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ORIGINAL ARTICLE

Safety and efficacy of targeted alpha therapy with ^{213}Bi-DOTA-substance P in recurrent glioblastoma

Leszek Królicki[1] · Frank Bruchertseifer[2] · Jolanta Kunikowska[1] · Henryk Koziara[3] · Bartosz Królicki[3] · Maciej Jakuciński[4] · Dariusz Pawlak[5] · Christos Apostolidis[2] · Saed Mirzadeh[6] · Rafał Rola[7] · Adrian Merlo[8] · Alfred Morgenstern[2]

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Abstract

Treatment options for recurrent glioblastoma multiforme (GBM) are very limited. GBM cells express high levels of the GPCR neurokinin type 1 receptor (NK-1R), and a modified substance P can be used as its ligand for the tumor cell targeting. Targeted alpha therapy with DOTA-Substance P labeled with the short range alpha emitter ^{213}Bi allows for selective irradiation and killing of tumor cells.

Material and methods

Twenty patients with recurrent GBM were included into the study following a standard therapy. 1–2 intracavitary or intratumoral port-a-cath systems were stereotactically inserted. Patients were treated with 1–7 doses of ^{213}Bi-DOTA-Substance P (^{213}Bi-DOTA-SP) in 2-month intervals. ^{68}Ga-DOTA-Substance P (^{68}Ga-DOTA-SP) was co-injected with ^{213}Bi-DOTA-SP to assess the biodistribution using PET/CT. Therapeutic response was monitored with performance status and MRI imaging.

Results

Treatment with activity up to 11.2 GBq ^{213}Bi-DOTA-SP was well tolerated with only mild and transient adverse reactions. The median progression free survival was 2.7 months. The median overall survival from the first diagnosis was 23.6 months and median survival after recurrence was 10.9 months. The median survival time from the start of ^{213}Bi-DOTA-SP was 7.5 months.

Conclusions

Treatment of recurrent GBM with ^{213}Bi-DOTA-SP is safe and well tolerated. The median overall survival after recurrence of 10.9 months compares favorably to the available alternative treatment options. Once the supply of high activity ^{225}Ac/^{213}Bi radionuclide generators is secured, targeted alpha therapy with ^{213}Bi-DOTA-SP may evolve as a promising novel option to treat recurrent GBM.

Keywords Glioblastoma multiforme · GBM · ^{213}Bi-DOTA-SP · ^{68}Ga-DOTA-SP · Targeted alpha therapy · TAT · Substance P

✉ Jolanta Kunikowska
jolanta.kunikowska@wum.edu.pl

[1] Nuclear Medicine Department, Medical University of Warsaw, ul. Banacha 1 a, 02-097 Warsaw, Poland

[2] European Commission, Joint Research Centre, Directorate for Nuclear Safety and Security, Karlsruhe, Germany

[3] Department of Neurosurgery, Institute of Psychiatry and Neurology, Warsaw, Poland

[4] Department of Nuclear Medicine, Brodnowski Hospital, Warsaw, Poland

[5] Radioisotope Centre POLATOM, National Centre for Nuclear Research, Otwock, Poland

[6] Nuclear and Radiochemistry Group, Nuclear Security and Isotope Technology Division, Oak Ridge National Laboratory, Oak Ridge, TN 38731-6229, USA

[7] Department of Neurology, Military Institute of Aviation Medicine, Warsaw, Poland

[8] Neurosurgery, Bern and University of Basel, Spitalgasse 32, Basel, Switzerland

Introduction

Glioblastoma multiforme (GBM), the most common malignant primary brain tumor, continues to present a poor prognosis with a median overall survival time of 10–15 months, despite extensive standard treatment [1–3]. Following the initial diagnosis, GBM debulking surgery and intensified chemotherapy, external beam radiotherapy and a combination of radio- and chemo-therapy based on temozolamide (TMZ) are customarily used with a limited response rate or prolongation of overall survival time [4–7].

Treatment options for recurrent GBM are even more limited. The median overall survival in this group is less than 6 months [8]. Only 25% of patients with progressive or recurrent GBM can be considered for repeat surgery [6]. The benefit from resection of recurrent GBM has been described only in patients under 70 years of age, with smaller tumors (<50 cm^3) and a preoperative Karnofsky performance score greater than 80% [8, 9]. When unfavorable patient characteristics are excluded, reoperation is not an independent predictor of survival [9]. Re-irradiation remains a palliative option only for a selected group of patients (KPS > 60%, tumor size <40 mm and progression more than 6 months) [10]. Repeat TMZ therapy is not effective in recurrent GBM, and the median OS ranged from 5.3–6.6 months [11, 12]. Nitrosoureas, in single or combination therapy, remain as a second-line treatment option with the median OS 5.1–7.5 months, but suffer from a limited safety profile [13]. Eisenstat et al. assessed the combination of TMZ and afatinib (an irreversible EGFR blocker). PFS6 was 10%, and serious adverse events (grade III) were observed [14]. Similar results and limitations were observed by using the anti-angiogenic agent Bevacizumab, a monoclonal antibody to vascular endothelial growth factor (VEGF). In monotherapy trials with Bevacizumab in TMZ-pretreated patients with recurrent or progressive GBM, PFS6 ranged 25–42% and OS 6.5–9.2 months [15–18].

Local application of targeting agents has been proposed as an alternative approach [19, 20], which allows for high drug concentrations within the targeted tumor area by delivering treatment through stereotactically inserted port-a-cath systems. Insertion of impregnated drug wafers into the postoperative resection cavity [21] and convection-enhanced delivery methods for macromolecules [22] represent modifications of this approach.

Several ligand-receptor systems have been tested for local brain tumor therapy, e.g. anti-tenascin antibodies which target the extracellular matrix protein tenascin, or radiolabeled somatostatin analogues due to overexpression of the SSTR-2 receptor system in about 80% of gliomas [23–25]. The NK-1R receptor system is one of most promising targets because of much higher and more specific expression levels on GBM cells [26–28]. The ligand for NK-1R is substance P (SP). This regulatory peptide with a molecular weight of only 1.8 kD (in its DOTA-chelated form) is currently one of the best candidates for intratumoral treatment of the glial tumors of WHO grades II-IV [26].

A further critical point in therapeutic efficacy, which determines the toxicity profile, is the type of delivered energy and the range of the emitted radiation leading to tumor cell DNA damage. Beta particle-emitting radionuclides (e.g. ^{131}I, ^{90}Y, ^{177}Lu) mainly induce radical formation leading to DNA single strand breaks while alpha particles, such as those from ^{225}Ac and ^{213}Bi, directly induce DNA double strand and cluster breaks that lead to cell death with high probability. Furthermore, beta-emitters have a higher toxicity profile for adjacent normal brain tissue due to the more dissipative properties of beta radiation, while alpha emitters not only have a much higher energy, but also a very narrow tissue range of less than 0.1 mm, effectively limiting toxicity to normal brain cells [26]. Clinically, the safety and remarkable therapeutic efficacy of targeted alpha therapy using peptides labeled with the alpha emitters ^{225}Ac and ^{213}Bi has already been demonstrated for the treatment of neuroendocrine tumors [29], prostate cancer [30–32] and secondary GBM [33].

This paper presents the results of targeted alpha therapy with radiolabeled ^{213}Bi-DOTA-SP in 20 patients with recurrent GBM. The primary aim was to study the feasibility and toxicity of the approach. The secondary aim was to report the outcome of therapy in terms of the progression free survival (PFS) and overall survival (OS).

Materials and methods

Twenty patients (14 males and 6 females) with an average age of 48.2 ± 11.8 years, with histologically confirmed recurrent glial tumor WHO grade IV following a standard therapy (surgery, radio- and chemotherapy), were included in the study over the course of 3 years. The study was approved by the Ethical Committee of the Medical University of Warsaw. Informed consent was obtained from all individual participants included in the study.

The following inclusion criteria were applied:

- Histopathologically confirmed recurrent primary glial tumor, grade IV (WHO);
- Tumor volume below 90 mL as defined by the T1-weighed contrast-enhanced MRI;
- Absence of obstruction of CSF circulation or decompensating intracranial pressure;
- Karnofsky performance score > 40;
- No pregnancy or lactation;
- Age higher than 18 years, absence of psychological, familial, sociological conditions potentially hampering compliance with the study protocol.

Radionuclides and radiolabeling

^{225}Ac was obtained by radiochemical extraction from ^{229}Th sources at the Directorate for Nuclear Safety and Security of the Joint Research Centre of the European Commission in Karlsruhe, Germany, and at Oak Ridge National Laboratory, Oak Ridge, US and was loaded on a ^{225}Ac/^{213}Bi radionuclide generator using AG MP-50 cation exchange resin (Bio-Rad) [28–30].

^{68}Ge/^{68}Ga generators (iThembaLABS, Republic of South Africa and Galliapharm generator, Eckert & Ziegler, Germany) were used for labeling ^{68}Ga-DOTA-SP. DOTA-[Thi^{8}, Met$(O_2)^{11}$]-substance-P (Bachem, Austria and piChem, Austria) was used for preparing ^{213}Bi-DOTA-SP and ^{68}Ga-DOTA-SP. The labeling and quality control of ^{213}Bi-DOTA-SP and ^{68}Ga-DOTA-SP was performed as previously described [27].

Study protocol and injection of the radiopharmaceutical

One or two catheters connected to a subcutaneous port (Medtronic, USA) prepared for multiple punctures were implemented into the postsurgical cavity stereotactically or intratumorally, 2–4 weeks before treatment. To confirm the proper catheter position and to exclude connection with ventricular or cisternal CSF system, a local test injection into the port system was performed using gadolinium contrast agent (1.0–1.5 ml dissolved in saline solution in proportion of 1:20) for MRI imaging (Fig. 1) before therapy.

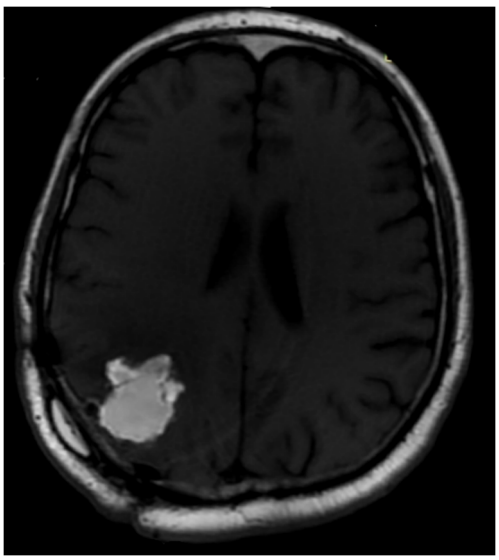

Fig. 1 MRI after injection to the cath-path reservoir of gadolinium contrast for confirmation of catheters' positions and exclusion of connection with CSF space of the ventricular and the cisternal system

For each therapeutic cycle, 1 to 3 injections (total up to 2.1 GBq, median 1.7 GBq) were performed depending on the activity of ^{213}Bi available from the ^{225}Ac/^{213}Bi generator.

Depending on the clinical status, patients were treated with 1–7 cycles (1 cycle in 8 patients, 2 cycles in 2 patients, 3 cycles in 2 patients, 4 cycles in 6 patients, 6 cycles in 1 patient, 7 cycles in 1 patient) of ^{213}Bi-DOTA-SP in 2 month intervals.

The MRI evaluation, injection procedure of ^{213}Bi-DOTA-SP and PET/CT after co-injection of ^{68}Ga-DOTA-SP with therapeutic doses of ^{213}Bi-DOTA-SP were performed as a previous described protocol [33].

Statistical methods

Parameters were characterized by the mean (± SD). The progression free survival (PFS) was defined as the time from the start of radioisotope treatment to the first evidence of progression or relapse, or to death. The 6-month PFS (PFS6), 12 month PFS (PFS12) and 18 month (PFS18) rate was defined as the number of subjects who had not progressed or died prior to 6 months/12 months from the date of their first dose of ^{213}Bi-DOTA-SP, divided by the number of subjects in the Cohort.

The overall survival (OS) from the diagnosis was defined as the time from the first diagnosis of the tumor to death from any cause (OS-d); OS from recurrence was defined as the time from the diagnosis of recurrence to death from any cause (OS-r). OS from the start of treatment was defined as the time from the first cycle of ^{213}Bi-DOTA-SP treatment to death from any cause (OS-t). OS, PFS, PFS6, PFS12 and PFS18 were calculated using the Kaplan-Meier estimator and compared using the log-rank test. Calculations were performed using GraphPad PRISM 5 (GraphPad Software Inc).

Multivariate analysis was performed using Cox proportional hazard models to reveal significant risk factors of worse patients' prognosis. Factors correlating with each other were excluded from the model consequently. Multivariate analysis was performed with Statistica v. 13.1 (TIBCO Software Inc., USA), p value <0.05 was considered as a statistically significant.

Results

Patient characteristics and functional status

The functional status of patients before the treatment and during the follow up was assessed using the Karnofsky status and Barthel Index. The median pre-therapeutic Karnofsky status was 70 (ranged from 40 to 100), and Barthel Index 90 (ranged from 35 to100). These parameters were evaluated during therapy and the follow up period. At the last course of therapy, the median Karnofsky status was 60 (ranged from 40 to 90) and

Barthel Index 65 (ranged from 45 to 100). Three months after the last course, the Karnofsky status was 60 (ranged from 40 to 80) and Barthel Index 60 (ranged from 30 to 95).

Depending on the clinical status, patients were treated with 1–7 cycles of ^{213}Bi-DOTA-SP in 2 month intervals. The median total injected activity was 3.3 GBq (ranged from 1.6 to 11.2 GBq).

MRI of the brain demonstrated postoperative changes with surgical margin enhancement and diffuse T2 and FLAIR changes consistent with edema and/or non-enhancing neoplasm. The median tumor volume measured in MRI (defined on T1 image) was 23.5 mL (ranged from 2.6 to 90 mL). Detailed data of patients are given in Table 1.

^{68}Ga-DOTA-SP post-therapeutic imaging

Post-therapeutic scans were performed to evaluate the tracer whole body biodistribution and expression of NK-1 receptor at the target site. In all cases, the uptake in the tumor area was increased as illustrated in a typical PET/CT image in Fig. 2. The whole body scans presented very low distribution in kidney and urine, with less than 5% of activity in the bladder. Consequently, ^{213}Bi activities found in the blood pool typically corresponded to less than 3% of the activities injected intratumorally and peaked at 1 h post-injection. Only in a few cases with leaky tumor cavity, the activity in blood was found to be <6% of the time-corrected injected dose.

Side-effects of treatment with ^{213}Bi-DOTA-SP

Local treatment with ^{213}Bi-DOTA-SP was well tolerated. In only 2 patients, some flush of face was observed as systemic SP effects following absorption of small amounts of tracer into the blood stream. In one patient, ventricular enhancement was seen in MRI without clinical symptoms (as an effect of flow of a small amount of ^{213}Bi-DOTA-SP to the ventrical system). This patient received high doses of corticosteroids. Epileptic seizures were observed in 10 patients within 2–5 days after injection, however, in all these cases, seizures were noted sporadically also before radioisotope treatment, despite treatment with anti-epileptic drugs. In one patient, transient (5 days) worsening of paresis was observed. No severe adverse events occurred.

Therapeutic outcome

Out of 20 evaluable patients, while one of them is still alive, 17 patients have died due to progressive disease and 2 patients died due to non-treatment related causes (pulmonary embolism in both cases). The median overall survival time from the primary diagnosis (OS-d) was 23.6 months and the median

Table 1 Detailed patients' data treated with ^{213}Bi-DOTA-SP

	Initials	Age	Tumor volume T1Vol [ml]	Karnofsky status	Barthel index	No of courses	Total activity [GBq]
1	ŚJ	51	14,7	70	70	2	3,1
2	JT	38	78,5	50	50	1	1,7
3	KE	58	38,2	80	95	6	11,2
4	ZA	53	26,2	60	70	1	2,1
5	WJ	37	53,7	70	100	4	7,8
6	GA	40	90,0	70	80	1	1,7
7	ML	54	2,6	70	100	4	7,6
8	KH	47	83,7	60	50	1	2,0
9	ŻZ	68	62,7	50	35	1	1,9
10	KI	41	15,8	90	100	3	5,0
11	JA	45	14,5	40	60	1	1,7
12	KG	57	33,4	90	90	1	1,8
13	RJ	27	6,6	100	100	7	10,8
14	GJ	53	20,8	60	85	1	1,6
15	GZ	43	14,5	90	100	2	3,4
16	SzE	48	20,2	90	100	4	7,4
17	KT	66	84,0	100	100	4	6,3
18	WA	22	73,6	60	85	4	6,2
19	ZA*	51	17,0	90	90	4	4,3
20	CP	65	14,3	70	95	3	3,1

*still alive

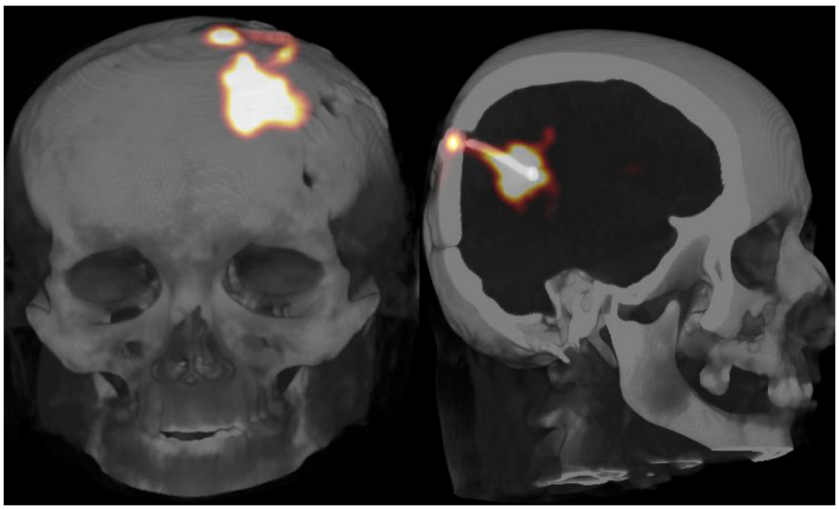

Fig. 2 PET/CT after local co-injection of 10 MBq ^{68}Ga-DOTA-SP with a therapeutic dose of ^{213}Bi-DOTA-SP into the resection cavity of a glioblastoma. Most of the activity is concentrated within the lesion, little activity remains in the capsule and within the catheter

survival time from the diagnosis of the recurrence (OS-r) was 10.9 months.

From the onset of ^{213}Bi-DOTA-SP treatment, the median PFS was 2.7 months and the OS-t was 7.5 months. The results are summarized in the Kaplan-Meier estimator curve (Fig. 3). 55% and 40% and 30% of patients stayed alive during the 6 month, 12-month and 18 month follow up from the start of radioisotope treatment, respectively. An example of the therapeutic effect, observed in a 58-year-old patient suffering from recurrent GBM grade IV that manifested 6 months after the initial diagnosis, is shown in Fig. 4. MRI (T1 weighted after contrast injection) examinations revealed stabilization of the disease at the 8 month follow-up. Overall, the patient survived 23.8 months after the start of ^{213}Bi-DOTA-SP therapy (OS-r: 25.9 months).

The median total tumor volume (T1Vol), defined as solid tumor parts, resection cavity and putative necrotic areas on the T1-weighed gadolinium enhanced MRI images, was 23.5 mL (range: 2.6 to 90 mL) before therapy. Further imaging analysis disclosed the median volume of solid tumor elements contrasted by gadolinium (T1VolCE) to be 22.1 mL (range: 2.2–86.5 mL), and necrotic areas plus resection cavity (T1VolNec) to be 3.7 mL (range: 0–14.8 mL). On the T2 images, the median volume of the pathological signal (T2Vol) was 127.1 mL (range: 23.3 and 301.9 mL).

Changes in tumor volumes were analyzed 2–3 months after the last dose of ^{213}Bi-DOTA-SP in 13 evaluable patients (not available in 6 patients due to death, in 1 patient due to allergy to gadolinium). T1Vol increased to 41.9 mL (range: 0.3–126.6 mL), T1VolCE increased to 33.6 mL (range: 0.3–105.7 mL), and T1VolNec increased to 6.0 mL (range: 0.0–21.1 mL), and, finally, T2Vol decreased to 107.4 mL (range: 27.1 and 207.1 mL). These alterations in tumor volumes, however, did not reach statistical significance.

Analyses of survival parameters according to the Karnofsky and Barthel status were performed. In patients with Karnofsky ≤60 ($n = 7$) vs Karnofsky ≥70 ($n = 13$), PFS was 3.7 vs 3.7 months, OS-d 23.7 vs 23.7 months, OS-r 12.5 vs 14.8 months, OS-t 8.9 vs 12.0 months, respectively. The obtained data were not statistically significant. There was no statistically significant difference between all analyzed groups and patients with Karnofsky ≤60 and with Karnofsky ≥70.

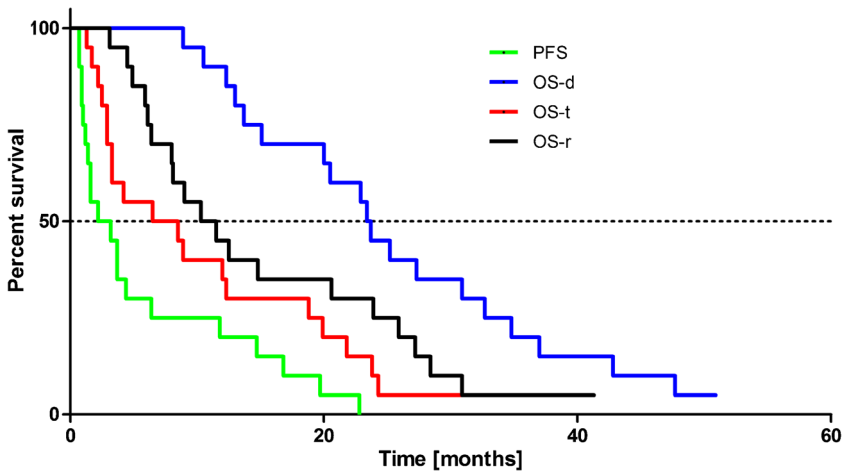

Fig. 3 The Kaplan-Meier estimator displays the progression free survival (PFS), overall survival following initial diagnosis (OS-d), overall survival following recurrence (OS-r) and overall survival after initiation of therapy with ^{213}Bi-DOTA-SP analogue (OS-t)

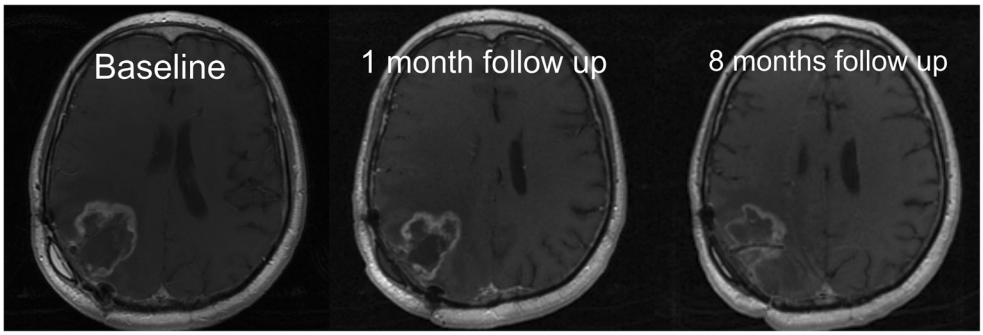

Fig. 4 MRI (T1 weighted after contrast injection) images of a 58-year-old male patient with recurrent GBM grade IV manifested 6 months after the initial diagnosis. Following standard treatment consisting of surgery, radio- and chemotherapy with TMZ, 6 cycles of ^{213}Bi-DOTA-SP were applied with a total activity of 11. 2 GBq. MRI images revealed stabilization of disease

In the group of patients with Barthel ≤70 ($n = 16$) vs Barthel ≥85 (n = 13), PFS was 3.7 vs 4.4 months, OS-d 23.4 vs 25.2 months, OS-r 12.5 vs 20.6 months and OS-t 8.9 vs 12.3 months, respectively. As in the previous analysis related to the Karnofsky status, no statistically significant difference was observed.

The NIH Recurrent GBM Scale provides stratification of prognosis of patients before surgery [9]. We used this scale to assess the influence of the same factors: KPS score ≤ 80, tumor volume ≥ 50 cm3, and MSM score ≥ 2 in PFS and OS in our group of patients. Our assessment rated 6 patients as NIH0, 7 patients as NIH1 and 7 patients as NIH2. No one in our group had NIH score 3.

In patients with NIH0 vs NIH1 vs NIH2, PFS was 5.4 vs 1.6 vs 0.9 months, OS-d 33.8 vs 20.0 vs 23.4 months, OS-r 27.8 vs 10.3 vs 8.1 months and OS-t 17.1 vs 4.2 vs 3.3 months, respectively. The statistical difference is shown in Table 2.

Because of inhomogeneous groups of patients, the Cox analysis to evaluate the effects of the relevant prognostic factors on the survival times and the independence of these variables was used.

Table 2 Statistical difference in PFS, OS-d, OS-r, OS-t according NIH scale

		p	Statistical significances
PFS	NIH0 vs NIH1	**0.0429**	**s**
	NIH1 vs NIH2	0.4025	ns
	NIH0 vs NIH2	0.0849	ns
OS-d	NIH0 vs NIH1	0.2543	ns
	NIH1 vs NIH2	0.9496	ns
	NIH0 vs NIH2	0.2567	ns
OS-r	NIH0 vs NIH1	**0.0190**	**s**
	NIH1 vs NIH2	0.7523	ns
	NIH0 vs NIH2	**0.0422**	**s**
OS-t	NIH0 vs NIH1	0.0606	ns
	NIH1 vs NIH2	0.7049	ns
	NIH0 vs NIH2	**0.0496**	**s**

* Bold entries statistically significant

Multivariate analysis revealed a strong positive influence of the number of courses and negative influence of the NIH score on patients' prognosis (Table 3). The hazard ratio (HR) was 1.90 for every point in the NIH score.

Therefore, an analysis in subgroups of patients receiving only one dose of ^{213}Bi-DOTA-SP and two or more doses of ^{213}Bi-DOTA-SP was performed. The median pre-therapeutic Karnofsky status was 60 (range: 40–90) in the group receiving only one dose of ^{213}Bi-DOTA-SP and 85 (range: 60–100) in the group receiving two or more doses of ^{213}Bi-DOTA-SP ($p < 0.005$), respectively, the Barthel Index was 65 (range: 35–90) vs 100 (range: 70–100) ($p < 0.01$). The median total tumor volume (T1Vol) was 48.1 mL (range: 14.5 to 90 mL) vs 16.4 mL (range: 2.6 to 84 mL) (ns, $p = 0.08$). PFS in the first group was 1.0 month, and in the second group 5.4 months, OS- r 6.2 vs 22.3 months, OS-t 2.7 vs 15.6 months, respectively ($p < 0.0001$) (Fig. 5). Therefore, the rapidly progressive cases all displayed larger tumor volumes and poorer clinical performance.

Discussion

In the present study, we report our experiences with local administration of ^{213}Bi-DOTA-SP in 20 patients with recurrent GBM. The treatment was well tolerated without severe adverse effects. These findings are in good agreement with the favorable safety profile observed in local ^{213}Bi-DOTA-SP therapy of nine patients diagnosed with secondary GBM reported earlier [33].

The median PFS from the start of radioisotope treatment in the group of patients with recurrent GBM was 2.7 months and PFS6 was 30%**.** The median OS from the initial diagnosis was 23.6 months and the median OS from the diagnosis of the recurrence was 10.9 months.

The optimization of patient recruitment must be taken into consideration in further studies. In our group of patients, there was no defined cut off-value of the Karnofsky and Barthel status, but in multivariate analysis, the results of TAT depend the NIH score, where Karnofsky is one of the components.

Table 3 Cox proportional hazards regression model

Parameter	Parameter estimate	P value	Hazard ratio	95% Confidential interval
Age (years)	0.0282	0.228	1.029	0.983 – 1.077
NIH score	**0.6405**	**0.049**	**1.898**	**1.000 – 3.599**
Number of courses	**-0.7196**	**0.002**	**0.487**	**0.312 – 0.759**

* Bold entries statistically significant

As a function of the NIH score we found statistically significant differences in PFS, OS-r and OS-t.

Additionally, multivariate analysis showed a strong statistically significantly impact of the number of cycles, with significant p value regardless of the small group of patients.

Patients who received only one dose of treatment were in worse clinical condition with rapid tumor progression and clinical deterioration within a couple of weeks after the first course of treatment. In the subgroup that received two or more doses of treatment, the clinical status at the time of treatment was stable or improved.

Statistically significant longer PFS and OS values were observed in the group that received 2 or more doses of ^{213}Bi-DOTA-SP (PFS 5.4 vs 1.0 months).

These data show that the proposed local treatment of recurrent GBM with high doses of radioisotopes represents a promising approach for this difficult clinical problem. OS observed in our group of 20 patients of 23.6 months compares favorably with historic control data: OS in GBM patients ranges between 9.7–15.9 months for first-line standard treatment [34–36]. OS was 6 months for patients with surgical resection only, 5 months for patients that received no intervention, 8 months for patients treated with chemotherapy alone, while 14 months for patients treated with surgery and adjuvant therapy combined ($p < 0.05$). Their surgical morbidity, however, was substantial (16 out of 33 patients, 48%) [37].

Table 4 The survival data of different therapies

Therapy	PFS 6 [%]	OS [months]
TMZ	27.3	3.6
TMZ + afatinib	10	
Bevacizumab	25-42	6.5-9.2
TAT	30	10.9

The RESCUE study which examined the effect of TMZ re-challenge based on the "temozolamide-free interval" showed that PFS6 and median OS were 27.3% and 3.6 months, respectively, for patients receiving re-challenge early, 7.4% and 1.8 months for patients receiving re-challenge after an extended period, and 35.7% and 3.7 months for patients receiving re-challenge after a prolonged interval [38]. In contrast to the local treatment, hematologic toxicity grades 3 and 4 during TMZ therapy were observed in most studies.

The survival data of different therapies is summarized in Table 4.

Critical issues for the successful local administration of radiopharmaceuticals are an adequate stereotactic positioning of catheters and a careful application of the compound to optimize its distribution. Co-injection of ^{68}Ga-DOTA-SP with therapeutic doses of ^{213}Bi-DOTA-SP [33] allows short time imaging of the tumor and study of the whole body distribution, and is recommended for monitoring adequate distribution. From a technical perspective, the implementation of therapy with ^{213}Bi-DOTA-SP in clinical practice does not pose particular challenges. ^{225}Ac /^{213}Bi radionuclide generators can be safely handled using established procedures and standard equipment typically available in nuclear medicine departments.

A limitation of our study lies in the small number of patients. To prove the efficacy of TAT with ^{213}Bi-DOTA-SP for treatment of recurrent GBM, more extensive studies with a larger number of patients are required. However, high

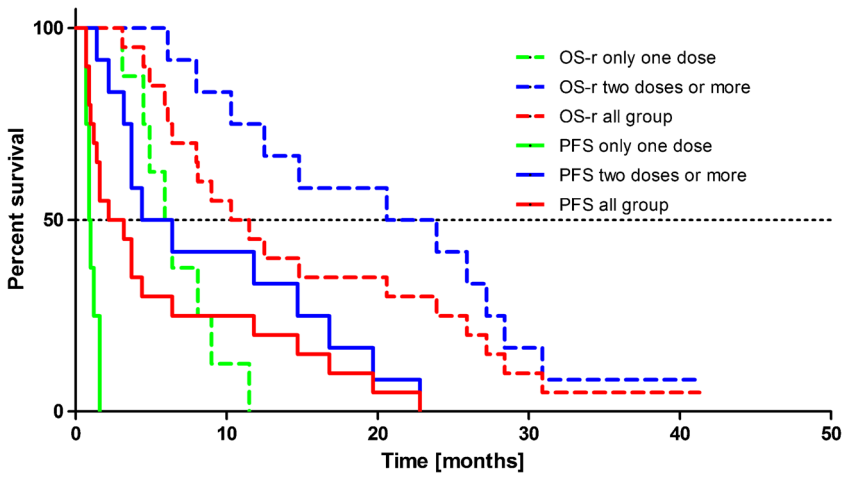

Fig. 5 The Kaplan-Meier estimator displays the progression free survival (PFS) and overall survival following recurrence (OS-r) in all patients, patients receiving only one dose of ^{213}Bi-DOTA-SP treatment and two or more doses of ^{213}Bi-DOTA-SP

activity ^{225}Ac /^{213}Bi radionuclide generators are currently still costly and in limited supply. For more extensive clinical studies, the supply of ^{225}Ac as mother nuclide for ^{225}Ac/^{213}Bi generators must be significantly increased beyond current levels. Accelerator-driven processes based on proton irradiation of ^{226}Radium [39] or ^{232}Thorium [40] that allow production of ^{225}Ac on a large scale have been developed and need to be further implemented to overcome these supply limitations.

Conclusions

Local treatment of recurrent GBM with ^{213}Bi-DOTA-SP is safe and well tolerated.

The median overall survival after recurrence of 10.9 months observed in our cohort of 20 patients compares favorably to standard treatments. More extensive studies are required to evaluate PFS and OS in a larger number of patients, and the optimization of patient inclusion criteria should be taken into consideration for further studies.

NIH scale seems to be good stratification factor for qualification to TAT.

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Compliance with ethical standards

This article does not contain any studies with animals performed by any of the authors.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent was obtained from all individual participants included in the study.

Conflict of interest All authors declare that they have no conflict of interest in relation to this article.

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