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Intra-arterial administration boosts ^{177}Lu-HA-DOTATATE accumulation in salvage meningioma patients

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ABSTRACT

INTRODUCTION: Intravenous ^{177}Lu-(HA-)DOTATATE has shown promising results for the treatment of surgery- and radiotherapy-refractory meningiomas. We aimed to investigate the added value of intra-arterial administration. **METHODS:** Patients underwent at least one intravenous ^{177}Lu-HA-DOTATATE treatment first and subsequent intra-arterial cycles. In(tra)-patient comparison was based on post-treatment ^{177}Lu-HA-DOTATATE imaging 24 hours post-injection. Technical success rates and adverse events were recorded. **RESULTS:** Four patients provided informed consent. Technical success rate was 100% and no angiography related or unexpected adverse events occurred. Intra-patient comparison showed an increased target lesion accumulation on both planar imaging (mean +220%) and SPECT/CT (mean +398%) after intra-arterial administration compared to intravenous. No unexpected adverse events during follow-up occurred. **CONCLUSION:** Intra-arterial PRRT significantly increases tracer accumulation, and is a safe and promising improvement for salvage meningioma patients. Future prospective studies on intra-arterial PRRT are needed to determine gain on efficacy and survival.

INTRODUCTION

Surgery- and external beam radiation refractory meningiomas are a difficult entity to treat. Reported outcomes of a wide range of systemic treatments in this end-stage setting are poor and progression free survival rates are rather limited (*1*). Somatostatin receptor is overexpressed in meningiomas and is one of the most specific immunohistochemical markers (*2*). In recent years, promising results of Peptide Receptor Radionuclide Therapy (PRRT), with either ^{177}Lu- or ^{90}Y-labelled compounds in salvage meningioma have been reported, and its potential was recently recognized in the European Neuro-Oncology (EANO) guidelines on meningioma (*3*). The number of studies conducted on PRRT in meningioma is limited and far less compared to neuroendocrine neoplasm (NEN)(*4*). Intra-arterial administration of ^{177}Lu-HA-DOTATATE may benefit meningioma patients, as it might result in higher tumor uptake, as previously shown in NEN (*5, 6*). The current study reports the preliminary results on in-patient comparison of intravenous versus intra-arterial treatment of salvage meningioma patients.

MATERIALS AND METHODS

Patient Population

The institutional medical ethics committee approved this retrospective study and the requirement to obtain informed consent was waived. All historically referred meningioma patients were included in this retrospective analysis, and only patients treated intra-arterially were included. Screening of patients included clinical assessment, laboratory examinations, and ^{68}Ga-DOTATOC PET/CT (Somakit, Advanced Accelerator Applications), to assess sufficient tracer accumulation in line with current guidelines (*7*). All patients were planned for four cycles of 7400 MBq ^{177}Lu-HA-DOTATATE (Scintomics). Four to five weeks after each cycle, patients returned to the out-patient clinic for physical examination and laboratory testing. Baseline and follow-up toxicity was recorded according to Common Terminology Criteria for Adverse Events (CTCAE) version 5 (*8*).

Procedures

The first treatment cycle was always intravenous and if logistically possible, subsequent cycle(s) where administered intra-arterially. A diagnostic angiogram was performed to identify the tumor feeding vessel(s) (TFV). In case of multiple TFVs a single more proximal injection was chosen to cover all TFV. A single injection position was preferred to avoid microcatheter manipulation and contamination of the angiosuite. In case of multifocal disease, the lesion causing the most complaints was selectively treated (defined as target lesion). Production and administration method of ^{177}Lu-HA-DOTATATE has been previously reported (*9*). Technical success rate and adverse events related to the angiography procedure were registered.

Image Analysis

In line with standard clinical care, post-treatment scintigraphy was acquired 24 hours post-injection. On planar and SPECT/CT imaging, target-to-background-ratios of intravenous and intra-arterial cycles were compared. On planar imaging, a background region-of-interest was drawn in the right hemithorax (diameter 7 cm) for comparison with the lesional region-of-interest. On SPECT/CT, a background volume-of-interest was placed in the contralateral neck muscles for comparison with the lesion volume-of-interest (40% threshold of the maximum pixel value). All regions- and volumes-of-interest were copied to the corresponding images of subsequent treatment cycles. Percentual difference was calculated by dividing the intra-arterial target-to-background-ratio by the intravenous target-to-background-ratio, times 100. Response was based on target lesions and defined according to RANO on gadolinium enhanced MRI (*10*) and SUV_{peak} measurements on ^{68}Ga-DOTATOC PET, both acquired two months after treatment.

RESULTS

Patients

Up to July 2020, seven patients were referred, of which four patients had intra-arterial ^{177}Lu-HA-DOTATATE after initial intravenous ^{177}Lu-HA-DOTATATE. These four patients were treated between March 2018 and September 2020 and included in the current analysis. Baseline and treatment characteristics are shown in Table 1. The first patient was published before (*5*). All patients had histopathological confirmation on primary resection specimen or additional biopsy, and had progressive disease on MRI prior to therapy. At baseline no hematological or biochemical abnormalities were present and tumor related complaints varied (Table 1).

Angiography Procedures

Technical success rate of intra-arterial administration was 100%. Single TFV could be identified in 3 patients and multiple TFVs in one patient (proximal injection position in the external carotid artery). No administration difficulties and no contamination of the angiography suite occurred.

Image Analysis and Efficacy

In-patient comparison between cycles showed increased accumulation on both planar imaging (mean +220%) and SPECT/CT (mean +398%) in the target lesion (table 2). In patients with multifocal disease, in-patient comparison at a single time point was possible, and a clear distinction could be made between intra-arterially and intravenously treated lesions (figure 1).

One World Health Organization (WHO) grade 3 meningioma patient had progressive disease clinically and on imaging during treatment, and therapy was terminated earlier (after three cycles; two intravenous and one intra-arterial). The patient died 6 months after initiation of ^{177}Lu-HA-DOTATATE therapy. The remaining three patients with a WHO grade 2 meningioma completed all four treatment

cycles. One with a partial response and two with stable disease according to RANO. Baseline clinical complaints of the three WHO grade 2 meningioma patients improved after treatment (figure 1). Median follow-up was 1.7 years (range 1 – 3 years). One of these patients had an additional surgical resection (one year after treatment) and the others continue to experience disease control. No other additional therapies have been initiated.

Toxicity

No significant clinical or biochemical toxicities were reported (CTCAE grade ≥3; Table 3). Significant hematological toxicity was limited to one patient, experiencing an isolated grade 3 leucopenia. No unexpected or angiography-related adverse events occurred.

DISCUSSION

Our preliminary results show a clear increase of ^{177}Lu-HA-DOTATATE accumulation after intra-arterial administration (+398% on SPECT/CT), compared to intravenous administration in an in-patient comparison. How these results translate to improved survival or a higher number of objective response rates, remains to be seen and should be an aim of future prospective studies on PRRT in meningioma.

Recent meta-analysis by Mirian et al. confirmed durable disease control rates, limited toxicity profile and long progression free survival rates (PFS) on different kinds of therapeutic somatostatin receptor targeted radiopharmaceuticals in salvage meningioma patients (*4*). Pooled analysis of 111 patients showed a 6- and 12-month PFS of 61% and 53%, respectively of the entire analyzed group. The poorer outcome of WHO grade 3 meningioma patients was consistent in all publications (6-month PFS of 94%/48%/0% for WHO grade 1/2/3 respectively). Objective response rate however are still far from promising, just 2%. However, as the authors describe, many unknowns in treating meningiomas with PRRT exist. A wide variety of total administered activities was used (1.7-29.8 GBq in 1–6 cycles), and

application as a monotherapy or concurrent with EBRT. However, compelling evidence of one treatment algorithm over another is lacking. Our used treatment algorithm was based on experience with PRRT in NEN, but not 'proven' for meningiomas (*11*). Unfortunately, like in many other studies, dosimetric analysis with multiple time point imaging was unavailable in our cohort. The current EANO guideline does not give any direction how to perform PRRT in salvage meningioma and only recommends it for WHO grade 3 tumors, which seems contradictory to the evidence (*3, 4*). As no distinct guideline based on evidence exists, preferred treatment algorithm, proper patient selection on pre-treatment PET/CT and potential dosimetric thresholds of PRRT in meningiomas remain unknown and an open field of research.

Literature on intra-arterial PRRT in neuro-oncology is sparse. To our knowledge, only one recent publication describes the in-patient comparison of intravenous versus intra-arterial ^{68}Ga-DOTATATE in meningioma (n=4), showing two- to five-fold increase in tumor uptake (*12*). Outside the scope of meningioma, a study in 2002 already reported results on intra-arterial ^{90}Y-lanreotide in six astrocytomas and one histiocytoma (*13*). Even though the results of these two previous reports and our findings are in line with previous results on intra-arterial PRRT in NEN, it is a difficult comparison, as it is a completely different entity and the treated organ (brain vs. liver) differs in (arterial) vascularization. Nonetheless, increased uptake of different radiopharmaceuticals after intra-arterial administration seem to be present in NEN (*6*). However more recently, Lawhn – Heath et al. published the direct opposite (*14*). Imaging analysis was based on the surrogate of ^{68}Ga-DOTATOC, comparing intravenous and intra-arterial administration, of which the intra-arterial ^{68}Ga-DOTATOC was simultaneously administered with a single intra-arterial cycle of ^{90}Y-DOTATOC. Interestingly, intra-arterial administration lead to a lower SUV_{max} overall. Not only in extrahepatic tumor deposition (median ratio 0.73), where one might expect this to occur, but also in the hepatic tumor deposition (median ratio 0.90)(*14*). One possible explanation for their results may be the interference of radiopharmaceuticals during simultaneous infusion, thus making their results difficult to interpret. Currently, two other trials are ongoing to define the added benefit of

intra-arterial over intravenous, and with multiple cycles instead of just one ((*15*) and NCT04544098), hopefully providing definite answers.

The presented data will be used to initiate a new prospective study to determine the clinical benefit of intra-arterial PRRT, its effect on objective response and survival in salvage meningioma.

CONCLUSION

Intra-arterial PRRT significantly increases tracer accumulation, providing a safe and promising improvement for salvage meningioma patients. Future prospective studies on intra-arterial PRRT in meningioma are needed.

KEY POINTS

Question: Does intra-arterial administration increase ^{177}Lu-HA-DOTATATE uptake in meningioma?

Pertinent findings: This retrospective cohort, in-patient comparison shows that intra-arterial administration results in a mean four-fold increase in tumor uptake, without additional side-effects.

Implications for Patient Care: Efficacy of ^{177}Lu-HA-DOTATATE in meningioma may be improved by intra-arterial administration.

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Tables

Table 1. Baseline characteristics

Median age (range)	57 (44–66)
Localization* (main complaint)	
Temporal (epilepsy)	2
Falx (nausea)	1
Optic Meningioma (proptosis-induced pain)	1
Previous treatments	
Surgical resection	4
External beam radiation therapy	4
Temozolomide	1
Unifocal / multifocal	2 / 2
Histopathology WHO grade 1 / 2 / 3	0 / 3 / 1
Median number of treatment cycles	4 (3-4)
Intravenous	2 (1-2)
Intra-arterial	2 (1-3)
Median activity per cycle in MBq (range)	7338 (3668†–7637)
Median interval per cycle in weeks (range)	6.3 (5.7–10)

*Largest or most symptomatic lesion only. †Final cycle of one patient was delayed with an activity reduction of 50% out of precaution, because of a grade 3 leucopenia.

Table 2. Imaging analysis results.

Response assessment	**Baseline**	**After therapy**	
Median maximum diameter on MRI in mm (range)	24 (19–32)	21 (15–45)	
Median SUV_{peak} on ^{68}Ga-DOTATOC PET (range)	6.33 (5.13–8.81)	7.1 (2.4–8.7)*	
Post-treatment imaging assessment (n=15)	**Intravenous**	**Intra-arterial**	**Mean Δ**
Median planar target-to-background-ratio (range)	1.7 (1.4–2.5)	3.7 (2.8–5.2)	+220%
Median SPECT/CT target-to-background-ratio (range)	15.0 (12.7–18.6)	59.8 (40.5–82.0)	+398%

*Not available in the single progressive patient.

Table 3. Reported adverse events.*

CTCAE version 5 grade	1	2	3
Clinical			
Nausea	1		
Fatigue	3		
Hair loss	1		
Hematological†			
Anemia	2		
Leucopenia	2		1
Biochemical†			
AST	1		
ALT	2		

*highest CTCAE grade during the whole treatment. †other laboratory investigations did not show any toxicity during follow-up.

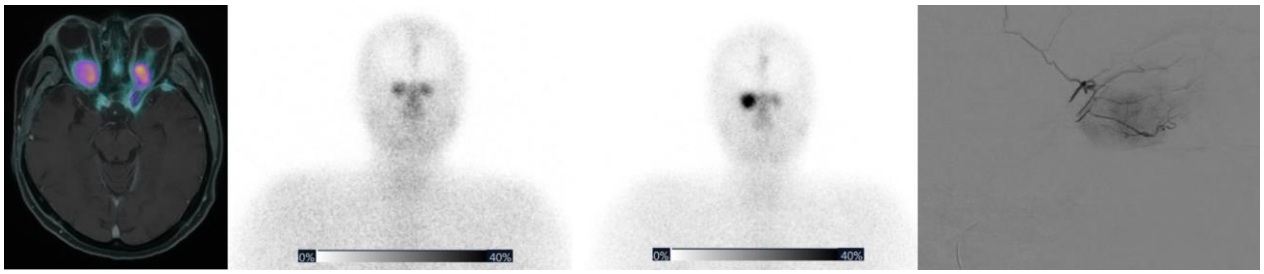

Figure 1. A. Pre-treatment ^{68}Ga-DOTATOC PET fused with MRI showing multiple meningiomas, especially bilateral optic meningiomas, causing blindness and proptosis induced pain complaints. Post-treatment ^{177}Lu-HA-DOTATATE planar image after intravenous (B) and intra-arterial treatment (C) showing a clear increased accumulation in the right optical meningioma (arrow) by intra-arterial treatment, but to the contralateral optical meningioma (treated by second pass). D. corresponding digital subtraction angiography of the intra-arterial administration. Patient had stable disease on imaging and proptosis induced pain complaints subsided.

Graphical Abstract