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REVIEW ARTICLE

An Overview of Targeted Alpha Therapy with ^{225}Actinium and ^{213}Bismuth

Alfred Morgenstern[1*], Christos Apostolidis[1], Clemens Kratochwil[2], Mike Sathekge[3], Leszek Krolicki[4] and Frank Bruchertseifer[1]

[1]*European Commission, Joint Research Centre, Directorate for Nuclear Safety and Security, Karlsruhe, Germany;* [2]*Department of Nuclear Medicine, University Hospital Heidelberg, Heidelberg, Germany;* [3]*Department of Nuclear Medicine, University of Pretoria and Steve Biko Academic Hospital, Pretoria, South Africa;* [4]*Department of Nuclear Medicine, Medical University Warsaw, Warsaw, Poland*

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Abstract: ***Background:*** Recent reports of the remarkable therapeutic efficacy of ^{225}Ac-labeled PSMA-617 for therapy of metastatic castration-resistant prostate cancer have underlined the clinical potential of targeted alpha therapy.

Objective and Conclusion: This review describes methods for the production of ^{225}Ac and its daughter nuclide ^{213}Bi and summarizes the current clinical experience with both alpha emitters with particular focus on recent studies of targeted alpha therapy of bladder cancer, brain tumors, neuroendocrine tumors and prostate cancer.

Keywords: Targeted alpha therapy, alpha emitter, actinium-225, bismuth-213, nuclide production, clinical application.

1. INTRODUCTION

The use of alpha emitters for cancer therapy has two distinct advantages over conventional therapies. The short range of alpha radiation in human tissue corresponding to only a few cell diameters (< 0.1 mm) allows the selective killing of targeted cancer cells while sparing surrounding healthy tissue. At the same time, the high energy of alpha radiation of several MeV and its associated high linear energy transfer leads to highly effective cell killing *via* DNA double strand and DNA cluster breaks, which are largely independent of cell cycle and oxygenation status [1, 2]. Consequently, alpha radiation can kill cells which otherwise exhibit resistance to treatment with beta- or gamma-irradiation or chemotherapeutic drugs, and can thus offer a therapeutic option for patients resistant to conventional therapies [3-5]. Only few alpha-emitting radionuclides are suitable for clinical application in targeted alpha therapy [6]. With the exception of the approved bone-seeking alpha emitter ^{223}Ra, by far most clinical experience is available with ^{225}Ac ($T_{1/2}$ = 9.9 d) and its short-lived daughter nuclide ^{213}Bi ($T_{1/2}$ = 46 min). Here we review methods for the production of ^{225}Ac / ^{213}Bi based on radiochemical extraction from ^{229}Th sources as well as accelerator driven processes and give an overview on the existing clinical experience with special focus on recent results in the treatment of bladder cancer, glioma, neuroendocrine tumors and prostate cancer.

*Address correspondence to this author at the European Commission, Joint Research Centre, Directorate for Nuclear Safety and Security, Karlsruhe, Germany; Tel: 497247951248; E-mail: alfred.morgenstern@ec.europa.eu

2. DECAY CHARACTERISTICS OF ^{225}AC AND ^{213}BI

^{225}Ac is a relatively long-lived alpha emitter with a half-life of 9.9 days [7]. It decays *via* a cascade of six short-lived radionuclide daughters to near stable ^{209}Bi ($T_{1/2}$ = 1.9x10^{19} y) (Fig. **1**) [8]. The predominant decay path of ^{225}Ac yields net four alpha particles with energies ranging from 5.8 to 8.4 MeV and associated tissue ranges of 47 to 85 µm [1]. In addition, the cascade includes two beta disintegrations of 1.6 and 0.6 MeV maximum energy. Gamma co-emissions useful for *in vivo* imaging are generated in the ^{225}Ac decay path from the disintegration of ^{221}Fr (218 keV, 11.6% emission probability) and ^{213}Bi (440 keV, 26.1% emission probability). Its long half-life and the multiple alpha particles generated in the decay chain render ^{225}Ac a particularly cytotoxic radionuclide.

^{213}Bi is a mixed alpha/beta emitter with a half-life of 46 min. It mainly decays via beta$^-$ emission to the ultra short-lived, pure alpha emitter ^{213}Po ($T_{1/2}$ = 4.2 µs, E_α = 8.375 MeV) with a branching ratio of 97.8% (Fig. **1**). The remaining 2.2 % of ^{213}Bi decays leading to ^{209}Tl *via* alpha particle emission (E_α = 5.549 MeV, 0.16%, E_α = 5.869 MeV, 2.01 %). Both ^{213}Po and ^{209}Tl finally decay via ^{209}Pb ($T_{1/2}$ = 3.25 h, beta$^-$) into long-lived ^{209}Bi ($T_{1/2}$ = 1.9x10^{19} y). The 8.375 MeV alpha particle emitted by ^{213}Po has a path length of 85 µm in human tissue. It is contributing more than 98% of the alpha particle energy emitted per disintegration of ^{213}Bi and can therefore be considered as mainly responsible for its cytotoxic effects. With 92.7 % the majority of the total particle energy emitted per disintegration of ^{213}Bi originates from alpha decay, while only 7.3 % of decay energy is contributed by beta particle emission, including the decay of ^{209}Pb [1]. The decay of ^{213}Bi is accompanied by the emission of a 440

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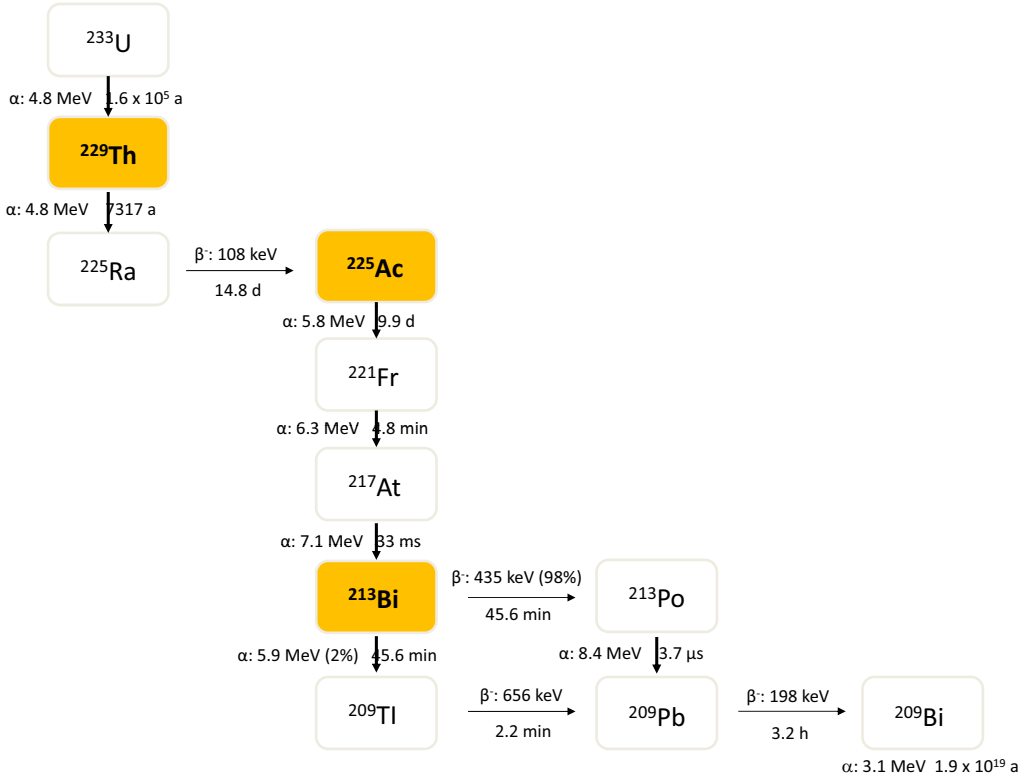

Fig. (1). Decay chain of ^{233}U.

keV photon (emission probability of 26.1%) that can be detected using SPECT gamma cameras equipped with commercially available high energy collimators, allowing the monitoring of ^{213}Bi-biodistribution and the conduction of pharmacokinetic and dosimetric studies.

3. PRODUCTION OF ^{225}AC AND ^{213}BI

3.1. Radiochemical Extraction from ^{229}Th

For more than two decades, the main process utilized for the production of ^{225}Ac and ^{213}Bi has been based on radiochemical extraction from ^{229}Th ($T_{1/2}$ = 7,317 y) [9] sources originating from the decay of fissile ^{233}U. To date, all clinical tests and the vast majority of pre-clinical research with ^{225}Ac and ^{213}Bi have been conducted using ^{225}Ac / ^{213}Bi obtained from the decay of ^{229}Th. Sources of ^{229}Th allowing the production of clinically relevant activities of ^{225}Ac / ^{213}Bi are available at the Directorate for Nuclear Safety and Security of the Joint Research Centre (JRC) of the European Commission in Karlsruhe, Germany (formerly known as Institute for Transuranium Elements) [10,11], Oak Ridge National Laboratory (ORNL), USA [12] and at the Institute of Physics and Power Engineering (IPPE) in Obninsk, Russia [13]. The ^{229}Th sources have been obtained by separation from aged, fissile ^{233}U originally produced by neutron irradiation of natural ^{232}Th. More recently, the isolation of a ^{229}Th source has also been reported from Canadian Nuclear Laboratories [14].

The production of ^{225}Ac from ^{229}Th at JRC Karlsruhe and ORNL has been described in detail in [10-12] and in a recent review [15]. JRC has been the first laboratory to provide ^{225}Ac / ^{213}Bi to clinical partners in the mid-1990's and since then, has produced approximately 13 GBq ^{225}Ac annually for preclinical research and clinical testing performed at JRC Karlsruhe or in collaboration with a wide network of clinical partners. The maximum annual production of ^{225}Ac at ORNL is approximately 33 GBq, while IPPE has reported a production of 22 GBq per year [13]. ^{225}Ac produced at JRC Karlsruhe and ORNL has been extensively applied for patient treatment and found safe for administration to humans. Direct clinical application of ^{225}Ac produced at IPPE has not been reported to date.

Overall the current worldwide production of ^{225}Ac from ^{229}Th amounts to approximately 68 GBq per year. This level of supply allows the conduction of pre-clinical studies and is sufficient for the treatment of several hundreds of patients per year, in particular when ^{225}Ac-labeled ligands are used where administered activities typically range from 4 – 50 MBq per therapeutic dose. However, the current supply of ^{225}Ac is certainly insufficient for widespread use and routine application in hospitals worldwide. Consequently, a variety of alternative methods for large-scale production of ^{225}Ac have been investigated.

3.2. Accelerator-Based Routes

Alternative ways of producing ^{225}Ac / ^{213}Bi, including the irradiation of ^{226}Ra targets using neutrons, protons, deuterons or gamma-rays and the irradiation of ^{232}Th targets with highly energetic protons have been investigated [16], but have not yet been implemented for a regular supply of ^{225}Ac / ^{213}Bi.

Among these routes, the production of ^{225}Ac by proton irradiation of ^{226}Ra targets in a cyclotron through the reaction

$^{226}Ra(p,2n)^{225}Ac$ is currently the most promising process for large-scale production of ^{225}Ac. The maximum cross-section for the nuclear reaction has been reported as 7.1 x 10^2 ± 68 mb at 16.8 MeV proton energy [17]. The production can be performed with high yields in a cost-effective manner in medium-sized cyclotrons at proton energies below 20 MeV. An important advantage of the process is that no other long-lived actinium isotopes such as ^{227}Ac ($T_{1/2}$ = 21.8 y) are co-produced, and chemical purification of the irradiated targets yields ^{225}Ac of high isotopic purity. Co-production of short-lived ^{226}Ac ($T_{1/2}$ = 29 h) and ^{224}Ac ($T_{1/2}$ = 2.9 h) according to the reactions, $^{226}Ra(p,n)^{226}Ac$ and $^{226}Ra(p,3n)^{224}Ac$ can be minimized through selection of appropriate proton energies. Furthermore, these short-lived actinium isotopes decay to low levels during the time required for target cooling and reprocessing. Although the handling of cyclotron targets made from ^{226}Ra is technically demanding, the production of ^{225}Ac via proton irradiation of ^{226}Ra is the method of choice for large-scale, cost-effective production and can be expected to provide the amounts of high purity ^{225}Ac required for widespread application in the mid-term future.

An alternative accelerator driven method for the production of ^{225}Ac has been developed in recent years based on the irradiation of ^{232}Th targets with high energy protons [18-23]. It has been demonstrated that spallation of ^{232}Th with high energetic protons available at large accelerators can produce significant amounts of ^{225}Ac and production yields in the range of several GBq have been reported for irradiations using intense proton beams and lasting 10 days [20, 21]. The spallation of ^{232}Th simultaneously leads to a significant co-production of radionuclidic impurities that must be removed through appropriate multi-step chemical separation steps [24-26]. However, the main disadvantage of the ^{232}Th based spallation process is the co-production of long-lived ^{227}Ac ($T_{1/2}$ = 21.8 y) at activity levels of 0.1 to 0.2% relative to the activity of ^{225}Ac at end of bombardment [22]. Since ^{225}Ac and ^{227}Ac isotopes cannot be chemically separated, the implications of the ^{227}Ac impurity for the clinical application of the ^{225}Ac product have to be carefully evaluated. Initial studies investigating the potential toxicity and dosimetric aspects of the ^{227}Ac impurity indicate that the consequences for patient safety might be acceptable [27]. However, issues related to the safe handling and disposal of long-lived ^{227}Ac in hospitals might compromise the clinical acceptance of the product and still have to be addressed.

4. ^{225}AC / ^{213}BI RADIONUCLIDE GENERATORS AND LABELLING CHEMISTRY OF ^{225}AC AND ^{213}BI

^{225}Ac / ^{213}Bi generators have been recently reviewed in detail [28]. Briefly, ^{225}Ac / ^{213}Bi generators based on AG MP-50 cation exchange resin are most established and have been used for all patient studies with ^{213}Bi to date. JRC Karlsruhe has developed a high activity generator system that allows reliable operation of the generator when loaded with activities up to 4 GBq ^{225}Ac [29]. A key feature of this generator is the homogeneous distribution of ^{225}Ac activity over approximately two-thirds of the generator resin in order to minimize radiolytic degradation of the organic resin and to assure reliable operation over several weeks. The generator has been successfully used for the preparation of therapeutic doses of up to 2.3 GBq ^{213}Bi-Substance P analogue (activity at the time of injection) for locoregional treatment of brain tumors.

The labelling chemistry of ^{213}Bi is well established. ^{213}Bi can be stably linked to biomolecules *via* derivatives of DTPA (diethylene triamine pentaacetic acid) or DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid). Derivatives of the open-chain chelating ligand DTPA are particularly suitable for ^{213}Bi-labelling of antibodies due to their fast complexation kinetics at room temperature. As Bismuth(III) complexes of the pre-organised derivative CHX-A"-DTPA (*N*-[(*R*)-2-amino-3-(*p*-aminophenyl)propyl]-*trans*-(*S,S*)-cyclohexane-1,2-diamine-*N,N,N*',*N*",*N*"-pentaacetic acid) are exhibiting very high *in vivo* stability [30, 31], CHX-A"-DTPA is the chelate of choice for ^{213}Bi-labelling of antibodies. Optimized protocols for ^{213}Bi labelling of antibodies in clinical settings allow the synthesis, sterile filtration and quality control of therapeutic doses within 15 min after end of generator elution [32].

Complexes of Bi(III) with the highly pre-organized, octadentate DOTA ligand are kinetically inert and also exhibit high stability *in vivo* [33, 34]. A synthesis protocol based on microwave heating to 95 °C at pH 9 was developed that allows rapid ^{213}Bi-labelling of DOTA-chelated peptides with radiochemical yields exceeding 99% and specific activities exceeding 50 MBq/nmol within less than 5 min reaction time [35]. Using this robust synthesis scheme, DOTA chelated peptides developed for peptide receptor radiotherapy, such as DOTA-Substance P targeting the neurokinin-1 receptor and the widely used somatostatin-analogs (*e.g.* DOTATOC, DOTATATE) can be labelled with ^{213}Bi in a straightforward manner.

Labeling of biomolecules with ^{225}Ac(III) is also typically performed *via* the DOTA chelate. Rapid synthesis can be performed *via* microwave heating to 95 °C for 5 min at pH 9 with radiochemical yields exceeding 99% at specific activities of 0.1 MBq /nmol [5]. For labelling of heat sensitive biomolecules at temperatures not exceeding 40 °C, slightly longer reaction times are required [36]. Recently, the 18-membered macrocycle N,N′-bis[(6-carboxy-2-pyridil)methyl]-4,13-diaza-18-crown-6 (H_2macropa) has been investigated for chelation of ^{225}Ac [37]. H_2macropa was found to rapidly bind kBq activities of ^{225}Ac at room temperature leading to a complex with high *in vivo* stability. Therefore H_2macropa might offer a valuable alternative for ^{225}Ac labelling of heat sensitive biomolecules. These highly promising results still need to be confirmed in further studies with therapeutic activities of ^{225}Ac in the MBq range.

5. CLINICAL EXPERIENCE WITH ^{225}AC AND ^{213}BI

Table **1** gives an overview of the current clinical experience with ^{225}Ac and ^{213}Bi. To date more than 500 patients have received ^{225}Ac- and ^{213}Bi-labeled radioconjugates for therapy of leukemia [38-40], Non-Hodgkins Lymphoma [41], malignant melanoma [42-44], bladder cancer [32, 45], glioma [46-48], neuroendocrine tumors [4, 49], and prostate cancer [5, 50, 51]. All clinical tests listed in Table **1** have been conducted using ^{225}Ac or ^{225}Ac / ^{213}Bi radionuclide generators produced and quality controlled at JRC Karlsruhe or ORNL. The radionuclides obtained from both sites have high radionuclidic and chemical purity, afford high labelling

Table 1. Overview of clinical experience with ^{225}Ac- and ^{213}Bi-labeled compounds.

Cancer type	Radioconjugate	Patients	References
Leukemia	^{213}Bi-HuM195mAb	49	[38,39]
-	^{225}Ac-HuM195mAb	36	[40]
Lymphoma	^{213}Bi-anti-CD20-mAb	12	[41]
Melanoma	^{213}Bi-9.2.27mAb	54	[42-44]
Bladder Cancer	^{213}Bi-anti-EGFR-mAb	12	[32,45]
Glioma	^{213}Bi-Substance P	68	[46-48]
-	^{225}Ac-Substance P	19	[48]
Neuroendocrine tumors	^{213}Bi-DOTATOC	25	[4]
-	^{225}Ac-DOTATOC	39	[49]
Prostate cancer	^{225}Ac-PSMA-617	190	[5,50,51]

yields and have been found safe for administration to humans by well-trained physicians following established protocols for radiolabeling and quality control.

In view of the currently strongly increasing interest in clinical application of particularly ^{225}Ac-labeled radioconjugates it is of utmost importance that ^{225}Ac obtained from sources other than JRC or ORNL is carefully evaluated for purity and safety before administration to humans is considered by physicians. ^{225}Ac sources of inferior purity may contain potentially toxic radionuclide impurities and may result in low radiochemical yields during radiolabelling. Appropriate purification and validation procedures must be implemented before application to humans. Synthesis and quality control of ^{225}Ac-labeled ligands for clinical application should be performed only by well-trained staff with experience in handling and analysing ^{225}Ac and its daughter nuclides.

5.1. Radioimmunotherapy with ^{213}Bi and ^{225}Ac

The pioneering first-in-human clinical investigations of ^{213}Bi-labeled antibodies for therapy of leukemia [38,39], melanoma [42-44] and Non-Hodgkins Lymphoma [41] have been reviewed in detail previously [15]. Based on the promising results of two studies investigating the safety and therapeutic efficacy of the ^{213}Bi-labeled anti-CD33 antibody lintuzumab for therapy of leukemia, clinical studies investigating the ^{225}Ac labelled analogue are conducted and are summarized in a separate review in this issue.

More recently, a pilot study on the locoregional treatment of bladder cancer (carcinoma in situ) using the ^{213}Bi-labelled anti-EGFR monoclonal antibody cetuximab has been conducted in collaboration of JRC Karlsruhe and Technical University Munich, Germany [32,45]. Carcinoma *in situ* (CIS) is a high-risk bladder cancer due to its tendency to invade neighbouring tissue. Standard treatment options for CIS include transurethral resection and intravesical instillation of Bacillus Calmette-Guerin (BCG). However, a significant fraction of patients eventually becomes unresponsive to BCG treatment and radical cystectomy is typically performed at this stage with an associated drastically reduced quality of life. In this pilot study of targeted alpha therapy, 12 patients scheduled for cystectomy were offered salvage treatment by intravesical instillation of 366-821 MBq ^{213}Bi-labelled anti-EGFR monoclonal antibody. 11 out of 12 patients were treated only once in this pilot study, while one patient was treated twice. The therapy was found to be safe and without any side effects, no activity of ^{213}Bi was detected outside the bladder. Remarkably, 3 out of 12 patients achieved complete remissions already after one (2/12) or two (1/12) treatments, thus avoiding or delaying cystectomy. These results show that locoregional targeted alpha therapy with ^{213}Bi-anti-EGFR-MAb is a promising new option for therapy of CIS. Escalation of the administered dose and increasing the number of treatments can be expected to further enhance the therapeutic efficacy and should be investigated in a follow-up study.

5.2. Peptide Receptor Alpha Therapy with ^{213}Bi and ^{225}Ac

Targeted peptide receptor alpha therapy with ^{213}Bi / ^{225}Ac has to date been clinically tested for treatment of brain tumors, neuroendocrine tumors and prostate cancer. Important advantages of utilizing low molecular weight ligands as targeting vehicles for ^{213}Bi and ^{225}Ac include fast tumor uptake and rapid clearance of unbound conjugates from circulation, thus reducing haematological toxicity. Internalizing ligands are particularly advantageous for application in combination with ^{225}Ac in order to harness the multiple alpha particles emitted in its decay chain.

5.3. ^{225}Ac- and ^{213}Bi-substance *P analogues* for Glioma Therapy

Peptide receptor alpha therapy of brain tumors has been tested for the first time in two patients as early as 1999 in collaboration of JRC Karlsruhe with University Hospital Basel [46] and subsequently, five more patients were treated in 2007/2008 [47]. The metabolically stabilized substance P analogue DOTA-[Thi^{8},Met$(O_2)^{11}$]-substance P was used as targeting vector. Substance P is the physiological ligand of the neurokinin-1 (NK-1) receptor that is consistently overex-

pressed in WHO grade II–IV gliomas and that has also been detected on tumour cells infiltrating the intra- and peritumoural vasculature [52]. The low molecular weight peptide (1.8 kDa) has been shown to diffuse rapidly and to be able to localise in remote satellite lesions [46]. In order to overcome the blood-brain barrier and to increase tumor uptake, administration of ^{213}Bi-[Thi^{8},Met(O$_2$)^{11}]-substance P was conducted locoregionally *via* an implanted catheter system with a subcutaneous port. The treatment was found to be safe without severe adverse effects. Remarkably, all 3 early patients diagnosed with grade II gliomas still do not show signs of recurrence or neurological impairments 10 years (2/3) and 18 years (1/3) after therapy.

Based on the promising outcome of these initial clinical experiences with a locoregional injection of ^{213}Bi-[Thi^{8}, Met(O$_2$)^{11}]-substance P, a follow-up investigation was conducted in collaboration of JRC Karlsruhe and Medical University Warsaw [48]. The patient group consisted of 61 patients with grade II to IV gliomas, including primary and secondary recurrent glioblastoma. Patients were treated with up to 14.1 GBq ^{213}Bi-[Thi^{8},Met(O$_2$)^{11}]-substance P, administered in up to 8 treatment cycles at two month intervals. Biodistribution was monitored via PET/CT after co-injection of ^{68}Ga-[Thi^{8},Met(O$_2$)^{11}]-substance P. The treatment was well tolerated, no severe adverse events were observed. PET/CT imaging demonstrated high retention of the radiolabelled peptide at the tumor site (Fig. **2**), less than 8% I.D. was found in the blood pool within five hours post injection. Fig. (**3**) shows magnetic resonance images of a patient with grade III glioma showing excellent response to locoregional treatment with ^{213}Bi-Substance P analogue. The patient was treated with 8 cycles of ^{213}Bi-[Thi^{8},Met(O$_2$)^{11}]-substance P with a cumulative activity of 14.1 GBq in two-month intervals. 44 months after administration of the 8th treatment cycle the patient is in excellent clinical condition. Overall analysis of the therapeutic efficacy in the 61 patients treated to date is ongoing, an interim subgroup analysis indicates prolonged survival times for grade IV patients in comparison to standard treatments [53].

Widespread glioma cell infiltration into normal adjacent brain areas is the main cause for failure of glioma treatment. Although low molecular weight substance P analogues exhibit relatively rapid diffusion, the short half-life of ^{213}Bi of 46 min might compromise the delivery of sufficient doses to remote tumor cells. In addition, high activity ^{225}Ac/^{213}Bi generators required for preparation of therapeutic activities

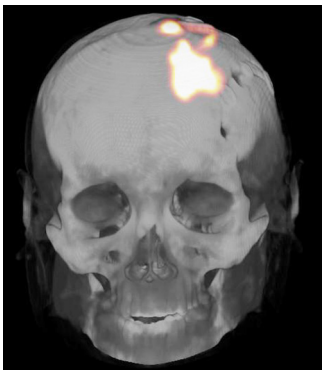

Fig. (2). ^{68}Ga-DOTATOC PET/CT image of a patient with recurrent glioblastoma after co-injection of 10 MBq ^{68}Ga-[Thi^{8},Met(O$_2$)^{11}]-substance P and 1.7 GBq ^{213}Bi-[Thi^{8},Met(O$_2$)^{11}]-substance P. The image taken at 1 hour post injection shows high retention of the radiolabelled compound in the tumor area, with some residual activity remaining in the catheter system.

in the multi GBq range are currently still very costly and in limited supply. Therapeutic application of longer-lived ^{225}Ac could overcome these limitations, and *in vitro* characterisation of the ^{225}Ac labelled derivative DOTA-[Thi^{8}, Met(O$_2$)^{11}]-substance P showed promising anti-tumor efficacy [54]. Recently an initial dose escalation study investigating the intratumoral/intercavitary injection of ^{225}Ac-DOTAGA-[Thi^{8},Met(O$_2$)^{11}]-substance P has been started [48]. To date, 19 glioma patients have been treated with activities ranging from 10 to 42 MBq ^{225}Ac-DOTAGA-[Thi^{8}, Met(O$_2$)^{11}]-substance P. The treatment has been well tolerated, analysis of therapeutic efficacy and patient recruitment is ongoing.

5.4. ^{225}Ac- and ^{213}Bi-DOTATOC for Therapy of Neuroendocrine Tumors

Peptide receptor alpha therapy of neuroendocrine tumors was first investigated clinically in collaboration JRC Karlsruhe and University Hospital Heidelberg. Twenty-five patients with multi-resistant neuroendocrine tumors refractory to therapy with ^{90}Y-/^{177}Lu-DOTATOC were treated with ^{213}Bi-DOTATOC. Administration was performed interarterially into the main tumor-feeding vessel in 21 patients, while 4 patients received intravenous injections. Cumulative activities ranging from 2.6 to 21 GBq of ^{213}Bi-DOTATOC were administered within 1-5 cycles in two-month intervals.

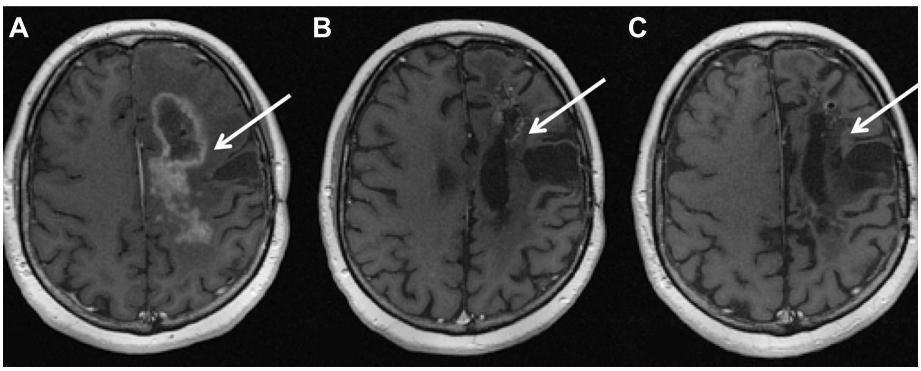

Fig. (3). Magnetic resonance images of a patient with grade III glioma showing excellent response to locoregional treatment with 8 cycles of ^{213}Bi-Substance P analogue with a cumulative activity of 14.1 GBq (2 months after first therapy (**A**); 8 months after 8th therapy (**B**); 33 months after 8th therapy (**C**)).

An interim analysis of the first 8 patients showed that chronic kidney toxicity was moderate and hematoxicity was less pronounced than with preceding beta therapies [4]. Remarkably, intravenous administration of 3.3 GBq of ^{213}Bi-DOTATOC in a patient with extensive bone marrow involvement did not lead to relevant acute haematological side effects, in accordance with the concept of selective tumor cell irradiation with the short-range alpha emitter. Although all patients reported in this investigation were in different challenging situations and had developed resistance against therapy with beta emitters, targeted alpha therapy with ^{213}Bi-DOTATOC resulted in a high number of long-lasting anti–tumour responses, including one complete remission. The results of this investigation provided convincing clinical data demonstrating that targeted alpha therapy can offer a valuable additional treatment option to patients refractory to therapy with beta emitters. Furthermore, the study also demonstrated that targeted alpha therapy with short-range alpha radiation is also effective against solid lesions, as impressively illustrated in the SNMMI image of the year 2012 [55]. ^{213}Bi-DOTATOC can evolve as a promising compound for therapy of neuroendocrine tumors once the supply limitations for high activity ^{25}Ac/^{213}Bi generators are resolved.

Therapy of neuroendocrine tumors using ^{225}Ac-DOTATOC was clinically tested in a follow-up investigation with 39 patients with progressive neuroendocrine tumors [56]. The investigation was conducted as an empiric dose escalation to find the Maximum Tolerable Dose (MTD) of a single cycle and fractionation concepts. The MTD of a single cycle ^{225}Ac-DOTATOC was considered to be 40 MBq. Multiple fractions were tolerated with 25 MBq every 4 months or 18.5 MBq every 2 months. Cumulative activities of 75 MBq were found tolerable in regard to delayed toxicity. The observed radiologic treatment response was without clear preference of a particular fractionation concept. An example of a partial response observed in a patient with a multi-resistant neuroendocrine tumor after two treatment cycles with 16 MBq (1st cycle) and 42 MBq (2nd cycle) ^{225}Ac-DOTATOC is shown in Fig. (**4**).

5.5. ^{225}Ac- PSMA-617 for Therapy of Prostate Cancer

The implementation of ^{225}Ac-PSMA-617 for therapy of metastatic castration-resistant prostate cancer constitutes a major advancement in targeted alpha therapy [57]. ^{225}Ac-PSMA-617 was first developed and characterised *in vitro* at JRC Karlsruhe in 2013/2014 and a microwave-assisted protocol for reliable synthesis and quality control of clinical doses was established. Based on the first reports of the promising clinical efficacy of PSMA-617 labelled with the beta emitter ^{177}Lu and the enhanced cytotoxicity of alpha compared to beta emitters, the concept of combining ^{225}Ac with the ligand PSMA-617 seemed highly promising. The key features of the pharmacokinetics of PSMA-617, including its fast tumor uptake, high internalization rate, extended tumor retention and rapid clearance of unbound ligand, are highly favourable for combination with an alpha emitter with a half-life of several days and multiple alpha emissions in its decay chain. Clinical testing is currently conducted in collaborations of JRC Karlsruhe with University Hospital Heidelberg, Steve Biko Academic Hospital Pretoria and Technical University Munich.

A dosimetry estimate comparing ^{225}Ac-PSMA-617 and ^{213}Bi-PSMA-617 demonstrated that short-lived ^{213}Bi is an inferior choice for targeted alpha therapy with PSMA-617. ^{213}Bi-PSMA-617 suffers from higher perfusion-dependent off-target radiation and a longer biological half-life of PSMA-617 in dose-limiting organs than the physical half-life of ^{213}Bi [58]. To our knowledge, there are no reports to date on the clinical application of ^{213}Bi-PSMA-617 except for a single case report and hence the subject is not discussed further [59].

The first report of the remarkable therapeutic efficacy of ^{225}Ac-PSMA-617 in patients with late-stage metastatic castration-resistant prostate cancer (mCRPC) presented complete remissions observed in two patients in highly challenging situations [5]. To develop a standardized treatment protocol for ^{225}Ac-PSMA-617 therapy in advanced-stage mCRPC patients, a dosimetry estimate was calculated on the basis of time–activity curves derived from serially obtained ^{177}Lu-PSMA-617 scans and salvage therapies empirically conducted with 50 to 200 kBq/kg of ^{225}Ac-PSMA-617 were evaluated retrospectively regarding toxicity and treatment response. For advanced-stage patients, a treatment activity of 100 kBq/kg of ^{225}Ac-PSMA-617 per cycle repeated every 8 weeks was found to present a reasonable trade-off between toxicity and biochemical response [50]. An interim analysis

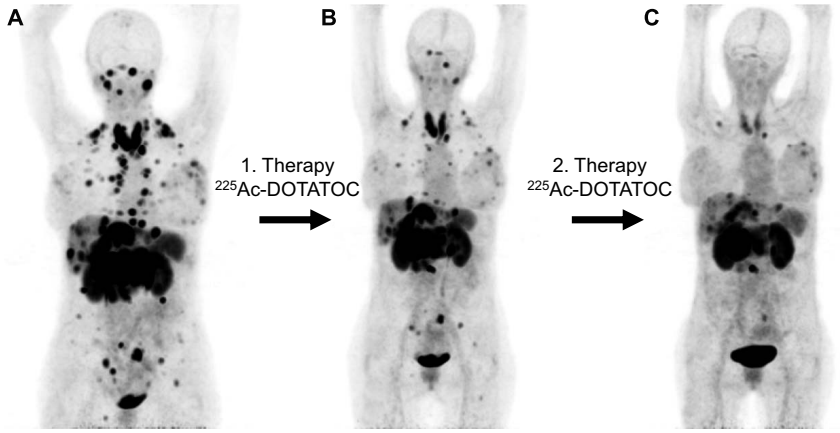

Fig. (4). ^{68}Ga-DOTATOC PET/CT images of a patient with a multi-resistant neuroendocrine tumor showing partial response after two treatment cycles with 16 MBq (1st cycle) and 42 MBq (2nd cycle) ^{225}Ac-DOTATOC. (**A**): before therapy (Oct 2011); (**B**): 4 months after first therapy with 16 MBq ^{225}Ac-DOTATOC (Feb 2012); (**C**): 3 months after second therapy with 42 MBq ^{225}Ac-DOTATOC (May 2012).

of the efficacy of this treatment protocol was conducted in a retrospectively analysed group of forty patients with mCRPC. Evaluation of PSA and radiological response demonstrated remarkable anti-tumor activity of ^{225}Ac-PSMA-617 and swimmer-plot analysis indicated the promising duration of tumor-control, especially taking into account the unfavorable prognostic profile of the selected advanced-stage patients. Xerostomia (dry mouth syndrome) was the main reason to discontinue therapy or to refuse additional administrations, indicating that further modifications of the treatment regimen with regard to side effects might be necessary to further enhance the therapeutic range [51]. One of the excellent examples of the therapeutic efficacy of ^{225}Ac-PSMA-617 in a patient with mCRPC that was progressive under conventional therapy is shown in Fig. (**5**). The patient was treated at Steve Biko Academic Hospital, Pretoria, with two cycles of ^{225}Ac-PSMA-617 with a cumulative activity of 14 MBq. Restaging with ^{68}Ga- PSMA PET/CT after 5 months showed a remarkable molecular imaging response. This patient also demonstrated a biochemical response with a decrease in PSA level from 1,301 to <0.05 ng/mL.

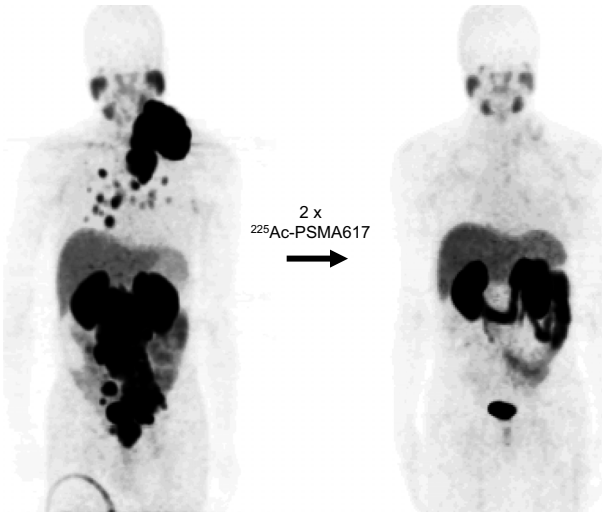

Fig. (5). Excellent response to therapy after 2 cycles of ^{225}Ac-PSMA-617 demonstrated by ^{68}Ga-PSMA-11 PET/CT images of patient with metastatic castration-resistant prostate cancer before (left panel) and after (right panel), with decrease in serum PSA level from 1,301 to <0.05 ng/mL. The patient was treated at Steve Biko Academic Hospital, Pretoria, with two cycles of ^{225}Ac-PSMA-617 with a cumulative activity of 14 MBq.

CONCLUSION

The recent reports on the remarkable therapeutic efficacy of ^{225}Ac-PSMA-617 for the therapy of mCRPC have significantly sparked interest in the clinical application of targeted alpha therapy. The implementation of ^{225}Ac-PSMA-617 does not only provide a promising therapeutic option for the second most frequent cancer in men, but also successfully underlines the significant potential of the concept of targeted alpha therapy as such. The clinical data recently obtained on targeted alpha therapy of neuroendocrine tumors and prostate cancer convincingly show that therapy with alpha emitters can overcome resistance to therapy with conventional drugs and also with beta emitters and can offer a valuable additional treatment option to patients that have failed established treatments. The combination of ^{225}Ac or ^{213}Bi with low molecular weight peptide ligands seems particularly promising due to the favourable pharmacokinetics of these ligands. The clinical experience with locoregional treatment of glioma with ^{225}Ac- and ^{213}Bi-labelled substance P analogues is promising and needs to be validated further. The intravesical therapy of bladder cancer with ^{213}Bi-anti-EGFR MAb is an intriguing approach that certainly deserves further study. For all these promising novel approaches formal clinical studies are highly warranted to compare the safety and efficacy against approved therapies under controlled conditions.

To satisfy the increased clinical demand for ^{225}Ac, accelerator driven production routes, preferably based on proton irradiation of ^{226}Ra in medium energy cyclotrons, should be rapidly implemented. In general, the safety of ^{225}Ac obtained from alternative sources should be carefully evaluated before its administration to humans is considered. ^{225}Ac and ^{213}Bi are highly cytotoxic radionuclides that can provide remarkable benefit to cancer patients. Their clinical application should be conducted by well-trained physicians, following established protocols and guidelines for radiolabeling and quality control.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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