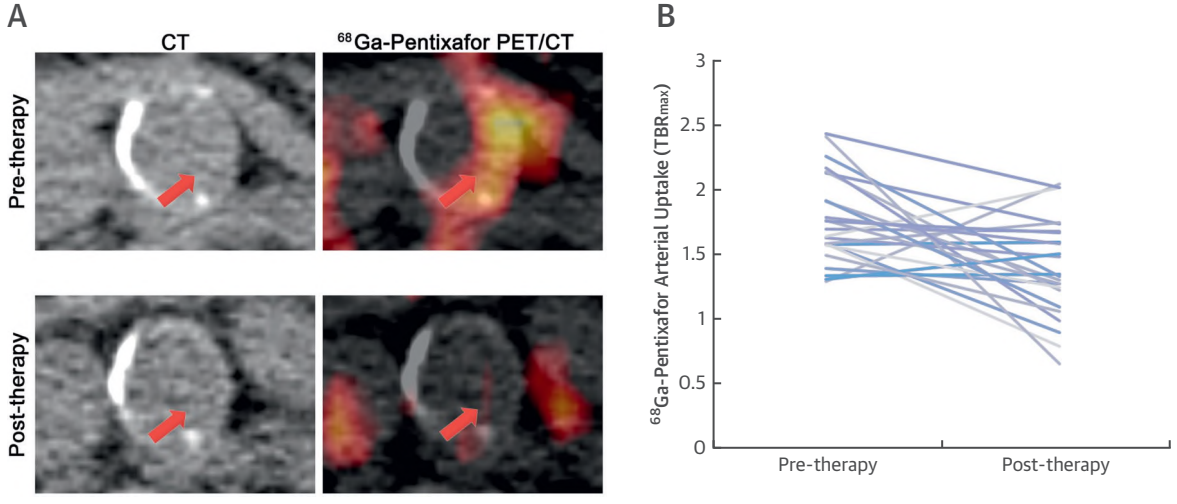
Anti-Inflammatory Effects on Atherosclerotic Lesions Induced by CXCR4-Directed Endoradiotherapy

Atherosclerosis is characterized by eccentric thickening of the arterial vessel wall due to the formation of atheromatous plaque in the intimal layer initially formed by infiltration of circulating monocytes, which subsequently undergo maturation to macrophages. The identification of high-risk patients with vulnerable atherosclerotic plaque (i.e., with increased risk of plaque rupture) has been a major challenge in the field of cardiovascular studies. Inflammatory activity in atherosclerotic plaques is recognized as a prominent factor of vulnerable lesions. C-X-C motif chemokine receptor 4 (CXCR4) plays an important role in the process of atherosclerosis progression, and pilot studies have demonstrated the ability of ^{68}Ga-Pentixafor, an antagonist on the CXCR4 for positron emission tomography (PET) imaging, to non-invasively visualize and quantify CXCR4 in inflammatory atherosclerotic lesions (1-3). Recently, a therapeutic compound (^{177}Lu-labeled Pentixather or ^{90}Y-labeled Pentixather) was introduced for radionuclide-based endoradiotherapy (ERT) of CXCR4-overexpressing hematologic malignancies (4,5). We aimed to assess the anti-inflammatory effect of CXCR4-directed ERT on atherosclerotic lesions.

Five patients with multiple myeloma referred for ERT with the compounds ^{90}Y-labeled Pentixather (n = 3) or ^{177}Lu-labeled Pentixather (n = 2) were included in this retrospective cohort. No patient had a history of vasculitis or prior cardiovascular events, and only a single patient was treated with antihypertensive medication. All patients underwent whole-body ^{68}Ga-Pentixafor PET/computed

FIGURE 1 **CXCR4-Targeted Modification of Inflammatory Activity in Atherosclerotic Plaques Detected by ^{68}Ga-Pentixafor PET/CT**



(A) Representative pre-therapeutic and post-therapeutic ^{68}Ga-Pentixafor positron emission tomography/computed tomography (PET/CT) imaging of an abdominal plaque in a multiple myeloma patient. PET signals were mainly localized in an area without CT calcification. After treatment, ^{68}Ga-Pentixafor PET demonstrated decreased maximum tissue-to-blood ratios (TBR_{max}) (TBR_{max} = 2.1 vs. TBR_{max} = 1.1) **(red arrows)**. **(B)** A decreasing trend for TBR_{max} values of ^{68}Ga-Pentixafor–positive lesions (n = 24) could be recorded after CXCR4-directed endoradiotherapy. CXCR4 = C-X-C motif chemokine receptor 4.

tomography (CT) (102 ± 33 MBq) on a PET/CT scanner (Biograph mCT 64; Siemens, Erlangen, Germany) before and after 1 cycle of treatment (^{177}Lu: 15.2 and 7.8 GBq, respectively; ^{90}Y: 5.1 ± 2.0 GBq). The median time interval between baseline and follow-up ^{68}Ga-Pentixafor PET/CT was 98 days (range: 56 to 126 days).

Eight arterial segments were screened for increased ^{68}Ga-Pentixafor uptake, including both carotids, the aortic arch, the ascending and descending aorta, the abdominal aorta, and both iliac arteries. Briefly, a 3-dimensional volume of interest was drawn along the arterial wall with present focal uptake of ^{68}Ga-Pentixafor. For analysis of follow-up scans, the same lesions that were detected at baseline were considered. Maximum standardized uptake values (SUV_{max}) were derived from these volumes of interest, and the mean of blood-pool radioactivity (SUV_{blood}) was determined from 3 volumes of interest in the superior vena cava. The normalized maximum tissue-to-blood ratio (TBR_{max}) was calculated by dividing SUV_{max} from tissue with SUV_{blood} from the blood pool.

Continuous variables were recorded as mean ± SD. The mean TBR_{max} of ^{68}Ga-Pentixafor pre-therapy and post-therapy were retrospectively assessed using the paired Student's *t*-test. Two-sided p values of <0.05 were considered significant.

At baseline, 24 arterial lesions with focal uptake of ^{68}Ga-Pentixafor (in a single patient, 9 focal lesions could be analyzed; in the remainder, 5 [n = 1), 4 [n = 1], and 3 [n = 2] lesions were assessed, respectively) were detected, and 3 of them (13%) showed arterial macrocalcification (with CT Hounsfield units ≥130).

ERT resulted in a substantial decrease of uptake ratios in 18 of 24 (75%) of initially ^{68}Ga-Pentixafor-positive lesions (mean TBR_{max} of the 24 lesions: 1.8 ± 0.3 vs. 1.4 ± 0.4; p = 0.08) (**Figure 1**). Post-therapeutic C-reactive protein levels did not differ significantly from pre-therapeutic values (post-therapy: 0.32 ± 0.20 mg/dl vs. pre-therapy: 0.24 ± 0.12 mg/dl; p = 0.27).

To summarize, in a small cohort of patients experiencing multiple myeloma, targeted ERT appeared to induce a reduction of arterial CXCR4 expression, as determined by ^{68}Ga-Pentixafor PET/CT. Although this initial observation suffers from small sample size, retrospective design, and lack to histologic confirmation, the interaction of CXCR4-directed treatment (also using non-radionuclide-based receptor antagonists) with vascular inflammatory pathophysiology should be considered for future applications and might open a new therapeutic option for high-risk atherosclerosis.

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