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^{90}Y-DOTATOC as Therapeutic Option for Complex Recurrent or Progressive Meningiomas

Brief Communication

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Abstract

Background: Standard treatment of meningiomas is surgery and/or radiotherapy. Complex, especially recurrent or progressive cases, may exhibit tumor growth involving critical neurovascular structures or diffuse growth, resulting in limited efficacy and higher risks of standard treatment. We evaluated, if somatostatin receptor-targeted radionuclide therapy with ^{90}Y-DOTATOC may be a therapeutic option.

Patients and methods: 15 patients with recurrent or progressive meningiomas after multimodal pretreatment and/or unfavorable medical risk profile were treated with systemic ^{90}Y-DOTATOC. Endpoints were progression free survival and toxicity.

Results: Usually applied doses were 7400 MBq/m^2 ^{90}Y-DOTATOC in two fractions. Mean observation time was 49.7 months (range 12-137). Overall median progression free survival was at least 24 months. Toxicity was moderate, mostly hematological (*n*=8) and transient.

Conclusion: ^{90}Y-DOTATOC therapy is feasible and may represent a promising second- or third-line option for complex meningiomas which are progressive or otherwise not treatable with reasonable risk-benefit ratio

Keywords: Meningioma, Peptide Receptor Radionuclide Therapy, Somatostatin-Receptor, DOTATOC, ^{90}Yttrium

Introduction

Meningiomas are benign (WHO I°, 80-90%), atypical (WHO II°, 5-15%), or malignant neoplasms (WHO III°, 1-3%). Depending on age, tumor size and treatment, 5-year survival was 70% for benign and 55% for malignant meningiomas (*1*). A subgroup exhibits diffuse *en plaque*-growth pattern, attachment of tumor segments to critical neural or vascular structures obviates complete resection. Attempts to resect meningiomas involving these critical structures may cause devastating vascular injury or disabling cranial neuropathies (*2, 3*). Tumor remnants are treated radiotherapeutically which leads to 5-year progression-free survival rates in 89% of benign and 48% of malignant cases (*4*). However, fractionated external beam radiotherapy may also cause serious neurological complications (*5*) and secondary tumors (*6*). Stereotactic radiotherapy represents an option for selected cases (*7*), leading to 5-year tumor control rates of 93% (*8*). Stereotactic GammaKnife (Elekta, Sweden) radiosurgery led to control rates of 92.5% in small meningiomas with permanent morbidity rates of 6.6% (*9*).

Regarding complex or recurrent meningiomas especially in proximity to critical vascular resp. neural structures or meningiomas with diffuse, meningiosis-like growth, there is so far no sufficient therapeutic option.

70-100% of meningiomas express somatostatin receptors (*10*), mainly subtype 2a (SSTR2a). Somatostatin analogues could be shown to effect progression-free survival in 44% of patients in a 6-month follow-up in recurrent meningiomas (*11*).

The aim of this prospective study was to investigate feasibility, toxicity and efficacy of targeted beta-radiotherapy for stabilization of complex meningiomas using the somatostatin analogue ^{90}Y-DOTA-D-Phe^{1}-Tyr^{3}-octreotide (DOTATOC), a metabolically stable cyclic octapeptide (*12*).

Patients and Methods

Study design

Clinical phase II single-center open label study investigating response, survival and safety. Approval by the Ethics Committee of Swiss Cantons Basel-Landschaft and Basel-Stadt and Swiss Federal authorities (Swissmedic). Evaluation of progression-free survival (PFS) as primary endpoint, toxicity as secondary endpoint.

Patients

Inclusion criteria were (a) SSTR2a-positivity, (b) recurrent or progressive meningiomas in functionally critical areas or (c) unfavourable medical risk profile or refusal of surgery. SSTR2a status was assessed by ^{111}In-DOTATOC-scintigraphy/SPECT or ^{111}In-OctreoScan (112.5 MBq ^{111}In). Tumor uptake was graded (*13*): lower than (grade 1), equal to (grade 2), greater than (grade 3) normal liver tissue or higher than normal spleen/kidney uptake (grade 4). Exclusion of preexisting grade II-IV hematologic/renal toxicities, also of Karnofsky performance status (KPS) <50.

Treatment Protocol

20 mg IV-dexamethasone pre-therapeutically. After initial dose modification according (*12*), ^{90}Y-DOTATOC-dose was fixed at 3,700 MBq/m^2 twice with 8-week interval. Simultaneous injection of ^{111}In-DOTATOC (112.5 MBq) to verify biodistribution and receptor binding. Imaging 6, 24 and 48 h after injection by γ-camera. Post-therapeutic tapering of dexamethasone. Therapeutic effects and adverse events were monitored by clinical examinations, blood sampling and Magnetic resonance-(MR-) imaging.

Kidney protection

Inhibition of renal re-uptake and retention by infusion of physiologic saline containing arginine (20.7 mg/mL) and lysine (20.0 mg/mL).

Radiotracers

GMP-compliant development of DOTATOC, a tetraazocyclo-dodecanetetraacetic acid modified somatostatin analogue (*14*). ^{111}In- and ^{90}Y-DOTA-D-Phe^1-Tyr^3-octreotide synthesized as (*12*). Preparation, affinity- and stability-calculations of ^{111}In- and ^{90}Y-labeled DOTATOC according (*15*). Radiolabeling yield determined by Sep-Pak C18 cartridge and HPLC was 99% or higher without peptidic radiolysis products, revealing radioligands with preserved receptor binding (K_d = 2.2±0.5 nM). Affinity of ^{90}Y-labeled DOTATOC determined by competition assay to 1.8±0.5 nM ^{123}In-labeled octreotide, stability as (*14*).

Toxicity

Scoring according to National Cancer Institute grading criteria (NCI-CTC V4.0). Hematology, liver and kidney parameters were examined pre-therapeutically and biweekly for at least 2 months post-therapeutically.

Tumor response

MR-imaging 4 weeks before and 6-8 weeks after treatment. Follow-up clinical and radiological examinations at 6-/12-month intervals depending on neurological status. Response evaluation according to RECIST 1.1 criteria to determine progression free survival (i.e. stable disease). Additional treatments were not allowed for at least 12 months.

Results

Patients

Fifteen patients (median 56 years, range 41-78) were included, see Table 1. All patients gave written informed consent. Median Karnofsky performance status at inclusion was 90 (50-100). Gender distribution (female *n*=12, male *n*=3) as reflected by epidemiological studies (*16*). WHO grading was I° (*n*=9), II° (*n*=2), and III° (*n*=1). Biopsy or surgery has not been performed due to high American Society of Anesthesiologists- (ASA-) score in three patients; the high diagnostic probability of meningioma was based on typical radiological patterns in CT-/MR-imaging and positive ^{111}In-octreotide or ^{111}In-DOTATOC-uptake. Fourteen tumors were SSTR2a-positive in ^{111}In-OctreoScan or ^{111}In-DOTATOC, uptake grades were "1" (*n*=2), "2" (*n*=5), "3" (*n*=7). Overall, 12 patients (80%) had been included with progressive tumors, 3 patients (20%) after subtotal resection. Ten patients had been treated by surgery (6 patients), surgery and radiotherapy (3 patients) or surgery and radiotherapy and chemotherapy (1 patient) before ^{90}Y-DOTATOC. These tumors were progressive (patients 1,3,4,6,7,8,15) or had been subtotally resected (patients 2,5,9). Four patients died from non-tumor related disease (patients 8,13,14,15). Mean follow-up was 49.7 months (range 12-137).

Tumor response

Stable disease (SD) was observed in 13 patients (86.7%) and progressive disease (PD) in 2 patients (13.3%). 8 out of 15 patients were ongoing stable and did not reach the endpoint PFS. With this statistical limitation, the overall median PFS was 24 at least months (range 0-137).

Evaluation of response is limited in two patients (13,14) due to non-tumor related death before tumor progression (pneumonia, cardiac failure). Two patients (8,15) were radiologically stable for 19 resp. 14 months, but died after 32 resp. 16 months (non-tumor related: pneumonia, hemolytic anemia).

Five of 6 remaining patients (83%) with confirmed WHO I° tumors (2,4,6,7,9) exhibit ongoing progression free survival (range 14–137 months), patient 5 experienced progression after 17 months.

Figure 1 illustrates a progressive skull base meningioma (patient 4) with brainstem compression, infiltration of cavernous sinus and affection of the optic chiasm. Surgical decompression was followed by two cycles of ^{90}Y-DOTATOC, resulting in ongoing stable disease for now 87 months.

One WHO II°-tumor (patient 1) did not respond, while WHO II°-patient 10 with craniocervical skull base meningioma responded to treatment (figure 2): after bioptic diagnosis of meningioma WHO II°, surgery was declined to avoid further risk for lower cranial nerves. ^{90}Y-DOTATOC (13,320 MBq) led to ongoing clinical stabilization and radiologically stable disease (now 83 months).

Patient 3 with a WHO III° meningioma was radiologically stable for 4 months after ^{90}Y-DOTATOC therapy (8,438 MBq).

Toxicity

Summary in Table 1S (supplemental data). Median follow-up was 6 months (range 2-45).

Overall hematological toxicity > grade II in 5 patients (33.3%). Reduction of RBC from pre-existing grade I to III (one patient, 6.7%), subsequent recovery. Transient thrombocytopenia (grade I, 3 patients, 20%). Transient grade I or II leukopenia (four patients, 26.6%); transient lymphocytopenia (4 patients grade II, 26.6%; 4 patients grade III, 26.6%).

Transient neurological toxicity (two patients, 13.3%): radiogenic edema with gait disturbance (patient 15) and one seizure (patient 13).

Creatinine-increase to grade II toxicity (one patient, 7.1%) over 14 months (clearance 15.8 ml/min).

Slight transient elevation of hepatic enzymes (5 patients, 33.3%), unclear relationship to ^{90}Y-DOTATOC due to accompanying morbidity.

Discussion

In most cases, surgical removal of meningiomas is an effective and definitive therapeutic approach. However, meningiomas involving cranial nerves, vascular structures or the brain stem can render surgery hazardous with considerable morbidity (*3*). Consequently, a subgroup of meningiomas is treated by standard external beam radiotherapy, fractionated stereotactic radiotherapy or stereotactic radiosurgery. These modalities have been shown to control tumor growth (*4*), especially in smaller meningiomas (*17*), but with complications (*5, 6*).

In complex meningiomas involving critical neurovascular structures, exhibiting diffuse growth or recurrence despite multimodal therapy or high perioperative risks, the aims of treatment need to be questioned and should be adapted from "complete resection without loss of neurologic function" to rather "prevention of further tumor growth with preserved quality of life".

With a median progression free survival of at least 24 months and ongoing progression free survival in 83% of confirmed WHO I° meningiomas (observation time-range 14-137 months) in our study, ^{90}Y-DOTATOC may represent a promising option for complex cases. Progression free survival in the WHO I°-patients in our cohort is somewhat longer than in the study cohort of Bartolomei et al. (*18*), which may potentially be attributable to higher total doses applied in our study (median dose 13 GBq vs. 10 GBq). However, the potential dose-effect relationship is interesting, since long-term tumor control can be achieved with relatively low doses by radiosurgery (*19, 20*).

Due to the small number of confirmed WHO II°- and III°-patients in our study, it remains unclear, if malignant meningiomas may potentially require higher doses than the applied doses. In the study of Bartolomei *et al.* (*18*), this group of patients was treated analogous to WHO I°-meningiomas with a median dose of 10 GBq. The outcome of the WHO II°- and III°-patients was significantly inferior compared to patients with WHO I° meningiomas, which might indicate the need for higher doses.

With regard to additive toxicity, the potential combination of radiotherapy and radiolabelled somatostatin analogues has raised concerns and has been addressed by Kreissl *et al.* (*21*). According to their results, a combination of ^{177}Lu-labelled somatostatin analogues with fractionated external beam radiotherapy is feasible and well tolerated. Consequently, ^{90}Y-DOTATOC treatment may

supplement surgery and the existing radiotherapeutic options with a promising second- or third line option for patients with otherwise poor alternatives. However, patients with impaired renal function have to be evaluated thoroughly before considering therapy with radiolabelled somatostatin analogues. Alternatively, according to the results of Minutoli *et al.* (*22*), ^{111}In-labelled somatostatin analogues might be used instead of β-emitting radionuclides in cases with a higher risk of renal toxicity

Conclusion

This study demonstrates feasibility and efficacy of ^{90}Y-DOTATOC treatment in patients with complex meningiomas. Hematological, neurological and renal toxicities were transient and moderate. ^{90}Y-DOTATOC may represent a promising second- or third-line therapeutic option for complex meningiomas which are progressive or otherwise not treatable with reasonable risk-benefit ratio.

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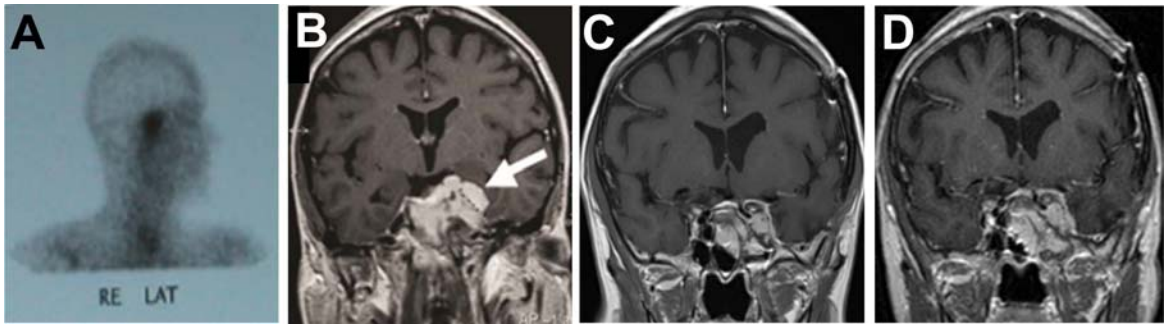

Fig. 1: WHO 1° meningioma, patient 4. (A) Scintigraphy 24 h after ^{111}In-DOTATOC displaying SSTR2a expression. (B) Contrast T1-MR-imaging at initiation of ^{90}Y-DOTATOC therapy. (C) MR-imaging 60 months, (D) 87 months after ^{90}Y-DOTATOC treatment. Arrow indicates tumor localization.

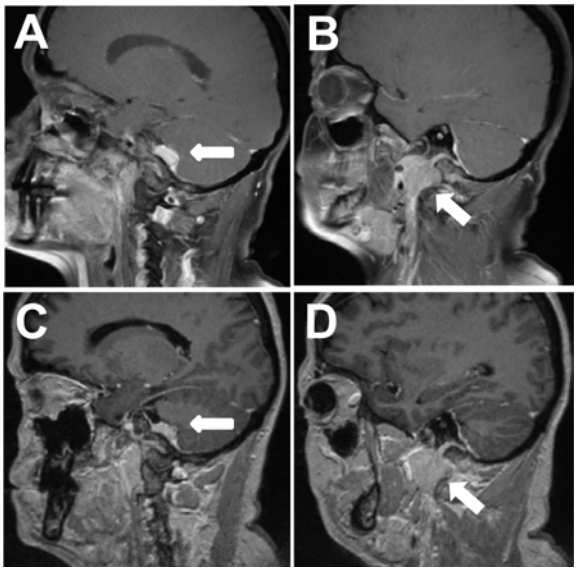

Fig. 2: WHO II°-meningioma, patient 10. Meningioma from cerebello-pontine angle to upper cervical spine. (A, B) Contrast T1-MR-imaging at initiation of ^{90}Y-DOTATOC therapy, intracranial (A) and vertebral (B) tumor (arrows). (C, D) MR-imaging 72 months after ^{90}Y-DOTATOC treatment. Arrows indicate tumor localization.

Pt. No.	Age	Sex	Location	WHO grade	Pre-THx	Octreo-uptake	Fractions/ [MBq]	KPS	Response RECIST	PFS/OS [months]
Treatment after subtotal surgery and other pretreatment/diffuse tumor growth										
1	63	M	Falx bifrontal	II	S, RT	na	2/1’688	80	PD	0/12
2	63	F	Skull base + parietal	I	S	2	3/4’500	90	SD	137+/137+
3	51	F	Convexity, multiple	III	S, RT, Chemo	3	4/8’438	90	PD	4/22
4	56	F	Skull base	I	S	3	2/13’500	90	SD	87+/87+
5	44	M	Skull base	I	S, RT	3	2/14’800	90	SD	17/48+
6	46	F	Skull base	I	S	1	2/12’580	80	SD	24+/24+
7	47	F	Skull base	I	S	3	2/12’950	80	SD	72+/72+
8	67	M	Convexity, multiple	I	S, RT	2	2/13’320	60	SD	19/32
9	56	F	Skull base	I	S	2	2/11’840	100	SD	14+/14+
Treatment due to severe medical comorbidity/refusal of surgical tumor resection										
10	54	F	Skull base	II	-	2	2/13’320	90	SD	83+/83+
11	64	F	Skull base + temporal	na	-	3	2/14’800	90	SD	68+/68+
12	43	F	Skull base	na	-	2	2/13’690	90	SD	56+/56+
13	41	F	Pineal region	I	-	3	2/11’250	50	SD	57/57
14	71	F	Skull base + parietal	na	-	3	2/12’210	80	SD	18/18
15	78	F	Skull base	I	S	1	2/13’320	70	SD	14/16

Table 1: Patient characteristics and treatment. Age: at initiation of ^{90}Y-DOTATOC; S: Surgery; RT: Radiotherapy; C: Chemotherapy; KPS: Karnofsky performance status; +: ongoing; multiple: ≥3 tumor locations); SD: stable disease; PD: progressive disease; PFS: progression-free survival; OS: overall survival.