapy.

Conditioning Chemotherapy and Stem Cell Transplantation

All patients except patient 2 received stem cell grafts from unrelated donors. Therefore, in these subjects additional conditioning chemotherapy included busulfan (in $n = 5$ patients)/treosulfan ($n = 1$), antithymocyte globulin (ATG Fresenius S; Neovii), fludarabine, and thiotepa. In patient 5, fludarabine was withheld because of chronic kidney failure.

Safety and Response Assessment

Adverse events were classified as in the *Medical Dictionary for Regulatory Activities* (24); severity was assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (25).

If available (in $n = 3$ patients), response was defined according to the Lugano criteria (26) after 6, 11, and 16 wk. Progression-free survival was defined as the time from RLT until disease progression, initiation of new antitumor therapy, or death.

TABLE 2
Overview of Administered Activities and Estimated Organ and Lymphoma Doses

Parameter	Patient no.					
	1	2	3	4	5	6
Pretherapy dosimetry						
¹⁷⁷ Lu-pentixather (MBq)	224	224	200	208	200	211
Kidney max_mL (Gy/GBq ¹⁷⁷ Lu)	0.8	2.9	1.3	0.8	*	1.3
Liver (Gy/GBq ¹⁷⁷ Lu)	0.2	0.6	0.7	0.4	0.6	0.9
Spleen (Gy/GBq ¹⁷⁷ Lu)	0.3	0.8	0.7	1.0	1.7	0.7
Bone marrow max_mL (Gy/GBq ¹⁷⁷ Lu)	†	†	*	4.8	2.4	0.9
Extramedullary lesion max_mL (Gy/GBq ¹⁷⁷ Lu)	0.9	1.9	4.5		5.5	1.9
RLT						
⁹⁰ Y-pentixather (GBq)	5.3	2.8	4.3	6.5	5.8	6.2
Added RLT with ¹⁸⁸ Re-anti-CD66 (GBq)					5.6	
Added RLT with ⁹⁰ Y-Zevalin (GBq)						1.4
Posttherapy dosimetry[‡]						
Kidney max_mL (no protection) (Gy/GBq ⁹⁰ Y)	3.5	11.3	4.9	3.8	*	5.7
Liver (Gy/GBq ⁹⁰ Y)	0.9	1.8	1.6	1.3	1.6	2.0
Spleen (Gy/GBq ⁹⁰ Y)	1.2	1.8	1.6	3.4	3.6	1.8
Bone marrow (Gy/GBq ⁹⁰ Y)	†	†	*	11.4	5.1	1.9
Extramedullary lesion max_mL (Gy/GBq ⁹⁰ Y)	3.9	5.3	10.4		16.7	7.1
Kidney max_mL (with protection [¶]) (Gy)	11.2	19.2	12.9	14.6	*	20.9
Liver (Gy)	5.0	5.1	7.1	8.4	9.5	12.2
Spleen (Gy)	6.6	5.2	7.0	21.8	20.7	11.1
Bone marrow max_mL (Gy)	†	†	*	73.8	29.4	11.7
Extramedullary lesion max_mL (Gy)	20.9	15.0	45.2		96.5	43.5

*Not evaluable because of malignant structures.
†No visible tracer accumulation.
[‡]⁹⁰Y-pentixather, recalculated from pretherapeutic dosimetry.
[¶]40% reduction of absorbed radiation dose of kidneys by coinfusion of amino acid solution (arginine/lysine).

RESULTS

Patient Characteristics

Between November 2015 and February 2017, 6 patients with advanced-stage, progressive DLBCL were enrolled. All subjects had been extensively pretreated and had undergone multiple lines of previous treatment (2–6 lines of treatment; median, 3 lines). At the time of presentation, multiple lymphoma manifestations in lymph nodes ($n = 5$ patients), bone ($n = 3$), lungs ($n = 3$), kidneys ($n = 3$), pleura ($n = 2$), spleen ($n = 2$), and muscle ($n = 2$), as well as in adrenal, pancreas, stomach, and thyroid ($n = 1$ each), were documented.

Pretherapeutic Dosimetry

The activities of ¹⁷⁷Lu-pentixather administered for the pretherapeutic dosimetry study and the measured specific absorbed doses in the kidneys, liver, spleen, bone marrow, and tumor are listed in Table 2. The kidneys were the dose-limiting organ for all patients (apart from expected myeloablation). Lymphoma doses of up to 5.5 Gy/GBq of ¹⁷⁷Lu-pentixather (16.7 Gy/GBq of ⁹⁰Y-pentixather) were deduced.

Therapy and Adverse Events

⁹⁰Y was administered as the radionuclide of choice in all patients. Because of the shorter half-life of ⁹⁰Y than of ¹⁷⁷Lu, the residual dose in the medullary cavities is reliably below 750 mGy after an interval of 14 d between RLT and subsequent SCT (in contrast to a much longer and more heterogeneous interval with ¹⁷⁷Lu). The tolerable activity of ⁹⁰Y-pentixather was estimated from the kinetics measured in the pretherapeutic dosimetry targeting at a 23-Gy kidney dose in the 1-mL volume with the highest measured activity concentration (max_mL). The actually infused activities (2.8–6.4 GBq of ⁹⁰Y), the tolerable activities without kidney protection, and the estimated actually absorbed doses in the kidney max_mL (assuming a 40% kidney dose reduction due to the amino acid solution) are listed in Table 2 for each patient.

During RLT application, no immediate toxic or allergic reactions or changes in vital signs occurred. No acute adverse renal, hepatic, or cardiac events were observed.

As expected, RLT (in combination with additional conditioning chemotherapy) resulted in neutropenia of less than 500/ μ L after a median of 8 d (range, 5–20 d) and complete myeloablation after a median of 13 d (range, 8–23 d) in all patients.

Allogeneic SCT was performed after a median of 17.5 d (range, 14–25 d).

Successful engraftment with an absolute neutrophil recovery of more than 500 could be observed in 5 of 6 patients after a median of 11 d (range, 9–13 d). The remaining patient (patient 3) experienced serious infectious complications during aplasia and died from fungal sepsis 34 d after RLT.

Antilymphoma Activity

Patient 1 died from central nervous system aspergillosis 29 d after RLT. Of the remaining 4 of 6 patients available for response assessment, a partial response was recorded for two (patients 5 and 6; Fig. 1) and a mixed response for the remaining two (patients 2 and 4). Both patients with a partial response had undergone CXCR4-directed RLT in combination with radioimmunotherapy.

Noteworthy, patient 2 presented with a complete remission of all CXCR4-positive lymphoma manifestations but the appearance of new receptor-negative lesions (associated with lumbar spine nerve roots), which were exclusively detected by ^{18}F -FDG PET/CT (Fig. 2).

During follow-up, another patient (patient 5) died of pneumogenic sepsis (while being in partial remission), and the remaining three (patients 2, 4, and 6) succumbed to lymphoma progression. Median progression-free survival was 62 d (range, 29–110 d), and median overall survival was 76 d (range, 29–334 d). In total, 3 patients died of infectious complications (patients 1 and 3 during aplasia, patient 5 after initial successful engraftment 89 d after RLT), and the remainder died of disease progression.

DISCUSSION

After the initial reports of the feasibility of RLT with ^{177}Lu - and ^{90}Y -labeled pentixather in patients with relapsed or refractory multiple myeloma, this is the first description, to our knowledge, of CXCR4-directed radionuclide therapy in relapsed or refractory DLBCL. In parallel with our previous experience with RLT in multiple myeloma and acute leukemia (19), ^{90}Y -pentixather as part of the conditioning regimen before allogeneic SCT was well tolerated and could readily be combined with additional treatment, including chemotherapy or radioimmunotherapy targeting CD20

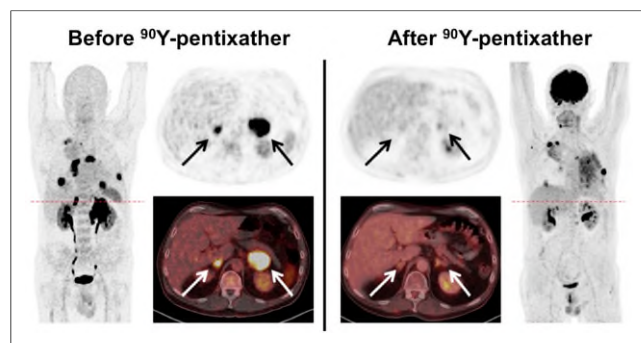


FIGURE 1. Example of partial response after CXCR4-targeted RLT (and additional radioimmunotherapy with ^{90}Y -Zevalin) as part of conditioning regimen before allogeneic SCT in DLBCL (patient 6). Shown is display of maximum-intensity projections (outer columns) and transaxial slices (inner columns, with PET at top and PET/CT at bottom) of pre-therapeutic CXCR4-directed and posttherapeutic ^{18}F -FDG PET/CT. Post-RLT imaging was performed 11 wk after SCT and demonstrated partial response of renal, adrenal (arrows), pulmonary, and most nodal DLBCL manifestations. Diffuse uptake on ^{18}F -FDG PET in left lung was caused by inflammatory changes due to pneumonia.

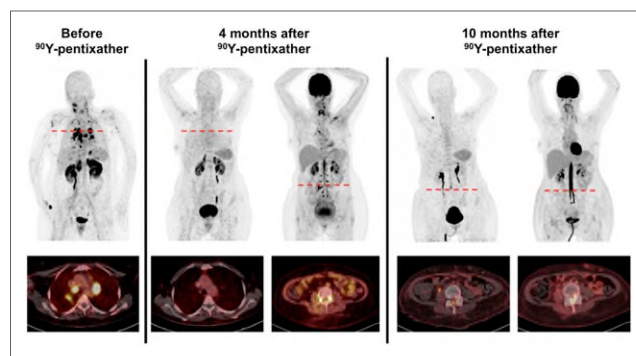


FIGURE 2. Emergence of viable, CXCR4-negative DLBCL after RLT. Shown is display of maximum-intensity projections and transaxial fused PET/CT images of patient 2 before, 4 mo after, and 10 mo after CXCR4-directed RLT with ^{90}Y -pentixather. Whereas RLT resulted in complete remission of all known lymph node, pulmonary, and adrenal lesions (as compared with pretherapeutic MRI), patient complained about new-onset bladder dysfunction. Additional ^{18}F -FDG PET/CT revealed emergence of new viable, CXCR4-negative lymphoma manifestations affecting spinal cord as well as dorsal root ganglia. Chemotherapy with trofosfamide was started. After initial response, restaging revealed progressive disease with numerous new paraspinal (still CXCR4-negative) lesions.

or CD66. Apart from the expected hematotoxicity resulting in myeloablation, no acute renal, hepatic, or cardiac adverse events were observed. No toxic or allergic reactions occurred. Because of infectious complications associated with aplasia, 2 patients died from fungal sepsis 29 and 34 d after RLT. Transplantation-related mortality was therefore within the reported ranges for allogeneic SCT and was not further increased by the addition of RLT. Successful donor stem cell engraftment could be recorded 10–13 d after transplantation and was not compromised by preceding radionuclide therapy.

An objective partial or at least mixed response could be observed in all patients available for response assessment. Noteworthy, the 2 patients who underwent additional conditioning radioimmunotherapy were those who achieved partial remission, and one might therefore speculate that patients could benefit from even further intensified treatment before SCT. However, this very preliminary finding needs to be confirmed in larger trials.

In this small cohort, treatment efficiency correlated with estimated absorbed tumor doses. The 2 patients with an objective response were estimated to achieve the highest lymphoma doses of more than 90 Gy (patient 5) and more than 40 Gy (patient 6) (and additional radioimmunotherapy).

However, response duration was rather short-lived in all cases, with a median progression-free survival of only 62 d. These results are quite comparable to the observations of our pilot studies in multiple myeloma, with an initial objective treatment response in more than 80% of cases but disease relapse in all cases after a median of 54 d (21). These rather disappointing results might directly reflect patient selection, with all subjects undergoing RLT after exhaustion of all alternative treatments. Given the fact that all patients presented with very advanced, highly refractory lymphoma, more durable responses would have been achieved at earlier disease stages or by adding consolidating or maintaining therapies directly after tumor-debulking CXCR4-directed RLT to better address lymphoma heterogeneity and to eradicate surviving DLBCL cell clones. Tumor heterogeneity or clonal evolution could impressively be demonstrated in one patient who presented

with complete disappearance of all former, initially CXCR4-expressing, lymphoma manifestations but emergence of new, chemokine receptor-negative, lesions. Although we have recently reported on the dynamic regulation of CXCR4 on the tumor cell surface in response to (bridging) chemotherapy (27), the phenomenon of receptor downregulation of a therapy-resistant subclone has not been observed yet. Future basic studies to further investigate and elucidate the underlying pathways are urgently needed. A better understanding of CXCR4 biology might also lead to the identification of synergistic therapy combinations to better address tumor heterogeneity and improve the efficacy and duration of CXCR4-directed RLT. Additionally, introduction of α -labeled therapeutic vectors (e.g., ^{213}Bi - or ^{225}Ac -labeled pentixather) could help to overcome the resistance of subclones as recently demonstrated for highly refractory prostate cancer (28–30). Over the short term, new insights will be generated in the COLPRIT trial (Eudra-CT 2015-001817-28), which will focus on the potential role of CXCR4-directed RLT in multiple myeloma and other lymphoproliferative cancers.

This study had several limitations. It was retrospective and comprised a very limited number of patients. Treatment protocols were not identical for all patients. Because of the obvious need to combine RLT with subsequent stem cell support, the antilymphoma efficacy of ^{90}Y -pentixather as a single agent could not be reliably assessed.

CONCLUSION

CXCR4-directed RLT as a conditioning regimen in relapsed or refractory lymphoma before allogeneic SCT is feasible and able to achieve objective responses in even very advanced disease stages. Given the short response duration, further assessment of this novel treatment earlier in the course of disease and in combination with other treatment approaches to enhance efficacy is needed.

DISCLOSURE

Hans-Jürgen Wester is founder and shareholder of Scintomics. No other potential conflict of interest relevant to this article was reported.

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