^{225}Ac-Labeled Somatostatin Analogs in Neuroendocrine Tumors Management

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The widespread use of peptide receptor radionuclide therapy (PRRT) represents a major therapeutic breakthrough in nuclear medicine, particularly since the introduction of ^{177}Lu-radiolabeled somatostatin analogs. These radiopharmaceuticals have especially improved progression-free survival and quality of life in patients with inoperable metastatic gastroenteropancreatic neuroendocrine tumors expressing somatostatin receptors. In the case of aggressive or resistant disease, the use of somatostatin derivatives radiolabeled with an alpha-emitter could provide a promising alternative. Among the currently available alpha-emitting radioelements, actinium-225 has emerged as the most suitable candidate, especially regarding its physical and radiochemical properties.

actinium-225 radionuclide production radiolabeling targeted radionuclide therapy targeted alpha-therapy radiobiology neuroendocrine tumors radiopharmaceuticals 225Ac–DOTATATE

1. Introduction

1.1. About Neuroendocrine Tumors

Neuroendocrine tumors (NETs) form a heterogeneous group of malignancies with a wide variety of histology and nomenclature. The term “neuroendocrine” is used to describe cells that are widely spread throughout the body, with both neurological and endocrine characteristics [1]. Neurological properties are based on the presence of dense granules similar to those found in serotonergic neurons that store monoamines [2]; endocrine properties refer to the synthesis and secretion of such mediators [3]. Thus, this broad definition includes neoplasms occurring in nerve structures (e.g., ganglia and paraganglia), in straight endocrine organs (e.g., pituitary gland, thyroid, parathyroid or adrenal) and in the diffuse neuroendocrine system of various organs.

1.2. Somatostatin Receptors and Octreotide Analogs

Although NETs are heterogeneous diseases in their pathophysiology and clinical expression, they usually share the characteristic of overexpressing somatostatin receptors (SSTRs) [4]. Five SSTR subtypes are described (SSTR1 to SSTR5), SSTR2 being the most frequently encountered in differentiated NETs [5]. However, several subtypes can be expressed concomitantly on tumor cells in various combinations and proportions [6][7]. NETs overexpressing SSTRs most often have a gastrointestinal, pancreatic, bronchial, pulmonary, or even thymic or breast origin.

SSTRs belong to the G-protein-coupled receptor family and are localized at the cell membrane. Their natural peptide ligand, somatostatin, is found in humans under two different forms: one of 14 amino acids (SS-14) and one of 28 amino acids (SS-28) (**Figure 1**) [8][9]. Natural somatostatin has been shown to be unsuitable for in vivo use due to its short plasma half-life (about 3 min) [10]. Analogues of this hormone, more resistant to enzymatic degradation, have therefore been developed by making various modifications to the natural molecule [11][12]. The introduction of D-series amino acids to improve in vivo stability, the retention of the minimum chain length to maintain biological activity, the use of the hexapeptide motif Cys-Phe-D-Trp-Lys-Thr-Cys and the elongation of the N- and C-terminal ends allowed the characterization, in 1982, of the most stable active somatostatin analog known as octreotide (**Figure 1**) [13].

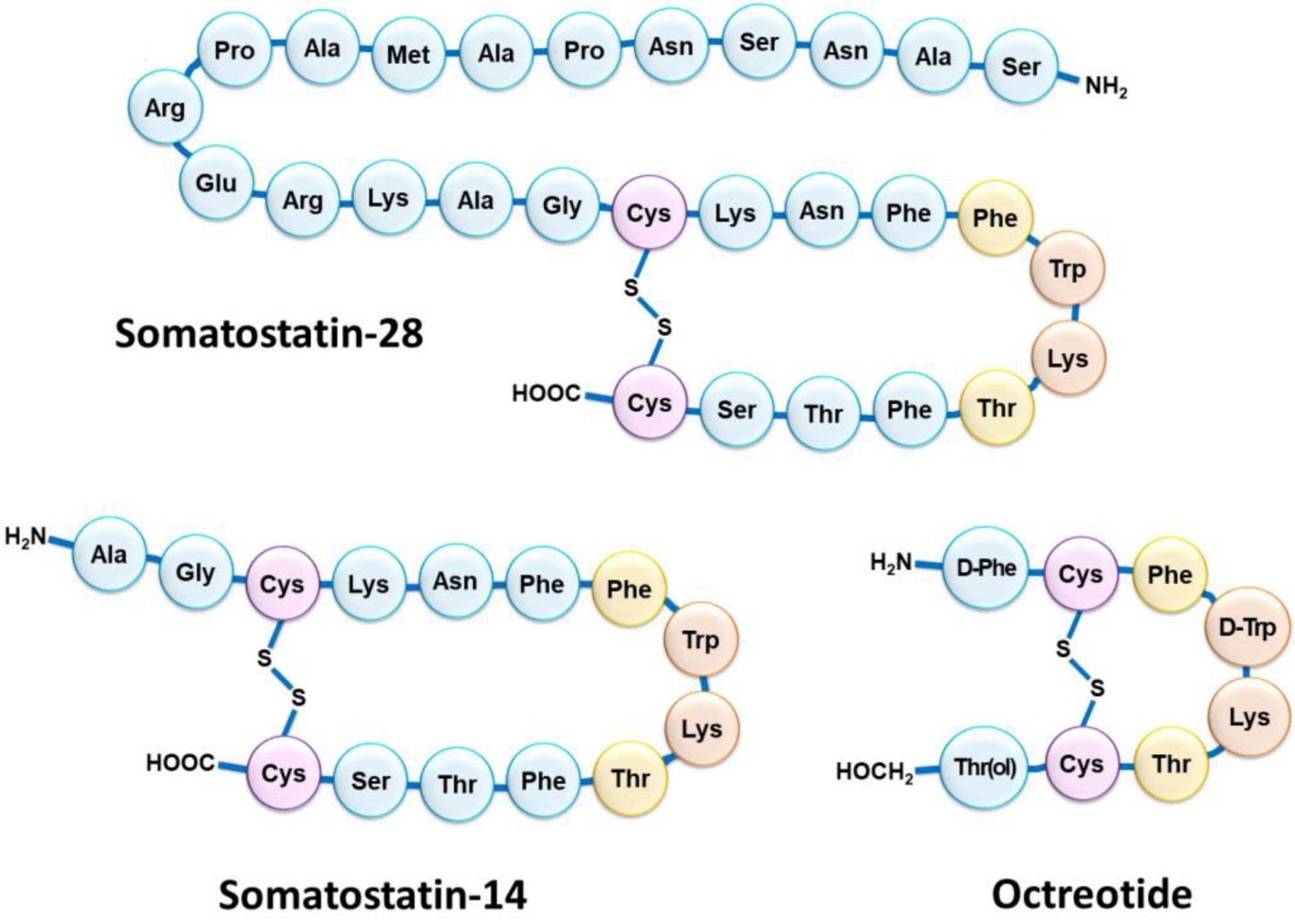

Figure 1. Schematic structure of the two natural isoforms of somatostatin (SS-14 and SS-28) and octreotide. The amino acid residues Cys (purple) form an intramolecular disulfide bridge; the amino acid residues Trp and Lys (orange) included in a β-turn are necessary for biological activity; the nearby amino acid residues Phe and Thr (yellow) are in favor of good biological activity but accept slight modulation.

1.3. SSTR Targeting for Peptide Receptor Radionuclide Therapy

Radionuclide therapy consists of the administration of a vector molecule labeled with a particle-emitting radioelement (either β or α) for therapeutic purposes. This approach is called radiopeptidotherapy or peptide receptor radionuclide therapy (PRRT) in the case of NETs, as the vector molecules used so far have been somatostatin analogs functionalized by a chelating agent [14]. This treatment method is recommended for metastatic or inoperable diseases with a positive expression of SSTR2. In NET radiopeptidotherapy, a first generation of molecules containing the Auger-emitter ^{111}In was developed and evaluated [15][16][17][18], followed by a second generation of PRRT agents radiolabeled with the beta-emitter ^{90}Y [19][20][21][22]. Subsequently, in the early 2000s, ^{177}Lu–[DOTA^{0},Tyr^{3}]octreotate emerged as an advantageous alternative, emitting both β- and γ-radiation [23]. The β- particles of ^{177}Lu are characterized by a maximum energy E_{max} of 0.5 MeV and a mean energy of 133.3 keV (lower than the ^{90}Y E_{max} of 2.28 MeV and E_{mean} of 932.9 keV, respectively, improving the irradiation of small tumors) [24] and an average path in the tissues of 2 mm (also lower than the ^{90}Y tissue penetration of 11 mm). This radioelement is characterized by a physical half-life of 6.7 days.

1.4. PRRT Using Somatostatin Analogs Radiolabeled with Alpha-Emitters

Although β-PRRT remains an approved treatment for unresectable metastatic NETs, some tumors show resistance to β-emissions despite somatostatin receptor expression [25]. Furthermore, not all treated patients achieve partial or complete response following SSTR-targeting ^{177}Lu-PRRT, and relapse is often observed in the years post-treatment [26]. Thus, among the strategies considered in an effort to overcome these drawbacks, octreotide derivatives radiolabeled with alpha-emitting radionuclides have received particular attention [27]. Within this group of radioisotopes, radium-223 (alkaline earth metal, group 2) has been extensively studied both in vitro and in vivo, and has paved the way for the use of alpha-emitting radioelements in patients [28]. To date, radium-223 is used in its dichloride form for the treatment of symptomatic bone metastases in patients with castration-resistant prostate cancer, without known visceral metastatic disease. However, due to its particular chemistry, ^{223}Ra is not suitable for DOTA-peptide radiolabeling. Thus, a special interest has emerged for several α-emitting lanthanides (e.g., ^{149}Tb) and actinides (e.g., ^{227}Th and ^{225}Ac), as well as some radioelements from their decay chain (e.g., ^{213}Bi) to achieve a convenient complex formation with DOTA [29]. An initial preclinical evaluation of ^{213}Bi–DOTATOC showed its potential value in NETs resistant to ^{177}Lu-PRRT [30][31][32][33], these properties being promptly confirmed in the clinic [34].

2. Actinium-225: Decay Characteristics, Radiobiological and Dosimetry Considerations

2.1. Physical Properties of Actinium-225

Actinium-225 is a relatively long-lived pure alpha-emitter, with a half-life of 9.9 days that is well-suited for radionuclide therapy applications and for centralized industrial production, distant from the (pre)clinical user sites. It is formed from the ^{229}Th decay product ^{225}Ra and decays via a cascade of six short-lived daughter radionuclides to the nearly stable bismuth-209 (**Figure 2**) [35]. These intermediates include francium-221 ($t_{1/2}$ = 4.8 min, 6.3 MeV α-particle and 218 keV γ-emission), astatine-217 ($t_{1/2}$ = 33 ms, 7.1 MeV α-particle), bismuth-213 ($t_{1/2}$ = 45.6 min, 5.9

MeV α-particle, 1.4 MeV β-particle and 440 keV γ-emission), polonium-213 ($t_{1/2}$ = 4.3 µs, 8.5 MeV α-particle), thallium-209 ($t_{1/2}$ = 2.2 min, 3.9 MeV β-particle) and lead-209 ($t_{1/2}$ = 3.2 h, 0.6 MeV β-particle) before reaching ^{209}Bi. Overall, the predominant decay pathway of ^{225}Ac produces four alpha-particles with energies ranging from 5.8 to 8.5 MeV and associated tissue ranges of 47 to 85 µm. In addition, the cascade includes two main beta-disintegrations of 1.4 and 0.6 MeV maximum energy. Therefore, ^{225}Ac is considered as an in vivo radionuclide generator or a "nanogenerator" with regard to its decay chain.

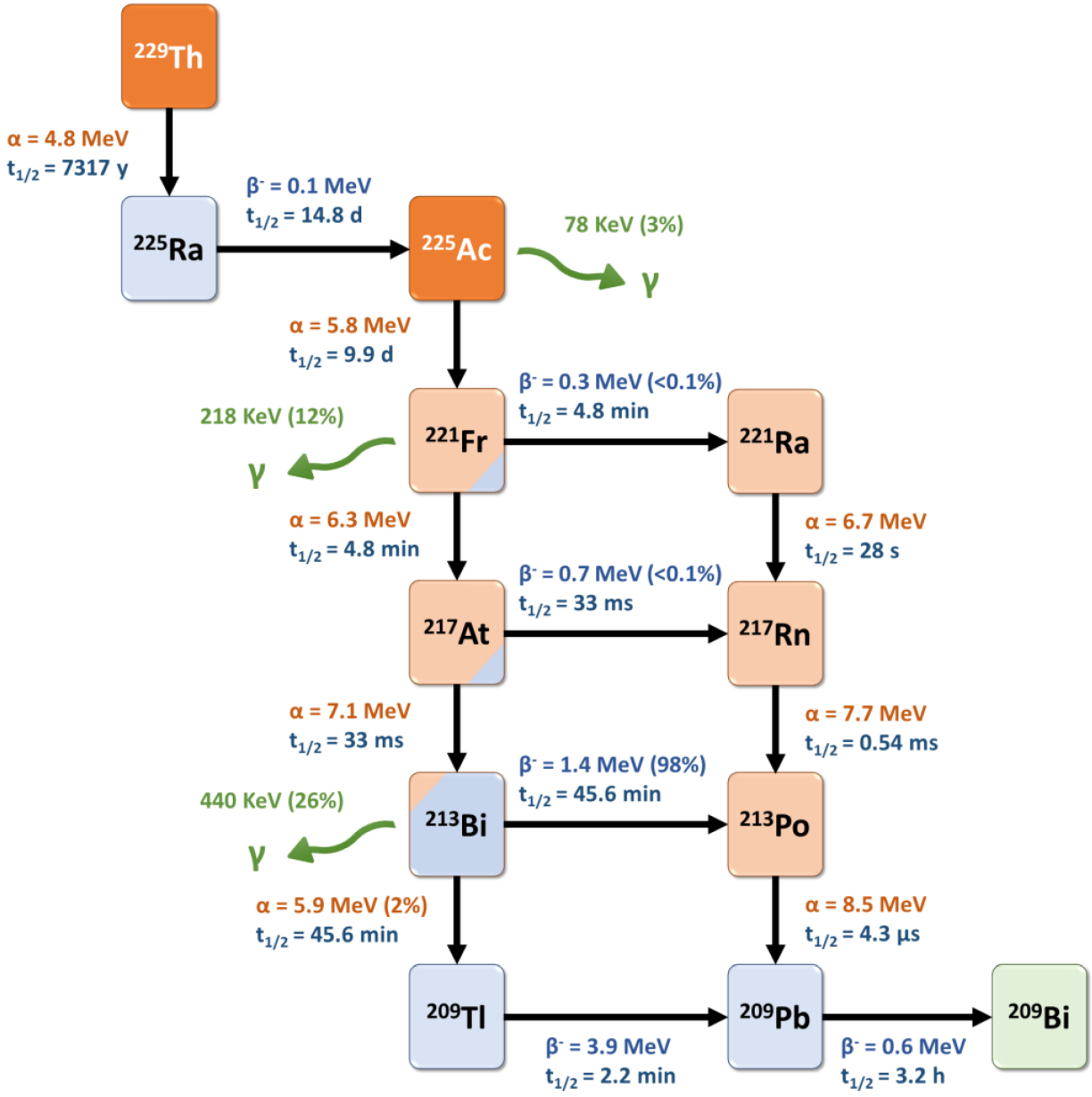

Figure 2. Decay scheme for one type of production and radioactive decay of ^{225}Ac.

2.2. Radiobiological Properties of Actinium-225

^{225}Ac appears as a particularly cytotoxic radionuclide, regarding its long half-life and the multiple alpha-particles generated in its decay chain.

Alpha-particles have a shorter range in tissues (<0.1 mm) than beta-particles (around 2 mm for ^{177}Lu), which allows the selective killing of targeted cancer cells and theoretically reduces the risk of toxicity to surrounding healthy tissues. In radiation therapy, tumor cell death is directly related to the absorbed doses (i.e., energy deposit, expressed in Grays, with 1 Gy = 1 J/kg) inducing DNA damage that may be direct or indirect (water ionization or excitation generating reactive oxygen species) after interaction with the ionizing particle or radiation. Damage to cell membranes and other cell components, such as mitochondria, may also result in cell death. For the same absorbed dose, the different types of radioactive particles do not have the same biological effects. Alpha-particle emitters have a higher linear energy transfer (LET), which represents the energy deposit by length (or volume), with values around 50–230 keV·µm^{-1} in water [36]. Compared to beta-particle emitters and for the same physical absorbed dose, alpha-particles generate a higher density of ionization and excitation along their track. This causes various types of damage that are more difficult to repair, especially DNA double-strand breaks, explaining the higher relative biological effectiveness (RBE) of alpha-particles (**Figure 3**).

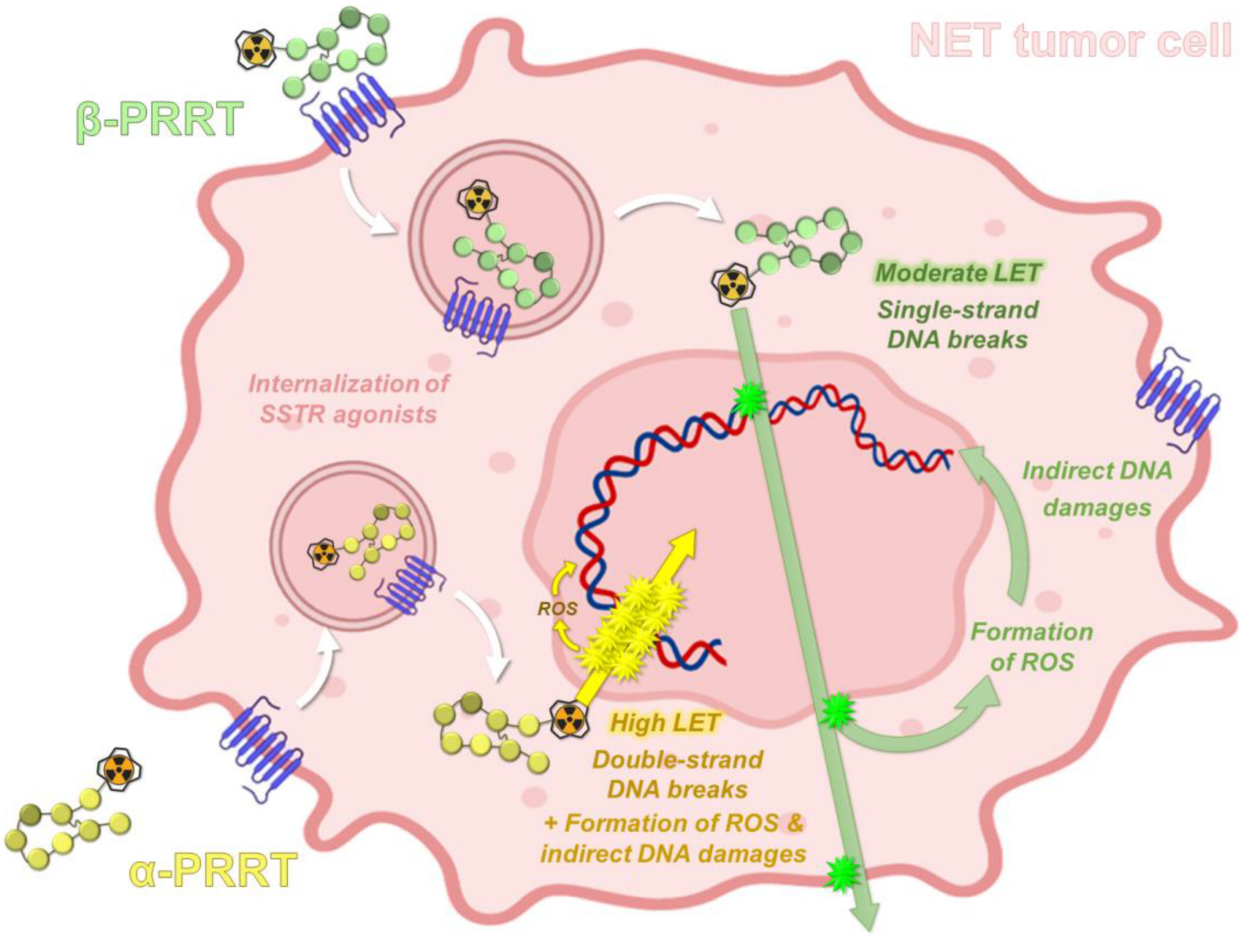

Figure 3. Principle of SSTR-targeting PRRT based on radiolabeled somatostatin analogues. PRRT: peptide receptor radionuclide therapy; SSTR: somatostatin receptors; LET: linear energy transfer; ROS: reactive oxygen species.

2.3. Dosimetry for Targeted Alpha-Therapy with ^{225}Ac

The purpose of dosimetry in radionuclide therapy is to understand or predict the likely biological effects, such as toxicity and efficacy, of a radiopharmaceutical drug on a patient. Evaluating the absorbed dose in relevant organs and tumors requires essential parameters including the spatial and temporal biodistribution of the administered radiopharmaceutical (in order to estimate the total number of radionuclide disintegrations in different tissues and tumors, determined by multi-time-point photon imaging) and information about both the physical properties of the radionuclide and the patient anatomy. In the case of alpha-emitter-labeled radiopharmaceuticals, accurate quantitative imaging is particularly challenging due to the low yield of imageable photons emitted, the very low activity administered, the short path length and heterogeneous distribution in tissue, and the multiple daughter radionuclide redistributions. However, biodistribution and dosimetry research involving ^{225}Ac has emerged in the last few years using different approaches. These include the direct detection of gamma-emissions by gamma-cameras [37][38], dosimetry based on a surrogate nuclide such as ^{177}Lu that can be imaged (particularly for [^{225}Ac]Ac–PSMA-617 treatment [39][40]), pharmacokinetic modeling [41], and small-scale and microdosimetry [42][43].

3. Radiochemical and Preclinical Development of [^{225}Ac]Ac–DOTATATE

3.1. Production of Actinium-225

Two isotopes of actinium, ^{227}Ac and ^{228}Ac, exist in nature within the natural decay chain of uranium-235 and thorium-232, respectively [44]. However, neither of these two isotopes is used in the clinic, with ^{228}Ac representing a minimal part of natural actinium and ^{227}Ac having a very long half-life ($t_{1/2}$ = 21.77 y). Therefore, ^{225}Ac is the only one of the more than 30 known actinium isotopes to be used in preclinical and clinical studies to date.

The main method for generating ^{225}Ac for clinical use is through radiochemical extraction following the decay of ^{229}Th ($t_{1/2}$ = 7397 y), which originates from reactor-bred ^{233}U [45][46]. The main sources of ^{229}Th in the world for ^{225}Ac used in preclinical and clinical studies are Oak Ridge National Laboratory (ORNL, Oak Ridge, TN, USA) [45], the Institute of Physics and Power Engineering (IPPE, Obninsk, Russia) [47], and the Directorate for Nuclear Safety and Security of the Joint Research Center of the European commission (JRC, Halstenbek, Germany), formerly the Institute for Transuranium Elements (ITE, Karlsruhe, Germany) [48]. More recently, the Canadian Nuclear Laboratories set up a ^{225}Ac production chain that could supply up to 3.7 GBq of this radioisotope annually [49].

Consequently, accelerator-based production techniques to obtain ^{225}Ac have been developed. The most promising approach to obtain ^{225}Ac at a large scale may be the cyclotron proton irradiation of a ^{226}Ra target, involving the ^{226}Ra(p,2n)^{225}Ac transformation [50][51]. With a high cross-section peak (710 mb) at 16.8 MeV, this convenient method can be performed on low-energy cyclotrons.

3.2. Chemistry of Actinium

3.2.1. Actinium in Aqueous Solution

Actinium is the chemical element with atomic number 89 and the first element of the actinide group, to which it gives its name. Nevertheless, actinium has rather similar chemical properties to lanthanum and other lanthanides. Actinium exists essentially in the +3 oxidation state in aqueous solution; additionally, Ac^{3+} is the largest +3 cation in the periodic table. It is also the most basic +3 ion due to its low charge density, directly related to its large size. Although the +3 state is the most stable in aqueous solution, the +2 oxidation state may also be encountered [52]. This second species is assumed because a reduction half-wave potential in a $^{225}Ac^{3+}$ aqueous solution can be observed. The progressive negative shift of this potential in the presence of increasing 18-crown-6 concentrations has been attributed to the formation of a complex between crown ether and divalent actinium [53]. However, without the effect of 18-crown-6 on the reduction of $^{225}Ac^{3+}$, the existence of stable $^{225}Ac^{2+}$ ions in aqueous solution remains unlikely regarding the low extraction yields of actinium using sodium amalgam in aqueous sodium acetate, an extraction technique usually efficient for lanthanides at a stable +2 oxidation state [54].

3.2.2. Coordination Chemistry of Actinium

The usefulness of actinium-225 as a radionuclide for therapeutic purposes has been limited for a long time by the unavailability of chelating agents that are both capable of being compatible with this bulky radionuclide and of controlling the fate of the resulting daughter emitters, particularly with regard to their alpha-recoil, which is related to the conservation of momentum laws that occurs upon release of an alpha-particle [55]. Nevertheless, the coordination chemistry of such a clinically relevant alpha-emitter has recently gained more and more interest [56].

Considering its low polarizability and despite its large ionic radius, the Ac^{3+} ion is considered a hard Lewis acid [57], showing a medium absolute chemical hardness value of 14.4 eV [58]. As such, it will complex more easily with hard ligands, such as anionic oxygen donors. The complexation reaction will preferentially occur under charge control and the acid–base bond will be essentially ionic. Indeed, Ac^{3+} displays an electrostatic interaction constant (E_A) value of 2.84 and a covalent interaction constant (C_A) value of 0.28 [56]. This predominance of charge interactions can be predicted from the character of the frontier molecular orbitals, which are centered on the nuclei of the donor and acceptor atoms; when these atoms are close together in space, the overlaps of the orbitals are negligible while the charge interactions are strong. This is mainly attributed to the density of the charge, which is very significant in ions of hard consistency.

The high ionic radius of the Ac^{3+} cation suggests that the most suitable chelators would be polydentate agents, with a high denticity between 8 and 12. Initial works investigated the suitability of linear polyaminocarboxylate chelators, such as CHX-A″-DTPA, for the chelation of the $^{225}Ac^{3+}$ cation [59][60]. These efforts were motivated by the advantageous radiolabeling kinetic properties of these ligands; however, the complexes obtained did not show sufficient in vivo stability. Subsequently, large macrocyclic chelators were considered and the 18-membered polyaminocarboxylic acid core HEHA was rapidly identified as particularly suitable for actinium complexation [60][61].

3.2.3. Relevance of DOTA in Actinium Radiopharmaceuticals

The in vivo fate of the ^{225}Ac–DOTA complex alone was initially shown to be safe, with only low activity amounts in liver and bone of BALB/c mice [60]. Subsequently, DOTA-bioconjugated constructs (either antibodies or peptides) also showed the sufficient stability of the complex, both in vitro [62][63][64][65] and in vivo [62][63]. Nevertheless, early studies raised some concerns about the compatibility of DOTA with actinium [60][66]. Indeed, the large ionic radius of the Ac^{3+} ion is not in favor of the good thermodynamic stability of the DOTA complex, which may also be subject to transmetalation with other cations. In order to minimize adverse in vivo effects associated with the loss of ^{225}Ac and its daughter radionuclides (especially ^{213}Bi, significantly increasing the kidney-absorbed dose [67]) from DOTA, several approaches have been considered, such as the co-administration of chelating agents or concomitant diuresis [68][69].

3.3. Somatostatin Analogs Radiolabeled with ^{225}Ac: Preclinical Studies

Only a few studies have reported preclinical efficacy results of ^{225}Ac-radiolabeled somatostatin analogues, due to this group of vector molecules having already been widely studied with beta-emitters such as ^{90}Y or ^{177}Lu [70].

Activities between 10 and 60 kBq were well-tolerated by the mice; however, activities over 30 kBq induced pathologic changes in the renal cortex, suggesting radiation-induced acute tubular necrosis in both the distal and proximal tubules. Similar results were obtained in another study on Sprague Dawley rats that received 111 or 370 kBq [^{225}Ac]Ac–DOTATOC and developed renal tubular nephrosis or renal glomerulopathy [71]. Only a slight accumulation in the liver was objectified, probably due to the release of free ^{225}Ac. After a single administration of the highest non-toxic activity (20 kBq), tumor weights 14 days after treatment were lower with [^{225}Ac]Ac–DOTATOC than with [^{177}Lu]Lu–DOTATOC (1 MBq), in accordance with previous studies investigating [^{213}Bi]Bi–DOTATOC [30][31].

4. Clinical Use of ^{225}Ac–DOTATATE

To date, [^{177}Lu]Lu–DOTATATE is considered as the standard PRRT treatment for GEP NETs. In this regard, the phase 3 randomized control trial NETTER-1 specifically demonstrated that [^{177}Lu]Lu–DOTATATE therapy plus long-acting octreotide was associated with a significantly longer PFS (28.4 vs. 8.5 months) than high-dose long-acting octreotide in advanced midgut GEP NET patients, although the OS endpoint of the study did not reach statistical significance (48 vs. 36.3 months, $p = 0.3$) [72][73]. Thus, this therapy offers a promising option as an early-line treatment for advanced NET [72][74]. Nevertheless, this type of pathology is known to frequently relapse, which may lead to patient retreatment. In this context, several studies have investigated the value of a renewed treatment with β-PRRT; furthermore, TAT protocols using somatostatin analogs, especially ^{225}Ac-based approaches, were also rapidly proposed as an alternative for patients that did not respond to β-PRRT.

Although it was used several years earlier, the first literature report of an alpha-PRRT with [^{225}Ac]Ac–DOTATOC in human dates from October 2018 [75]. Ten patients with metastatic NETs progressing after ^{90}Y– and/or [^{177}Lu]Lu–DOTATOC therapy were treated with intra-arterial [^{225}Ac]Ac–DOTATOC (~8 MBq). Overall, the treatment was well-

tolerated and effective, demonstrating its potential as a possible therapeutic alternative in advanced NETs resistant to β-PRRT.

Then, two major studies involving ^{225}Ac-labeled octreotide analogs were reported in patients with advanced-stage SSTR-expressing metastatic GEP NETs. These works primarily focused on the hematologic and renal toxicity of [^{225}Ac]Ac–DOTATOC, and on the long-term outcomes of this therapeutic, respectively.

5. Conclusions

Ahead of other α-emitters, TAT using ^{225}Ac-labeled somatostatin analogs seems to be a promising therapeutic approach for metastatic or inoperable NETs, especially considering its preliminary efficacy and safety results. Efforts to achieve the sufficient production of ^{225}Ac and extensive radiochemistry works aimed at optimizing the chelation of this radioelement reflect the high expectations for its clinical use, including in other pathologies such as prostate cancer with ^{225}Ac-labeled PSMA ligands [39][76][77][78][79][80], or even in hematological cancers such as acute myeloid leukemia [81]. However, the role of TAT versus β-PRRT in terms of OS, PFS and long-term toxicity is still difficult to define without formal comparative studies. Beforehand, the further investigation into the therapeutic use modalities of ^{225}Ac-radiolabeled somatostatin analogs will be required. Some of these questions may be answered by the ACTION-1 clinical trial (NCT05477576) [82], which is designed to determine the safety, pharmacokinetics, and recommended phase 3 dose of [^{225}Ac]Ac–DOTATATE and its efficacy compared to the investigator-selected standard of care therapy in patients with inoperable GEP NETs that progressed following ^{177}Lu–somatostatin analogues. Similarly, preliminary data on the efficacy of ^{225}Ac-labeled somatostatin analogs in other cancers such as paragangliomas [83] or pheochromocytomas [84] will need to be further consolidated. From a radiopharmaceutical perspective, the importance of developing a reliable method for measuring the radiochemical purity of ^{225}Ac conjugates produced in-house appears to be crucial and would certainly be a key requirement to obtain approval for clinical use from regulatory agencies. In addition, it will be interesting to develop a standardized dosimetric tool for the accurate estimation of adsorbed doses in target and non-target organs. For the time being, TATs constitute an emerging therapeutic alternative for patients with either highly resistant or late-stage disease, particularly in the context of compassionate access, depending on the country.

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